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REVIEW

Molecular and cellular pathways associated with chromosome 1p deletions during colon carcinogenesis

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Abstract: Chromosomal instability is a major pathway of sporadic colon carcinogenesis. Chromosome arm 1p appears to be one of the "hot spots" in the non-neoplastic mucosa that, when deleted, is associated with the initiation of carcinogenesis. Chromosome arm 1p contains genes associated with DNA repair, spindle checkpoint function, apoptosis, multiple microRNAs, the Wnt signaling pathway, tumor suppression, antioxidant activities, and defense against environmental toxins. Loss of 1p is dangerous since it would likely contribute to genomic instability leading to tumorigenesis. The 1p deletion-associated colon carcinogenesis pathways are reviewed at the molecular and cellular levels. Sporadic colon cancer is strongly linked to a high-fat/low-vegetable/low-micronutrient, Western-style diet. We also consider how selected dietary-related compounds (eg, excess hydrophobic bile acids, and low levels of folic acid, niacin, plant-derived antioxidants, and other modulatory compounds) might affect processes leading to chromosomal deletions, and to the molecular and cellular pathways specifically altered by chromosome 1p loss.

Keywords: chromosome 1p, colon carcinogenesis, molecular pathways, cellular pathways

Introduction

Chromosomal instability is a major feature of sporadic colon carcinogenesis.[1–11] Eighty-five percent of colorectal cancers are aneuploid, the remaining 15% being diploid.[5] Chromosome 1p deletions in colon tumors have been reported by laboratories from at least 15 countries around the world.[12–49] Chromosome 1p deletions occur at an early stage of colon carcinogenesis,[21,24,26–28,30,31,33,37,39,41–45] and are strongly linked to karyotypic evolution during colon cancer development.[43]

Many reports in the literature indicate that the macroscopically normal mucosa proximal or distal to a colon cancer exhibit aneuploidy (loss or gain of chromosomes or parts of chromosomes). Relevant to this review, Cianciulla et al[44] reported that deletions of chromosome 1p were simultaneously found in both the distant normal-appearing mucosa of 76% of patients who also harbored 1p deletions in their cancer. These findings indicate that the loss of chromosome 1p may be one of the "hot spots" among the numerous defects in the non-neoplastic mucosa associated with the possible initiation of colon carcinogenesis.[50–70]

The pioneering work of Paraskeva et al[71–75] indicated the likely involvement of chromosome 1p loss in in vitro immortalization[72,74] and in the progression of adenomas to carcinomas.[75] The functional importance of loss of distal 1p in colon tumorigenesis was demonstrated in 1993 by Tanaka et al[76] who introduced

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chromosomal band 1p36 into colon carcinoma cells and found that their tumorigenicity was suppressed.

Chromosome 1p deletions can affect distinct pathways of sporadic colon carcinogenesis, including both chromosomal instability and chromosomal instability-negative pathways. The underlying mechanisms associated with the loss of chromosome 1p that may contribute to genomic instabilty and drive colon carcinogenesis are loss of genes associated with DNA repair, spindle checkpoint function, apoptosis, multiple microRNAs (miRNAs), the Wnt signaling pathway, tumor suppression, antioxidant activities, and defense against environmental toxins.[77,78] Since centromeric instability and resulting telomeric fusions have been proposed as a mechanism for the loss of chromosome 1p,[79] the loss of genes located on chromosome 1p that function to ensure centromeric stability and telomere integrity, in turn, can exacerbate chromosomal instability throughout the genome. These 1p deletion-associated pathways that may lead to colon carcinogenesis will be reviewed at the molecular and cellular levels, and dietary factors that affect these pathways (eg, excess hydrophobic bile acids, and low levels of folic acid, niacin, plant-derived antioxidants, and other modulatory compounds) will be explored. It is likely that certain dietary factors prevent, initiate, or exacerbate genomic instability in colon epithelial cells and thus have importance for colon carcinogenesis.

Mechanisms of carcinogenesis associated with the loss of key genes on chromosome 1p

Chromosome 1, the longest human chromosome, is gene-dense with 3141 genes.[80] The genes located on chromosome 1 were identified with the assistance of the Weizmann Institute of Science websites:

GeneLoc (www.genecards.weizmann.ac.il/geneloc/index.shtml) and GeneCards – The Human Gene Compendium (www.genecards.org). Genes located on the *p* arm of chromosome 1 that are associated with protection against oxidative stress, DNA damage, mitotic perturbations, excessive cellular proliferation, development of apoptosis resistance, aberrant colonic cell differentiation, and environmental toxicity have been tabulated and the function of the gene products described (Tables 1–8). Since many of these genes have tumor suppressive capabilities, the simultaneous loss caused by a 1p deletion could initiate the formation of neoplastic clones and enhance tumorigenesis through Darwinian selection.[8]

Mechanisms protective against genomic instability

Cells with DNA damage, spindle damage, and dysfunctional telomeres signal DNA damage responses.[81–84] These DNA damage responses include the activation of numerous checkpoints that arrest the damaged cells in the G1, S, G2, or M-phase of the cell cycle, depending upon the nature of the damage or dysfunction and the stage of the cell cycle of the target cell. DNA-damage checkpoints are activated following direct damage to DNA.[85–91] Spindle assembly checkpoints are activated following damage to the mitotic machinery,[85,92–98] or as a result of DNA damage during mitosis.[99] Telomere checkpoints are activated by defective telomeres.[100–106] These checkpoints prevent the damaged cell from completing DNA replication and mitosis until all damage is repaired (Figure 1), and thus prevent 1) mutations that could be formed by replicating a damaged DNA template, 2) aneuploidy that could result from chromosome mis-segregation, and 3) telomere fusions that result in anaphase bridges, broken chromosomes, and translocations as a consequence of the well-known breakage–fusion–bridge cycles.[107–114]

However, cells with excessive direct DNA damage,[115–122] massive chromosome loss or chromosomal imbalances,[123] prolonged activation or inhibition of the spindle checkpoint pathways,[122–127] or excessively shortened or dysfunctional telomeres,[128–140] initiate a cascade of molecular events that ultimately leads to either caspase-dependent cell death,[141–143] caspase-independent cell death,[144] or a special form of apoptosis referred to as mitotic catastrophe[145–148] (Figure 2). (Brightfield micrographs are shown in Figure 3 illustrating the cellular alterations that accompany apoptosis [Figure 3A], mitotic perturbation [Figure 3B], mitotic catastrophe [Figure 3C], and micronuclei formation [associated with aneuploidy] [Figure 3D]). The cell-destructive and cell-protective pathways are downstream of a common signal transduction network that responds to DNA damage.[149] The repair/survival and non-repair/cell death pathways are probably activated simultaneously.[149] The repair, checkpoint, and cell death response to DNA damage are, however, well co-ordinated,[150] the interplay of positive and negative regulatory loops resulting in a delayed death response to DNA damage.[149]

DNA repair and the DNA damage response (DDR) (Table 1)

The genes on chromosome 1p associated with DNA repair or the DNA damage response (DDR) include CLSN, DCLRE1B (APOLLO), DDI2, GADD45α, MSH4, MUTYH,

Table 1 DNA repair and DNA damage response genes

Gene	Function
CLSN	Claspin homolog (*Xenopus laevis*); upstream regulator of checkpoint kinase 1 (Chk1) and triggers checkpoint arrest of the cell in response to inhibition of DNA replication or to DNA damage induced by ionizing and UV radiation; binds specifically to BRCA1 and Chk1 and facilitates the ATR-dependent phosphorylation of both proteins; Chk1 is required to maintain Claspin stability; ring-shaped DNA-binding protein with high affinity for branched DNA structures and associates with S-phase chromatin following formation of the pre-replication complex; acts as a sensor which monitors the integrity of DNA replication forks.
DCLRE1B	DNA cross-link repair 1B (PSO2 homolog, *S. cerevisiae*); aliases: APOLLO, SNM1B; one of several evolutionarily conserved genes involved in the repair of interstrand cross-links which prevent strand separation, thereby blocking transcription, replication, and segregation of DNA; functions in the HSP70-mediated DNA damage response; APOLLO is stabilized when bound to the telomere-binding protein TRF2, and protects human telomeres in S phase; reduced levels result in an increased number of telomere-induced DNA damage foci and telomeric fusions in S-phase, suggesting that APOLLO contributes to a processing step associated with the replication of chromosome ends; interacts with astrin (microtubule binding protein) and is required for the prophase cell cycle checkpoint in response to spindle stress.
DDI2	DNA-damage inducible 1 homolog 2 (*S. cerevisiae*); protein has aspartic-type endopeptidase activity; very little is known as to the function of this gene product in the DNA damage response.
GADD45α	Growth arrest and DNA-damage-inducible 45 alpha; multifunctional protein; responds to environmental stresses by mediating activation of the p38/JNK pathway via MTK1/MEKK4 kinase; the DNA damage-induced transcription of this gene is mediated by p53-dependent and -independent mechanisms; exhibits checkpoint function in response to oxidative DNA damage; responsive to p53 and modifies DNA accessibility on damaged chromatin; involved in base excision repair; stimulates DNA excision repair and inhibits entry of cells into S phase; level of expression modulated by glutathione peroxidase-1 and quercetin; deficiency associated with multidrug resistance; interacts with Aurora-A and inhibits its kinase activity; mediator of CD437-induced apoptosis; demethylation of 5′ CpG island in GADD45α leads to apoptosis; increased expression arrests the cell cycle at the G2/M phase; GADD45α-mediated apoptosis is activated by DNA mismatch repair; induces Bim dissociation from the cytoskeleton and translocation to mitochondria; regulates beta-catenin distribution and maintains cell-cell adhesion.
MSH4	MutS homolog 4 (*E. coli*); multifunctional protein; physically interacts with MSH5, MLH1, MLH3, RAD51, DMC1, and von Hippel-Lindau tumor suppressor-binding protein 1 during meiosis; required for reciprocal recombination and proper segregation of homologous chromosomes at meiosis; ATP binding by MSH4-MSH5 results in the formation of a sliding clamp that dissociates from the Holliday Junction crossover region embracing 2 duplex DNA arms; evidence is lacking at present for functional involvement of MSH4 and MSH5 in mismatch repair; in addition to meiosis, MSH4 and MSH5 are thought to play roles in mitotic DNA double strand break repair and the DNA damage response in human cells.
MUTYH	MutY homolog (*E. coli*); DNA glycosylase involved in oxidative DNA damage repair; the enzyme excises adenine bases from the DNA backbone where adenine is inappropriately paired with guanine, cytosine, or 8-oxo-deoxyguanosine (a major DNA lesion caused by oxidative stress); mutations in this gene result in heritable predisposition to colon and stomach cancer; the protein is localized to the nucleus and the mitochondria; excessive activity of MUTYH in response to oxidative DNA damage results in cell death. See text and Figure 4 for an in-depth discussion of the functions of MUTYH in base excision repair and cell death.
RAD54L	RAD54-like (*S. cerevisiae*); aliases: HR54, hRAD54, RAD54A. DNA repair and recombination protein RAD54-like; protein product is a double-stranded DNA-dependent ATPase belonging to the DEAD-like helicase superfamily (Swi2/Snf2 protein family), and shares similarity with *Saccharomyces cerevisiae* Rad54, a protein involved in the repair of DNA double-strand breaks through homologous recombination; belongs to the RAD52 epistasis group that additionally includes RAD50, RAD51, RAD52, RAD55, RAD57, RAD59, MRE11, and Nbs1/XRS2; the binding of Rad54 to double-stranded DNA utilizes the energy from ATP hydrolysis to induce topological changes in DNA, believed to facilitate homologous DNA pairing and stimulate DNA recombination in the Rad52 DNA repair pathway; essential for strand invasion of the homologous donor sequence and may involve disruption or movement of nucleosomes (chromatin remodeling activity) that might block joint molecule formation and/or branch migration; dissociates Rad51 from nucleoprotein filaments formed on single-stranded DNA; Rad54 oligomers (dimer to particles >40 nm in diameter) possess a unique ability to cross-bridge or bind double-stranded DNA molecules positioned in close proximity. The combination of the cross-bridging and double-strand DNA translocation activities of Rad54 stimulates the formation of DNA networks, leading to rapid and efficient DNA strand exchange by Rad51; also plays an essential role in telomere length maintenance and telomere capping in mammalian cells through the Rad51 recombination pathway.
TP73	Tumor protein 73; member of the p53 family of transcription factors involved in cellular responses to stress; the family members include p53, p63, and p73 which have high sequence similarity to each other allowing p63 and p73 to transactivate p53-responsive genes causing cell cycle arrest and apoptosis; regulated by tyrosine kinase c-Abl in the apoptotic response to DNA damage; induces apoptosis via PUMA transactivation and Bax mitochondrial translocation; inactivated by human papillomavirus E6 proteins; has a role in mitotic exit and caspase-independent cell death; regulates DRAM-independent autophagy that does not contribute to programmed cell death; has a role in E2F1-induced apoptosis; may be a tumor suppressor protein.

Table 2 Mitosis-related and spindle checkpoint genes

Gene	Protein function
APITD1	Apoptosis-inducing, TAF9-like domain 1; centromere protein and component of the CENPA-CAD complex found at the distal nucleosome; this complex is recruited to centromeres where it is involved in the assembly of kinetochore proteins, mitotic progression and chromosome segregation; has a role in apoptosis.
AURKAIPI	Aurora kinase A interacting protein 1; functions as a negative regulator of AURKA by degrading AURKA through several mechanisms involving the proteasomal pathway and ubiquitin-independent pathways involving antizyme 1; the inhibition of Aurora A has the effect of canceling the mitotic delay that occurs as a result of perturbation of cellular microtubules.
CCDC28B	Coiled-coil domain containing 28B; localizes to centrosomes and basal bodies.
CCNL2	Cyclin L2; a novel RNA polymerase II-associated cyclin located in nuclear speckles; transcriptional regulator involved in regulating the pre-mRNA splicing process; contains a RS region (arginine-serine dipeptide repeat) within the C-terminal domain which is the hallmark of the SR family of splicing factors; co-localizes with splicing factors; pro-apoptotic protein which modulates the expression of a critical apoptotic factor, leading to apoptosis.
CDC2L1	Cell division cycle 2-like 1 (PITSLRE proteins); aliases: CDK11B, p58CDC2L1, galactosyl transferase-associated protein kinase p58/GTA; a member of the p34Cdc2 protein kinase family known to be essential for eukaryotic cell cycle control; has multiple roles in cell cycle progression, cytokinesis, and apoptosis; during Fas or tumor necrosis factor-induced apoptosis, CDK11 p110 isoforms are cleaved by caspases.
CDC2L2	Cell division cycle 2-like 2 (PITSLRE proteins); aliases: CDK11A, PITSLRE protein kinase beta; this gene encodes a member of the p34Cdc2 protein kinase family and is in close proximity to CDC2L1, a nearly identical gene in the same chromosomal region; has multiple roles in cell cycle progression, cytokinesis (maintains sister chromatid cohesion) and apoptosis.
CDC7	Cell division cycle 7 homolog (*S. cerevisiae*); kinase activity of CDC7 is critical for the G1/S transition of the cell cycle; functions in replication stress and mediates Claspin phosphorylation in DNA replication checkpoint control.
CDC14A	CDC14 cell division cycle 14 homolog A (*S. cerevisiae*); alias: dual specificity protein phosphatase CDC14A; required for centrosome separation, chromosome segregation and subsequent cytokinesis during cell division; phosphorylates the APC (anaphase-promoting complex) subunit FZR1/CDH1, thereby promoting APC-FZR1-dependent degradation of mitotic cyclins and subsequent exit from mitosis; interacts with and dephosphorylates tumor suppressor protein p53, thereby regulating p53 function; interacts with KIF20A to localize CDC14 to the midzone of the mitotic spindle.
CDC20	Cell division cycle 20 homolog (*S. cerevisiae*); acts as a regulatory protein by interacting with several proteins at multiple points in the cell cycle; required for 2 microtubule-dependent processes, nuclear movement prior to anaphase and chromosome separation; required for full ubiquitin ligase activity of the APC; regulated by MAD2L1 resulting in an inactive ternary complex (MAD2L1-CDC20-APC) in metaphase; in anaphase the binary complex (CDC20-APC) is active in degrading its targeted substrates.
CDC42	Cell division cycle 42; 25 kDa GTP binding protein; small GTPase of the Rho-subfamily which regulates multiple signaling pathways including cell cycle progression G1 to S; controls spindle orientation of adherent cells; antagonistic cross-talk between Rac and Cdc42 GTPases regulates generation of reactive oxygen species; Cdc42 is a substrate for caspases and influences Fas-induced apoptosis.
CDCA8	Cell division cycle associated 8; alias: BOREALIN; component of a chromosomal passenger complex (CPC) required for stability of the bipolar mitotic spindle; The CPC consists of survivin, CDCA8, INCENP, and Aurora-B; the CPC functions at the centromere to ensure correct chromosome alignment and segregation; CDCA8 is required for chromatin-induced microtubule stabilization and spindle assembly; CDCA8 may be required to direct the CPC to centromeric DNA; major effector of the TTK kinase in the control of "attachment-error-correction" and chromosome alignment.
CDKN2C	Cyclin-dependent kinase inhibitor 2C; alias: p-18-INK4C; this protein is a member of the INK family of cyclin-dependent kinase inhibitors; interacts strongly with CDK6 and weakly with CDK4 and prevents the activation of the CDK kinases; inhibits cell growth and proliferation in the presence of retinoblastoma protein 1 (RB1) and acts as a tumor suppressor.
CROCC	Ciliary rootlet coiled-coil protein; aliases: rootletin, Tax1-binding protein 2, ROLT; major structural component of the ciliary rootlet; forms centriole-associated filaments and contributes to centrosome cohesion before mitosis; recombinant rootletin forms detergent-insoluble filaments radiating from the centrioles; the homopolymeric rootletin protofilaments bundle into variably shaped thick filaments; interacts with C-Nap1 and may function in centrosome cohesion by acting as a physical linker between the pair of centrioles/basal bodies; ciliary rootlet interacts with kinesin light chains and may provide a scaffold for kinesin-1 vesicular cargos; rootletin is phosphorylated by Nek2 kinase and is displaced from the centrosomes at the onset of mitosis, resulting in the binding of beta-catenin to rootletin-independent sites on centrosomes (an event that is required for centrosome separation); overexpression of rootletin in cells results in the formation of extensive fibers resulting in multinucleation, micronucleation and irregularity of nuclear shape and size, indicative of defects in chromosome separation.
E2F2	E2F transcription factor 2: member of the E2F family of transcription factors; transcription activator that binds DNA cooperatively with DP (differentiation regulated transcription factor proteins) through the E2 recognition site, 5′-TTTC[CG]CGC-3′, found in the promoter region of a number of genes whose products are involved in cell cycle regulation

(*Continued*)

Table 2 (*Continued*)

Gene	Protein function
	or in DNA replication; the E2F family plays a crucial role in the control of the cell cycle and action of tumor suppressor proteins (eg, p14 (ARF); binds specifically to unphosphorylated retinoblastoma protein pRB in G0/G1, leading to the repression of E2F target genes; subsequent phosphorylation of pRB by cyclin-dependent kinases in late G1 inactivates pRB, liberating free E2F, which then functions to activate the expression of target genes required for S-phase entry and cell cycle progression; although E2F1-3 transcription factors were classified as positive regulators of the cell cycle (E2F activators), they also cause transcriptional repression, indicating that their specific effects may be cell type-specific; represses the expression of survivin, a dual mediator of apoptosis resistance and cell cycle progression; can function as a tumor suppressor in epithelial tissues, perhaps by limiting proliferation in response to Myc; hemizygosity of the E2F2 locus is sufficient to increase tumor incidence in the Myc-transgenic mouse model of tumorigenesis in the skin and oral cavity.
HDAC1	Histone deacetylase 1: in addition to effects on gene expression, histone deacetylase activity plays an important role in regulating the assembly of kinetochores, the activation of the mitotic checkpoint and the process of cytokinesis; decreased activity or aberrant control of HDAC activity can result in altered kinetochore assembly by disrupting pericentromeric heterochromatin, failure of appropriate chromosome segregation, and defects in the mitotic spindle checkpoint, resulting in mitotic slippage and chromosome instability; HDACs 1, 2, and 4 are closely related Zn^{++}-dependent enzymes; HDAC1 is part of a complex that binds to the promoter of TBP-2 (thioredoxin binding protein-2), resulting in repression of TBP-2 transcription, increasing the activity of thioredoxin and protecting cells against oxidative stress.
KIF1B	Kinesin family member 1B; motor protein that transports mitochondria and synaptic vesicle precursors; involved in the movement of chromosomes during mitosis; functions as a haploinsufficient tumor suppressor by inducing apoptotic cell death; acts downstream of EglN3 to induce apoptosis.
KIF2C	Kinesin family member 2C; aliases: MCAK (mitotic centromere-associated kinesin); Aurora B regulates MCAK at the mitotic centromere; phosphorylated by STK12 and regulates the association of centromeres and kinetochores; promotes the ATP-dependent removal of tubulin dimers from microtubules in association with the process of microtubule depolymerization and turnover; functions in chromosome segregation during mitosis; contains the microtubule tip localization signal (MtLS) motif; phosphorylated after DNA damage, probably by ATM or ATR.
KIF17	Kinesin family member 17; proteins of the kinesin family are microtubule-dependent molecular motors that transport organelles within cells and move chromosomes during cell division.
MAD2L2	Mitotic arrest deficient-like 2 (yeast)-Like 2; component of the mitotic spindle assembly checkpoint that, like MAD2, may prevent the onset of anaphase until all chromosomes are properly aligned at the metaphase plate; suppression of MAD2L2 confers sensitivity to a range of DNA-damaging agents, especially a DNA cross-linker, such as cisplatin; in MAD2L2-depleted cells there is a significant decrease in the cisplatin-induced sister chromatid exchange rate, a marker for homologous recombination-mediated post-replication repair; Unlike MAD2, MAD2L2 has not been shown to have a dual-role mitotic/pro-apoptotic function; interacts with the small GTPase RAN, which may play a role in the control of the spindle checkpoint during mitosis and the regulation of nucleocytoplasmic trafficking during interphase.
PLK3	Polo-like kinase 3; aliases: FNK, PRK; multifunctional serine/threonine protein kinase involved in stress response pathways; required for entry into S phase; regulates the M phase of the cell cycle; activated by genotoxic stress, through a Chk3-mediated priming phosphorylation followed by an ATM-mediated full activation; functions as a centrosome localization signal, overexpression of which causes mitotic arrest, cytokinesis defects, and apoptosis; involved in checkpoint-mediated cell cycle arrest to ensure genetic stability; links DNA damage to cell cycle arrest and apoptosis, in part through the p53 pathway; may also be part of the signaling network that controls cellular adhesion.
PSRC1	Proline/serine-rich coiled-coil 1; alias: DDA3; functions as a microtubule destabilizing protein that controls spindle dynamics and mitotic progression by recruiting and regulating microtubule depolymerases; the N-terminal domain of PSRC1 regulates the spindle association of the microtubule depolymerase Kif2a and controls the mitotic function of PSRC1; regulated by p53 and may participate in p53-mediated growth suppression; direct transcriptional target of p53 and p73.
RCC1	Regulator of chromosome condensation 1; a protein with a 7-bladed propeller structure that is involved in the regulation of onset of chromosome condensation in S phase; binds to chromatin and promotes the exchange of Ran-bound GDP by GTP; phosphorylation of RCC1 by cdc2 kinase in mitosis is essential for producing a high RanGTP concentration on chromosomes and for chromatin-induced mitotic spindle formation; perturbation of the chromosomal binding of RCC1, Mad2 and survivin causes spindle assembly defects and mitotic catastrophe; the RCC1/Ran complex, in conjunction with other proteins, acts as a component of a signal transmission pathway that detects unreplicated DNA.
RCC2	Regulator of chromosome condensation 2; alias: telophase disk protein of 60 kDa (TD-60); has an essential role in the prometaphase to metaphase progression and required for the completion of mitosis and signaling cytokinesis; may function as a guanine nucleotide exchange factor for the small GTPase RAC1; interacts with microtubules; appears in the nucleus at G2, then concentrates at the inner centromere region of chromosomes during prophase, then redistributes to the midzone of the mitotic spindle during anaphase where it covers the entire equatorial diameter from cortex to cortex; phosphorylated upon DNA damage, probably by ATM and ATR.
SASS6	Spindle assembly 6 Homolog (*C. elegans*); necessary for centrosome duplication and functions during procentriole formation to ensure that each centriole seeds the formation of a single procentriole per cell cycle; part of a ternary complex of SASS6, CENPJ, and CEP350.

Table 3 Apoptosis-related genes

Gene	Protein function
BCL2L15	Bcl-2-like protein 15 has a pro-apoptotic function; alias Bfk; human bfk mRNA is found in cerebellum, colon, small intestine, testis, and uterus, but the protein is predominantly expressed in tissues of the gastrointestinal tract; in the transition from normal human colonic mucosal tissue to tumors, 80% of colon tumors show a substantially reduced expression of Bfk; gene expression appears to be regulated by female sex hormones.
BCL10	B-cell lymphoma 10; wild-type bcl10 is a pro-apoptotic protein that suppresses cellular transformation, whereas mutant forms lose this activity and display gain-of-function transforming activity; the bcl10 protein contains an amino-terminal CARD (caspase recruitment domain) found in many apoptotic-related molecules; the BCL10 gene often exhibits a frameshift mutation resulting in truncation distal to the CARD; has a high mutation frequency in hepatocellular carcinoma (57% of cases); the frequency of mutation in other cancers is as follows: lymphoma (45%), colon cancers with the microsatellite mutator phenotype (13%), mesothelioma, male germ cell tumors, adenocarcinoma cell lines (12%), gastric cancers with the microsatellite mutator phenotype (10%); the presence of the bcl10 protein highly correlates with the expression of phosphorylated p65 NF-kappaB in peripheral T-cell lymphomas and is associated with a better clinical outcome than bcl10-negative tumors.
CASP9	Caspase-9 (cysteine-aspartic acid protease, family member 9) precursor; aliases: APAF-3 (apoptotic protease-activating factor 3), apoptosis-related cysteine peptidase, MCH6, ICE-LAP6, ICE-like apoptotic protease 6; caspase-9 and APAF1 bind to each other via their respective NH2-terminal CED-3 homologous domains in the presence of cytochrome C and ATP to form the apoptosome, a high-molecular-weight complex; the caspase-9 precursor then becomes activated, which in turn activates the downstream caspases, caspase-3, and caspase-2, in response to genotoxic stress.
DFFA	DNA fragmentation factor, 45 kD, alpha polypeptide; alias ICAD (inhibitor of caspase-activated DNase, DFFB); DFF is a heterodimeric protein consisting of 45 kD (DFFA) and 40 kD (DFFB) subunits; DFF becomes activated when DFFA is cleaved by caspase 3 and dissociates from DFFB (DFFB is the active component of DFF involved in both DNA fragmentation and chromatin condensation during the process of apoptosis [see below]).
DFFB	DNA fragmentation factor, 40 kD, beta polypeptide (caspase-activated DNase; alias CPAN; enzyme activity is inhibited by DFFA; its Mg^{++}-dependent endnuclease activity degrades DNA and induces DNA fragmentation; the fragmented DNA results in chromatin condensation during apoptosis, and is responsible for the typical crescents and margination of chromatin that are characteristic morphological features of the nucleus during apoptosis.
THAP3	THAP domain containing, apoptosis-associated protein 3; the THAP-family C(2)CH zinc-coordinating DNA-binding proteins function in diverse eukaryotic cellular processes, including transposition, transcriptional repression, stem-cell pluripotency, angiogenesis, neurological function, and apoptosis; the specific mechanism by which THAP3 contributes to apoptosis is unknown.
TNFRSF25	Tumor necrosis factor receptor superfamily, member 25; aliases: death receptor 3; DR3; translocating chain-association membrane protein; apoptosis inducing receptor; APO3; lymphocyte-associated receptor of death; LARD; apoptosis-mediating receptor TRAMP; a death domain-containing receptor related to TNFR-1 and CD95 (Apo-1/Fas); receptor for TNFSF12/APO3L/TWEAK; interacts with the adaptor TRADD; DR3 signal transduction is mediated by a complex of intracellular signaling molecules including TRADD, TRAF2, FADD, and FLICE.

RAD54L, and TP73. The functions of these gene products are described in Table 1. The pathways that lead to the prevention of genomic instability are diagrammatically shown in Figure 4. DNA damage elicits a well orchestrated and highly interactive series of events called the DDR, which causes cells to undergo growth arrest so that DNA damage can be adequately repaired. Although p53 mutation or loss of heterozygosity (LOH) is a late event in colon carcinogenesis,[151] the loss of p73 (found on chromosome 1p) through chromosomal deletion events may act early in colon carcinogenesis. P73 is an important isoform of the p53 family, since it performs many of the transcriptional functions of p53, and may even target the same genes as p53 during the DDR. In addition, TP73 has distinct transcriptional targets and harmonizes with p53 and p63 to maintain genomic stability.[152–158] In addition to its role in growth arrest after DNA damage to allow DNA repair to take place, p73 plays an active role in spindle dynamics, mitotic exit and chromosomal stability. The PSRC1 (proline/serine-rich coiled-coil 1) gene found on chromosome 1p (see Table 2) encodes a protein which is a direct transcriptional target of both p53 and p73.[159] PSRC1 functions as a microtubule destabilizing protein that controls spindle dynamics and mitotic progression by recruiting and regulating microtubule depolymerases.[160] Through its transcriptional activity, p73 is important for the M-to-G1 transition during mitosis.[161] Functional knock-out of p73 gene expression by small interfering RNAs alters mitotic progression, resulting in an increase of ana-telophase cells, the accumulation of aberrant late mitotic figures, and the appearance of abnormalities in the subsequent interphase.[161] This novel pathway involves the p73-mediated transcription of Kip2/p57, a cyclin-dependent kinase inhibitor, and the coordination of mitotic exit and transition to G1.[161,162] Like p53, p73 has been confirmed to be a tumor suppressor.[163–167] Therefore, a loss of p73 should have a major impact in the development of genomic instability during carcinogenesis.

Table 4 MicroRNAs (miRNAs) and components of the miRNA processing complex

MicroRNA	Function
30c-1	A genetic variant of 30c-1 is associated with familial breast cancer in noncarriers of BRCA1/2 mutations.
30e	A functional variant of pre-miRNA-30e is strongly associated with schizophrenia.
34a	Major pro-apoptotic miRNA that is regulated by p53; induced by treatment of pancreatic β cells with IL-1β and TNF-α, and responsible, in part, for cytokine-triggered cell death; expression frequently lost in pancreatic ductal adenocarcinoma cells.
101-1	MiR-101 is downregulated in stage II MSS and MSI colon cancers compared to normal mucosa, hepatocellular carcinoma, prostate cancer and transitional cell carcinoma of the bladder; miR-101 inhibits cell proliferation, represses the expression of the Polycomb group protein EZH2, and induces apoptosis.
137	MiR-137 exhibits decreased levels of expression in colon tumors compared to normal mucosa; frequently upregulated in rectal cancer in response to capecitabine chemoradiotherapy; changes level in reaction to xenobiotic challenge; targets MITF (micropthalmia-associated transcription factor) in melanoma cell lines.
186	Expression of miR-186 significantly reduces the abundance of FOXO1, a tumor suppressor, in endometrial cancer, resulting in deregulated cell cycle control and impaired apoptotic responses; downregulates expression of the pro-apoptotic purinergic P2X7 receptor; dysregulated in human myocardial infarction.
197	Target miRNAs not experimentally verified.
200a	Involved in the regulation of the Wnt/β-catenin signaling pathway; miRNAs-200a, -200b, and -429 are all encoded on a 7.5 kb polycistronic primary miRNA transcript.
200b	Involved in the regulation of the Wnt/β-catenin signaling pathway; miRNAs-200a, -200b, and -429 are all encoded on a 7.5 kb polycistronic primary miRNA transcript.
320b-1	MiR-320 shows highest expression in the proliferative compartment of the crypts; the decrease in miR-320 in stage II colon cancers is predictive of a metastatic recurrence independent of age, differentiation grade, and histologic subtype; targets the transferrin receptor 1 and inhibits proliferation; expression of miRNA-320 in myocardial microvascular endothelial cells (MMEC) impairs angiogenesis by decreasing proliferation and migration of MMEC; overexpression of miR-320 in mouse hearts increases apoptosis and infarction; targets heat-shock 20 mRNA; potentially targets the mRNA of the p85 subunit of phosphatidylinositol 3-kinase; exhibits a 50-fold increase in insulin-resistant 3T3-L1 adipocytes; affects cell cycle progression of bronchial epithelial cells exposed to benzo[a] pyrene.
429	Involved in the regulation of the Wnt/β-catenin signaling pathway; miRNAs-200a, -200b, and -429 are all encoded on a 7.5 kb polycistronic primary miRNA transcript; regulates the differential expression of miR200.
551a	Target mRNAs not experimentally verified.
552	MiR-552 exhibits decreased levels of expression in proficient mismatch-repair colon tumors relative to deficient mismatch-repair tumors; target mRNAs not identified.
553	Target mRNAs not identified.
760	Regulated by 17β-estradiol and may affect a number of transcripts belonging to estrogen-responsive gene clusters.
942	Target mRNAs not experimentally verified.
1256	Target mRNAs not experimentally verified.
1262	Targets the HLA-G mRNA.
1290	Target mRNAs not experimentally verified.
1302-2	Controlled by the multifunctional Y-Box protein 1 (YB-1); upregulated more than 1.5-fold in drug-sensitive gastric carcinoma cells.
MiRNA processing	
Ago1	Argonaute 1; aliases: protein argonaute 1, EIF2C1 (eukaryotic translation initiation factor 2C1), putative RNA-binding protein Q99, GERP95 (Golgi endoplasmic reticulum protein 95); encodes a member of the Argonaute family of proteins which binds to miRNAs and plays a role in gene silencing through RNA interference; may interact with dicer1; highly basic protein which contains a PAZ domain and a PIWI domain; found in a tandem cluster of closely related argonaute proteins, Ago3 and Ago4 on chromosome 1p; lacks endonuclease activity and does not appear to cleave target mRNAs.
Ago3	Argonaute 3; aliases: protein argonaute 3, EIF2C3 (eukaryotic translation initiation factor 2C3); encodes a member of the Argonaute family of proteins which binds to miRNAs and plays a role in gene silencing through RNA interference; highly basic protein which contains a PAZ domain and a PIWI domain; found in a tandem cluster of closely related argonaute proteins, Ago1 and Ago4 on chromosome 1p; lacks endonuclease activity and does not appear to cleave target mRNAs.
Ago4	Argonaute 4; aliases: protein argonaute 4, EIF2C4 (eukaryotic translation initiation factor 2C4); encodes a member of the Argonaute family of proteins which binds to miRNAs and plays a role in gene silencing through RNA interference; may interact with dicer1; highly basic protein which contains a PAZ domain and a PIWI domain; found in a tandem cluster of closely related argonaute proteins, Ago1 and Ago3 on chromosome 1p; lacks endonuclease activity and does not appear to cleave target mRNAs.

Table 5 Genes associated with the Wnt signaling pathway

Gene	Protein function
CTNNBIP1	Catenin, beta interacting protein 1: aliases: ICAT (inhibitor of beta-catenin-interacting protein ICAT), inhibitor of beta-catenin and Tcf-4; 9-kDa negative protein regulator of the Wnt signaling pathway; prevents interaction between beta-catenin and Tcf-4 family members, thereby repressing beta-catenin-Tcf-4-mediated transactivation; in intestinal tissue, ICAT is upregulated in the mature, non-dividing enterocyte lining the villi, and is absent in the beta-catenin/TCF signaling region of the crypts; does not protect the soluble pool of beta-catenin from degradation by the APC (adenomatous popyposis coli); has a pro-apoptotic function in certain situations (see text).
DVL1	Dishevelled-1; aliases: DVL, segment polarity protein dishevelled DVL-1; the human homolog of the Drosophila dishevelled gene (dsh) encodes a cytoplasmic phosphoprotein that regulates cell proliferation, acting as a transducer molecule for developmental processes; dishevelled family proteins are cytoplasmic mediators of the Wnt/beta-catenin signaling pathway linked to cancer with Dvl considered to be a middle molecule in the pathway; Dvl, Axin and GSK form a ternary complex bridged by Axin, and Frat1 can be recruited into this complex by Dvl; the Dvl-binding domain of either Frat1 or Axin is able to inhibit Wnt-1-induced LEF-1 activation, suggesting that the interactions between Dvl and Axin and between Dvl and Frat may be important for the Wnt/beta-catenin signaling pathway; Wnt-1 appears to promote the disintegration of the quaternary Frat1-Dvl-GSK-Axin complex, resulting in the dissociation of GSK from Axin and the formation of the Dvl/Frat-1 complex that leads to the activation of the Wnt signaling pathway.
WNT2B	Wingless-type MMTV integration site family, 2B; aliases: WNT13, XWNT2, protein Wnt-2b; member of the WNT family of highly conserved, secreted signaling factors that regulate cell growth and differentiation; ligand for members of the frizzled family of seven transmembrane receptors with an extracellular WNT-binding domain and a cytoplasmic dishevelled-binding domain; may be a signaling molecule that affects the development of discrete regions of tissues; is likely to signal over only a few cell diameters; WNT2B is one of the canonical WNTs transducing signals through Frizzled and LRP5/LRP6 receptors to beta-catenin-TCF/LEF signaling pathway; functions as a stem cell factor during embryogenesis and during carcinogenesis.
WNT4	Wingless-type MMTV integration site family, 4; aliases: WNT-4, SERKAL; member of the WNT family of highly conserved, secreted signaling factors that regulate cell growth and differentiation; ligand for members of the frizzled family of seven transmembrane receptors; is likely to signal over only a few cell diameters; activates the canonical beta-catenin-mediated Wnt pathway and binds Frizzled-6 receptor; WNT4 promoter harbors 2 p63/p73 response elements which contributes to an increase in WNT gene expression; WNT4 gene expression can be negatively regulated by Notch1 activation through p21WAF1/Cip1.

Since base excision repair (BER) removes damage that would otherwise be mutagenic in mammalian cells,[168–170] BER is one of the most important DNA repair pathways in the gastrointestinal tract. BER ameliorates environmentally induced DNA damage in addition to the alkylation, oxidation, and deamination events that occur during normal metabolic processes.[171,172] A critical enzyme in the base excision repair pathway is MUTYH (MutY homolog or A/G-specific adenine DNA glycosylase), whose germline mutation is a known cause of MAP (MutYH-associated polyposis), a recently described autosomal recessive colorectal adenoma predisposition syndrome with a very high risk of colorectal cancer.[173] *Myh* deficiency enhances intestinal tumorigenesis in multiple intestinal neoplasia ($Apc^{Min/+}$) mice.[174] Interestingly, *Myh* deficiency in mice has a larger effect on tumor initiation than on progression in the small bowel.[174] Since 1p deletions are observed in the human non-neoplastic mucosa of patients with colon cancer,[44] it is possible that Myh-deficient field defects may initiate the process of colon carcinogenesis in humans as it does in the mouse model. Since MUTYH-null mouse embryonic stem cells exhibit a mutator phenotype,[175] the loss of MUTYH can affect multiple pathways associated with colon carcinogenesis. The role of MUTYH in the repair of oxidative DNA damage begins with the formation of 8-oxo-guanine (8-oxoG) (see Figure 4), which then causes a mispairing of the oxidized guanine base with adenine upon DNA replication. Mismatch repair processes are activated and MUTYH excises adenine leaving an apurinic (AP) site resulting, after AP endonuclease action, in a DNA single strand (ss) break.[176–180] The activity of MUTYH, in conjunction with other glycosylases and the spontaneous generation of AP sites, may be quite extensive, since about 9000 AP sites/cell occur daily.[168] The AP site is then correctly repaired by the sequential action of several enzymes which catalyze template-directed insertion of one or a few nucleotides at the previously damaged site.[172]

In addition to their role in DNA repair or the DDR, MUTYH and p73 play important roles in the death of cells that experience either excessive oxidative DNA damage or chromosomal instability. The MUTYH-mediated cell death pathway is described in the next section followed by a section on the p73-mediated cell death pathway, which utilizes part of the MUTYH pathway in its mediation of cell death in response to excessive mitotic perturbation.

MUTYH/PARP/AIF pathway of cell death

MUTYH-mediated cell death has, as a central player, the activation of PARP-1 [poly(ADP-ribose) polymerase-1] (Figure 5).

Table 6 Tumor suppressor genes

Gene and genomic locus (ensembl cytogenetic band)	Functions
CHD5 (1p36.31)	Chromodomain helicase DNA binding protein 5; aliases: ATP-dependent helicase CHD5; belongs to a group of SWI/SNF proteins called CHD proteins, which contain a SWI/SNF-like helicase/ATPase domain, as well as a DNA-binding domain and a chromodomain that directly modifies chromatin structure; chromatin is maintained in a transcriptionally active state by CHD5 which can affect the expression levels of many genes at once and can affect the quick progression of a tumor; appears to be involved in early tumorigenic processes and controls proliferation, apoptosis, and senescence via the $p16^{Ink4a}$ and $p19^{Arf}$ pathway; overexpression of CHD5 increases apoptosis through a $p19^{Arf}$/p53 pathway; mice heterozygous for CHD5 are prone to spontaneous tumor formation; expression is downregulated through methylation, which may explain the higher level of colon cancer incidence in African Americans (78% with methylated CHD5) compared with Iranians (47% with methylated CHD5).
DEAR1 (1p35.1)	Ductal epithelium-associated RING chromosome 1; alias: TRIM62 (tripartite motif-containing 62); member of the RING-B-box-coiled-coil (RBCC)/TRIM subfamily of RING finger proteins which regulate tissue architecture; first member of the TRIM family that localizes to the cell–cell junction; down regulation in normal mammary epithelial cells results in formation of aberrant acinar structures with a loss of normal cell polarity and decreased rates of apoptosis.
APITD1 (1p36.22)	Apoptosis-inducing, TAF9-like domain 1; see Table 2 for general description; contains a predicted domain with similarity to the human TATA box-binding protein-associated factor, TAFII31, which is required for p53-mediated transcriptional activation; since loss of function for APITD1 is a mechanism by which tumor cells can overcome the cell growth-regulating and apoptosis-inducing properties of p53, it is considered to have tumor-suppressive properties.
PRDM2 (1p36.21)	PR domain containing 2, with ZNF domain; aliases: RIZ1, Zinc finger protein RIZ, HUMHOXY1, MTB-ZF, KMT8, retinoblastoma protein-interacting zinc finger protein, Lysine N-methyltransferase, MTE-binding protein, GATA-3-binding protein G3B, PR domain zinc finger protein 2; this tumor suppressor is a member of the nuclear histone/protein methyltransferase superfamily involved in chromatin-mediated gene expression; encodes a zinc finger protein that can bind to the retinoblastoma protein, estrogen receptor, and the macrophage-specific TPA-responsive element (MTE) of the heme oxygenase 1 (HO-1) gene; the PR domain is responsible for its tumor suppressing activity; the S-adenosyl-L-methionine-dependent histone methyltransferase activity of PRDM2 specifically methylates "Lys-9" of histone H3; regulates normal cell division and function using a "Yin-Yang" fashion; overexpression induces a G_2-M cell cycle arrest and/or apoptosis (cell death independent of Rb and p53); expression and activity are reduced in many cancers; loss of activity results in decreased apoptosis and differentiation and enhanced proliferation; common target of frameshift mutation in microsatellite-unstable cancers; gene expression epigenetically silenced through promoter hypermethylation; upregulated by a methyl-balanced diet accompanied by the repression of the oncogene, c-jun.
SDHB (1p36.13)	Succinate dehydrogenase complex, subunit B, iron sulfur (1p); SDH1, Ip (iron-sulfur protein), GL4, succinic dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial; one of 4 nuclear-encoded subunits of complex II of the mitochondrial respiratory chain, specifically involved in the oxidation of succinate and the transfer of electrons from FADH to CoQ (ubiquinone); this iron-sulfur subunit is highly conserved and contains three cysteine-rich clusters which comprise the iron-sulfur centers of the enzyme; responsible for specifically transferring electrons from succinate to CoQ; decreased activity results in altered mitochondrial metabolism, the activation of pseudohypoxia and a shift to glycolytic respiration; SDHB-silenced cells can result in >400 genes either 6-fold or more upregulated or downregulated (dysregulated genes involve those involved in proliferation, adhesion, and the hypoxia pathway); DDHB-silenced cells display characteristic features of the tumor phenotype (eg, greater capacity to adhere to extracellular matrix components, including fibronectin and laminin) suggesting a possible mechanism of tumor initiation and enhanced tumorigenesis.
PRDX1 (1p34.1)	Peroxiredoxin 1; see Table 7 for description; *Prdx1* knockout mice generate malignancies in intestines, lymphomas, and sarcomas; prdx1–/– mouse cells show a shift in intracellular ROS from the cytoplasm to the nucleus with increased oxidative DNA damage; prdx1-deficient mouse cells show increased sensitivity to oxidative DNA damage; lower expression of PRDX1 found in tumors of the oral cavity and correlates with larger tumor size, lymph node metastasis, and clinically advanced stages. PRDX1 acts as a tumor suppressor in esophageal cells and induces apoptosis after activation by histone deacetylase inhibitors; interacts with a region of the c-Myc transcriptional regulatory (Myc box II) domain that is essential for transformation, and selectively alters its biological function and target gene expression; inhibits c-Abl kinase activity by interacting with its SH3 domain.
PTCH2 (1p34.1)	Patched homolog 2 (Drosophila); aliases: patched (Drosophila) homolog 2, PTC2, protein patched homolog 2; gene encodes a transmembrane receptor of the patched gene family; functions as a tumor suppressor by inhibiting another transmembrane protein SMO (smoothened), which functions in the hedgehog signaling pathway; receptor for Sonic Hedgehog, a secreted molecule implicated in the formation of embryonic structures and in tunorigenesis.

(*Continued*)

Table 6 (*Continued*)

Gene and genomic locus (ensembl cytogenetic band)	Functions
CAMTA1 (1p36.31)	Calmodulin binding transcription activator 1; cell cycle regulatory gene; in cases with 1p LOH, its expression is reduced by half, suggesting a functional effect caused by haploinsufficiency.
AJAP1 (1p36.32)	Adherens junctions associated protein 1; aliases: SHREW1, Mot8, transmembrane protein SHREW1; membrane protein that targets to the basolateral membrane of polarized epithelial cells through cytoplasmic sorting motifs that include three tyrosines and a dileucine; interacts with E-cadherin-catenin complexes of adherens junctions; functions to inhibit cell adhesion and migration.
UBE4B (1p36.22)	Ubiquitination factor E4B (UFD2 homolog, yeast); UBOX3, ubiquitin-fusion degradation protein 2, homozygously deleted in neuroblastoma-1; binds to the ubiquitin moieties of preformed conjugates and catalyzes ubiquitin chain assembly in conjunction with the E1, E2, and E3 classes of ubiquitin-activating enzymes; activity linked to cell survival under stress conditions; involved in protecting the cell from environmental stress; cleaved by caspase 6 and granzyme B during apoptosis.
NBL1 (1p36.13)	Neuroblastoma, suppression of tumorigenicity 1; aliases: zinc finger protein DAN, DAND1, Dan domain family member, NO3; founding member of the evolutionarily conserved CAN (cerberus and DAN) family of proteins which contain a domain resembling the CTCK (C-terminal cystine knot-like) motif found in a number of signaling molecules; secreted protein which acts as BMP (bone morphogenetic protein) antagonist by binding BMPs and preventing them from interacting with their receptors; plays an important role in growth and development; contains a putative p53/p73-binding site in the 5′-upstream region of the gene; acts as an inhibitor of cell cycle progression; may play an important role in preventing cells from entering the final stage (G1/S) of the transformation process; functional association exists between NBL1 and p73 during cisplatin-induced cell death.
PLA2S-II (1p36.13)	The secretory type II phospholipase A2; aliases: MOM1 (modifier of MIN-1), group IIA phospholipase A2, non-pancreatic secretory phospholipase A2, phosphatidylcholine 2-acylhydrolase 2A; catalyzes the hydrolysis of the sn-2 fatty acid acyl ester bond of phosphoglycerides, releasing free fatty acids and lysophospholipids, liberating arachidonic acid (AA) and prostaglandin D2, a metabolite of AA; participates in the regulation of phospholipid metabolism in biomembranes and the maintenance of membrane asymmetry; other known functions are related to microbial defense mechanisms (bactericidal activity) and the inflammatory response; human homolog of the MOM (modifier of min [APC]) gene, which suppresses polyp number during intestinal tumorigenesis in the min mouse model, possibly by altering the cellular microenvironment within the intestinal crypt or inducing AA metabolite-mediated apoptosis in pre-neoplastic or neoplastic cells.
ST7L (1p13.2)	Suppression of tumorigenesis 7 like; aliases: related to the tumor suppressor gene, ST7, found at the chromosome 7q31 genomic locus; ST7L gene is clustered in a tail-to-tail manner with the WNT2B gene on chromosome 1p (analogous to the clustering of ST7 with the WNT2 gene on chromosome 7q; the related gene, ST7, induces changes in genes involving the re-modeling of the extracellular matrix, such as SPARC, IGFBP5 and several matrix metalloproteinases; may act as a tumor suppressor by modification of the tumor microenvironment.
RAD54L (1p34.1)	RAD54-like (*S. cerevisiae*); see Table 1 and text for description.
E2F2 (1p36.12)	E2F transcription factor 2; see Table 2 for description.
TNFRSF25 (1p36.31)	Tumor necrosis factor receptor superfamily, member 25; see Table 3 for description.
PLK3 (1p34.1)	Polo-like kinase 3; see Table 2 for description.
GADD45α (1p31.3)	Growth arrest and DNA-damage-inducible 45 alpha; see Table 1 for description.
CTNNBIP1 (1p36.22)	Alias ICAT; see Table 5 for description.
MUTYH (1p34.1)	MutY homolog (*E. coli*); see Table 1 and text for description.
CDKN2C (1p32.3)	Cyclin-dependent kinase inhibitor 2C; see Table 2 for description.
DFFA (1p36.22) DFFB (1p36.32)	DNA fragmentation factor; see Table 3 and text for description.
KIF1B (1p36.22)	Kinesin family member 1B; see Table 2 and text for description.
TP73 (1p36.32)	Tumor protein 73; DNA damage response protein and pro-apoptotic tumor suppressor; see Table 1 and text for description.
MiR-34a (1p36.22)	miRNA-34a; see Table 4 and text for description.
MiR-101-1 (1p31.3)	miRNA-101-1; see Table 4 and text for description.

Excessive DNA ss breaks caused by the action of MUTYH and AP endonuclease in the nucleus results in the activation of PARP-1, which attaches polymers of ADP-ribose to proteins, thereby opening up the chromatin to allow access of DNA repair proteins.[181,182] PARP initially serves as a survival protein facilitating the rapid repair of DNA strand breaks, and also prevents DNA degradation, in part, by inhibiting the activity of deoxyribonucleases through the process of poly(ADP) ribosylation.[183] Since the synthesis of ADP-ribose polymers consumes nicotinamide adenine dinucleotide (NAD^+),[184] and NAD^+ is largely found in mitochondria where it participates in the production of ATP (bottom right side of Figure 5), sustained

Table 7 Genes associated with antioxidant function

Gene	Protein function
GCLM	Glutamate-cysteine ligase, modifier subunit; aliases: gamma-glutamylcysteine synthetase, GSC light chain; the first rate limiting enzyme of glutathione synthesis; the enzyme consists of a heavy catalytic subunit and a light (30.8 kDa) regulatory subunit.
GPX7	Glutathione peroxidase 7; non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase; alleviates oxidative stress generated from polyunsaturated fatty acids.
PRDX1	Peroxiredoxin 1; aliases: thioredoxin peroxidase 2, thioredoxin-dependent peroxide reductase 2, TDPX2, natural killer cell-enhancing factor A, PAG, PAGB; member of the peroxiredoxin family of antioxidant enzymes which reduce hydrogen peroxide and alkyl hydroperoxides; the enzyme reduces peroxides using reducing equivalents provided through the thioredoxin system, not through glutaredoxin; plays an important role in eliminating peroxides generated during metabolism; participates in the signaling pathways of growth factors and tumor necrosis factor-alpha by regulating the intracellular concentrations of hydrogen peroxide; overoxidized peroxiredoxins (eg, cysteines oxidized to cysteine sulfinic or sulfonic acids) are regenerated by p53-regulated sestrins (homologs of a bacterial AhpC which reduces bacterial peroxiredoxins), thus re-establishing the antioxidant firewall.
TXNDC12	Thioredoxin domain containing 12; aliases: endoplasmic reticulum protein ERP19, ERP19, hTLP19, protein disulfide isomerase family A (member 16), endoplasmic reticulum thioredoxin superfamily member, 18 kDa; members of this superfamily possess a thioredoxin fold with a consensus active-site sequence (CxxC) and have roles in redox regulation, defense against oxidative stress, refolding of disulfide-containing proteins, and regulation of transcription factors; induced at the transcriptional level by the unfolded protein response (UPR), a signaling pathway that responds to the accumulation of misfolded proteins; possesses significant protein thiol-disulfide oxidase activity; inhibits the induction of apoptosis by agents that cause ER stress, including brefeldin A, tunicamycin, and dithiothreitol; smallest member of the protein disulfide isomerase (PDI) family of proteins to contain a Cys-Xxx-Xxx-Cys active site motif; like the catalytic domains of PDIs; TXNDC12 adopts a thioredoxin fold with a thioredoxin-like active site located at the N-terminus of a long kinked helix that spans the length of the protein.

PARP activation will consume energy reserves, resulting in cell death, usually through the process of necrosis.[185–188] A marked deficiency in energy reserves may cause the ATP-dependent Na^+/K^+ transport proteins, which maintain ionic balance, to fail, resulting in cell swelling and lysis of the cell,[189] one of the hallmarks of necrosis.[190]

In addition to the above energy catastrophe caused by excessive PARP activity in the nucleus, persistent single-stranded gaps in newly replicated DNA initiated by the action of MUTYH *in mitochondria* can result in the fragmentation and depletion of mitochondrial DNA (mtDNA)[191,192] accompanied by the loss of mitochondrial function culminating in cell death[191,193] (bottom right side of Figure 5). Dysfunctional mitochondria can release Ca^{++} into the cytosol which can activate calpains, causing Bax activation, lysosomal rupture, and the release of cathepsins into the cytosol[191,194] resulting in a caspase-independent mode of cell death. Calpain activation can also result in Bax activation, followed by Bax oligomerization and mitochondrial damage, resulting in the loss of the mitochondrial membrane potential.

There is another unique mechanism that can lead to PARP-mediated cell death after excessive MUTYH activity, in addition to the fragmentation of mtDNA, energy catastrophe and calpain/lysosomal rupture/cathepsin pathways of mitochondrial failure described above. The main product of PARP-1 activity is the generation of polymers of ADP-ribose (PAR). Although these polymers are usually covalently bound to proteins, free PAR polymers are themselves toxic[195–197] and function as a death signal.[197–199] The PAR polymers bind to mitochondria and induce the release of tAIF (truncated apoptosis-inducing factor) from the mitochondria into the cytosol[199] (lower left side of Figure 5). tAIF is then translocated to the nucleus where it binds to DNA,[200–202] causes DNA condensation[203] and recruits DNA degrading factors (eg, endogenous endo- and exo-nucleases) resulting in DNA degradation[198,204] (upper left side of Figure 5). This series of events is part of an intricate program of caspase-independent cell death,[203–213] and is currently an active area of research.

Several mechanisms have been proposed to explain how tAIF is released from the mitochondria into the cytosol.[210,214] Prior to truncation, AIF is embedded in the inner mitochondrial membrane,[215] and the release of AIF requires its cleavage[215,216] from a 62 kDa AIF mitochondrial form to a truncated 57 kDa soluble AIF form (tAIF).[217,218] Calpain-I, which is activated by Ca^{++},[219] and Ca^{++}-independent cathepsins B, L, and S[218,220] can cleave intramitochondrial AIF.[221–223] The calpains and cathepsins can truncate AIF in the same position at Gly102/Leu103.[218] Calpain-I, however, appears to be the critical enzyme regulating AIF processing in which the AIF pathway is important for cell death.[219] Oxidative modifcation of AIF markedly increases the susceptibility of AIF to calpain-I-mediated processing, most probably through the exposure of a normally hidden calpain cleavage site.[219] Since the PAR polymer is a highly negatively charged molecule, it could depolarize mitochondria leading to opening of the mitochondrial membrane permeability transition pore (MPTP) followed by the release of tAIF.[197,199] PAR polymers

Table 8 Genes associated with protection against environmental and metabolic toxicity

Gene	Protein function
AADACL3	Arylacetamide deacetylase-like 3; the enzymatic activity of the family of arylacetamide deacetylases carry out the deacetylation of carcinogenic arylacetamides such as 4-acetylaminobiphenyl, 2-acetylaminofluorene, and 2-acetylaminaphthalene.
AADACL4	Arylacetamide deacetylase-like 4; the enzymatic activity of the family of arylacetamide deacetylases carry out the deacetylation of carcinogenic arylacetamides such as 4-acetylaminobiphenyl, 2-acetylaminofluorene, and 2-acetylaminaphthalene.
AKR1A1	Aldo-keto reductase family 1, member A1; aliases ALDR1, ARM, dihydrodiol dehydrogenase 3; member of the aldo/keto reductase superfamily; catalyzes the NADPH-dependent reduction of a variety of biogenic/xenobiotic aromatic and aliphatic aldehydes to their corresponding alcohols; oxidizes proximate carcinogen trans-dihydrodiols to o-quinones.
AKR7A2	Aldo-keto reductase family 7, member A2; aliases: succinic semialdehyde reductase, SSA reductase, AFAR1; catalyzes the NADPH-dependent reduction of succinic semialdehyde to gamma-hydroxybutyrate; can reduce the dialdehyde protein-binding form of aflatoxin B1 (AFB1) to the non-binding AFB1 dialcohol.
AKR7A3	Aldo-keto reductase family 7, member A3; aliases: AFAR2, AFB1 aldehyde reductase 2; involved in the detoxification of aldehydes and ketones; can reduce the dialdehyde protein-binding form of aflatoxin B1 (AFB1) to the non-binding AFB1 dialcohol.
AKR7L	Aldo-keto reductase family 7-like; aliases: AFAR3, AFB1 aldehyde reductase 3; involved in the detoxification of aldehydes and ketones; can reduce the dialdehyde protein-binding form of aflatoxin B1 (AFB1) to the non-binding AFB1 dialcohol; this family member encodes a selenoprotein, which contains a selenocysteine residue; the selenocysteine is encoded by the UGA codon that normally signals translational termination.
CYP2J2	Cytochrome P450, family 2, subfamily J, polypeptide 2; aliases: microsomal monooxygenase, flavoprotein-linked monooxygenase, arachidonic acid epoxygenase; the cytochrome P450 superfamily of enzymes catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids; this protein localizes to the endoplasmic reticulum and is the predominant enzyme responsible for epoxidation of endogenous arachidonic acid pools in cardiac tissue; also functions in the gastrointestinal tract; epoxygenase-derived eicosanoids have anti-inflammatory properties.
CYP4Z1	Cytochrome P450, family 4, subfamily Z, polypeptide 1; catalyzes the in-chain hydroxylation of lauric acid and myristic acid; single-pass type II membrane protein found in the endoplasmic reticulum.
CYP4A11	Cytochrome P450, family 4, subfamily A, polypeptide 11; aliases: fatty acid omega-hydrolase, lauric acid omega-hydrolase, alkane-1 monooxygenase, 20-hydroxyeicosatetraenoic acid synthase; this CYP450 member localizes to the endoplasmic reticulum and catalyzes the omega- and omega-1-hydroxylation of medium-chain fatty acids such as laurate, myristate and palmitate; oxidizes arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE).
CYP4A22	Cytochrome P450, family 4, subfamily A, polypeptide 22; aliases: fatty acid omega-hydroxylase, lauric acid omega-hydrolase; this CYP450 member localizes to the endoplasmic reticulum and catalyzes the omega- and (omega-1)-hydroxylation of medium-chain fatty acids such as laurate and palmitate; shows no activity toward arachidonic acid and prostaglandin A1.
CYP4B1	Cytochrome P450, family 4, subfamily B, polypeptide 1; aliases: microsomal monooxygenase, P-450HP; this enzyme is located in the endoplasmic reticulum and oxidizes a variety of structurally unrelated compounds, including steroids, fatty acids and xenobiotics; involved in an NADPH-dependent electron transport pathway; can be induced to high levels in the liver and other tissues by various foreign compounds, including drugs, pesticides, and carcinogens.
CYP4X1	Cytochrome P450, family 4, subfamily X, polypeptide 1; aliases: CYPIVX1, MGC40051; located in the endoplasmic reticulum and may be involved in neurovascular function in the brain.
GSTM1	Glutathione S-transferase Mu 1; aliases: glutathione S-alkyltransferase M1, S-(hydroxyalkyl)glutathione lyase M1, HB subunit 4; glutathione transferases may serve as an antioxidant system preventing degenerative cellular processes; the genes encoding the mu class of enzymes are organized in a gene cluster on chromosome 1p13.3 and are known to be highly polymorphic; this enzyme conjugates glutathione to a wide number of endogenous and exogenous toxins and carcinogens; null mutations of class mu genes have been linked with an increase in a number of cancers, most likely caused by an increased susceptibility to environmental toxins and carcinogens; specific genetic polymorphisms are associated with susceptibility to colorectal cancer.
GSTM2	Glutathione S-transferase Mu 2; aliases: glutathione S-alkyltransferase M2, S-(hydroxyalkyl)glutathione lyase M2; this enzyme conjugates glutathione to a wide number of endogenous and exogenous toxins and carcinogens; alleviates benzo[a]pyrene-diolepoxide-DNA damage.
GSTM3	Glutathione S-transferase Mu 3; aliases: glutathione S-alkyltransferase M3, S-(hydroxyalkyl)glutathione lyase M3; this enzyme conjugates glutathione to a wide number of endogenous and exogenous toxins and carcinogens; GSTM1 and GSTM3 allele variants are a risk-modulating factor in colorectal cancer patients.
GSTM4	Glutathione S-transferase Mu 4; aliases: glutathione S-alkyltransferase M4, S-(hydroxyalkyl)glutathione lyase M4; this enzyme conjugates glutathione to a wide number of endogenous and exogenous toxins and carcinogens; active on 1-chloro-2,4-dinitrobenzene.

(*Continued*)

Table 8 (*Continued*)

Gene	Protein function
GSTM5	Glutathione S-transferase Mu 5; aliases: glutathione S-alkyltransferase M5, S-(hydroxyalkyl)glutathione lyase M5; this enzyme conjugates glutathione to a wide number of endogenous and exogenous toxins and carcinogens.
MTF1	Metal response element binding transcription factor 1; transcription factor that induces the expression of metallothioneins and other genes involved in metal homeostasis in response to heavy metals such as cadmium, zinc, copper and silver; is a nucleocytoplasmic shuttling protein that accumulates in the nucleus upon heavy metal exposure and binds to promoters containing a metal-responsive element; nucleocytoplasmic shuttling of MTF1 is regulated by diverse signals.
MTF2	Metal response element binding transcription factor 2; alias: polycomb-like protein 2; binds to the metal-regulating element of the metallothionein-1A gene promoter, which is zinc-dependent.

of increasing complexity and molecular weight are more toxic than simple PAR polymers of low molecular weight.[197] The PAR polymer could also bind to PAR polymer binding proteins associated with mitochondria, which then release AIF.[199,224–226] This results in AIF cleavage producing a tAIF, which is soluble and enters the cytosol. The release of tAIF may also be caused by a significant but not excessive decrease in NAD^+ (as a result of PARP activity), ATP, and the mitochondrial membrane potential, resulting in the opening of the MPTP (mitochondrial permeability transition pore).[186,196,211] The release of tAIF may also be caused by other caspase-independent pathways involving molecules that are often found in the downstream execution phase of apoptosis, such as tBid (truncated Bid),[227–229] Bax oligomers (formed after

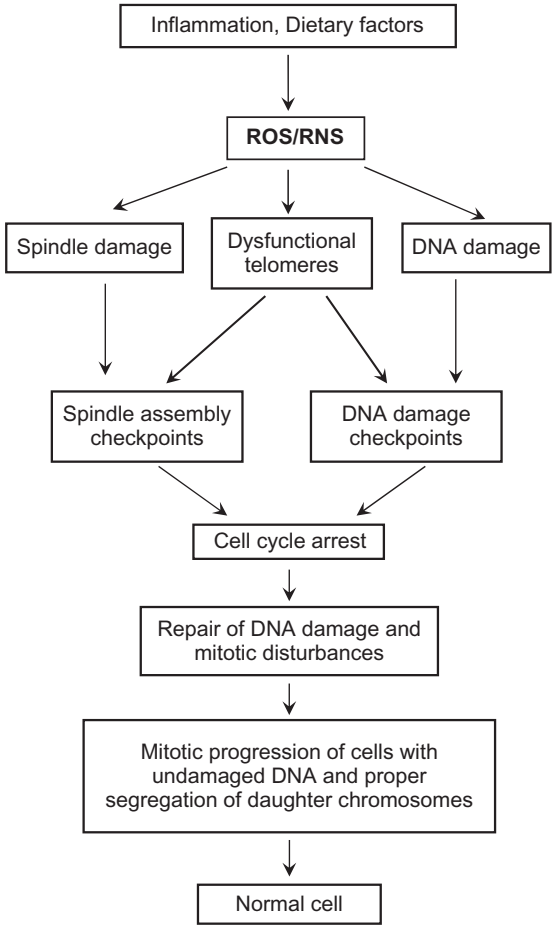

Figure 1 The damaging effects of dietary factors and inflammatory conditions on the colonic epithelium. Damage to DNA, the mitotic spindle, and to telomeres is mediated through the generation of ROS (reactive oxygen species) and/or RNS (reactive nitrogen species). This damage results in the activation of spindle and DNA damage checkpoints, which delay mitosis until repairs are made.

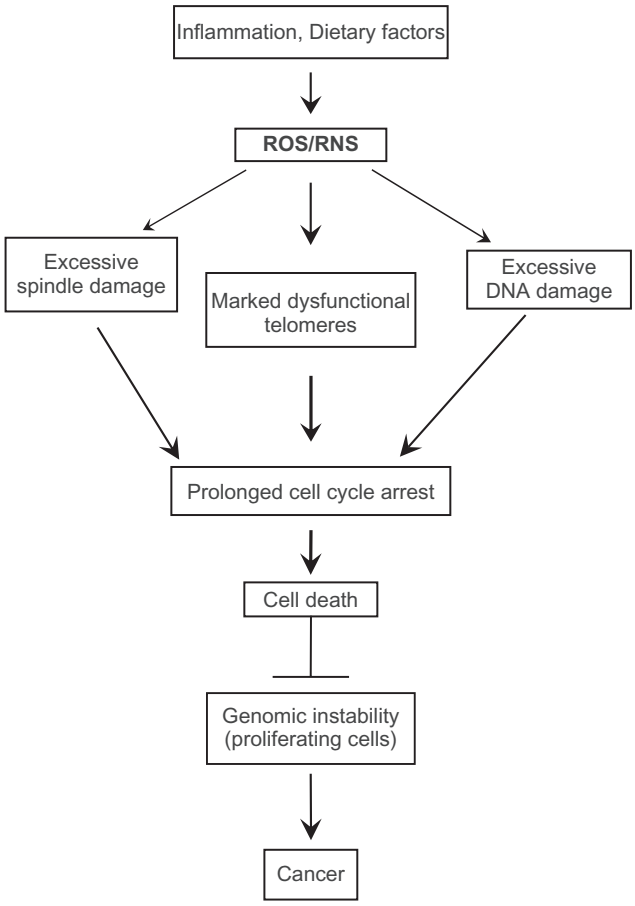

Figure 2 Excessive spindle damage, dysfunctional telomeres, or DNA damage can result in a prolonged cell cycle arrest which activates pro-cell death pathways. This activation of pro-cell death pathways leads to removal of cells with unrepaired damage to the mitotic spindle, the chromosome ends, and DNA and prevents the potential propagation of cells with many types of genomic instability.
Abbreviations: ROS, reactive oxygen species; RNS, reactive nitrogen species.

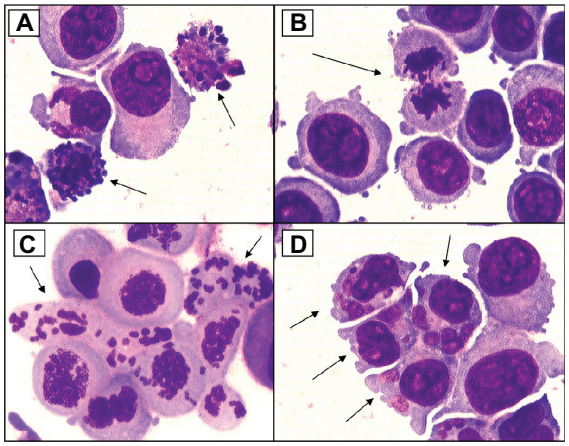

Figure 3 Examples of cellular alterations that accompany apoptosis (**A**), mitotic perturbation during anaphase (**B**), mitotic catastrophe with complete chromosome/spindle disruption (**C**), and abundant micronuclei formation associated with aneuploidy (**D**). Panels A, B, and D are examples of HCT-116 cells treated with 10 μM camptothecin. Panel C represents cells treated with 5 μM phenstatin (drug obtained through courtesy of Dr GR. Pettit, Arizona State University) (cytospin preparations of Giemsa-stained cells; ×100 oil objective lens)

activation of Bax by Ca^{++}-dependent calpains),[211,217] Bak,[230] and Bim-EL.[231,232] The activation of PARP also activates other stress-response pathways such as the RIP/TRAF2/JNK pathway,[233–235] which may be responsible, in part, for generation of tBid[228] and the phosphorylation of Bim-EL. The phosphorylation of Bim-EL releases Bim-EL from sequestration by the microtubular dynein motor complex,[236] allowing it to bind to bcl-2,[231] thereby enhancing the cell death process.

Mechanisms that interfere with tAIF release include the 1) degradation of the PAR polymer by PARG (PAR glycohydrolase),[237] 2) inhibition of tAIF translocation to the nucleus by Bcl-2, Bcl-xl, HSP70, or Iduna, and 3) interference of transcription of the AIF gene by BNIP3.[238] PARG, Bcl-2, Bcl-xl, HSP70, Iduna, and BNIP3 have been shown to be upregulated during carcinogenesis, consistent with the development of tumor cell resistance to cell death. In addition, pro-cell death molecules involved in this MUTYH/PARP/AIF pathway, such as AIF, Bid, Bax, Bak, and Bim-EL, have been reported to be downregulated during carcinogenesis. Thus, overall, MUTYH likely has an important role in the death of cells exposed to excessive reactive oxygen species/reactive nitrogen species (ROS/RNS)-induced DNA damage, and interference with the MUTYH cell death pathway is associated with carcinogenesis.

P73 and caspase-dependent cell death

Like p53, p73 is responsible for the induction of apoptosis in response to excessive DNA damage that cannot be repaired.[239] P73 has the ability to upregulate the transcription of numerous classic apoptosis-related genes such as caspases 3, 6, and 8, Bcl-2 family members, and death receptors (Figure 6). In order for p73 to function as a transcription factor, it must be phosphorylated. The c-Abl kinase, activated by DNA damage, phosphorylates and activates p73 on tyrosine 99.[240] The stress-induced mitogen-activated protein kinase, p38 MAPK, phosphorylates and activates p73 on threonine residues.[239] The degradation of p73 by the E3 ubiquitin-like protein, Itch, is prevented by the Yes-associated protein, YAP. E2F1, p53, and c-jun (located on chromosome 1p; Figures 4 and 6) may also have a role in p73 activation in different cell types.[241,242] One mechanism by which p73 induces apoptosis includes the transcription of PUMA (p53 upregulated modulator of apoptosis), which in turn causes Bax translocation to the mitochondria with the release of cytochrome *c*.[243] A second mechanism involves the transcription of scotin, which causes endoplasmic reticulum (ER) stress and subsequent apoptosis.[244,245] Unlike p53, a direct role of p73 in the apoptotic process (eg, mitochondrial translocation and perturbation) has not been verified. The role of p73 in the regulation of the miRNA processing complex will be discussed in the section "MiRNAs and miRNA processing". As noted above, loss of p73 through chromosome 1p deletion occurs early in colon carcinogenesis, contrary to the loss of p53 which is a late event.

Mitosis-related and spindle checkpoint function (Table 2)

There are 24 genes on chromosome 1p whose gene products affect many different aspects of the mitotic process, and include kinases, phosphatases, centromere proteins, centrosome proteins, cyclins, regulatory mitotic proteins, motor spindle proteins, regulators of chromosomal condensation, a mitosis-related transcription factor, a deacetylase, and a major spindle checkpoint protein (Table 2). The large number of mitosis-related genes that are lost if there is a chromosome 1p deletion could potentially be responsible for colon cancer initiation and progression, since cancer epidemiology studies show that abnormal expression of mitosis-related genes is frequent in different tumor types.[246,247] Mitotic checkpoints, and specifically the spindle assembly checkpoint, are major targets for tumor-associated alterations.[247] The mitotic spindle assembly checkpoint is essential for ensuring that all chromosomes are properly aligned on the metaphase plate, with every chromosome

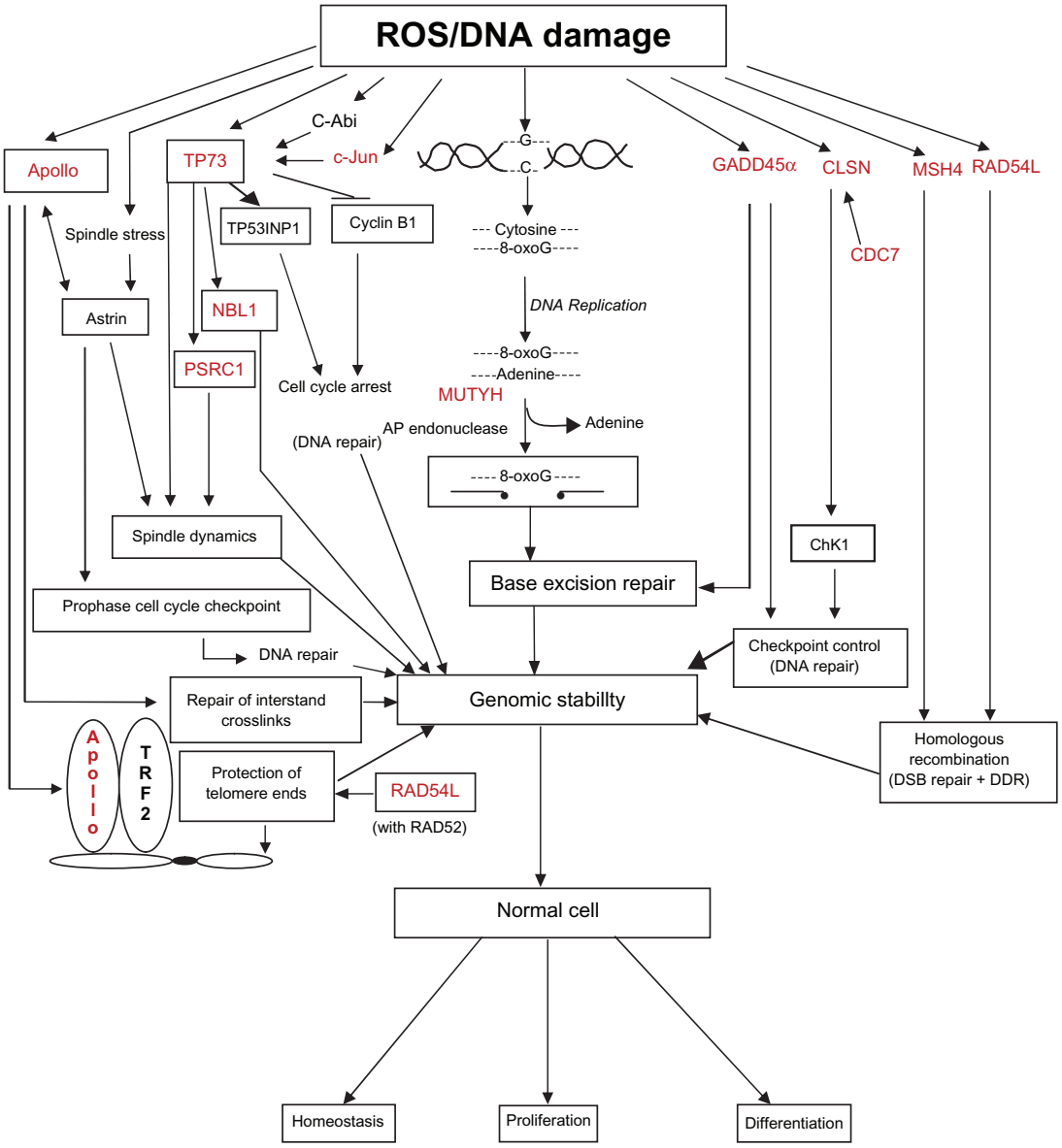

Figure 4 DNA damage causes several downstream molecular and cellular events. The DNA damage response involves several DNA repair proteins and transcription factors that allow the cell cycle to be arrested at several points to enhance genomic stability. All of the genes associated with these damage response pathways that are also found on chromosome 1p are highlighted in red, and reference to the appropriate tables (contain functions of gene products) in the text is provided below. The large number of molecular and cellular events affected by the loss of chromosome 1p is apparent.

Notes: Genes: CLSN, DCLRE (APOLLO), GADD45α, MSH4, MUTYH, TP73, RAD54L (Table 1); CDC7 (phosphorylates claspin in response to DNA damage), PSRC1 (DDA3) (Table 2); NBL1 (Table 6). Additional protein functions in diagram not discussed in text: astrin (microtubule binding protein involved in the functional and dynamic regulation of mitotic spindles); CHK1 (checkpoint homolog of S. pombe; serine/threonine-protein kinase required for cell cycle arrest in response to DNA damage or presence of unreplicated DNA); cyclin B1 [regulatory protein involved in mitosis; complexes with p34 (cdc2) to form the maturation-promoting factor, MPF; expressed predominantly during G2/M]; TP53INP1 (tumor protein p53-inducible nuclear protein 1; in response to DNA damage, it promotes p53 phosphorylation on "Ser-46" and promotes cell cycle arrest; promotes apoptosis if DNA damage is excessive); TRF2 (telomeric repeat binding factor 2; component of the shelterin complex that binds the telomere double-stranded – TTAGGG – repeat and protects telomere ends).

Abbreviations: DDR, DNA damage response; ROS, reactive oxygen species; RNS, reactive nitrogen species.

attached to a spindle microtubule by its kinetochore to prevent aneuploidy.[97] If these processes fail to occur and the cell undergoes a prolonged mitotic arrest (Figure 2), the cell may be eliminated through caspase-dependent or caspase-independent cell death mechanisms[147] to ensure genomic stability (Figure 7).

Oxidative stress is a major factor that can induce disturbances in spindle organization,[248,249] induce centrosome amplification, cause proteolysis of the anaphase inhibitor securin and mitotic cyclins,[250] affect components of the anaphase-promoting complex,[251] and override the spindle checkpoint,[250] thereby affecting chromosomal stability.

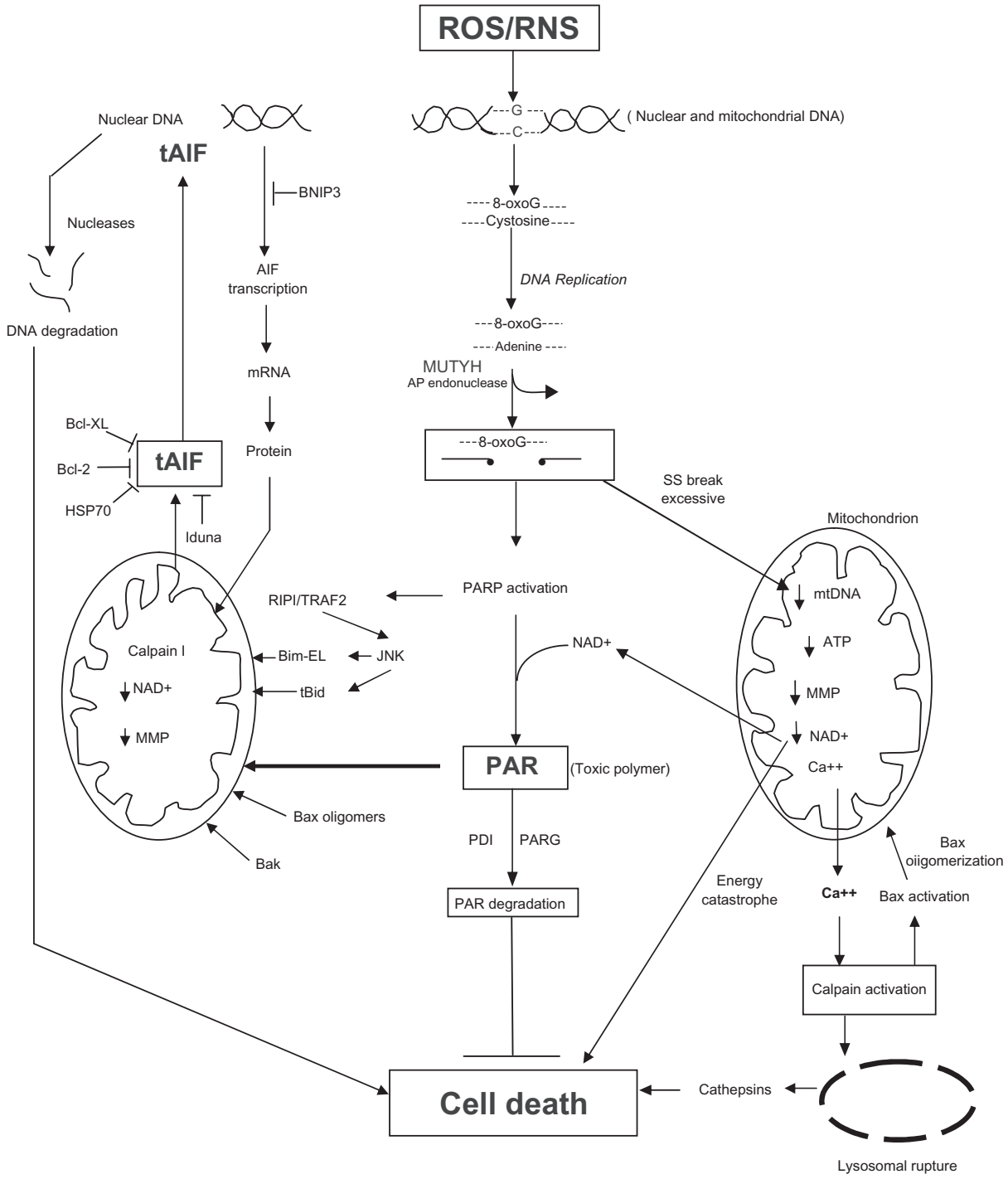

Figure 5 The mechanisms by which excessive activity of MUTYH and AP endonucleases can lead to cell death through the activation of PARP and the generation of toxic poly(ADP)ribose (PAR) polymers and mitochondrial DNA (mtDNA) damage (see text for detailed description).
Abbreviations: ROS, reactive oxygen species; RNS, reactive nitrogen species.

During the process of mitosis, direct oxidative damage to chromosomes resulting in double-strand breaks, or oxidative damage to telomeres can activate p53 (Figure 7) or p73 (Figure 6), major DNA damage response proteins that elicit apoptosis through multiple caspase-dependent mechanisms. In addition, caspase-independent mitotic cell death can also occur during a mitotic catastrophe (Figure 3C, Figure 7), which is a prestage to distinct modes of cell death that may be caspase-dependent or caspase-independent.[148]

The length of time that a spindle is destabilized may determine the mode and timing of cell death after mitotic exit.[123,124,126] It has been suggested that prolonged mitotic

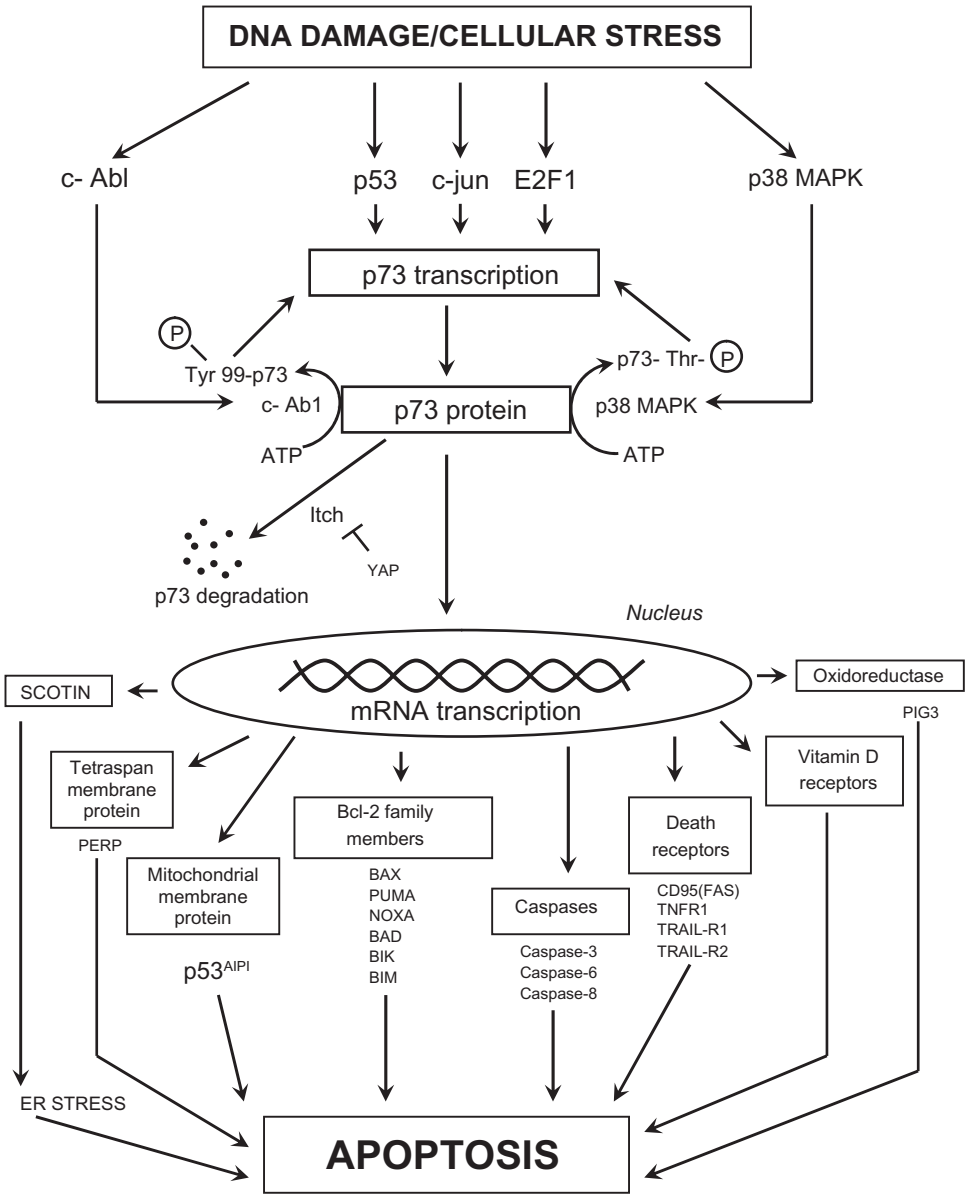

Figure 6 The possible mechanisms by which p73 transcription and activation can lead to cell death through classic apoptotic mechanisms. Definitions of proteins not included in the main text: PERP (p53 apoptosis effector related to PMP22; tetraspan membrane protein and component of intercellular desmosome junctions); p53AIP1 (p53 apoptosis-inducing protein 1; promoter activated by acetylated p73); FAS (CD95) (member 6 of the TNF receptor superfamily which contains a death domain); TNFR1 (member 1A of the TNF receptor superfamily); TRAIL-R1 (member 10A of the TNF receptor superfamily); TRAIL-R2 (member 10B of the TNF receptor superfamily; death receptor 5); PIG3 (p53-induced gene 3 protein; quinone oxidoreductase involved in the generation of ROS and cell death).
Abbreviation: ER endoplasmic reticulum.

delay can lead to the decay of anti-apoptotic messenger RNAs (mRNAs)[252,253] and/or the gradual accumulation of pro-apoptotic signals.[252,254] Of the 24 mitosis-related genes (Table 2), the products of 7 genes have dual-role mitosis/pro-apoptotic functions. These dual-role mitosis/pro-apoptotic genes include APITD1, CCNL2, CDC2L2, CDC42, E2F2, KIF1B, and PLK3 (Table 2). Cells may become genomically unstable if they evade mitotic checkpoints through a process referred to as mitotic slippage, mitotic arrest slippage, or mitotic checkpoint slippage[255–263] (Figure 7). With mitotic slippage, the cell exits mitosis prematurely, carrying broken chromosomes, abnormal numbers of chromosomes, and unrepaired DNA damage into the daughter cells. In addition to loss of pro-apoptotic proteins, it has been reported that the gradual loss of the checkpoint effector, cyclin B, releases the mitotic arrest induced by spindle disruptive agents, despite the continued presence of spindle damage and upstream checkpoint proteins.[14,258,260] In order for a DNA-damaged cell to survive after mitotic slippage, it must evade both apoptosis in the subsequent G1 phase of the cell

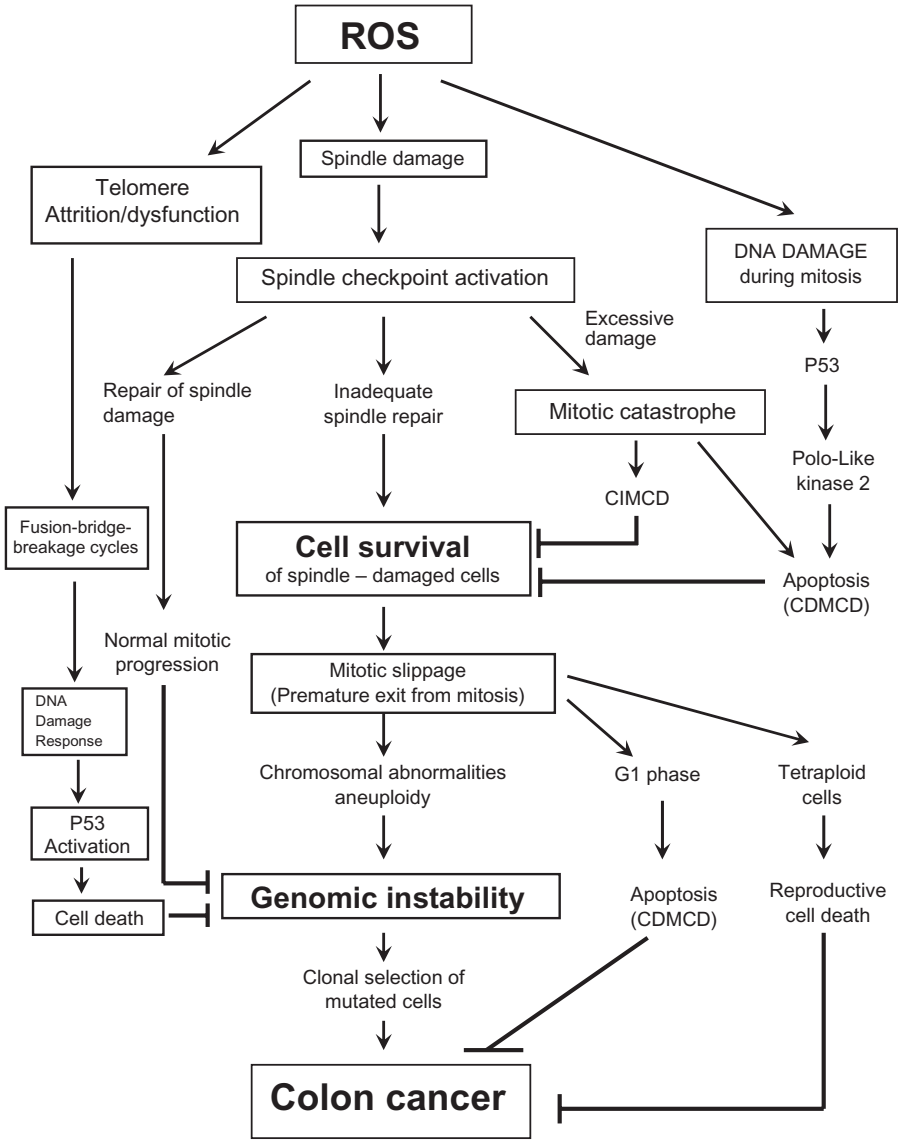

Figure 7 The different cellular fate following spindle, telomere and DNA damage during mitosis. Cells with excessive genomic damage can undergo caspase-dependent cell death (CDMCD) or caspase-independent mitotic cell death (CIMCD). DNA-damaged cells may, however, exit from mitosis by defying cell death pathways through a process referred to as mitotic slippage. These preneoplastic cells with DNA damage and chromosomal abnormalities can then be clonally expanded to produce a tumor and eventually develop into a malignancy through continued cycles of damage to the genome.
Abbreviation: ROS, reactive oxygen species.

cycle[124] (Figure 7) and reproductive cell death that can follow centrosome amplification and the generation of tetraploid cells[264] (Figure 7).

Thus, a decrease in pro-apoptotic mitotic/cell cycle-related genes located on chromosome 1p (APITD1, CCNL2, CDC2L2, CDC42, E2F2, KIF1B, PLK3) (Table 2) may result in resistance to cell death, a critical event that drives tumorigenesis.[52,54,265–267]

Apoptosis-related genes (Table 3)

Seven genes associated with apoptosis are located on chromosome 1p. Bcl-10 and Bcl2L15 are Bcl-2 family members, THAP3 is a zinc-coordinating DNA-binding protein, DNA fragmentation factor A (DFFA) and B (DFFB) are the two subunits of DFF, caspase-9 is a major initiator caspase in the apoptotic proteolytic cascade, and TNFRSF25 is a death domain-containing receptor related to TNFR-1 and CD95 (Apo-1/Fas). The deletion of 3 of these genes would have important implications for carcinogenesis through the increase in apoptosis resistance, and will be discussed in some detail.

DFF is a heterodimeric protein composed of a catalytically active 40 kD subunit, DFFB (CAD [caspase-activated DNase]), and an inhibitory 45 kD subunit, DFFA (ICAD

[inhibitor of CAD]).[268,269] When bound to DFFB, DFFA inhibits the nuclease activity of DFFB.[268,269] During apoptosis, caspase-3 cleaves DFFA at amino acids 117 and 224 and dissociates it from DFFB, thereby releasing the inhibition of DFFB.[270] DFFB activity results in chromatin condensation[271] and the formation of the typical crescents and margination of chromatin that are characteristic of classic apoptotic cells at the ultrastructural level.[190,266,272–276] Characteristic ultrastructural features of apoptotic cells treated with a ROS-generating and DNA-damaging agent are shown in Figure 8. At the molecular level, the action of DFF on DNA results in the initial cleavage of DNA into 50- to 300-kb long fragments,[277,278] representing the dismemberment of the higher order organization of chromatin into chromosomal loop domains, and the fragmentation of DNA into oligonucleosomal sized fragments that form a "ladder" on agarose gel electrophoresis.[279] The importance of DFF in suppressing tumorigenesis[280] was demonstrated by Yan et al[281] using DFF40-null mice. DFF-deficient cells exhibit significant increases in mutation, chromosomal instability, and survival compared with wild-type control cells.[281] This is probably a result of the inhibition of cell death of DNA-damaged cells resulting from the failure to undergo DNA fragmentation.[282,283] DFF is reported to avoid chromosome instability in a p53-independent manner.[284] Irradiation of cells with a caspase-resistant form of DFFA led to increased clonogenic survival of cells with increased chromosomal aberrations and aneuploidy.[284] The ability of DFF to maintain chromsosomal stability appears to be the result of the DNA fragmentation-induced death of cells with excessive DNA damage.[284] Although DFFB has intrinsic DNAse activity, both DFFA and DFFB are required to generate DNase activity,[140,269] and must be co-expressed.[280] DFFA has been postulated to stabilize the synthesis of DFFB,[270,271] or mediate the correct folding and chromatin localization of DFFB.[271] The absence of DFF results in an increased frequency of cell transformation and enhanced susceptibility to radiation-induced carcinogenesis, indicating that DFF is a tumor suppressor.[280] Recently, it has been reported that the expression of DFFA protein, but not DFFA mRNA, is regulated by a specific miRNA, miR-145, suggesting a mechanism of translational regulation.[285] The regulation of DFFB by miRNA has not been investigated, and, so far, none of the miRNAs found on chromosome 1p (Table 4) have been determined to have DFFA or DFFB as target mRNAs for translational regulation.

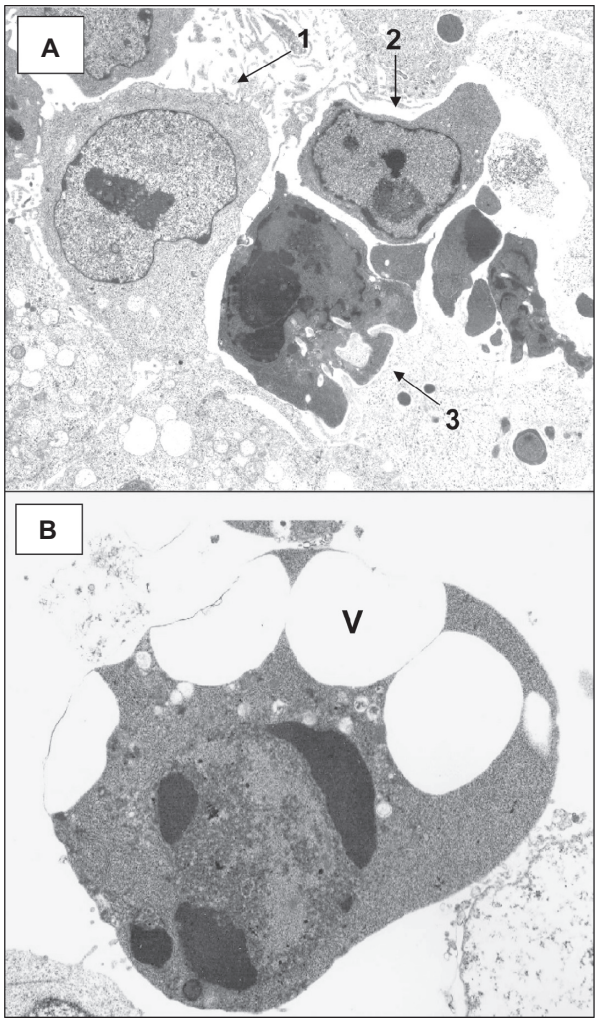

Figure 8 Transmission electron micrographs of HCT-116 cells reacted with 0.5 mM sodium deoxycholate for 2 hours. **A**) Normal cell (arrow 1) with prominent nucleolus and dispersed chromatin; arrow 2 points to a cell in early apoptosis, showing margination of chromatin, a nucleolus showing nucleolar segregation, and an increase in electron density compared with the normal cell; arrow 3 points to a cell in a late stage of apoptosis showing condensed chromatin, a marked increase in electron density compared with the cell above, and apoptotic body formation. **B**) Apoptotic cell in a late stage of apoptosis showing condensed chromatin (including crescent formation), an increase in electron density, and cytoplasmic vacuole (V) formation. (Uranyl acetate, lead citrate stains.)

Caspase-9 is a member of the family of cysteine-aspartic acid-specific proteases (caspases), and is also referred to as Apaf-3 (apoptotic protease-activating factor 3). In the presence of cytochrome *c* and dATP, Apaf-1 binds to procaspase-9[286] via a CARD (caspase activation recruitment domain),[287] forming a complex referred to as the apoptosome.[286,288,289] The cellular oxidative state can affect apoptosome formation by promoting an interaction between caspase-9 and Apaf-1 via disulfide formation.[290] In the apoptosome, caspase-9 is activated to process other downstream caspases, including caspase-3 and caspase-2.[291] Caspase-9 plays an important role in apoptosis induced by genotoxic stress.[292,293] The caspase-9-induced apoptotic pathway can result from mitochondrial membrane depolarization, formation of the apoptosome,

and the activation of multiple caspases, including caspase-3 and caspase-2.[294] Loss of caspase-9 is therefore important to carcinogenesis, since it can result in apoptosis resistance and the propagation of DNA-damaged cells.[295] If caspase-9 is lost, caspase-3 cannot be activated, and thus cannot cleave many substrates including DFFA, an essential endonuclease in apoptosis (see previous page). Similarly, if caspase-9 is lost, caspase-2 may not be activated. Caspase-2 plays a specific role in genotoxic stress-induced apoptosis in some cell types.[296,297] (However, there is another pathway for activation of caspase-2. Activation of p53 by DNA damage can result in the p53-mediated transcription of the death domain protein PIDD [p53-induced protein with a death domain], which, together with RAIDD or RIP1, can form a multiprotein complex called the PIDDosome[298–300] which then activates caspase-2[298]). DNA damage can also activate caspase-2 through the activation of c-Abl.[301] C-Abl binds directly to caspase-9, phosphorylates it on Tyr-153, which then results in the autocleavage and activation of caspase-9 resulting in the apoptosis of excessively DNA-damaged cells.[301] Caspase-9 also mediates apoptosis caused by ER stress.[302] ER stress first activates caspase-12,[302] which is located on the outer membrane of the ER;[303] caspase 12 then activates caspase-9 through a cytochrome *c*-independent mechanism.[302] In some cells, ER stress can result in caspase-8 activation, formation of tBid, mitochondrial damage, release of cytochrome *c* and the activation of caspase-9 through the formation of the apoptosome.[304] Therefore, ER stress can activate caspase-9 through both mitochondrial-independent and -dependent mechanisms.

MiRNAs and miRNA processing (Table 4)

miRNAs are evolutionarily conserved, endogenous, small (21 to 24 nucleotides) non-coding RNAs cleaved from 70 to 100 nucleotide hairpin-shaped precursors that reduce translation and stability of target mRNAs through RISC (RNA interference effector complex)-mediated mRNA degradation and translational suppression via sequence-recognition interactions with the 3′ untranslated region of their targeted mRNAs.[305–315] The diverse cellular functions affected by miRNAs[306,316,317] is underscored by the prediction that thousands of genes are potential miRNA targets.[318–320] At least 800 different miRNAs predicted by computational scanning in the human genome have been documented (http://microrna.sanger.ac.uk). Individual miRNAs have the potential to downregulate large numbers of target mRNAs with seed region complementary sites in their 3′ untranslated regions.[321–323] It has been speculated that miRNAs could regulate ~30% of the human genome.[306] MiRNAs function in proliferation, cell cycle control, the prevention of replicative stress, differentiation, and apoptosis.[324–333] More than half of the known human miRNAs are located at fragile sites, as well as at sites of LOH, amplification, and common breakpoint regions, which are particular genomic regions that are prone to alteration in cancer cells.[327] The overexpression or underexpression of miRNAs as a result of chromosomal additions or deletions, respectively, in individual cells can have dramatic effect on hundreds to thousands of target genes. It is, therefore, not surprising that aberrant expression of miRNAs is associated with cancerous tissues,[334–340] and that characteristic miRNA expression profiles are features of certain human cancers.[341–350] Impaired miRNA processing enhances cellular transformation and tumorigenesis,[351,352] and certain miRNAs are even classified as tumor suppressors and oncogenes.[353–355] Alterations in a series of specific miRNAs have been associated with the age of onset of colon cancer, the growth of colon cancer cells, and certain stages of colon carcinogenesis.[344,356–369] Human colon cancer profiles from 80 colon tumors and 28 samples of normal mucosa show differential miRNA expression depending on mismatch repair status and are characteristic of undifferentiated proliferative states.[367] Examination of the genomic regions containing differentially expressed miRNAs revealed that they were also differentially methylated in colon cancer at a far greater rate than would be expected by chance.[367] MiRNA profiles could accurately predict microsatellite status in a set of 39 colon cancer studied by Lanza and colleagues.[370] This is probably a reflection of the presence or near absence of chromosomal instabilty in the respective microsatellite stable vs unstable cancers.[371]

There are 20 miRNAs and 3 components of the miRNA processing complex (Argonaute proteins 1,3,4) encoded on chromosome 1p (Table 4). One of the 20 miRNAs, miR-34a, is known to be regulated by p53.[309,330,372–376] Tarasov et al[375] evaluated the differential regulation of 74 miRNAs by p53; 50 miRNAs were either positively or negatively regulated by p53, miR-34a showing the highest fold increase (33.4 fold). Although the 20 miRNAs found on chromosome 1p can have pleiotropic effects on cells, miR-34a is the most well studied for its role in cell cycle arrest and apoptosis in response to DNA damage.[309,330,374,377,378] The miR-34 family of miRNAs is one of only 18 mammalian miRNA families[379] that are present in flies and worms.[309] It is probable that links between p53 and the miRNA-34 family may have arisen early in the evolution of the stress-related p53 network.[309] Because of its central role in preventing carcinogenesis, miR-34a has been

classified as a tumor suppressor.[372,377] MiR-34a has numerous downstream targets, including bcl-2 (major anti-apoptotic protein), NOTCH1, Delta1 (ligand for NOTCH1), NOTCH2 (found on chromosome 1p), CDK4, CDK6, Cyclin D1, Cyclin E2, c-Met, MYCN, SIRT1 and E2F3.[319,362,374,375,377,380–384] The inhibition of NOTCH1 by miR-34a would enhance apoptosis since NOTCH1 is known to inhibit p53 activity[385,386] and to have an anti-apoptotic role[387,388] in tumorigenesis. The inhibition of SIRT1 by miR-34a contributes to p53-dependent apoptosis[389] through deacetylating and stabilizing p53 leading to an increase in p21 and PUMA.[384] The E2F3 transcription factor is not known to have a role in apoptosis; however, it is a novel repressor of the ARF/p53 pathway[390] and a potent transcriptional inducer of cell-cycle progression.[377] Therefore, the downregulation of E2F3 by miRNA-34a would have a growth inhibitory effect.[362,374] MYCN has important roles in both cell proliferation and apoptosis, and MYCN amplification is almost always associated with the loss of chromosome 1p36.[382] It is probable that the effects of miR-34a on cellular molecular pathways is widespread, since enforced expression of 34A shows a dramatically altered gene expression profile with upregulation of 532 mRNA transcripts and downregulation of 681 mRNA transcripts highly enriched for those genes that regulate cell-cycle progression, apoptosis (BCL2, BIRC3 [baculoviral IAP repeat-containing 3], DcR3 [decoy receptor 3]), DNA repair, and angiogenesis.[330] In conclusion, although p53 is a late event in colon carcinogenesis, the deletion of a major downstream target of p53, miR-34a, as a result of chromosomal 1p deletion, could have dramatic effects on colon tumorigenesis.

MiR-101 is a miRNA that, like 34a, is pro-apoptotic[391] and considered to be a tumor suppressor.[391,392] The nomenclature of miR-101-1 (Table 4) and miR-101-2 is based on the fact that miR-101-1 is produced from a genomic locus on chromosome 1p31 and miR-101-2 from a genomic locus on chromosome 9p24.[392] Loss of heterozygosity at both 1p and 9p are known to be associated with cancer.[392] The mechanism by which miR-101 induces apoptosis is by targeting and decreasing the expression of the multifaceted anti-apoptotic protein Mcl-1 (myeloid cell leukemia sequence 1).[391] Mcl-1 undergoes rapid turnover which may serve as a convergence point for signals that affect global translation, thereby coupling translation to cell survival and the apoptotic machinery.[393] (The DNA damage response can also result in Mcl-1 destruction and the initiation of apoptosis.[394,395]) Mcl-1 specifically inhibits apoptosis, in part, by sequestering the pro-apoptotic Bim, Bak, tBid, and Noxa, in an inactive state. Since Mcl-1 can interact with tBid and inhibit its induction of cytochrome *c* release, it plays an important role in resistance to TRAIL and TNFα-induced apoptosis.[396,397] Therefore, Mcl-1 can inhibit apoptosis induced by both the death receptor (extrinsic) and mitochondrial (intrinsic) pathways. Mcl-1 is targeted for proteasome-mediated degradation by the E3 ubiquitin ligase MULE[398] and is rapidly degraded with a half-life of 30 minutes to 3 hours.[393] Its short half-life relates to the presence of a long proline-, glutamic acid-, serine-, and threonine-rich (PEST) region upstream of the Bcl-2 homology domains.[398] The inhibition of translation with cycloheximide can cause the rapid degradation of Mcl-1 within 30 minutes, thereby triggering the apoptotic machinery through the release of Bim and the activation of Bak and Bax.[393] Although full-length Mcl-1 does not interact with Bax, the caspase-mediated cleavage of Mcl-1 at Asp127 generates a fragment that induces apoptosis through direct interaction with Bax.[399] Phosphorylation of Mcl-1 can affect its function and degradation.[400] The phosphorylation of Mcl-1 is prominent in cells that accumulate in the G2/M phase of the cell cycle as a result of exposure to microtubule disrupting agents, and in synchronized cells passing through this phase.[401] This phosphorylation, especially at serine 64, enhances the anti-apoptotic function of Mcl-1,[400] thereby allowing cells to properly align their chromosomes prior to anaphase. In colorectal mucosa, the Mcl-1 protein is found in the apical cells of the crypt,[402,403] whereas the distribution is more diffuse in the malignant cells.[403]

In addition to the development of apoptosis resistance, the loss of miR-101 also leads to cancer progression through the overexpression of histone methytransferase EZH2 (enhancer of zeste homolog 2), a polycomb group member, with concomitant dysregulation of epigenetic pathways.[392,404] MiR-101 also represses the expression of FOS (v-fos FBJ murine osteosarcoma viral oncogene homolog) oncogene, a key component of the AP-1 (activator protein-1) transcription factor, MYCN (a gene amplified in many tumors), and COX-2, an enzyme involved in the production of prostaglandins from the metabolism of arachidonic acid.[405] Enhanced expression of miRNA-101 also has an effect on the late stages of cancer, since it inhibits invasion and migration.

The p53/p63/p73 family of tumor suppressors are known to regulate the major components of the miRNA processing complex,[164,406] which include Drosha-DGCR8, Dicer-TRBP2, and Argonaute proteins. Drosha (RNASEN) is an RNAse III endonuclease; DGCR8 is a double stranded RNA binding protein; DICER contains an RNA helicase motif required for the formation of RISC (RNA induced silencing complex);

TRBP2 (trans-activation-responsive RNA binding protein 2) is a component of the miRNA loading complex (composed of DICER1, AGO2, and TRBP2) required for the formation of RISC. Argonaute proteins are endonucleases that aid in the maturation of pre-miRNAs of 60 to 70 nucleotides to mature miRNAs of 21 to 24 nucleotides; the tethering to mRNA mimics the miRNA-mediated repression of protein synthesis.[164,407,408] There are 8 members of the Argonaute family in the human genome;[409] 4 belong to the PIWI subfamily and are expressed mainly in the testis, whereas the other 4 belong to the elF2C/AGO subfamily and are expressed in a variety of adult tissues. Ago1 and Ago2 (catalytic engine of RISC) reside in 3 complexes with distinct DICER and RNA-induced proteins involved in RNA metabolism.[410] Three of the 4 members of the elF2C/AGO subfamily are found in a tandem cluster of closely related Argonaute non-nucleolytic proteins,[411] Ago1, Ag3, and Ago4 on chromosome 1p (Table 4). Therefore, loss of chromosome 1p should have a major impact on the process of miRNA processing in the affected cells.

A family of miRNAs on chromosome 1p of particular interest to colon carcinogenesis is the miR-200 family, which includes miR-200a, -200b, and -429 (Table 4). These 3 family members are all encoded on a 7.5-kb polycistronic primary miRNA transcript and help determine the epithelial phenotype of cancer cells through the regulation of the Wnt/β-catenin signaling pathway.[412,413] Wnt growth factors activate a cascade of intracellular events, known as the canonical Wnt pathway, which ultimately leads to a coordinated proliferation, differentiation, and sorting of the epithelial cell population that forms the colonic crypts.[414] In colorectal cancer, epithelial cells that acquire mutations in the Wnt/β-catenin signaling pathway gain inappropriate proliferative capabilities mimicking the effect of a permanent Wnt stimulation.[414] Beta-catenin is a transcription factor that translocates to the nucleus and activates target genes involved in stimulation of the cell cycle and inhibition of apoptosis. E-cadherin binds directly to β-catenin in the cytoplasm, which restricts the movement of β-catenin to the nucleus. ZEB1 and ZEB2 are proteins that repress the transcription of E-cadherin. Members of the miR-200 family were found to directly target the mRNA of ZEB1 and ZEB2,[412,415–418] upregulate E-cadherin expression in cancer cell lines, and reduce cellular motility.[412] Conversely, downregulation of one miR-200 family member that was tested, miR-200a, was shown to promote tumor growth by reducing E-cadherin and activating the Wnt/β-catenin signaling pathway.[413] Cancer progression has some similarities with embryonic development and wound healing, in which a process of epithelial-to-mesenchymal transition (EMT) occurs.[419] Although the EMT normally occurs as a process of stem cell differentiation, the EMT that occurs during carcinogenesis involves a change from a differentiated tumor to a more invasive dedifferentiated tumor.[412,419,420]

The loss of the miR-200 family of miRNAs, coupled with the loss of 4 proteins associated with the Wnt/β-catenin signaling pathway (Table 5 below), and the loss of the pro-apoptotic miR-34a and the miRNA transcriptional protein, p73, should have a significant impact on the initiation and progression of colon cancer.

Wnt/β-catenin signaling pathway (Table 5)

The Wnt signaling pathway is critical for the differentiation and sorting of the epithelial cell population necessary for the organization of the colonic crypts and for the regulation of crypt cell renewal and homeostasis.[414,421] Wnt signaling is initiated by the binding of extracellular Wnt factors to receptors on the cell surface, which triggers a signaling cascade that leads to the accumulation of β-catenin.[414,422] In the absence of Wnt signals, β-catenin is degraded by a multicomplex complex composed, in part, of APC (adenomatous polyposis coli), GSK3β (glycogen synthase kinase-3-beta), and the scaffold proteins Axin1 and Axin2/conductin,[423–425] forming the β-catenin destruction box. This destruction box is responsible for the GSK3β-mediated phosphorylation of β-catenin and its subsequent degradation by the ubiquitin-proteasome pathway. The Wnt signals block this phosphorylation and degradation, resulting in the accumulation of β-catenin. Cytoplasmic β-catenin accumulation and translocation to the nucleus allows β-catenin to associate with TCF/LEF (T cell factor/lymphocyte enhancer factor) transcription factors which target genes that enhance cell survival and proliferation (ie, *c-myc*, *cyclin D1*).[426–428] Mutations in APC, β-catenin, Axin1, or ICAT (inhibitor of beta-catenin and Tcf-interacting protein) result in the deregulated accumulation of β-catenin and the constitutive activation of Wnt signaling,[429–431] a major cause of cancer, including colorectal cancer.[418,424,425,432]

There are 4 genes located on chromosome 1p that are directly involved in the Wnt signaling pathway (CTNNBIP1, DVL1, WNT2B, and WNT4) (Table 5). WNT2B and WNT4 are secreted signaling factors and Dvl1 is a cytoplasmic molecule that associates with Frat-1 to activate the Wnt signaling pathway. The loss of these positive regulators of the Wnt signaling pathway as a result of a chromosomal 1p deletion may contribute to the dysregulation of crypt

organization that could initiate the carcinogenic process.[433] CTNNBIP1/ICAT (Table 5), on the other hand, is a negative protein regulator of the Wnt signaling pathway. ICAT disrupts β-catenin–TCF interactions,[434–436] thereby downregulating gene expression associated with proliferation and cell survival. The crystallographic structure of ICAT indicates the mechanism by which ICAT interferes with β-catenin function. The NH_2-terminal domain of ICAT binds to armadillo repeats 10–12 of β-catenin, whereas the COOH-terminal domain of ICAT binds to the groove formed by armadillo repeats 5–9.[435,437] The armadillo repeats 5–9 are crucial for the binding of β-catenin to both TCF and E-cadherin.[438] The importance of ICAT in the prevention of carcinogenesis is underscored by the fact that ICAT is a multipotent inhibitor of β-catenin[438] by interfering with the binding of β-catenin to TCF, cadherins, and APC, with consequences for transcription, cell adhesion, and cytoskeletal function.[438–440] The cytoplasmic and nuclear location of ICAT, using an immunohistochemical approach, is consistent with a broader role for ICAT than previously reported.[440]

In addition to the effects on transcription and cell adhesion, ICAT can function as a pro-cell death molecule in certain situations. Overexpression of ICAT in colorectal tumor cells results in growth arrest and cell death, and serves to eliminate cells with a constitutively activated Wnt signaling pathway.[441] Using flow cytometry, the cell death was evidenced by a sub-G1 peak of the cell cycle, and the forced entry of cells into an illegitimate DNA synthetic phase without having undergone a prior mitosis (enhanced trypan exclusion of >4N cells).[441] Transgenic mice expressing ICAT also make activated T cells (dependent on β-catenin–TCF signaling for survival[442,443]) highly susceptible to apoptosis (using annexin V staining), by reducing the expression of Bcl_{xL} below a critical threshold.[436] The mechanism by which ICAT reduces Bcl_{xL} expression is not known at the present time.

Since chromosomal instability is a major feature of colon carcinogenesis, it is appropriate to consider the role of the Wnt signaling pathway in mitotic control and aberrant Wnt signaling in the generation of chromosomal aberrations. A precedent for exploring the role of aberrant Wnt signaling in chromosomal instability are the findings that 1) multiple signaling pathways converge to orient the mitotic spindle in *Caenorhabditis elegans* embryos;[444] 2) APC and EB1 (a microtubule-associated protein) have the ability to maintain proper spindle positioning in the developing nervous system of *Drosophila*;[445,446] 3) binding of APC protein to microtubules increases microtubule stability and is regulated by GSK3β;[447] 4) APC has a role in chromosome segregation;[448] 5) β-catenin is a component of the mammalian mitotic spindle and functions to ensure proper centrosome separation and subsequent establishment of a bipolar spindle;[449] 6) GSK3β has a role in mitotic spindle dynamics and chromosome alignment,[450] and localizes to the centrosome and specialized cytoskeletal structures;[451] 7) dishevelled genes are involved in mitotic progression in cooperation with polo-like kinase 1;[452] and 8) conductin/axin2 and Wnt signaling regulates centrosome cohesion.[453] It is now well established that aberrant Wnt/β-catenin signaling can induce chromosomal instability in cancer, including colon cancer.[454–458] An understanding of the mechanisms by which specific components of the Wnt signaling pathway affect mitosis, mitotic slippage and other aspects of the cell cycle, including interaction with spindle checkpoint proteins, needs to be experimentally determined.

Tumor suppressors (Table 6)

Experiments involving somatic cell fusion and chromosome segregation established the concept that certain genes are capable of suppressing tumorigenesis.[459,460] Tumor suppressors are genes whose miRNA or protein products reduce the formation of tumors and prevent malignant progression by decreasing proliferation, regulating the cell cycle, maintaining chromosome integrity, enhancing DNA repair, inducing apoptosis, and, by reducing angiogenesis, invasion, migration, and cell adhesion. Classic tumor suppressor genes that, when deleted or mutated, contribute to tumorigenesis in many types of tumors include p53, RB, INK4a (p16), and ARF.[461] In colorectal cancer, mutations and LOH of the tumor suppressor, APC, can affect both the initiation and progression of cancer, whereas the loss of p53 is a late event. Therefore, when the loss of chromosome 1p became associated with many types of cancer, including colon cancer, several groups began the quest to identify the specific tumor suppressor gene or genes located on 1p.[462–467] Several genomic loci were identified as "hot spots" for tumor suppressor genes, which included 1p36 and 1p34. It became evident that many genes, both inside and outside of these "hot spots", could be classified as tumor suppressors; 26 tumor suppressor genes, their genomic loci, and the function of their gene products are listed in Table 6. (Note: 11 genes classified as tumor suppressors in Table 6 are not listed in other tables [Tables 1–5 and 7]).

Several tumor suppressors are haploinsufficient,[468] and cell cycle regulatory tumor suppressor genes seem especially dosage-sensitive.[469] These findings indicate that the loss of

only one copy of a gene in a diploid cell could have a biologic effect.[469] Such a loss could contribute to cellular transformation, with the process of selection driving clonal expansion of pre-neoplastic cells.[8]

Certain tumor suppressors play a more prominent role in tumorigenesis than others in particular tissue types. However, it is probable that the loss of numerous tumor suppressor genes as a result of a chromosomal deletion probably plays a prominent role in the initiation and progression of cancer through a "combination" of different and/or complementary adverse cellular and molecular events.[461,467]

Antioxidants (Table 7)

Four genes on chromosome 1p are associated with defense against oxidative stress (Table 7). Two of these (peroxiredoxin 1 [PRDX1] and endoplasmic reticulum protein ERP19 [TXNDC12]) utilize reducing equivalents provided through the thioredoxin system, and 2 (glutamate-cysteine ligase [modifier subunit] or GCLM and glutathione peroxidase 7 [GPX7]) utilize glutathione. One of the most important genes associated with oxidative stress is glutamate-cysteine ligase (GCL) (also called gamma-glutamylcysteine synthetase), the first rate limiting enzyme of glutathione synthesis.[470,471] This enzyme requires coupled ATP hydrolysis to form an amide bond between the γ-carboxyl group of glutamate and the amino group of cysteine to form γ-glutamylcysteine. The enzyme consists of a heavy catalytic subunit (73 kDa) and a light (31 kDa) regulatory subunit (GCLM); the light chain or modifier subunit is found on chromosome 1p. It has been known for the past 2 decades that the ultimate formation of glutathione is required for intestinal function.[472] The long-term ingestion of reduced glutathione has recently been shown to suppress the accelerating effect of a beef tallow diet on colon carcinogenesis in rats.[473] The specific importance of GCLM to protection against oxidative stress is underscored in GCLM (–/–) knock-out mice, which are severely compromised in the oxidative stress response.[474]

GCL can be increased by oxidative stress or glutathione depletion[475,476] through the inhibition of SHP-1[477] and the activation of jun N-terminal kinase (JNK).[477,478] The increase in GCL can protect against mitochondrial injury and numerous cellular processes that are depend on the generation of glutathione, such as cell cycle progression, inhibition of caspases (protection against apoptosis), activity of detoxification enzymes (see GSTM genes in Table 8; discussed below), and DNA repair.[479–482] Recent studies indicate that a reduced state of proteins in the nucleus is an important environment that induces heterochromatin formation[482] and the regulation of histones and PARP activities.[483]

Defense against environmental and metabolic toxicity (Table 8)

Chromosome 1p contains 19 genes associated with protection against toxins/carcinogens derived from the environment, dietary/cooking-derived components, and metabolism (Table 8). These genes consist of 2 arylacetamide deacetylase-like enzymes, 4 members of the aldo-keto reductase family, 6 members of the cytochrome P450 family of polypeptides, all 5 members of the mu class of glutathione-S-transferases (GSTs), and 2 metal response element binding transcription factors. A compilation of the 10 most significant transcripton factors capable of targeting the 5′-upstream promoter regions of these 19 genes (GeneCards [SABiosciences' database; UCSC Genome Browser]) indicates the possible involvement of 95 distinct transcription factors that control their expression. In addition, the Wnt/beta-catenin signaling pathway has been shown to activate various P450 family and GST mu class enzymes in mouse models.[484] Since transcription factors respond to different cellular demands and stresses, the presence of these genes on chromosome 1p indicates that the loss of this chromosome arm could compromise the cell's ability to respond to a variety of environmental toxins/carcinogens that could damage DNA.

It is of interest that all 5 genes of the mu class of GSTs are located on chromosome 1p. The 5 genes are arranged in tandem in the physical order 5′-M4-M2-M1-M5-M3-3′.[485,486] The M4-M2-M1-M5 sequence in the gene cluster is oriented in a head-to-tail orientation, whereas the M3 gene is oriented tail-to-tail with respect to the adjacent M5 gene, and is therefore transcribed in the reverse orientation relevant to the other 4 GST mu genes.[485] This GST mu gene cluster functions in the detoxification of electrophilic compounds by conjugating glutathione to a wide number of endogenous and exogenous toxins/carcinogens.[487] Genetic polymorphisms in GSTM1 increase susceptibility to gastric and colorectal adenocarcinomas.[488] In addition, about 70% of human loci is deleted for GSTM1 and 50% of the human population is homozygous deleted for GSTM1.[485] This deletion is a result of unequal crossing-over between the two 2.3 kb repeated regions in the intergenic regions that flank the GSTM1 gene. Homozygous deletion of GSTM1 results in increased baseline chromosomal aberrations in lymphocytes among smokers, indicating the role of epoxides and other reactive metabolites of polycyclic aromatic hydrocarbons in inducing

genomic instability in these compromised cells.[489] All 5 GSTM genes have distinct promoter regions that respond to a different array of transcription factors. Therefore, the loss of chromosome 1p would compromise cellular defenses against toxins/carcinogens, especially in individuals harboring the GSTM1 deletion or other specific polymorphisms.

Development of resistance to cell death and the propagation of cells with DNA damage and chromosomal defects (summary)

We have described in this review how the combination of the persistent damage to a cell's genome with the inability of that cell to adequately repair the damage or die in response to the excessive damage, is a dangerous situation which can result in clonal selection and the development of colon carcinogenesis. The molecular and cellular mechanisms that are associated with the death of cells are most complex, and include both caspase-dependent and caspase-independent processes. Listed in Tables 1–7 are 27 pro-apoptotic/pro-cell death genes found on chromosome 1p, whose simultaneous loss caused by a chromosome 1p deletion could have a major impact on the development of resistance to cell death. In Table 9, we extract from those tables the specific genes whose products contribute to cell death. Caspase-9 and both subunits of DNA fragmentation factor are on the downstream execution phase of apoptosis, and the consequences of their loss are obvious. However, the loss of other gene products (eg, TP73, miR-34a) can have pleiotropic effects on cell death pathways because of multiple transcriptional or translational targets. In addition, TP73, KIF1B, and E2F2 are classified as haploinsufficient genes, with loss of function implied with the presence of only 1 allele.[490] Some gene products have dual DNA repair/pro-cell death functions (eg, MUTYH) and dual mitosis/pro-cell death functions (KIF1B). One can see (Table 9) that, in addition to classic pro-apoptotic genes, there are dual role cell survival/pro-cell death genes, DNA damage-response genes, various tumor suppressor genes, genes associated with mitosis, miRNAs, Wnt signaling, and protection against the generation of peroxides. The mechanism of action of these 27 genes in the control of cell fate is an active area of investigation and beyond the scope of this review. This detailed study of the implications of the loss of chromosome 1p serve as an example of how specific chromosomal deletions can have a major impact on carcinogenesis.

Role of dietary factors in colon carcinogenesis (Table 10[491–538])

In this section we first address what alteration in specific dietary factors can lead to the loss of chromosome segments or entire chromosome arms in general to produce loss of heterozygosity. Second, we will consider how the consequences of the loss of genes located on chromosome 1p might be affected by pro-carcinogenic and anti-carcinogenic dietary factors. Our approach is to show how specific dietary factors may influence the molecular and cellular processes affected by chromosome 1p loss that were described in previous sections. Links of diet to any of the specific genes lost by the 1p deletion (see Tables 1–8) are listed in Table 10.

Diets high in fat,[473,539–547] but low in fiber,[540,548–551] low in vegetable intake,[552–555] and micronutrient deficient[556–560] induce oxidative stress and DNA damage and adversely affect many molecular pathways that prevent genomic instability and apoptosis resistance, 2 major processes that, together, enhance the development of sporadic colon cancer.

Table 9 Summary of pro-cell death genes on chromosome 1p

Pro-cell death genes	Reference tables
GADD54α, MUTYH, TP73	Table 1 DNA repair and DNA damage response genes
APITD1, CCNL2, CDC2L2, CDC42, E2F2, KIF1B, PLK3	Table 2 Mitosis-related and spindle checkpoint genes
BCL2L15, BCL10, CASP9, DFFA, DFFB, THAP3, TNFRSF25	Table 3 Apoptosis-related genes
miR-34a, miR-101-1, miR-320b-1	Table 4 MicroRNAs (miRNAs) and components of the miRNA processing complex
CTNNBIP1 (ICAT)	Table 5 Genes associated with the Wnt signaling pathway
CHD5, DEAR1, PRDM2, NBL1, PLA2S-II	Table 6 Tumor suppressor genes
PRDX1	Table 7 Genes associated with antioxidant function

Abbreviations: APITD1, Apoptosis-inducing, TAF9-like domain 1; CL2L15, B-Cell Lymphoma-2-like protein 15; BCL10, B-Cell Lymphoma 10; CASP9, cysteine-aspartic acid protease, family member 9; CCNL2, Cyclin L2; CDC2L2, Cell Division Cycle 2-like 2; CDC42, Cell Division Cycle 42; CHD5, Chromodomain Helicase DNA Binding Protein 5; CTNNBIP1 (ICAT), Catenin, beta interacting protein 1 (Inhibitor of beta-catenin-interacting protein 1); DEAR1, Ductal Epithelium-Associated RING Chromosome 1; DFFA, DNA Fragmentation Factor A; DFFB, DNA Fragmentation Factor B; E2F2, E2F transcription factor 2; GADD45α, Growth Arrest and DNA-Damage-inducible 45 alpha; KIF1B, Kinesin family member 1B; miR-34α, microRNA-34α; miR-101-1, microRNA-101-1; miR-320b-1, microRNA-320b-1; MUTYH, MutY Homolog (E. coli); NBL1, Neuroblastoma, suppression of tumorigenicity 1; PLA2S-II, The Secretory Type II Phospholipase A_2; PLK3, Polo-like Kinase 3; PRDM2, PR Domain Containing 2; PRDX1, Peroxiredoxin 1; THAP3, THAP domain containing; TNFRSF25, Tumor Necrosis Factor Receptor Superfamily, Member 25; TP73, Tumor Protein 73.

Table 10 Preventive effects of dietary factors on processes and signaling pathways associated with genes located on chromosome 1p

Process	Dietary factor(s) and food sources	Effect(s) of dietary factors and references
DNA repair and DNA repair proteins	1) Polyphenols occur in fruits and vegetables, wine, tea, coffee, herbs, extra virgin olive oil, chocolate, and other cocoa products	1) Stimulates DNA repair[491,492] and increases levels of DNA repair proteins (eg, PARP-1 and PMS2) by chlorogenic acid and metabolites[493] and GADD45 by dihydroxyphenylethanol[494] and quercetin.[495]
	2) Vitamins	2) Ascorbate upregulates MLH1 and p73.[496]
MicroRNA expression	1) Folate	1) Exerts cancer-protective effects through modulation of miRNA expression;[497] rats fed a methyl-deficient diet exhibited decreased expression of miRNA-34a with the concomitant increase in E2F3.[498]
	2) Retinoids	2) Exert cancer-protective effects through modulation of miRNA expression.[497,499]
	3) Curcumin (component of the Indian spice, turmeric)	3) Exerts cancer-protective effects through modulation of miRNA expression.[497,500]
	4) Polyphenols	4) Quercetin and metabolites modulate inflammatory miRNA gene expression.[501]
	5) Fish oil	5) n-3 polyunstaurated fatty acids modulate carcinogen-directed non-coding miRNA signatures in rat colon.[502]
	6) Vitamins	6) Differences in dietary vitamin E affect hepatic miRNA concentrations in vivo.[503]
Wnt signaling pathway	1) Stilbenes (polyphenols) present in grapes, berries, peanuts, and red wine	1) Reduced nuclear and cytoplasmic immunostaining of β-catenin in the AOM rat model of colon carcinogenesis.[504]
	2) Curcumin	2) Curcumin has an inhibitory effect on Wnt signaling[505,506] through a) suppression of β-catenin response transcription activated by Wnt3a,[507] b) induction of caspase-3-mediated degradation of β-catenin,[508] c) downregulation of p300, a positive regulator of the Wnt/β-catenin pathway,[507] d) reduction of expression of the Frizzled-1 Wnt receptor.[509]
	3) Triterpene lupeol found in a variety of fruits, vegetables, and some medicinal herbs	3) Lupeol treatment resulted in a) an increase of apoptosis, b) a decrease in β-catenin transcriptional activity, c) a restriction of the translocation of β-catenin from the cytoplasm to the nucleus, d) a decrease in expression of the Wnt target genes, c-myc, cyclin D1, e) a decrease in expression of the proliferation markers, PCNA, Ki-67, and f) a decrease in expression of the invasion marker, osteopontin.[510]
Antioxidant gene expression	1) Polyphenols (eg, red wine, black tea)	1) Activate endogenous antioxidant defense systems, which include the glutathione peroxidases;[511,512] enhancement of glutathione and γ-glutamylcysteine synthetase.[513–517]
	2) Curcumin	2) Curcumin alters EpRE and AP-1 binding complexes and elevates glutamate-cysteine ligase expression.[518]
	3) Diterpenes (eg, kahweol, cafestol)	3) The coffee-derived diterpenes (eg, kahweol, cafestol) can induce γ-glutamylcysteine synthetase and glutathione levels in the liver, kidney, lung, and colon of the rat.[519]
Environmental/ metabolic toxicity genes	1) Polyphenols and orto-phenols	1) Activate endogenous detoxification defense systems,[511,520] including GSTM2;[513] p-coumaric acid, a coffee compound.[521] can increase the mRNA levels of GSTM2.[522]
	2) Diallyl disulfide (DADS)	2) DADS increases tissue activities of quinone reductase and glutathione transferase in the gastrointestinal tract of the rat.[523]
	3) Butyrate	3) Butyrate can induce GSTM2 expression in human colon cells.[524]
	4) Diterpenes (eg, kahweol, cafestol)	4) The coffee-derived diterpenes (eg, kahweol, cafestol)[521] can enhance glutathione S-transferase activities.[519,525]
Oxidative DNA damage	1) Polyphenols include flavonoids (quercetin, luteolin, kaempferol, naringenin; myricetin), oleuropein, protocatechuic acid, hydroxybenzoic acids, flavones, hydroxycinnamic acids, lignans, anthocyanins, isoflavones, stilbenes, propanoid glycosides, chlorogenic acid, and metabolites	1) Polyphenols have the capacity to act as antioxidants (chain breakers or free radical scavengers,[526] thereby preventing the induction of oxidative DNA lesions,[527–530] and stimulating DNA repair;[492] black tea complex polyphenols inhibit 1,2-dimethylhydrazine-induced oxidative DNA damage in rat colonic mucosa;[531] 4-coumaric acid, a coffee component, can reduce oxidative DNA damage in rat colonic mucosa.[522]

(*Continued*)

Table 10 (*Continued*)

Process	Dietary factor(s) and food sources	Effect(s) of dietary factors and references
	2) Fish oils, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA)	2) Fish oils reduce oxidative DNA damage in rat colonocytes.[532]
	3) Monounsaturated fatty acid (eg, oleic acid) obtained from olive oil.	3) In a study of the effect of olive oils on biomarkers of oxidative DNA stress in Northern and Southern Europeans, 25 mL of 3 olive oils with low, medium, and high phenolic content were administered to 182 males daily for 3 weeks, resulting in a significant reduction of DNA oxidation by 13%.[533] The olive oil intake led to marked increase in monounsaturated fatty acid intake independent of the phenolic compounds; lifelong feeding of monounsaturated fatty acid-rich olive oil led to a lower level of oxidative DNA damage and DNA double strand breaks compared with polyunsaturated fatty acid-sunflower oil.[534]
	4) Short-chain fatty acids (eg, butyrate)	4) Pre-incubation of normal human colonocytes ex vivo and HT-29 colon cancer cells in vitro with physiological concentrations of butyrate reduced H_2O_2-induced DNA damage using the comet assay;[535] butyrate protects human colon cells from genetic damage by 4-hydroxynonenal.[536]
	5) Garlic organosulfur compounds (OSC), such as allicin, diallyl sulfide, diallyl disulfide, S-allyl cysteine, allyl mercaptan, are derived from garlic	5) OSC decreased the genotoxicity of hydrogen peroxide and methanesulfonate, assessed using the comet assay.[537]
	6) Vitamins	6) Ascorbic acid (vitamin C) protects against endogenous oxidative DNA damage.[538]

Abbreviations: AOM, azoxymethane; AP-1, activator protein 1; c-myc, avian myelocytomatosis viral oncogene homolog; DADS, diallyl disulfide; DHA, docosahexaenoic acid; E2F3, E2F transcription factor 3; EPA, eicosapentaenoic acid; EpRE, electrophile response element; GADD45, Growth Arrest and DNA-Damage-inducible 45; GSTM2, Glutathione S-Transferase Mu 2; Ki-67, antigen identified by monoclonal antibody Ki-67; miRNA-34a, microRNA-34a; MLH1, mutL homolog 1; mRNA, messenger ribonucleic acid; OSC, organosulfur compounds; P73, Tumor Protein 73; PARP-1, poly(ADP-ribose) polymerase-1; PCNA, proliferating cell nuclear antigen; PMS2, postmeiotic segregation increased 2; Wnt, wingless-type.

The effects of diet likely occur early in the carcinogenesis process, since an altered vegetable intake is known to affect pivotal carcinogenesis pathways in the colonic mucosa from adenoma patients and controls.[561] Although 2 alleles are associated with each gene, and the loss of 1 allele may be compensated for by the other, many genes are reported to be haploinsufficient, including those associated with the mitotic checkpoint.[562] It is relevant that TP73, KIF1B, and E2F2, found on chromosome 1p, have also been reported to be haploinsufficient,[490,563,564] and could have dramatic consequences for colon tumorigenesis if only 1 allele is expressed in colonic epithelial cells. It is possible that many other genes may be found to be haploinsufficient in the future, since a map of 1079 probable haploinsufficient genes has been compiled by systematic identification of genes unambiguously and repeatedly compromised by copy number variation among 8458 apparently healthy individuals.[565] Those genes with a high probability of exhibiting haploinsufficiency were enriched among genes implicated in human dominant diseases and among genes causing abnormal phenotypes in heterozygous knockout mice.[565] In addition, the loss of several genes on the same chromosome arm that affect a particular molecular pathway (see Tables 1–8) may *together* have a significant effect on that pathway, although the loss of a single gene may have little effect. Specific dietary factors may decrease the protein levels of certain genes through post-translational mechanisms (eg, proteasomal degradation), thereby inducing a functional pseudo-biallelic loss of a gene, one through a physical loss of the chromosomal segment harboring that gene, and the other an actual degradation of the gene product.

Although dietary factors may affect many processes associated with carcinogenesis, we will evaluate specific factors associated with oxidative stress/inflammation, since these genotoxic processes are known to have major effects on the initiation and progression of cancer, including colon cancer.[566–578] Direct damage to DNA, assessed by immunohistochemical staining of 8-oxoG, correlates with poor survival in colorectal cancer.[579] ROS can cause excessive DNA double strand breaks, resulting in the loss of chromosome segments or entire arms, depending on the location of the break. In addition, several DNA repair proteins are degraded through an oxidative mechanism,[580,581] thereby affecting DNA repair and increasing susceptibility to cancer.[582] Oxidative stress can affect spindle organization, induce centrosome amplification, cause proteolysis of components of the anaphase-promoting complex, and override the spindle checkpoint, thereby affecting chro-

mosomal stability. Therefore, oxidative stress can induce a mutator phenotype in affected cells.[583] The big question is what dietary factors contribute directly to oxidative DNA damage and aneuploidy (alteration in the number of whole chromosomes or chromosomal segments). We now address several dietary factors that may be associated with these forms of genomic instability. Although the literature on dietary factors associated with genomic instability is substantial, we have chosen to discuss the effects of a high-fat diet, folate deficiency, and niacin deficiency, since the molecular and cellular mechanisms associated with the overabundance or deficiency of these factors have been especially well studied.

A high-fat diet derived from beef tallow or corn oil (eg, linoleic acid, palmitic acid) is one of the major causes of sporadic colon cancer. Long-chain nonesterified ("free") fatty acids (FFA) and some of their derivatives and metabolites can modify the intracellular production of ROS, in particular superoxide anions and hydrogen peroxide, in part, through their interference with the mitochondrial electron transport chain.[584] FFA can also interfere with the glutathione system and stimulate the generation of superoxide anions from phagocytic NADPH oxidases.[584] Chronic exposure of cells to FFA (eg, palmitic acid) can also alter miRNA expression (eg, miR-34a, miR-146).[585]

The genotoxicity associated with a high-fat diet is also caused, in part, by high concentrations of hydrophobic bile acids released into the gastrointestinal tract in response to high-fat meals where they act as detergents to aid in the digestion of fats. Our research group showed that deoxycholic acid (a major hydrophobic bile acid in the human colon) induces ROS[586–589] in vitro, and oxidative DNA damage,[590] sessile adenomas,[591] and colon cancer[592] in dietary-related mouse models. In addition to the bile acid-induced formation of 8-oxoG in guanine bases of DNA and the induction of DNA strand breaks (activation of γ-H2AX[593] and PARP[594]), we have shown that deoxycholic acid affects genomic instability at the chromosomal level.[595] Evidence indicating the induction of chromosomal damage by deoxycholic acid include the formation of micronuclei and aberrant mitoses, attenuation of activation of the nocodazole-induced spindle checkpoint, and decrease in protein expression of major spindle checkpoint proteins (eg, Mad2, BubR1, securin). The dramatic effect of deoxycholic acid on the process of mitosis is underscored by the finding that deoxycholic acid modulates 71 mitosis-related genes at the mRNA and/or protein levels in vitro and in vivo using mouse models.[8] The induction by hydrophobic bile acids of both DNA and chromosomal damage indicates that hydrophobic bile acids are endogenous carcinogens that, at high pathophysiologic concentrations, are capable of contributing to the initiation and progression of colon cancer.[8,189,595–597] In addition to causing genomic instability, deoxycholic acid can activate survival pathways (eg, NF-κB[594] and autophagy[598]), which allow for the survival and selection of cells with genomic instability.[8,599]

Coffee drinkers have a lower incidence of cancer, including that of the colon and rectum.[600–603] One coffee compound that we found to prevent the formation of bile acid-induced proximal colon cancer in a mouse model is chlorogenic acid (CGA), the ester of caffeic acid with quinic acid.[592] CGA is one of the most abundant polyphenols in the human diet, with coffee, fruits (eg, blueberry, strawberry, raspberry, apple), and vegetables (eg, eggplants, potato, carrot, tomato) as its major sources.[493,604] CGA and its metabolites are likely responsible, in part, for the lower risk of rectal cancer associated with the consumption of decaffeinated coffee in 2 large prospective cohort studies.[603] One possible mechanism by which polyphenols can reduce colon cancer in this model is through the reduction in deoxycholic acid levels.[605] In this study, Han et al[605] report that when rats on a high-fat diet (30% beef tallow) received dietary curcumin (component of the Indian spice turmeric) or caffeic acid (metabolite of CGA), the fecal concentration of deoxycholic acid was substantially reduced. In addition, dietary supplementation of this high-fat diet with caffeic acid, catechin (plant polyphenol), rutin (citrus flavonoid glycoside), and ellagic acid (plant polyphenol) significantly reduced the levels of fecal lithocholic acid, a second major hydrophobic bile acid and risk factor for colon cancer.[605]

The induction of double-strand breaks is a major cause of the production of chromosomal fragments and the deletion of hundreds to thousands of genes. An important DNA repair protein in preventing large chromosomal deletions is Parp-1[606] (Figure 5). DNA strand breakage is directly caused by ROS (which would be enhanced due to the loss of genes encoding antioxidant proteins in the chromosome 1p deletion [Table 7]) or as a result of the activity of base excision repair enzymes (see Figure 5). Strand breakage activates Parp-1, which is involved with opening up chromatin and allowing DNA repair processes to occur, including base excision repair, single-strand and double-strand repair (Figure 5). Shibata et al[606] carried out mutation analysis using *Parp*-1 knockout *(Parp*$^{-/-}$*)* mice, and found that PARP deficiency enhanced deletion mutations, especially >1 kbp. A dietary micronutrient whose deficiency has a major effect on PARP activity is niacin (vitamin B_3) obtained from meat and corn. The term niacin

refers to nicotinic acid and nicotinamide, which are both used by humans to form NAD^+. PARP-1 utilizes NAD^+ to make poly(ADP-ribose) needed for poly(ADP-ribosyl)ation of proteins. In keeping with the protective effect of PARP, we determined that pre-treatment of cells in vitro with nicotinic acid and nicotinamide protected against bile acid-induced apoptosis,[607] presumably by enhancing PARP-mediated DNA repair of bile acid-induced DNA damage and replenishing the NAD^+ levels in mitochondria. In addition, we showed that pre-treatment of cells with nicotinic acid and nicotinamide upregulated the mRNA levels of the glycolytic enzymes, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and glucose-6-phosphate dehydrogenase (G6PD).[608] GAPDH and G6PD may protect against oxidative stress, in part through the generation of the reduced pyridine nucleotides, NADH and NADPH, respectively, from NAD^+.[608] Niacin supplementation was even reported to improve pellagra (severe niacin deficiency) in a patient with Crohn's disease,[609] a pre-cancerous inflammatory condition[610] associated with oxidative DNA damage.[611] Pellagra most probably developed in these Crohn's disease patients through a combination of intestinal malabsorption of niacin/nicotinic acid[612,613] and the high demand for NAD^+ that accompanies DNA damage-induced PARP-1 activity (see Figure 5). Work from our laboratory indicated that CGA and its metabolites, caffeic acid, *m*-coumaric acid, and 3-(*m*-hydroxyphenyl) propionic acid, increased PARP-1 protein expression.[493] The modulation of PARP-1 protein levels by CGA may explain, in part, the colon cancer preventive properties of CGA when added as a supplement to the bile acid-induced colon cancer mouse model.[592]

The mechanisms by which chromosome segments are deleted and translocated can be most complex. Deletions and translocations can arise from centromeric instability and telomeric instability.[7,614] and have been proposed as possible mechanisms for chromosomal aberrations associated with chromosome 1.[615–617] Centromeric instability can result from hypomethylation or acetylation of pericentromeric heterochromatin, resulting in decondensation/uncoiling/disruption of the centromere[618–620] and loss of the affected chromosome arms. Telomeric instability is characterized by telomeric fusions, formation of anaphase bridges during mitosis, broken chromosomes upon the stress of cell division, and fusion of chromosomal fragments to chromosome ends. This cycle of chromosomal abberations is referred to as breakage–fusion–bridge cycles.[107–114,621] Six genes found on chromosome 1p (APITD1, CCDC28B, CDCA8, HDAC1, KIF2C, RCC2) are associated with centomeres (see Table 2), and whose loss would affect centromeric instability. A deficiency of HDAC1, for example, has been reported to disrupt pericentromeric heterochromatin.[622] In addition to its role in the repair of interstrand cross-links,[623] APOLLO (aka DCLRE1B [DNA cross-link repair 1 B]) is also involved in the protection of telomeres (see Table 1). APOLLO is stabilized when bound to the telomere-binding protein TRF2, and protects human telomeres in S phase[624] (Figure 4). A reduced level of APOLLO results in an increased number of telomere-induced DNA damage foci and telomeric fusions in S-phase,[624] suggesting that APOLLO contributes to a processing step associated with the replication of chromosome ends. Hydrophobic bile acids, probably through the generation of oxidative stress, can modulate 71 genes associated with mitosis[8] and decrease the protein expression of 3 major spindle checkpoint proteins (eg, Mad2, BubR1, securin).[8] These alterations in gene expression, coupled with direct oxidative damage to components of the mitotic apparatus, may be responsible, in part, for the observed bile acid-induced mitotic aberrations.[595] It is, therefore, possible that bile acids may contribute to the loss of chromosome 1p through its effects on centromere instability and telomeric fusions.

Another mechanism by which large chromosomal deletions can occur is through folic acid deficiency.[625,626] Folic acid can attenuate the loss of heterozygosity of the DCC tumor suppressor gene in the colonic mucosa of patients with colorectal adenomas,[625] indicating that folic acid deficiency can affect allelic deletion and associated micronuclei formation.[627,628] Folates are a group of water-soluble B vitamins (obtained from leafy, green vegetables, the whole grain quinoa, and lentils) whose deficiency contributes to colon cancer.[629–633] Folates maintain DNA stability through their ability to donate one-carbon units for cellular metabolism and particularly for DNA biosynthesis, repair, and methylation.[629,633] Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in one-carbon metabolism. MTHFR catalyzes a unidirectional reaction that determines the balance between cellular availability of 5,10-methylenetetrahydrofolate, used for thymidylate and purine synthesis, and methyltetrahydrofolate used for biological methylation.[629] Folate deficiency, therefore, enhances carcinogenesis by impairing normal methylation and nucleotide synthesis, and creates an imbalance between the partitioning of cellular folates into these two pathways. Inhibition of folate metabolism results in excessive uracil misincorporation into DNA[633,634] with approximately 4 million uracil bases/cell.[559] The repair of 2 adjacent uracil residues on opposite strands of DNA can result in a double-strand break,

leading to chromosomal breakage and aneuploidy.[558,629,634] Folate deficiency also induces hypomethylation and inhibits DNA excision repair in immortalized normal human colon epithelial cells[633] and in the rat colon.[635]

Recent studies have implicated folate deficiency in the modulation of miRNA expression.[497,636] Using microarrays of 385 known human miRNAs, it was determined that folate deficiency in vitro in cultured cells induced a statistically significant fold-change in 24 miRNAs.[636] One of these miRNAs was miR-34a, which is found on chromosome 1p and involved in p53-mediated signaling (see Table 4 and the section on MiRNA and MiRNA Processing). MiRNAs were also determined to be altered in patients on a folate-deficient diet.[636] In addition to folate deficiency, polymorphisms of MTHFR and altered folate levels are associated with colon cancer risk.[637–640] The fact that MTHFR is located on chromosome 1p at 1p36.22 indicates that the loss of this chromosome arm, coupled with folate deficiency, can have major effects on genomic instability.

In this section we have considered how dietary factors such as niacin, folic acid, and a low-fat diet associated with low bile acid levels, together with antioxidants that protect against oxidative DNA damage (Table 10), might affect the processes relevant to carcinogenesis that are altered by chromosome 1p loss. In addition to a deficiency in dietary factors that prevent oxidative DNA damage, a deficiency of certain dietary factors that modulate DNA repair proteins, miRNA expression, antioxidant enzymes, defenses against environmental toxicity, and the Wnt signaling pathway (Table 10) can exacerbate the effects of the loss of chromosome 1p. An understanding of the complex molecular and cellular pathways that are affected by dietary factors is an enormous undertaking, but one that has become a focus of colon cancer prevention.

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Disclosure

The authors declare no conflicts of interest.

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