The roles of beta-adrenergic receptors in tumorigenesis and the possible use of beta-adrenergic blockers for cancer treatment: possible genetic and cell-signaling mechanisms

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Abstract: Cancer is the leading cause of death in the USA, and the incidence of cancer increases dramatically with age. Beta-adrenergic blockers appear to have a beneficial clinical effect in cancer patients. In this paper, we review the evidence of an association between β-adrenergic blockade and cancer. Genetic studies have provided the opportunity to determine which proteins link β-adrenergic blockade to cancer pathology. In particular, this link involves the major histocompatibility complex class II molecules, the renin–angiotensin system, transcription factor nuclear factor-kappa-light-chain-enhancer of activated B cells, poly(ADP-ribose) polymerase-1, vascular endothelial growth factor, and the reduced form of nicotinamide adenine dinucleotide phosphate oxidase. Beta-adrenergic blockers also exert anticancer effects through non-genomic factors, including matrix metalloproteinase, mitogen-activated protein kinase pathways, prostaglandins, cyclooxygenase-2, oxidative stress, and nitric oxide synthase. In conclusion, β-adrenergic blockade may play a beneficial role in cancer treatment. Additional investigations that examine β-adrenergic blockers as cancer therapeutics are required to further elucidate this role.

Keywords: β-adrenergic blocker, neoplasm, β-adrenergic antagonism, non-genomic factor

Introduction
The relationship between β-adrenergic antagonism and cancer has been well established in the literature. The function of β-adrenergic receptors was demonstrated in the cell membranes of breast cancer cells by the significant increase in cyclic adenosine monophosphate (cAMP) production induced by different concentrations of isoproterenol compared with cells that were unstimulated (control). Further, β-adrenergic receptors were implicated in the regulation of cell growth in lung cancer cell lines via the cAMP signaling pathway. Beta-adrenergic receptors were more highly expressed in oral squamous-cell carcinomas than in normal controls, and their expression was correlated with cervical lymph node metastasis, age, tumor size, and clinical stage. The β2-adrenergic receptor density in hepatocellular carcinoma (HCC) cellular membranes was higher than the β1-adrenergic receptor density in nonadjacent non-tumor liver cell membranes. Isoproterenol significantly increased cell proliferation via β-adrenergic receptors in a dose-dependent manner, with the concomitant activation of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathway in pancreatic cancer cells. In several experimental cancer models, the activation of the sympathetic nervous system promotes the metastasis of solid epithelial
and the dissemination of hematopoietic malignancies via the β-adrenergic receptor-mediated activation of protein kinase A (PKA) and the activation of exchange proteins by the adenylate cyclase signaling pathways. Interestingly, common haplotypes of the β₂-adrenergic receptor, which affect its translational efficiency, are associated with longevity in men and the level of β₂-adrenergic receptor protein is inversely associated with male lifespan. These findings may well have clinical implications for treating patients with β-adrenergic receptor agonists or antagonists.

Beta-blockers, used in a clinical context, reduced the rates of progression of several solid tumors. Chronic stress can accelerate the progression of human acute lymphoblastic leukemia via β-adrenergic signaling. Psychological stress promotes the progression of pancreatic cancer xenografts via neurotransmitter-induced activation of multiple pathways and increases systemic and tumor levels of norepinephrine (NE), epinephrine, cortisol, vascular endothelial growth factor (VEGF), and cAMP. Social stress also stimulates non-small cell lung carcinoma (NSCLC) by increasing nicotinic acetylcholine receptor-mediated stress neurotransmitter signaling. These findings are consistent with sympathetic effects on cell growth in cancer.

Epinephrine significantly increased the esophageal squamous-cell carcinoma cell proliferation that accompanied the elevation of intracellular cAMP levels, which were decreased by β-adrenergic antagonists. The development of lumbar lymph node metastases of human prostate cancer cells in athymic BALB/c nude mice increased with the application of NE via micro-osmotic pumps, and propranolol inhibited this effect. Exposure to nicotine either by tobacco smoke or nicotine supplements facilitates the growth and progression of NSCLC, and pharmacological intervention with β-blockers may lower the risk of NSCLC development among smokers. In elderly malnourished cancer patients, atenolol and propranolol treatment reduced resting energy expenditure, and propranolol decreased patient’s basal metabolic rates. Beta-blockers have also been associated with reduced prostate cancer-specific mortality, a 54% reduction in epithelial ovarian cancer death, a reduced risk in progression of thick malignant melanoma, the inhibition of astrocytoma cell proliferation, the induction of human gastric cancer cell apoptosis, the stimulation of cell cycle arrest, and the prevention of pancreatic cancer. In breast cancer, β-blocker use improved relapse-free survival in all patients with breast cancer; this effect was particular pronounced in patients with triple-negative breast cancer. The use of β-blockers resulted in a 57% reduction in the risk of metastasis and a 71% reduction in the 10-year mortality rate, and β-blockers could potentially be administered concomitantly with chemotherapy to increase treatment efficacy in breast cancer patients.

Following β-adrenergic-receptor stimulation, receptor activator of nuclear factor kappa-B ligand (RANKL) expression was induced in bone marrow osteoblasts and increased the migration of metastatic breast cancer MDA-231 cells in vitro. Further, RANKL expression can be blocked with the β-blocker propranolol in MDA-231 cells. Beta-blockers and drugs that interfere with RANKL signaling, such as denosumab, could increase patient survival if used as an adjuvant therapy to inhibit the early colonization of bone by metastatic breast cancer cells. In a retrospective study, propranolol treatment decreased the incidence of HCC in patients with compensated hepatitis C virus cirrhosis.

Carvedilol was a very potent inhibitor of cell proliferation in cells derived from breast tumors (MDA-MB-361), melanoma (Fem-x), cervix adenocarcinomas (HeLa) and human myelogenous leukemia. In addition, ICI 118551, a β₁-adrenoceptor blocker, significantly synergized the antiproliferative and pro-apoptotic effects induced by gemcitabine to inhibit the proliferation of pancreatic cancer cells. The use of propranolol as an adjunctive treatment has been reported for severe recurrent respiratory papillomatosis. Propranolol enhanced the sensitivity of gastric cancer cells to radiation by inhibiting β-adrenergic receptors and the downstream nuclear factor kappa-B cells (NF-κB)-VEGF/epidermal growth factor receptor/cyclooxygenase (COX)-2 pathway. Propranolol also had antiproliferative and apoptotic effects on multiple myeloma cells. These findings suggest that β-adrenergic blockade might play a role in cancer treatment.

Based on the evidence described above, in this review, we discuss the role of β-adrenergic blockers in cancer.

Figure 1 illustrates the signaling pathways and their connections to β-adrenergic receptors.

Genetic factors that relate to β-adrenergic inhibition and cancer

The major histocompatibility complex (MHC) class II molecules play an important role in the immune system and are essential in the defense against infection. The human MHC class II molecules are encoded by three different human leukocytic antigen (HLA) isotopes: HLA-DR, HLA-DQ, and HLA-DP. Published studies have suggested that several genes within the MHC region promote cancer susceptibility. A chimeric DR4 homozygous transgenic mouse line was reported to spontaneously develop diverse hematological...
malignancies at a high frequency. Most of these neoplasms were highly similar to the types of neoplasms that are found in human diseases. HLA-DR antigen expression was correlated with histopathological type and with the degree of cell differentiation in cutaneous squamous-cell carcinomas. In southern Tunisia, the \( DRB1^*03 \) and \( DR-B1^*13 \) alleles were significantly more frequent in patients with nasopharyngeal carcinoma (NPC). The \( DRI \) gene was shown to be strongly associated with thyroid carcinoma. HLA-DR was also increased in poorly differentiated thyroid carcinoma and in the anaplastic type of this carcinoma in particular. In Chinese populations, the \( DQA1^*0102 \) and \( DPB1^*0501 \) alleles have been reported to be significantly more common in patients with HCC than in controls. Among Korean study populations, the frequency of the \( DRB1^*0404 \) allele was significantly higher in gastric cancer patients than in gastritis patients. However, the frequencies of the \( DRB1^*0405 \) and \( DQB1^*0401 \) alleles were increased in Japanese patients with intestinal-type gastric cancer compared with controls. Somatic mutations affecting HLA class II genes may lead to a loss of HLA class II expression due to the formation of microsatellites in unstable colorectal carcinomas (CRCs). The \( DRB1^*15 \) allele and the \( DRB1^*15 DQB1^*0602 \) haplotype have been associated with human papillomavirus-16 positive invasive cervical cancer in Mexican women. It has been demonstrated that the \( DRB1^*0410 \) allele is the susceptibility allele in Japanese patients with testicular germ cell carcinoma. Furthermore, the frequencies of the \( DRB1^*09 \) and \( DQB1^*03 \) alleles were increased in patients with non-Hodgkin’s lymphoma and diffuse large B-cell lymphoma compared with normal controls. In a study of Turkish children, the frequencies of the \( DRB1^*04 \) and \( DRB1^*15 \) alleles were significantly higher in patients with acute leukemia than in controls. In Eastern Canada, the \( DRB1^*16 \) allele was a marker for a significant risk of chronic myelogenous leukemia. The \( DRB1^*04 \) and \( DRB5 \) alleles were associated with disease progression in Iranian patients with chronic lymphocytic leukemia. Moreover, cardiac \( \beta \)-adrenergic receptors and adenylyl cyclase activity in dilated cardiomyopathy were shown to be modulated by circulating autoantibodies against the cardiac \( \beta \)-adrenoceptor; the presence of these autoantibodies is controlled by the HLA-DR. Furthermore, propranolol-abrogated interferon-gamma increased HLA class II expression and interleukin-1-beta (IL-1\( \beta \)) secretion. HLA-DR was significantly reduced in the lymphocytes of carvedilol-treated chronic heart failure patients. These findings suggest that \( \beta \)-adrenergic blockers may have an effect on cancer by suppressing the expression of MHC class II antigens.

The primary function of the renin–angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. The angiotensin-converting enzyme (ACE) is a key enzyme in the RAS that converts angiotensin (AT) I to the potent vasoconstrictor AT II. The local RAS may influence tissue angiogenesis, cellular proliferation, apoptosis, and inflammation. Epidemiological and experimental studies have suggested that the RAS might contribute to the paracrine regulation of tumor growth. Renin levels are elevated in patients with liver cirrhosis and HCC and have been positively correlated with \( \alpha \)-fetoprotein. The overexpression
of ACE has been reported in extra-hepatic cholangio-carci-
mona,55 leukemic myeloid blast cells,56 and macrophages in
the lymph nodes of Hodgkin’s disease patients.57 AT II recep-
tors were also shown to be expressed in all human gastric
cancer lines,58 premalignant and malignant prostate cells,59
human lung cancer xenografts,60 and ovarian cancer.61 The
RAS mutation in codon 61 was the most common genetic
alteration in poorly differentiated thyroid carcinomas.62 The
ACE I/D polymorphism has been identified as a possible
target for developing genetic markers for breast cancer
in Brazilian women.63 The ACE I/D polymorphisms were
shown to play an important role in breast cancer risk and
disease-free survival in Caucasian postmenopausal women.64
Carriers of the high-activity DD genotype exhibited an
increased risk of breast cancer compared with low activity
II/ID genotype carriers.65 The DD genotype was associated
with patients with an aggressive stage of prostate cancer.66
ACE2 expression was decreased in NSCLC and in pancreatic
ductal adenocarcinoma, in which AT II levels were higher
than in controls.67,68 ACE2 has been suggested as a potential
molecular target for pancreatic cancer therapy.69 The AT II
concentration was significantly higher in the gastric cancer
region than in adjacent tissue.70 Furthermore, angiotensin
II-receptor blockers suppressed the cell proliferation effects
of AT II in breast cancer cells.71 The addition of ACE inhibi-
tors or angiotensin II-receptor blockers to platinum-based
first-line chemotherapy contributed to prolonged survival in
patients with advanced lung cancer72 and positively affected
the prognosis of advanced pancreatic cancer patients receiv-
ing gemcitabine.73 RAS inhibitors also improved the outcome
of sunitinib treatment in metastatic renal cell carcinoma.74
Moreover, catecholamines can alter the release of AT II.
Ming et al75 demonstrated that isoproterenol enhances the
stimulatory effect of dexamethasone on the expression of the
AT gene via β2-adrenergic receptors in mouse hepatoma cells.
Isoproterenol promoted an increase in the release of AT II
from isolated perfused mesenteric arteries, and this release
was blocked by propranolol.76 In other studies, isoproterenol
also increased the secretion of AT II in neuronal cultures,
cultured bovine aortic endothelial cells, and the brachial
arteries of hypertensive subjects.77,78 Propranolol treatment
reduced plasma renin activity, AT I, AT II, and AT 1-2, in the
portal vein and periphery in cirrhotic patients compared
with non-treated patients.80 Carvedilol inhibited basal and
stimulated ACE production in human endothelial cells81 and
exhibited beneficial effects on ACE activity and plasma renin
activity levels in chronic heart failure patients.82 In addition,
proliferating infantile hemangioma expressed two essential
components of the RAS, namely ACE and the AT II recep-
tor, that accounted for the propranolol-induced accelerated
involution of large proliferating infantile hemangioma.83-85
Thus, taken together, these findings suggest that the RAS is
activated in cancer patients and β-adrenergic blockers may
play a role in cancer by modulating the RAS.

The transcription factor NF-κB is a hetero-dimeric,
sequence-specific transcription factor that is expressed in
many cell types. NF-κB has been implicated in chronic
inflammatory diseases and is a key regulator of genes that are
involved in responses to infection, inflammation, and stress.
The NF-κB family of transcription factors plays a crucial role
in inflammation as well as in the development and progression
of cancer. The NF-κB pathway is dysregulated in prostate
cancer and has been implicated in the progression to the
androgen-independent state that ultimately leads to patient
death.86 NF-κB activity has been correlated with the progres-
sion and prognosis of pancreatic cancer in a mouse model.87
NF-κB expression was higher in renal cancer specimens than
in a control group,88 and NF-κB is known to play an important
role in endometrial cancer pathogenesis.89 NF-κB signaling is
important for medulloblastoma tumor growth, and the inhibi-
tion of NF-κB reduced tumor size and viability in vivo.90 It
has been reported that the association of the RE-1-silencing
transcription factor with NF-κB increases risks of CRC, colon
cancer, and rectal cancer.91 NF-κB alleles are associated with
oral carcinogenesis.92 NF-κB, and NF-κBIA polymorphisms
are associated with an increased risk for sporadic colorectal
cancer in a southern Chinese population.93 A homozygous
NFκBα rs17103265 deletion is a novel genetic risk factor
for gastric carcinogenesis, particularly for the development
of certain subtypes of gastric cancer in a southern Chinese
population.94 NF-κB1 insertion/deletion promoter poly-
morphism increases the risk of advanced ovarian cancer in
Chinese populations.95 The functional NF-κB1-94 insertion/
deletion ATTG (adenine-thymidine-thymidine-guanine)
polymorphism was associated with cervical squamous-cell
carcinoma, particularly in individuals who were 35 years of
age or younger.96 A meta-analysis revealed that a common
insertion/deletion (NF-κB1-94 insertion/deletion ATTG,
rs28362491) polymorphism in the NF-κB1 gene might be
associated with a decreased cancer risk, especially in Asian
populations.97 Moreover, cardiac collagen volume fraction
and apoptotic cell numbers were elevated in ketamine-
treated rats compared with control animals; these effects
were prevented by the co-administration of metoprolol. The
NF-κB cells were increased after ketamine treatment and
sharply reduced after metoprolol administration.98 Carvedilol
blocked in vitro human peripheral blood T-cell activation by downregulating NF-κB activity. Propranolol repressed gastric cancer cell growth through downstream NF-κB. Beta₂-adrenergic antagonists suppressed the activation of NF-κB and potentiated the antiproliferative effects of gemcitabine by inducing apoptosis in pancreatic cancer cells. Taken together, the evidence indicates that β-adrenergic antagonists may suppress NF-κB activation in cancer.

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that contributes to both cell death and survival under stressful conditions. PARP-1 catalytic activity is stimulated by DNA strand breaks. Parp-1-deficient cells exhibited enhanced sensitivity to the lethal effects of ionizing radiation and alkylating agents, whereas Parp-1 knock-out mice developed spontaneous mammary and liver tumors. The overexpression of PARP-1 has been reported in Ewing’s sarcoma, malignant lymphomas, CRC, HCC, breast cancer, pediatric central nervous system tumors, and ovarian cancer. In a meta-analysis, PARP-1 mRNA expression was correlated with higher grades, medullary histological types, tumor sizes, worse metastasis-free survival rates, and decreased overall survival rates in human breast cancer. PARP-1 polymorphisms have been associated with gastric cancer, prostate cancer, esophageal squamous-cell carcinoma, and lung cancer in Han Chinese individuals but with a reduced risk of non-Hodgkin lymphoma in Korean males. PARP-1 polymorphism reduced PARP-1 catalytic activity by 30%-40%. A meta-analysis found no significant association between PARP-1 V762 polymorphism and cancer risk. However, the A variant allele of the PARP-1 V762 polymorphism was associated with an increased risk of cancer among the Asian population but a decreased risk among Caucasians, particularly with respect to glioma. Moreover, rabbits treated with ketamine exhibited decreased left ventricular ejection fractions, reduced ventricular conduction velocity, and increased susceptibility to ventricular arrhythmia. Metoprolol treatment prevented these pathophysiological alterations. The expression of PARP-1 and apoptosis-inducing factor were increased after ketamine treatment and sharply reduced after metoprolol administration. Propranolol treatment markedly suppressed PARP activation in the skeletal muscle biopsies of pediatric burn patients. Propranolol also protected against staurosporine-induced DNA fragmentation and PARP cleavage in SH-SY5Y neuroblastoma cells. The nonselective β-blocker carvedilol significantly inhibited apoptosis and suppressed activated PARP-1 cleavage in human cardiac tissue. Carvedilol significantly decreased ischemia-reperfusion-induced poly- and mono(ADP-ribosyl)ation in heart perfusion and in a rheological model. Carvedilol also decreased PARP activity in the hippocampus and protected neurons against death after transient forebrain ischemia. Metipranol blunted sodium nitroprusside-induced breakdown of PARP-1 in rat eyes and retina. These findings suggest that PARP-1 is activated in cancer patients and β-adrenergic antagonists may have an effect on cancer by suppressing PARP-1.

Angiogenesis is a complex process that involves the coordinated steps of endothelial cell activation, proliferation, migration, tube formation, and capillary sprouting and requires the participation of many intracellular signaling pathways. VEGF is a key mediator of angiogenesis. Vascular changes associated with angiogenesis typically occur in cancer, but they have also been reported in inflammatory diseases. Statistically significant increases in VEGF expression relative to normal tissue have been reported in gastric cancer tissue, urothelial cell carcinoma of the urinary bladder, pancreatic cancer, thyroid cancer, esophageal gastric cancer, gastric cancer, osteosarcoma, HCC, inflammatory breast cancer, and ovarian cancer. VEGF polymorphisms were found to be a critical risk factor for genetic susceptibility to lung cancers in the ethnic Han Chinese of North China. A meta-analysis has suggested that the VEGF-405T/C, VEGF-634G/C, and VEGF-2578C/A polymorphisms are associated with CRC. A weak association between the VEGF-405G/C polymorphism and malignancy susceptibility was reported in an African population. VEGF-A and VEGF-D overexpression suggested poor prognosis in patients with gastric cancer and VEGF was identified as a marker of poor prognosis for patients with head and neck cancer. NE and isoproterenol significantly enhanced VEGF production in the ovarian cell lines and cultured NPC tumor cells. These effects were blocked by the β-adrenergic antagonist propranolol, supporting a role for β-adrenergic receptors in these effects. NE also induced the invasiveness of all NPC cell lines in a dose-dependent manner, which was blocked by propranolol. Propranolol significantly decreased VEGF activity in a phorbol myristate acetate-activated human leukemic cell line. Further, propranolol repressed gastric cancer cell growth through downstream effects on VEGF. NE increased the expression of VEGF and this effect was inhibited by propranolol in pancreatic cancer cells. In addition, epinephrine enhanced the expression of VEGF in colon adenocarcinoma cells. The stimulatory action of
adrenaline on colon cancer growth was blocked by atenolol and ICI-118,551, which are β₁ and β₂-selective antagonists, respectively.143 These findings suggest that β-adrenergic antagonists may modulate VEGF expression in cancer.

The reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme complex mediates critical physiological and pathological processes including cell signaling, inflammation, and mitogenesis through the generation of reactive oxygen species (ROS) from molecular oxygen. It has been demonstrated that NOX1 is required for Ras oncogene-induced cell transformation.144 The NOX subunit p22phox was reported to inhibit the function of the tumor suppressor protein tuberin in renal carcinoma cells.145 The activation of NOXs has been demonstrated in the development of numerous cancers, including melanoma,146 leukemia,147 esophageal adenocarcinoma,148 HCC,149 prostate cancer,150 colon cancer,151 glioblastoma multiforme,152 and multiple myeloma.153 NADPH polymorphisms were reportedly associated with myelodysplastic syndrome, de novo acute myeloid leukemia,154,155 esophageal cancer,156 lung cancer,156,157 non-Hodgkin lymphoma,158,159 childhood acute leukemia,160 postmenopausal breast cancer,161 and gastric cancer.162 Moreover, nebivolol, a third-generation selective β-adrenoceptor, improved left ventricle dysfunction and survival early after myocardial ischemia and inhibited cardiac NOX activation.163 Treatment with nebivolol was associated with improvement in insulin resistance, reduced proteinuria, and decreased NOX activity/levels of ROS in kidney and skeletal muscle tissue in the transgenic TG(hRen2)27 rat.164,165 Nebivolol also improved diastolic relaxation, fibrosis, and remodeling in Zucker obese rats, with reductions in NOX-dependent superoxide.166 Carvedilol attenuated the increased protein expression of NOX subunits in the heart and kidney in daunorubicin-induced cardiotoxicity and nephrotoxicity in rats.167 NOX activity in whole blood and isolated neutrophils was inhibited in a dose-dependent manner by nebivolol, whereas atenolol, metoprolol, and carvedilol were markedly less effective in Watanabe heritable hyperlipidemic rabbits.168 Celiprolol, a specific β₁-antagonist with weak β₂-agonistic action, suppressed NOX p22phox, p47phox, gp91phox, and NOX1 expression in the left ventricle of doxycorticosterone acetatesalt hypertensive rats.169 Thus, taken together, findings suggest that β-adrenergic antagonists may have a role in cancer by suppressing NADPH expression.

The role of β-adrenergic blockers in cancer

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for extracellular matrix remodeling and the regulation of leukocyte migration through the extracellular matrix, an important step in inflammatory and infectious pathophysiology. MMPs are produced by many types of cells, including lymphocytes, granulocytes, astrocytes, and activated macrophages. Activation of MMPs contributes to tumor angiogenesis and metastasis. MMP-1 expression has been linked to sarcoma cell invasion.170 MMP-2 expression has been found increased in gastric cancer cells125 and CRC.171 MMP-9 was shown to be expressed in many cancer cells, including those associated with NSCLC,172 lymph node metastasis in human breast cancer,173 ovarian cancer invasion and metastasis,174 glioblastoma multiforme,175 and adamantinous craniofacial dysplasia.176 The secretion of MMP-2 and MMP-9 by leucemic cells increased the permeability of the blood–brain barrier of the central nervous system by disrupting tight junction proteins.177 In gastric cancer, MMP-2 and MMP-9 were shown to play important roles in tumor invasion and metastasis.178 The risks for the development of hypophyseal adenoma and cervical neoplasia were greater in patients with MMP-1 polymorphisms179 than in those with the wild-type allele. The MMP-2 polymorphism contributed to prostate cancer susceptibility in Northern India151 and to the clinical outcomes of Chinese patients with NSCLC treated with first-line platinum-based chemotherapy.182 The MMP-7 polymorphisms were associated with esophageal squamous-cell carcinoma, gastric cardiac adenocarcinoma, NSCLC, and CRC.115,160,183 The single-nucleotide polymorphisms (SNPs) in the MMP-2 and MMP-9 region are associated with susceptibility to head and neck squamous-cell carcinoma in an Indian population.184 The SNPs of genes encoding MMPs (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13, and MMP-21) were shown to be related to breast cancer risk, progression, and survival.185 Based on a meta-analysis, an MMP-2 allele (-1306T) may be a protective factor against digestive cancer risk.186 The MMP-9 polymorphism was associated with a lower risk of CRC187 and polymorphisms in the promoter regions of MMP-1, MMP-3, MMP-7, and MMP-9 were associated with metastasis in certain cancers.188 A meta-analysis revealed that polymorphisms of MMP-1 (-1607) and MMP-3 (-1612) increase the risk of CRC.189 Moreover, propranolol inhibited tubulogenesis of human brain endothelial cells and MMP-9 secretion.190 A selective β₃-adrenoceptor agonist prevented human myometrial remodeling and the activation of MMP-2 and MMP-9 in an in vitro model of chorioamnionitis.191 NE treatment increased MMP-2 and MMP-9 levels in cultured NPC tumor cells, which was inhibited by propranolol. NE also induced the invasiveness of all NPC cell lines in...
a dose-dependent manner, which could be blocked by an MMP inhibitor and propranolol.141 Propranolol significantly decreased MMP-2 activity in a phorbol myristate acetate-activated human leukemic cell line.142 Propranolol-induced growth inhibition was associated with G0/G1 arrest, G2/M arrest, and repressed gastric cancer cell growth through the downstream inhibition of MMP-2 and MMP-9.21 NE increased the expression of MMP-2 and MMP-9 and these effects were inhibited by propranolol in pancreatic cancer cells.190,192 Epinephrine upregulated MMP-9 activity in human colon adenocarcinoma HT-29 cells, which was blocked by atenolol, a β1-selective adrenergic antagonist, or ICI-118,551, a β2-selective adrenergic antagonist.143 These studies suggested that β-adrenergic antagonists may play an important role in the pathological process of cancer by downregulating the level of MMPs and regulating the level of tissue inhibitors of metalloproteinases.

The MAPK pathways provide a key link between the membrane-bound receptors that receive these cues and changes in the pattern of gene expression, including the ERK cascade, the stress-activated protein kinases/c-jun N-terminal kinase (JNK) cascade, and the p38 MAPK high osmolarity glycerol HOG cascade.193 MAPK activation was higher in renal cancer specimens than in control group specimens. Renal tumor diameter and grade increase were directly correlated with p38 MAPK expression.90 The p38 levels were significantly higher in the HCC patients with a larger tumor (≥3 cm) and satellite tumors, and were significantly correlated with p-JNK levels. High p38 and low p-JNK expression was associated with poor survival in HCC patients.194 Increased MAPK activity and mitogen-activated protein kinase phosphatase-1 overexpression were associated with the carcinogenesis of human gastric adenocarcinoma.195 Overexpression of the Ras and MAPK proteins (Ras p21, ERK-1, JNK-1, and p38) conferred a progressive tendency toward invasive growth, advanced-stage cancer, and decreased levels of estrogen receptor-α protein in advanced-stage human breast cancer.196 The MAPK pathway was shown to be critical to oncogenic signaling in the majority of patients with malignant melanoma.197 The tumor suppressive actions of transforming growth factor beta-1 decreased cell viability and induced apoptosis in invasive prostate cancer and bladder cancer cells via the Akt-independent, p38 MAPK, and stress-activated protein kinases/JNK-mediated activation of caspases.198 Genetic variation in the MAPK-signaling pathway influenced colorectal cancer risk and survival after diagnosis.199 Expression of the MAPK phosphatase DUSP4 was associated with microsatellite instability in CRC and caused increased cell proliferation.200 Moreover, the stimulation of β-adrenergic receptors can activate cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) and mitogen-activated protein kinase (MAPK) pathways in pancreatic cancer cells. Pathways in pancreatic cancer cells. The β2-adrenergic antagonists suppressed invasion and proliferation by inhibiting both cAMP/PKA and Ras, which regulate activation of the MAPK pathway.100 NE stimulates pancreatic cancer cell proliferation, migration and invasion via β-adrenergic receptor-dependent activation of the p38 MAPK pathway. These stimulatory effects were completely stopped by propranolol or p38 MAPK-inhibitor SB203580.201 Propranolol was shown to exert its suppressive effects on hemangiomas through the hypoxia-inducible factor-1α–VEGF-A–angiogenesis axis, with effects mediated by the phosphoinositide 3-kinase/Akt and p38 MAPK pathways.202 Thus, these findings suggest that β-adrenergic antagonists may have a role in cancer by suppressing the MAPK pathway.

Prostaglandins play a role in inflammatory processes. COX participates in the conversion of arachidonic acid into prostaglandins. Tumor inflammation is now recognized as one of the hallmarks of cancer. The overexpression of COX-2 is associated with resistance to apoptosis, increased angiogenesis, and increased tumor invasiveness in various cancers. Increased COX-2 expression was reported in endometrial adenocarcinoma,203 breast cancer,204 reno-medulary interstitial cell tumor,205 CRC,206 gastric cancer,207 carcinoma of the cervix,208 and familial adenomatous polyposis.209 The deletion of COX-2 in mouse mammary epithelial cells delayed breast cancer onset.210 COX-2 inhibitors also decreased the growth and induced regression of human esophageal adenocarcinoma xenografts in nude mice211 and retarded murine mammary tumor progression by reducing tumor cell migration, invasiveness, and angiogenesis.212 Genetic variability in enzymes could have an impact on the disease risk. COX-2 polymorphisms were reported to be associated with bladder cancer,213 biliary tract cancer,214 lung cancer,215 nonmelanoma skin cancer after organ transplantation,216 esophageal squamous-cell carcinoma,217 NPC,218 pancreatic cancer,219 invasive ovarian carcinoma,220 breast cancer,221 gastric carcinoma,222 acute myeloid leukemia,223 prostate cancer,224 head and neck cancer,225 colorectal adenoma,226 and HCC.227 In a meta-analysis, the COX-2 1195G>A polymorphism was significantly associated with an increased risk for digestive system cancers, particularly in Asian populations.228 In addition, the COX-2 -765G>C polymorphism may have caused an increased risk of CRC and esophageal cancer in patients of Asian descent, whereas the 8473T>C polymorphism may have caused a decreased risk of breast and lung cancer.229
addition, prostaglandin E\(_2\) (PGE\(_2\)) has been reported to be associated with colorectal adenoma,\(^{230}\) pancreatic tumor,\(^{231}\) and childhood neuroblastoma.\(^{232}\) Suppression of PGE\(_2\) receptors inhibited human lung carcinoma cell growth.\(^{233}\) Moreover, adrenaline increased PGE\(_2\) release in human colon adenocarcinoma HT-29 cells, which can be blocked by COX-2 inhibitor or by atenolol, a \(\beta\)-selective adrenergic antagonist, or ICI-118,551, a \(\beta\)_blocker.\(^{143}\) The \(\beta\)_selective adrenergic antagonists suppressed COX-2 expression in pancreatic cancer cells.\(^{108}\) Propranolol inhibits cell proliferation and represses gastric cancer cell growth through the downstream COX-2 pathway.\(^{21,22}\) In addition, propranolol and COX-2 inhibitor administration, which can be applied perioperatively in most cancer patients with minimal risk and at low cost, counteracted several immunologic and endocrinologic perturbations and improved recurrence-free survival rates in mice undergoing primary tumor excision.\(^{234,235}\) Celiprolol activates endothelial nitric oxide synthase (NOS) through the phosphatidylinositol 3-kinase/Akt pathway via NF-\(\kappa\)B induced by oxidative stress.\(^{169}\) These findings suggest that \(\beta\)-adrenergic antagonists may play a role in modulating the inflammatory process in cancer.

ROS play a major role in various cell-signaling pathways. ROS activate various transcription factors and increase the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. ROS have been shown to play an important role in the initiation and progression of many cancers.\(^{236–241}\) SNPs of antioxidant defense genes may significantly modify the functional activity of encoded proteins. Women with genetic variability in the iron-related oxidative stress pathways may be at increased risk for post-menopausal breast cancer.\(^{242}\) The \(\text{ala}\) variant of superoxide dismutase was associated with a moderately increased risk of prostate cancer.\(^{243}\) Based on a meta-analysis, manganese superoxide dismutase polymorphisms may contribute to cancer development (Val-9Ala)\(^{244}\) and prostate cancer susceptibility (Val-16Ala)\(^{245}\) but not to breast cancer susceptibility (Val-16Ala).\(^{246}\) Moreover, myocardial tissue sections revealed increased ROS after traumatic brain injuries. Treatment with propranolol decreased ROS levels.\(^{247}\) Carvedilol can modulate ROS-induced signaling. Carvedilol significantly decreased the ischemia-reperfusion-induced free-radical production and nicotinamide adenine dinucleotide catabolism, and decreased the lipid peroxidation and red blood cell membrane damage as determined by free malondialdehyde production in heart perfusion and in a rheological model.\(^{129}\) Nebivolol improved diastolic dysfunction and myocardial remodeling through reductions in oxidative stress in the transgenic (mRen2) rat.\(^{248}\) These findings suggest that \(\beta\)-adrenergic antagonists modulate oxidative stress in cancer.

NOS is an enzyme that is involved in the synthesis of nitric oxide (NO), which regulates a variety of important physiological responses including cell migration, immune response, and apoptosis. NO and calcium were reported to regulate mitochondrial biogenesis in follicular thyroid carcinoma cells.\(^{249}\) There is a link between NO and the induction of apoptotic cell death in head and neck squamous-cell carcinoma.\(^{250}\) Cytokines, especially interferon-gamma, induced apoptosis in acute leukemia via the NO and caspase-3 pathways.\(^{251}\) The reduction of NO levels enhanced the radiosensitivity of hypoxic NSCLC.\(^{252}\) Increased NO may be a sign of subclinical cardiotoxicity of doxorubicin.\(^{253}\) High NO concentrations at the periphery of a melanoma may contribute to metastasis by stimulating cell proliferation, inhibiting apoptosis, or acting as a lymphangiogenic factor.\(^{254}\) Inducible NOS mRNA expression was considerably higher in glioblastoma specimens than in meningioma specimens.\(^{255}\) Inducible NOS expression has been correlated with angiogenesis, lymphangiogenesis, and poor prognosis in gastric cancer patients and estrogen receptor-negative breast cancer patients.\(^{256}\) NOS inhibition enhanced the antitumor effect of radiation in the treatment of squamous carcinoma xenografts.\(^{258}\) NOS polymorphisms were reported to be associated with bladder cancer,\(^{259}\) urothelial carcinoma,\(^{260}\) gastric cancer,\(^{261}\) colorectal cancer,\(^{262}\) and non-Hodgkin’s lymphoma.\(^{263}\) In a meta-analysis, endothelial NOS 894G>T polymorphism was associated with breast cancer.\(^{264}\) Moreover, metipranolol blunted NO-induced lipid peroxidation in rat eyes and retinas.\(^{114}\) Nebivolol prevented vascular NOS III uncoupling in experimental hyperlipidemia.\(^{158}\) Propranolol suppressed hemangioma growth by inhibiting the expression of endothelial NOS protein and the subsequent production of NO.\(^{265}\) These findings suggest that \(\beta\)-adrenergic antagonists may have a role in cancer by inhibiting the expression of NOS.

**Conclusion**

Beta-adrenergic blockade may play a role in the prevention and treatment of cancer. Genetic studies have provided the opportunity to determine the proteins that link \(\beta\)-adrenergic antagonism to cancer pathology. Beta-adrenergic inhibition also exerts its effect on cancer via non-genomic mechanisms. Further investigation of the relationship between \(\beta\)-adrenergic antagonists and cancer is required.
Disclosure

The authors declare no conflicts of interest in this work.

References


