The retinoblastoma protein: a master tumor suppressor acts as a link between cell cycle and cell adhesion

Abstract: RB1 was the first tumor suppressor gene discovered. Over 4 decades of work have revealed that the Rb protein (Rb) is a master regulator of biological pathways influencing virtually every aspect of intrinsic cell fate including cell growth, cell-cycle checkpoints, differentiation, senescence, self-renewal, replication, genomic stability, and apoptosis. While these many processes may account for a significant portion of RB1’s potency as a tumor suppressor, a small but growing stream of evidence suggests that RB1 also significantly influences how a cell interacts with its environment, including cell-to-cell and cell-to-extracellular matrix interactions. This review will highlight Rb’s role in the control of cell adhesion and how alterations in the adhesive properties of tumor cells may drive the deadly process of metastasis.

Keywords: cadherin, integrin, Rb, cancer, aggressiveness, metastasis

Introduction
Cancer cells are known to have many hallmarks that distinguish them from their normal counterparts. Two prominent hallmarks of cancer cells are the ability to survive and proliferate under inappropriate circumstances, and the ability to migrate from their original tissue location to distant places and there continue to proliferate. This cellular migration is thought to be dependent upon the cancer cell’s ability to change its cell-to-cell and cell-to-matrix adhesive properties and to survive during the process. Interestingly, accumulating evidence suggests that the RB1 tumor suppressor gene may regulate both of these key cancer hallmarks, explaining its prominence as a tumor suppressor.

The retinoblastoma protein (Rb): the classic paradigm
Existence of the RB1 gene was predicted in 1971 from epidemiological evidence from retinoblastoma families, and the RB1 gene was identified over 15 years later. The initial characterization of Rb function was guided by studies of DNA tumor viruses which pointed to Rb’s role as a regulator of the G1/S transition. It is now known that both the G1/S and G2/M phases of the mammalian cell cycle are controlled by a complex and redundant molecular pathway (highlighted schematically in Figure 1) that involves members of the E2 promoter binding factor (E2F), dimerization partner, Rb, cyclin-dependent kinase (CDKs), cyclin, and CDK inhibitor (CDKN) families. This pathway is disrupted in most, if not all, solid tumors.

While initial work on the function of Rb in the cell cycle highlighted its role in the G1/S transition, work over the last 3 decades demonstrates that Rb controls most cellular processes related to cell fate and DNA metabolism, including cell-cycle checkpoints,
Every component of the Rb pathway that represses cell cycle progression is subject to mutational inactivation in some human cancers and every component that induces cell cycle is subject to oncogenic upregulation, providing genetic evidence that the pathway as a whole is essential in tumor development. CDKN proteins are subjected to inactivating mutations and epigenetic silencing. Cyclins, CDKs, and, rarely, E2Fs themselves are upregulated by translocations and gene amplifications.26–29 The rate of RBl gene mutation varies significantly among different tumor types, but is highest in retinoblastoma, osteosarcoma, and small-cell lung cancer (SCLC).23,30 Mutations targeting the RBl gene directly affect Rb function by either completely abrogating its expression or by producing a nonfunctional protein.31 Other cancer types bearing wild-type RBl alleles still have impaired Rb function due to alterations in genes coding for upstream Rb regulators. These alterations range from inactivating mutations, deletions, or epigenetic silencing of the p16INK4a locus (a CDKN family member), to alterations leading to cyclin D or CDK4 overexpression.27 The latter scenario results in Rb inactivation by chronic hyperphosphorylation. Therefore, oncogenesis usually entails either a complete loss of Rb expression or its inactivation by hyperphosphorylation.

**Deregulation of adhesion proteins in cancer**

Figure 2 highlights the role that cell adhesion is thought to play in cancer spread and metastasis. Cadherins are calcium-dependent cell adhesion proteins that mediate cell-to-cell adhesion. They are named for the tissue that they were first identified in (eg, E-cadherin, N-cadherin, and OB-cadherin family member), to alterations leading to cyclin D or CDK4 overexpression.27 The latter scenario results in Rb inactivation by chronic hyperphosphorylation. Therefore, oncogenesis usually entails either a complete loss of Rb expression or its inactivation by hyperphosphorylation.

**Notes:** This schematic illustrates two key features of cell adhesion that are regulated by Rb. The specific examples of cadherins and integrins are for the purpose of illustration, based on the limited data at this time. In presence of sufficient Rb, normal epithelial cells express adequate levels of E-cadherin (or other tissue-specific cadherins such as OB-cadherin) to allow appropriate cell–cell contacts as well as adequate and appropriate integrins to maintain tight adherence to the ECM. However, upon loss of Rb function, epithelial cells may make a transition to a more mobile cell type (generally referred to as the epithelial–mesenchymal transition) that can leave their normal physical location (eCM 1) and adhere to an alternative eCM (eCM 2), which might ultimately result in a distant metastasis.

**Abbreviations:** ECM, extracellular matrix; Rb, retinoblastoma protein.
respectively), but are not restricted exclusively to those tissues. Cadherins, together with catenins, are the main components of adherens junctions, which are membrane protein complexes that are stabilized by association with actin filaments densely packed under the cell membrane. Their disruption is part of the epithelial–mesenchymal transition (EMT) during oncogenic progression and contributes to metastasis by facilitating detachment of cancer cells from the primary tumor. This disruption consists of a “cadherin switch” whereby expression of E-cadherin is repressed and N-cadherin is upregulated.

Alterations in integrin expression have also been noted in cancers. Similar to the “cadherin switch” occurring during EMT, an “integrin switch” has been observed in multiple solid tumors consisting of overexpression of integrin β4, and underexpression of integrins α7, α8, and α10. Integrins are a family of 26 cell-to-extracellular matrix (ECM) adhesion receptor subunits. Each functional integrin heterodimer consists of two type-1 (single membrane-spanning domain with the C-terminus located cytoplasmically) transmembrane subunits: one α- and one β-subunit. Integrins bind to multi-adhesive ECM components, organizing the cytoskeleton and activating intracellular signaling pathways. They have been shown to affect cell shape, polarization, cytoskeletal organization, cell motility, proliferation, survival, and differentiation. Integrins are unusual among transmembrane receptors in that they signal bidirectionally, carrying both mechanical and chemical signals. “Inside-out” signaling, known as “priming”, is responsible for a conformational change in the integrin heterodimer which extends outward and induces adhesiveness to the ECM. Adhesion is further strengthened by the lateral reorganization of integrins into clusters, which may progress to dot-like focal complexes that mature into larger focal adhesions and finally into streak-like fibrillar adhesions. The “integrin adhesome” is comprised of 156 signaling, structural, and adaptor molecules that contribute to cytoskeletal reorganization and catalytic activity as integrin tails have no catalytic activity of their own. Integrin signaling, and the associated crosstalk with adjacent receptor tyrosine kinases, has been linked to many pathways important in human cancer including the Ras/Raf/MEK/MAPK, PI3K/PtP/AKT, NF-κB, and Rb/E2F pathways.

**New roles for Rb in cell adhesion: regulation of cadherin- and integrin-mediated adhesion**

Cancer types showing high frequencies of mutational inactivation of the RB1 gene are very aggressive relative to tumors with chronically hyperphosphorylated wild-type Rb. An example is osteosarcoma, which at the time of diagnosis was consistently high grade and poorly differentiated. These patients have a poor prognosis, with 20% of diagnosed cases already having detectable metastases and only 10% achieving long-term disease-free intervals. Osteosarcoma incidence is increased 1,000-fold in patients who inherit RB1 mutations relative to the general population, implicating Rb loss in osteosarcoma formation. Rb loss occurs in over 70% of sporadic osteosarcomas, and loss of RB1 heterozygosity is present in 60%–70% of osteosarcomas and is indicative of a poor prognosis.

Like osteosarcoma, SCLC is characterized by a high rate (~90%) of mutational inactivation of the RB1 locus. Patients with SCLC have a 5-year survival rate of only 6%, which can increase to 54% if detected at a localized stage. Unfortunately, only 15% of SCLCs are detected at the localized stage. This extreme aggressiveness is in stark contrast to the 5-year survival rates of tumors with lower rates of RB1 mutations such as breast, prostate, and colorectal cancers when detected at a localized stage, which are 99%, 100%, and 90%, respectively, according to the American Cancer Society Cancer Facts and Figures, 2014. Interestingly, lung cancer survival rate triples to 18% in the non-SCLC (NSCLC) subtype, which usually bears wild-type RB1 alleles but instead exhibits preferential loss of the p16INK4A locus with consequent Rb hyperphosphorylation. The differences in survival rates between SCLC and NSCLC suggest that increased aggressiveness may be associated more with direct alterations of the RB1 locus than with chronic Rb hyperphosphorylation resulting from alterations in other loci.

This RB1 effect is also observed in epithelial cancers. Although RB1 mutations are rare in prostate cancer, a recent analysis of 50 castration-resistant prostate cancer patients demonstrated that patients with inactivating RB1 mutations have a 35-month reduction in median overall survival relative to patients with WT RB1 (P=0.025). Specifically, the 16 patients with RB1 mutations had a median overall survival of 70 months, versus 105 months in 34 patients with WT RB1.

The data discussed above highlight the association between direct mutational targeting of the RB1 gene and high mortality as demonstrated by the low 5-year survival rates of Rb-null cancers. Given that metastases indicate aggressiveness and cause over 90% of cancer deaths, we propose that Rb deficiency leads to a proclivity for early metastasis, that is, for early detachment of tumor cells from the primary tumor and invasion of adjacent and distal tissues. If so, blocking
that OB-cadherin, the predominant osteoblast cadherin, is phenotype (see herin and the acquisition of mesenchymal and migratory repressors. Slug and ZEB-1, which are known E-cadherin transcriptional regulation of several EMT-related transcriptional factors including implicating Rb loss in EMT, Rb depletion results in upregulation of Rb-proficient versus Rb-deficient osteoblasts, which found that Rb affects the expression of a variety of cell adhesion genes beyond cadherins, and that cellular processes related to cell adhesion are strongly affected by Rb. Integrins were also found among the cell adhesion genes whose expression is strongly affected by Rb, and cellular pathways involved in integrin-mediated cell-to-ECM adhesion were also found to be under Rb control. In a follow-up study, it was shown that Rb induces transcription of integrin α10 in osteoblasts, regardless of Rb phosphorylation status, with a corresponding increase in osteoblast binding to a collagen substrate. This suggests that Rb mediates not only cadherin-dependent cell-to-cell adhesion, but also promotes integrin-dependent cell-to-ECM adhesion. Taken together, the studies summarized above indicate a strong influence by Rb on cell adhesion that can either be activating or repressive depending on the genes involved, upregulating adhesion genes in differentiated cells (eg, integrin α10) while downregulating expression of adhesion genes associated with invasiveness and metastasis (eg, N-cadherin).

Rb appears to regulate the formation of functional cell adhesion structures beyond transcriptional regulation of cell adhesion genes, including facilitating the assembly of cell adhesion gene products at the cell membrane. In the absence of Rb, the Rho GTPase Rac1 and its effector, the p21-activated protein kinase (Pak1), become upregulated with consequent phosphorylation of the Merlin tumor suppressor at Serine 518 by Pak1, which in turn causes Merlin to detach from the cell membrane. Therefore, Rb seems to promote adherens junction assembly at the cell membrane by blocking the inactivating phosphorylation of Merlin by Pak1. Merlin is a membrane-bound tumor suppressor and cytoskeleton adapter that stabilizes adherens junctions by anchoring them to the cortical actin cytoskeleton under the plasma membrane. Merlin loss, which is frequent in the human cancer syndrome neurofibromatosis type 2, results in adherens junction disruption with consequent inactivation of contact-dependent growth arrest. In summary, studies
demonstrate that in the absence of functional Rb, transcrip-
tion of adherens junction components as well as their
assembly at the cell membrane are both compromised. This
explains the observation that in Rb-deficient tumors, such
as retinoblastoma and osteosarcoma, not only do adherens
junction proteins show diminished expression, but they also
fail to anchor to the cell membrane, instead showing aberrant
cytoplasmic localization.45–47

Invasiveness and metastases arise from a combination of:
loss of cell adhesion, onset of migration facilitated by
cytoskeletal reorganization and loss of cell polarity, and
the capacity to degrade basal laminae in order to escape
the primary tumor site and penetrate adjacent tissues. The
data summarized above link Rb loss predominantly to per-
urbanations in cell adhesion, but Rb loss could exacerbate
invasiveness by affecting other aspects of metastasis. For
example, Rb loss has been linked to increased expression of
the matrix metalloproteinases that remodel the ECM during
cell invasion and metastasis.54,55 Matrix metalloproteinase
genes such as MMP9, MMP14, and MMP15, which are
usually overexpressed in NSCLC, have been shown to be
regulated by Rb.56 Rb reactivation was sufficient to inhibit
MMP transcription, to reduce the invasion and migra-
tion of cancer cells in vitro, and to reduce metastatic foci
development in a tail vein lung metastasis model in mice.57
Rb depletion also exacerbates the invasiveness of erbB2-
positive breast cancer, suggesting that Rb loss may play a
predominant role in the progression of in situ breast ductal
cellular carcinoma to the invasive stages of the disease.58

The data implicating Rb control of cell adhesion in cul-
tured cells are abundant and provide mechanistic insights
that were lacking in early correlative studies. There are also
data providing insights into the consequences of Rb loss for
in vivo tissue morphogenesis. When a mouse model of osteo-
sarcoma was generated by conditionally knocking out Rb in
osteoblasts,59 structural defects indicative of impaired osteo-
blast adhesion were observed in the calvaria of Rb knock-
out mice. Specifically, Rb knockout mice lacked properly
organized osteoblast layers, and showed osteoblasts that had
migrated away from their proper position in the calvaria and
invaded the adjacent cartilage.51 Rb-deficient osteoblasts also
expressed elevated levels of ezrin, a membrane-cytoskeleton
linker and osteosarcoma metastasis marker.51,57,58 Other
mouse models of osteosarcoma based on abrogation of Rb
function have resulted in mice that develop fully penetrant,
highly metastatic early onset osteosarcomas.59 Given the
importance of cell-to-cell adhesion for osteoblast dif-
ferentiation, Rb loss can be predicted to alter osteoblast
differentiation and lead to the formation of osteosarcoma.
Osteoblasts originate from pluripotent mesenchymal stem
cells that differentiate into stroma, adipocytes, myoblasts,
chondroblasts, fibroblasts, or osteoblasts.60,61 Stem cells
committed to osteoblastic differentiation are sorted from
the rest of the mesenchymal precursors and align with, and
adhere to, each other. Homotypic, cadherin-based cell-to-cell
interactions play a major role in sorting the pluripotent stem
cells into distinct lineages. Consistently, osteoprogenitor
cells express a spatio-temporally regulated repertoire of
cadherins that provide cues for their alignment into a distinct
subpopulation within the bone marrow that will later differen-
tiate into mature osteoblasts.62,63 Adherens junction loss in
Rb-null osteoblasts is accompanied by abnormal expression
patterns of the predominant osteoblast-specific cadherins
OB- and N-cadherins, suggesting that the timing of cadherin
expression during osteoblast differentiation can be altered by
Rb loss.51 This in turn suggests that Rb is required to ensure
that expression of specific cadherins proceeds with the right
timing during differentiation, and that Rb loss could hamper
proper homotypical intercellular contacts, resulting in defec-
tive osteoblast differentiation with consequent disruption of
bone integrity and/or formation of bone tumors. Based on
in vivo observations, it is plausible that Rb is instrumental
in the orchestration of cell proliferation and cell adhesion as
part of differentiation and bone morphogenesis – disruption
of which may be central to the molecular etiology of osteo-
sarcomas, which are characterized by poor differentiation
and high frequencies of RB1 mutations.

A link between cell cycle control and cell adhesion
In metastatic cancer cells, adhesion is aberrantly regulated
by a variety of pathways, resulting in loss of cell-to-cell
and cell-to-ECM contact and dissemination of cancer cells
throughout the body. While more work is needed to elucidate
those pathways, in many instances this loss of adhesion has
been tied to cell cycle regulators, including members of the
Rb–E2F pathway.

Signaling from integrins through their downstream path-
ways occurs cooperatively through cross talk with growth
factor receptors and has been linked to a variety of pathways
involved with cell cycle progression. Integrin-mediated cell-
to-ECM adhesion acts as a checkpoint for cell cycle entry.
For example, in early work using Rb-positive LNCaP and
Rb-negative RU145 prostate epithelial cell lines, loss of β1
integrin contact to ECM inhibited G1/CDK activity leading to
an accumulation of hypophosphorylated Rb and subsequent
Bcl-2-mediated apoptosis. More recently, Wang et al found that overexpression of integrin α5 and knockdown of integrin α6 decreased pulmonary metastasis of the highly invasive breast cancer cell line 4T1 by inhibiting entry to S-phase through p27 upregulation, resulting in downregulation of cyclin E/CDK2 complexes. They also found that this modulation of integrin expression upregulated E2F, which may then induce expression of Chk1 to regulate cdc25A/Cyclin E/CDK2/Rb in a feedback loop. These findings implicate integrin α5 as a metastasis suppressor and α6 as a metastasis promoter in breast cancer. For a comprehensive review of how integrins control downstream entry to cell cycle progression, see the review by Moreno-Layseca and Streuli.

Expression of E2Fs 1–3 was shown to indirectly increase integrin β4 mRNA, protein, and cell surface expression. These E2Fs were found to be downstream of active H-Ras in SUM-159 breast carcinoma cells. Integrin α6β4 has been previously shown to enhance carcinoma invasion, so the mechanism proposed by Yoon et al links active H-Ras, active E2Fs, and integrin α6β4 in a single pathway to promote invasion.

Long-term treatment of 3 NSCLC cell lines with recombinant cysteine-rich 61 (CCN1), a secreted matrix-associated molecule, led to permanent cell cycle arrest in G0. Addition of CCN1 increased abundance of hypophosphorylated Rb and increased levels of p53 and p21 accumulation. A CCN1 mutant defective for binding integrin α6β1 and coreceptor heparan sulfate proteoglycans was incapable of inducing senescence.

The finding that Rb’s effect on integrin expression is unaltered by its phosphorylation state is particularly informative of the mechanisms linking Rb to cell adhesion and of the coupling between cell cycle and cell adhesion. As discussed above, phosphorylation is a mechanism of regulation of Rb function that abrogates Rb’s capacity to bind and block E2F transcription factors. The integrin α10 findings suggest that regulation of cell cycle progression and cell adhesion by Rb may be mechanistically uncoupled since, while Rb hyperphosphorylation abrogates Rb’s capacity to bind E2F and repress the cell cycle, it leaves intact the capacity to induce integrin-mediated cell-to-ECM adhesion. This could shed some light onto the aggressive behavior of Rb-deficient tumors. The tendency of Rb-deficient tumors to metastasize early in their development could be explained by the loss of both cell cycle control and cell adhesion resulting from Rb loss. The residual Rb activity retained by tumors with chronically hyperphosphorylated Rb, while not enough to halt initial tumor growth, may result in a less aggressive tumor and in deterring metastasis by helping to anchor the tumor structure.

The data discussed above expand the paradigm of Rb function beyond cell cycle to include roles in cell adhesion, and therefore implicate Rb loss in later stages of tumor metastasis. Figure 3 shows a model depicting how Rb can integrate cell cycle control and cell adhesion. These dual roles of Rb mechanistically explain how impairment of Rb function contributes to the aggressive nature of some tumor types, expands Rb’s arsenal of tumor suppressive abilities, and explains the potency of this preeminent tumor suppressor more adequately than the notion that Rb acts predominantly as a cell cycle repressor.

**Targeting Rb loss and aberrant adhesion**

The activity of the Rb kinases, the CDKs, is central to the Rb pathway. For this reason, small molecule CDK inhibitors are being developed and examined in clinical trials for a number of malignancies.

Aberrant adhesion has been determinant of potential treatment options in several cancers. For example, in erlotinib-resistant lung cancer cells harboring activating EGFR mutations, there was increased expression of Src, integrins β1, α2, and α5 along with increased adhesion. Silencing of integrin β1 restored erlotinib sensitivity. There

---

**Figure 3** Rb links cell cycle and cell adhesion.

**Notes:** This schematic illustrates the central role of Rb in both cell cycle and cell adhesion. Each molecule represented in this figure is discussed in the text of the review. Red objects represent tumor-suppressing proteins, whereas green objects represent tumor-promoting proteins. Pointed arrows indicate a direct stimulatory interaction. Blunt arrows indicate direct inhibitory interaction. Dotted lines represent indirect interaction or interactions via a mechanism that has not been fully elucidated.

**Abbreviations:** CDKN, cyclin-dependent kinase inhibitor; MMP, matrix metalloproteinase.
was also increased expression of integrins β1, α2, and/or α5 in refractory tumor samples from patients treated with erlotinib and/or gefitinib.  

Furanodiene, a natural terpenoid derived from *Curcuma Wenyujin*, was found to have antiproliferative activity in 95-D human lung cancer cells when combined with paclitaxel. These effects included downregulation of protein levels of cyclins D1 and B1, CDK6, and c-Myc, as well as downregulation of expression of integrin β4, focal adhesion kinase, and paxillin. Previous studies had shown that combining furanodiene and paclitaxel had synergistic antiproliferative effects in NCI-H1299 and 95-D human lung cancer cell lines, and that furanodiene decreased integrin β1 expression in breast cancer cells in a concentration-dependent manner.  

Unsurprisingly, aberrant integrin signaling has been implicated in several human cancers and specific therapies are being developed to target the integrin pathway in a number of diseases including development of anti-integrin α4 antibodies (eg, Natalizumab), integrin-linked kinase (ILK), and arginylglycylaspartic acid peptides such as eptifibatide. Perhaps most relevant to cancer, focal adhesion kinase (FAK) inhibitors such as GSK2256098 are in multiple clinical trials in solid tumors. Unfortunately, integrins are also known mediators of cell adhesion-mediated drug resistance. Specifically, melanoma cells expressing α4β1 and α5β1 integrins are resistant to doxorubicin and melphalan once bound to their fibronectin ligands. This resistance is the result of cell cycle arrest in G1 and is associated with increased levels of the CDKN p27 and its inhibition of cyclins A and E.  

Ligand-induced adhesion, an integrin-mediated Rap1-independent pathway that allows unstimulated leukocytes to adhere to and migrate through exposed endothelial matrix or high-density ligand, is CDK4-mediated, but Rb-independent. CDKNs were able to block this leukocyte adhesion and migration.  

The treatment options listed above are all designed to target either the Rb pathway or the process of adhesion. With the new work being pioneered on the link between these two pathways, it is our hope that, by either combining these drug classes or developing new drugs to specifically target this newly discovered link, treatment options will be more tailored to individual cancers and will be increasingly effective in the future.  

**Conclusion: implications for Rb as a metastasis suppressor**  
Recent work linking Rb to cell adhesion should reinvigorate the Rb field by challenging the classic paradigm of Rb acting predominantly as a cell cycle regulator. New information about Rb, as well as other oncogenes and tumor suppressors discovered decades ago, continues to uncover novel effects and potentialities beyond cell cycle control.  

In the currently accepted model of tumor evolution, a stepwise accumulation of mutations results in the progressive acquisition of aberrant cellular behaviors, with each behavior elicited by a particular mutation or sets of mutations. Mutations that inactivate tumor suppressors like *RB1* or that activate proto-oncogenes like *KRAS* would contribute to early stages of tumor evolution by conferring a proliferative advantage to incipient tumor cells. These mutations target cell cycle control by rendering cells capable of bypassing proliferative arrest, contributing to unchecked tumor growth. However, a paradigm in which Rb acts predominantly as a cell cycle repressor does not explain how Rb inactivation in early tumorigenesis would contribute to later stages of metastasis, particularly to the detachment of tumor cells from their original site and dispersion to distant tissues. The current model mandates the acquisition of additional secondary mutations that confer metastasis potential at later stages of tumor evolution. This multistep model has been challenged, however, and deemed conceptually inconsistent since the additional genetic hits that confer metastatic capabilities at later stages of tumorigenesis do not necessarily exacerbate the proliferative advantage conferred by the initial hits that disrupt cell cycle control. In a tumor history that is essentially a microevolutionary process, if secondary metastasis-related mutations do not further enhance the previously acquired replicative advantage, the cells that acquired them will remain rare within the tumor mass, outcompeted by more proliferative counterparts. Rather, it has been suggested that mutations acquired by incipient tumor cells early in tumorigenesis confer not only the replicative advantage that allows the initial tumor growth, but also later in tumorigenesis the proclivity to metastasize. Thus, the tendency to metastasize could be determined by mutant alleles acquired early in tumor history. This revised model predicts that fewer mutations are required for a full-blown malignant phenotype if they target multifunctional genes such as *RB1*. Several lines of evidence support this. First, primary human breast cancers can shed malignant cells into the bone marrow even when tumors are small and well-localized; second, DNA microarray analyses reveal that metastatic tumor cells show gene expression profiles remarkably similar to the cells contained in the primary tumor from which they were derived; third, certain early gene expression profiles in primary breast cancer tumors strongly predict metastasis and can be detected before metastasis.
The hope to achieve an understanding of the complex process of neoplastic transformation at the cellular level in terms of a small number of genetic changes.

Disclosure

The authors report no conflicts of interest in this work.