Regulation of Tumor Growth and Metastasis: The Role of Tumor Microenvironment

Hadi A. Goubran¹, Rami R. Kotb²,³, Julie Stakiw¹, Mohamed E. Emara¹ and Thierry Burnouf⁴

¹Saskatoon Cancer Centre and College of Medicine, University of Saskatchewan, SK, Canada. ²Medical Oncology, BC Cancer Agency, Victoria, BC. ³Department of Medicine, University of British Columbia, Vancouver, BC, Canada. ⁴Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan.

ABSTRACT: The presence of abnormal cells with malignant potential or neoplastic characteristics is a relatively common phenomenon. The interaction of these abnormal cells with their microenvironment is essential for tumor development, protection from the body’s immune or defence mechanisms, later progression and the development of life-threatening or metastatic disease. The tumor microenvironment is a collective term that includes the tumor’s surrounding and supportive stroma, the different effectors of the immune system, blood platelets, hormones and other humoral factors. A better understanding of the interplay between the tumor cells and its microenvironment can provide efficient tools for cancer management, as well as better prevention, screening and risk assessment protocols.

KEYWORDS: tumor, metastasis, regulation, tumor microenvironment, stroma, immune, platelets, hormones

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CORRESPONDENCE: hadigoubran@gmail.com; hadi.goubranmessiha@saskcancer.ca

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Introduction

Humans are continuously exposed to a variety of carcinogenic and mutagenic stimuli, including environmental toxins, radiation and viral as well as other infections. This stimulation results in cells bearing abnormal characteristics reported in a relatively important number of otherwise healthy persons.¹,² Tumors, however, can only grow if their complex tissue environment provides them with a milieu that can sustain their growth and spread. A complicated bidirectional interaction is therefore happening at the interface between the genetically unstable malignant cells and their stable milieu, a process that will determine the degree of tumor promotion and proliferation, invasiveness, potential for spread and even tumor-host (patient) prognosis.³

Metastasis, on the other hand, is a multistage process that requires cancer cells to escape from the primary tumor, survive in the circulation while hiding from tumor surveillance mechanisms, seed at distant sites, establish themselves and grow. Each of these processes involves multiple mechanisms that are influenced and occasionally modulated solely by the non-malignant cells of the tumor milieu.³

In the absence of malignancy, normal tissue homeostasis rules apply, with a stable tissue structure and tightly controlled cellular proliferation and cellular death. However, alterations of tissue homeostasis by infection or inflammation,⁴ aging, environmental toxins or radiation can compromise stromal structural integrity and affect tumorigenesis. In the past, tumors were viewed as a disease involving simple aberrant mutations in tumor cells. It is now evident that the role played by a deregulated tumor microenvironment [TME] is crucial for tumor growth and spread.³,⁵

Immunosurveillance, the process whereby the immune system eliminates damaged, senescent and pre-malignant or malignant cells, appears to play a major homeostatic function
in maintaining tissue integrity and stability. Accumulating evidence indicates that defects in the molecular and cellular circuitries that underpin immune responses accelerate the course of chronic diseases, cancer development and progression. Immunosurveillance seems therefore to be a key regulator in the tumor milieu.  

Another integral factor in tumor proliferation and protection from immune destruction is the establishment of adequate blood supply, through angiogenesis and the provision of tumor growth factors. Platelets and, potentially, platelet-derived microparticles [PMPs] fulfill this role and may contribute to immunosuppression. Finally, many tumors are hormone-sensitive, by virtue of their cells of origin or by their potential to express hormonal receptors that modulate their growth and spread. 

In the current review, we will discuss how the stroma, the immune system, the platelets and hormones (collectively referred to as tumor milieu), interplay to regulate tumor growth and metastasis (Fig. 1).

**Stromal Cells and Deregulated Tissue Homeostasis**

In the absence of malignancy, cellular proliferation and death are tightly controlled to ensure tissue stability. Tissue-specific function is achieved by interactions between the cell and its surrounding extracellular matrix (ECM), through a model of dubbed dynamic reciprocity. According to this model, a dynamic bidirectional communication between the ECM and the cell is extended to the broad realm of gene expression by connecting ECM receptors to the cell cytoskeleton, then to the nuclear matrix, and eventually to chromatin of the adjacent cells and back again. Maintaining normal tissue homeostasis can prevent neoplastic transformation by ensuring tissue stability. The majority of cell adhesion molecules involved in the process fall into three families, integrins (namely β1-integrins), those in the immunoglobulin superfamily, and cadherins (Epithelial (E)-cadherins). In addition, β-catenin, a component of the adhesion complex, plays a significant role in signal transduction, cellular proliferation and migration. 

Fibroblasts present in the tumor microenvironment deposit the ECM in the milieu and regulate the differentiation of cells. In addition, fibroblasts modulate the immune response in the tumor milieu. Cancer-associated fibroblasts differ from normal ones and may arise during disease progression under the effect of cytokines delivered in the milieu, eliciting a pro-tumorigenic function.

![Figure 1](image-url). The stroma, immune system, platelets (direct and indirect actions) as well as hormones interplay to regulate tumor growth and spread.
The epithelial-mesenchymal transition (EMT) is the process by which epithelial cells are transcriptionally reprogrammed to lose their polarity and adhesion, and gain migratory potentials in developmental processes or migratory and invasive properties in the context of cancer. EMT-inducing transcription factors dynamically modulate cell adhesion and promote metastasis by regulating the expression of the cadherin family of proteins. E-cadherin expression is repressed (a hallmark of EMT) with a switch to N-cadherin expression. 16

Matrix metalloproteinases, or matrixins, are endopeptidases that belong to a family of zinc-dependent proteases with more than 21 human forms. Their main substrates are matrix molecules such as collagen, but many non-matrix substrates have also recently been identified. They are important in many aspects of invasion and metastasis, and play a part in remodeling the ECM. 15

Finally, stem cells are a key factor in tissue homeostasis. Their activity is tightly regulated during development and in adult tissues through the combined action of local and systemic effectors. While stem cells and their microenvironments are capable of sustaining homeostasis in normal physiological circumstances, they also provide host tissues with a remarkable plasticity to respond to perturbations. This is because tissue homeostasis and regenerative capacity rely on these rare cells, endowed with the potential to self-renew and differentiate. 17 For these reasons, stem cells may also contribute to the establishment and continuous growth of tumors when tissue homeostasis is unbalanced.

Any alteration affecting the components of tissue homeostasis can result in tumorigenesis.

Aging. During aging, many tissues show a decline in regenerative potential coupled with a loss of stem cell function. At this point, the mechanisms that protect normal cell function begin to fail. 18 Therefore, a lot of cancers are age-related diseases. In the US, 50% of all malignancies occur in people aged 65–95. By 2020, 60% of all cancers are expected to be diagnosed in elderly patients. 19

This has led to the coining of the term “geroncogenesis”, alluding to the mechanism behind age-induced malignancies. Oncogenesis in the elderly is frequently attributed to the “multi-hit hypothesis” and the time required to accumulate genomic mutations. Wu et al (2013) proposed that aging not only allows time for cells to accumulate sufficient mutations to push them over a certain mutagenic threshold and into full-blown carcinogenesis, but also brings a decline in oxidative metabolism that is an early and important “hit” altering tissue homeostasis and driving tumorigenesis. 20 For instance, aging leads to both a decreased regenerative capacity in the brain and an increased risk of tumorigenesis, as is the case with the most common adult-onset brain tumor, glioma. A shared factor contributing to both phenomena is thought to be age-related alterations in neural progenitor cells, which impair the regenerative capacity of the tumor milieu. 21 Similarly, an aged bone marrow microenvironment seems to be associated with the elevated incidence of age-associated leukemias. 22

Another interesting mechanism often alluded to in geroncogenesis is inflammation. As senescent stromal cells accumulate in aging tissue, the local microenvironment changes to a state resembling chronic inflammation. Cells containing DNA mutations proliferate, which can ultimately lead to cancer. 23

Furthermore, the immune system provides a unique mechanism of defense against pathogens and possibly cancers. However, there is evidence that the immune system of the aged individual is eroded, a phenomenon termed immunosenescence. Both the innate and adaptive immunity are altered with aging. This, coupled with low-grade inflammation, contributes to increased tumorigenesis. 24

Inflammation/Infection. The link between inflammation and cancer was first proposed by Virchow, who observed leukocytes infiltrating tumor sites. 25 Statistically, tissues subjected to chronic inflammation generally exhibit a higher cancer incidence, reflecting a deregulated microenvironment. 4, 5

At the molecular level, free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and posttranslational modifications of key cancer-related proteins. Other products of inflammation include cytokines, growth factors, and transcription factors such as nuclear factor-kappa B. These control the expression of cancer genes (eg, suppressor genes and oncogenes) and key inflammatory enzymes such as inducible nitric oxide synthase and cyclo-oxygenase. The pro-cancerous outcome of chronic inflammation includes increased DNA damage, increased DNA synthesis, cellular proliferation, disruption of DNA repair pathways of the cellular milieu, inhibition of apoptosis, and promotion of angiogenesis and invasion. The stromal cells fail to maintain normal homeostasis and become maladaptive. 26 Chronic inflammation is also associated with immunosuppression, which is a general risk factor for cancer. 27

Clinical evidence in support of the inflammation-cancer link includes the higher incidence of hepatocellular carcinoma in patients with cirrhosis due to iron overload, alcohol or infection, 27 colorectal carcinomas in patients with inflammatory bowel disease, 28 gastric carcinomas and MALT (mucosa-associated lymphoid tissue) lymphomas in association with Helicobacter pylori and chronic gastritis, 29 and even the known association of papilloma viruses with chronic cervicitis and cervical carcinoma. 30

Of the 12.7 million new cancer cases that occurred in 2008 worldwide, 16.1% (around 2 million) were associated with infections and their ensuing inflammation. This fraction was higher in less developed countries (22.9%) than in others (7.4%), varying from 3.3% in Australia to 32.7% in sub-Saharan Africa. Applying public health recommendations to prevent and control infections could have a substantial beneficial effect on the future burden of cancer worldwide. 31
Finally, exposure to radiation is also an important determinant of the stromal response to tumorigenesis as it induces both inflammation and tissue-specific dysfunction in repair processes with deregulated tissue homeostasis.32

**Immune Regulation of Tumour Growth and Propagation**

Since Israel Penn’s observation (1970) that an organ transplant recipient maintained on chronic immunosuppressive therapy has 5–6% chance of developing a *de novo* cancer in the first few years following transplantation,33,34 attention has focused on the regulatory role played by the immune system in oncogenesis. Furthermore, HIV-acquired immunosuppression results in a significantly higher incidence of AIDS-related and non-AIDS-related malignancies, highlighting the regulatory role of the immune system on tumor growth and propagation.35 Evasion and suppression of the host immune system is also crucial for the progression of incipient tumors.36

Most of the immune cell populations in the tumor microenvironment play distinct roles in the modulation of the tumor milieu, favoring or inhibiting tumorigenesis. Figure 2 illustrates the different myeloid and lymphoid cell lineages present in the tumor milieu and their effects on tumor progression, as explained below.

**Myeloid cells.** Macrophages, often referred to as tumor-associated macrophages (TAMs) when present in the tumor milieu, are either recruited from the bone marrow or reside in the original stromal environment. They interact with a wide range of growth factors, cytokines and chemokines, which are thought to educate the TAMs and determine their specific phenotype and, hence, functional role as tumoricidal/static or tumor promoters.37 TAMs therefore range from M1 to M2 polarization, with M1 producing initially type I pro-inflammatory cytokines with a tumoricidal/static role. By contrast, M2 polarization, induced by the cytokines endothelin-2 and vascular endothelial growth factor (VEGF) released in the tumor milieu, produces type II cytokines acting as tumor promoters.38

Myeloid-derived-suppressor cells [MDSCs] arising in the context of aberrant myelopoiesis in cancer patients are a heterogeneous population of immune cells from the myeloid lineage that execute strong immunosuppressive activities. They are mobilized to the tumor milieu, where they infiltrate the growing tumor, favoring neo-vascularization and interfering...
significantly with the different mechanisms of immune surveillance.\(^39\)

Dendritic cells, also known as accessory cells, are the major antigen processing and presenting cells in the tumor milieu and usually act as the link between the innate and the adaptive immune systems,\(^40\) presenting the antigen on their surface to the recruited T-cells. MDSCs interfere significantly with this surveillance process.\(^39\)

The role played by the very abundant neutrophils, on the other hand, is markedly controversial. These cornerstone cells of the innate immune system are phenotypically plastic, performing opposing roles in cancer regulation.\(^31\)

Mast cells, the resident granulocytes in most tissue, are recruited to the tumor milieu and act as reservoirs, releasing tumor promoter cytokines.\(^41\)

**Lymphocytes.** The role played by lymphocytes attracted to the tumor site is also a complex one. The key cytotoxic tumoricidal lymphocyte is the natural killer cell (NK). In the presence of the released interferon and interleukin-2 in the milieu, NK cells are transformed into a more active effector, known as lymphokine activated killers (LAK).\(^42\) Unlike other cytotoxic lymphocytes, NK cells kill stressed cells independent of their MHC protein, through their strong perforin. Furthermore, NK cells are also regulatory cells engaged in reciprocal interactions with dendritic cells, macrophages, \(T\) cells and endothelial cells.\(^43\) Their role in tumor surveillance is primordial. MDSCs interfere significantly with the NK surveillance process.\(^39\)

NK cell population is now known to be divided into different subpopulations; the \(CD56^{dim}\) phenotype is the majority present in peripheral blood and is highly cytotoxic, whereas \(CD56^{bright}\) NK cells make up only 5%–15% of the circulating NK cells and are mainly cytokine producers.\(^44\) A preserved \(CD56^{dim}/CD56^{bright}\) ratio is important in the fight against cancer.\(^44\)

The \(T_H (\) Helper) population bearing the marker \(CD3+\) and \(CD4+\) performs a dual function, based on the subsets and the ratio of their populations. \(T_H1\) cells mediate a tumor suppressor inflammatory reaction, whereas \(T_H2\) can mediate a tumor promoter reaction.\(^45\) B-lymphocytes mediating humoral immunity can promote cancer progression by altering the \(T_H1/T_H2\) ratio to favor tumorigenesis.\(^46\)

Cytotoxic T lymphocytes, bearing the \(CD8+\) marker, can identify and destroy cancer cells through their MHC recognition when recruited to the tumor milieu.\(^47\)

Regulatory \(T\) cells (Tregs) are crucial for peripheral tolerance as they maintain the homeostasis of innate cytotoxic lymphocytes, regulating the expansion and activation of \(T\) and \(B\) cells. They are intimately involved in immunological diseases and cancer.\(^48\) In certain cancers (e.g., breast and hepatocellular carcinoma), increased Tregs promote cancer progression by interfering with immune surveillance. Conversely, in other types of cancers with an inflammatory component, such as colorectal, Tregs can inhibit cancer progression by dampening inflammation.\(^49\) The mechanism underlying the divergent Tregs role in cancer remains mysterious.\(^48\)

With immunosenescence, many changes may decrease the capacity of the immune system to combat the emerging or progressing tumor. The most important changes that may decrease immune response efficiency are the changes in \(T\) cell functions and phenotypes, concomitant with the presence of a low-grade inflammation. Deregulated immune responses in the elderly also produce directly pro-tumor molecules and induce the accumulation of immunosuppressive immune cells either systemically or in the tumor milieu. Furthermore, the adaptive immune system, due to both weakness of the innate immune response and the intrinsic alterations occurring with aging, cannot perform its tumor-eradicating activity, which is dependent on clonal expansion and IL-2 production.\(^50\)

The various components of the immune system seem to interplay with the stromal factors, regulating tumor growth and dissemination. It seems therefore evident that immune modulation should be a crucial component in the fight against cancer. The presence of suppressive factors in the tumor microenvironment, however, may explain the limited activity observed with previous immune-based anti-cancer therapies and why these therapies may be more effective in combination with agents that target other steps of the cycle. Emerging clinical data suggest that cancer immunotherapy is likely to become a key part of the clinical management of cancer.\(^51\) Furthermore, examining the effects of tumor-host interactions on clinical outcome and prognosis represents an evolving interdisciplinary field. Evaluation of pathological immunity may provide information on prognosis and help identify patients who are more likely to benefit from immunotherapy.\(^52,53\)

**Platelets and Platelets-Derived Microparticles**

The platelets are key players in hemostasis and thrombosis, and they also have much broader roles in balancing health and disease. They are crucial in repairing vascular damage and, through the myriad of growth factors stored in their granules, they play a central role in healing processes. Their membrane receptors interact with one another and with the vessel wall to stop acute blood loss, and they also interact with inflammatory and immune cells, mediating between inflammation and thrombosis.

Their role in tumor-induced thrombosis has long been known.\(^54\) Reciprocally, there is a growing body of evidence that complex interactions between tumor cells and circulating platelets play an important role regulating tumor growth, dissemination and angiogenesis.\(^8-10\) Platelet-derived microparticles (PMPs) also share a pathological function in this complex interaction.\(^55,56\)

**Direct surface platelet interactions.** By virtue of the platelet’s vast array of surface receptors and glycoproteins, platelet-receptor/tumor cell interactions play crucial roles in tumor biology.
Platelet P-selectin, a membrane glycoprotein mediating hemostasis-inflammatory cross-talks, binds a large number of cancer cell lines, aiding their leak in the circulation during the metastatic process and subsequent endothelial attachment. In the circulation, tumor cells come into contact with more platelets. Platelet-coated tumor cells co-express platelet markers and platelet MHC class I transferred onto their surfaces, escaping T-cell-mediated immunity. They are therefore shielded from natural killer cell destruction. Platelet-tumor cell aggregates also help the microvascular arrest of tumor cells at remote sites. Figure 3 illustrates the role of direct platelet interaction in the metastatic process.

Furthermore, some tumor cell lines express integrins normally found on platelets, namely GPIb and αIIbβ3 (GPIIb/IIIa), adding to their malignant potential. P2Y receptors are also sometimes shared between platelets and tumor cells, mediating a platelet-tumor-endothelial interaction as tumor nucleoside diphosphate kinase supports metastases and mediates angiogenesis via P2Y receptor signaling.

**Indirect role of platelet growth factors.** Platelets are nothing but cell fragments, 2–3 µm in diameter, derived from precursor megakaryocytes in the bone marrow. They act as huge reservoirs of growth factors, which are stored in their granules, unleashing their cargo and byproducts when activated. Their angiogenic potential has been explored for nearly two decades as they contain more than 30 growth regulatory proteins. The myriad of functional molecules in the platelet granules not only supply essential coagulation factors to reinforce hemostasis but also to deliver growth factors supporting endogenous stem cell differentiation, tissue regeneration, healing and neo-vascularization.

Platelets are attracted to the tumor milieu and are activated through the process of tumor cell-induced platelet aggregation (TCIPA) following direct and indirect cellular interaction with tumor cells. Following their initial activation, the dense granule contained-ADP is released, activating more platelets through P2Y₁ and P2Y₁₂ receptors. ADP is also considered to be an angiogenic protein promoting neo-vascularization and tumor cell proliferation.

VEGF stimulates cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. It is known to occur as at least six
differentially spliced variants, giving rise to mature isoforms containing 121, 145, 165, 183, 189 and 206 amino acids, all inducing vasculogenesis and angiogenesis.\textsuperscript{64–66}

Solid cancers cannot grow beyond a limited size without an adequate blood supply; cancers that can express VEGF are able to grow and metastasize. Platelets attracted to the tumor sites release large amounts of VEGF, acting as tumor promoters. Clinicopathological data also suggest that the lymphatics are an initial signal route for the spread of solid tumors with sentinel nodes providing significant information on staging. The proliferation of new lymphatic vessels (lymphangiogenesis) is in part under the control of VEGF.\textsuperscript{64}

Another important \(\alpha\)-granule-derived growth factor is transforming growth factor \(\beta\) [TGF-\(\beta\)] that intervenes in osteoclastic degradation of bone matrix, necessary for the establishment of bone metastasis.\textsuperscript{71,72} Furthermore, TGF-\(\beta\) exhibits immunomodulatory functions, altering the T-cell response by transforming T\(_H\) cells to T\(_{reg}\) and suppressing NK cell activity.

Other platelet cytokines of interest are insulin-like growth factor-I (IGF-I), a strong mitogen,\textsuperscript{73} and platelet factor 4 (PF-4), which seems to bind newly formed blood vessels and paradoxically inhibits angiogenesis.\textsuperscript{74}

**Microparticles: tumor-microvesicles and platelet-derived microparticles.** Microparticles (MP) and microvesicles (MV) are small plasma membrane remnants shed from cells upon their activation or apoptosis. They are an important intercellular communication tool and, through the activation of signaling pathways, may modify cellular conformation and behavior.\textsuperscript{75}

MP/MV load consists of proteins, lipids, and nucleic acids, including microRNA, which may be transferred horizontally between cells. In cancer, oncogenic pathways drive production of MP/MV, and oncoproteins could be incorporated into the MV (oncosomes). Oncogenic pathways also stimulate production of MP/MV harboring tissue factor (TF) that contributes to cancer-induced thrombosis.\textsuperscript{76} MP also correlates with processes related to cell aggressiveness including primary tumor growth, invasion, and metastasis.\textsuperscript{77} TF-bearing MV can be transferred between different populations of cancer cells and may therefore contribute to the propagation of the aggressive phenotype among heterogeneous subsets of cells in a tumor.\textsuperscript{77} Figure 4 illustrates the indirect role played by platelets and MPs in tumorigenesis.

**Hormones in Tumor Growth and Metastasis**

The relationship between hormones and cancer has long been established. Thomas Beatson, an Edinburgh University graduate in the 19\textsuperscript{th} century, developed an interest in the relation of the ovaries to milk formation in the breast. He decided to test

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**Figure 4.** Indirect action of platelets: platelets attracted to the tumor site are activated and, together with PMPs, they provide a rich source of growth factors which, for most of them, support tumor growth, angiogenesis and lymphogenesis. Furthermore, TGF-\(\beta\) interferes with immunesurveillance.

**Abbreviations:** PMP, platelet microparticles; ADP, adenosine diphosphate; IGF-1, insulin growth factor-1; PF4, platelet factor 4 (or CXCL4); VEGF, vascular endothelium growth factor; TGF-\(\beta\), transforming growth factor-\(\beta\); NK, natural killer cell; TC, lymphocyte T cytotoxic; T\(_{reg}\), regulatory T cell.
oophorectomy as a treatment line in advanced breast cancer and discovered the stimulating effect of the female ovarian hormone (estrogen) on breast cancer, even before the hormone itself was discovered. His work provided the foundation for the understanding of the promoter role of estrogen on breast, ovarian and other malignant tumors and the modern use of anti-hormone therapy, such as tamoxifen and the aromatase inhibitors, to treat or prevent breast cancer.  

The interplay between sex hormones (estrogen in particular) and other cancers has also been considered and reviewed since the early 20th century.  

Half a century after Beatson’s discovery, Charles Huggins, a urologist at the University of Chicago, reported dramatic regression of metastatic prostate cancer after the testicles were removed. Later, drugs that blocked male hormones were found to be effective treatment for prostate cancer.  

Furthermore, there is a growing body of evidence that various tumors express high levels of some hormones and their cognate receptors, indicating the possibility of a role in progression of cancer. Hormones such as luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid-stimulating hormone have been reported to stimulate cell proliferation and act as tumor promoters in a variety of hormone-dependent cancers including gonads, lung, thyroid, uterus, breast, prostate and others.  

These glycoprotein hormones bind their own receptors in respective target cells, regulating a large number of genes encoding nuclear, cytoplasmic and secreted proteins featuring the characteristics of growth factors. They are thus able to induce proliferation when the cells are in an undifferentiated state and promote functional parameters when they are differentiated. Cancer cells recruit these hormones and their receptors to promote their own growth and progression.  

Several findings suggest that the patient’s hormonal context plays a crucial role in determining the outcome of cancer. The exact nature of thyroid hormone action on tumor growth has been controversial, with contrasting data showing thyroid hormones to have a promoting or an inhibiting action on cancer cell proliferation depending on the case. Recent data point to a tissue specificity, and to specific mutations during tumoral development that alter the sensitivity of tumor cells to thyroid stimulation.  

Interestingly, certain hormones exert a negative effect on tumor growth, spread and tethering. Recently, four cardiac hormones, namely atrial natriuretic peptide, vessel dilator, kaliuretic peptide, and long-acting natriuretic peptide, reduced up to 97% of all cancer cells in vitro. These four cardiac hormones eliminated up to 86% of human small-cell lung carcinomas, two-thirds of human breast cancers, and up to 80% of human pancreatic adenocarcinomas growing in athymic mice via a complex mechanism involving specific kinases.  

In summary, hormones reaching the tumor milieu can be involved in tumorigenesis, enhancing the growth of hormone-receptor bearing cells or acting as growth factors. On the other hand, they can function as tumor suppressors through a complex kinase inhibition. Hormonal suppression and promotion are therefore useful therapeutic adjuvant tools in the fight against malignancy.  

Concluding Remarks  
Tumors are aberrant cells bearing abnormal characteristics reported in a relatively important number of otherwise healthy persons. It is now widely accepted that tumors contain cancer stem cells (CSC) bearing self-renewal potential and resistant to conventional cancer therapy with greater invasiveness and metastatic behavior. Identification of these cells and their niche is critical for identifying molecular targets in order to inhibit their growth and to destroy their niche.  

Tumor cells, however, can grow only if their environment provides them with a milieu that can sustain their growth, invasion and allow their escape from their original site to survive a hostile, immune patrolled circulation and seed at a distant location. A complex interaction therefore happens at the interface between the tumor and its surrounding. A deregulated TME and stromal structure due to chronic infection, inflammation, aging or radiation favors tumorigenesis. The role played by the innate and adaptive immune systems, interlinked by the dendritic cells, in regulating tumor growth is also crucial. Numerous immune cells interplay to prevent (or promote) the local growth of tumors and their spread, with the NK cells, TAM and MDSCs and T cells acting as central players. Tumor cells, as well as immunosenescence, may reduce immunosurveillance in the tumor milieu. The regulatory role played by platelets and, likely, PMPs in establishing adequate angiogenesis, supplying the growth factors needed for tumor proliferation and protecting disseminating cells for immune destruction, is integral. Many tumors are also hormone-sensitive by virtue of their cell of origin or by their potential to express hormonal receptors modulating their growth and spread. Therefore, the stroma, immune system, platelets and hormones, collectively referred to as tumor milieu, interplay intimately to regulate tumor growth and metastasis, and are a focus of anti-cancer therapy.  

Author Contributions  
Wrote the first draft of the manuscript: HAG. Contributed to the writing of the manuscript: RRK, JS, MEE, TB. Jointly developed the structure and arguments for the paper: HAG, RRK, JS, MEE, TB. Made critical revisions and approved final version: RRK, JS, MEE, TB. All authors reviewed and approved of the final manuscript.  

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