Yin-Yang Activities and Vicious Cycles in the Tumor Microenvironment

Isaac P. Witz

Introduction

A solid tumor is an ecosystem composed of tumor cells, resident and infiltrating nontumor cells, and molecules present in proximity to these cells. This ecosystem can be collectively described as the tumor microenvironment. Both the tumor cells as well as the neighboring nontumor cells take part in establishing the specific conditions existing in the microenvironmental milieu.

Stephen Paget postulated more than 100 years ago the concept of "seed and soil" as an explanation of site-specific metastasis in breast cancer. Studies published in the last three to four decades supported Paget’s concept and established that the tumor microenvironment does not only serve as a binary and passive growth medium for cancer cells but also, or mainly, as an interaction arena between microenvironmental components and tumor cells. Each of the interaction partners is capable of regulating gene expression in all the other partners, thereby shaping their phenotype. Moreover, the microenvironmental components may exert selective pressures on tumor cells. As such, the "soil" operates primarily as an active "educational/inductive/selection" venue in which the "seed" is directed into one of several molecular evolution pathways. In other words, by exerting regulatory functions and selective pressures, the tumor microenvironment determines and shapes the malignancy phenotype of cancer cells and as such drives tumor progression and metastasis (1).

It is now well recognized that oncogenes and tumor suppressor genes are not specifically associated with the metastatic stage (2) and that the tumor microenvironment plays a pivotal role in conferring the metastatic phenotype on cancer cells (1, 3). These developments have allowed for the establishment of a new treatment paradigm targeting interactions between the tumor cell and its microenvironment.

In searching for such new targets, one must consider the unique characteristics of the tumor microenvironment. These include an overwhelming complexity of intertwined signaling pathways, an abnormality of its "normal" nonmalignant compartment, opposing (yin-yang) effects of some of its components on tumor progression, and a plethora of vicious cycles (1).

This review will provide principles, rather than a comprehensive review, related to the yin-yang activities of tumor microenvironmental components and to vicious cycles operating in it and discuss the implications of these two characteristics on cancer therapy.

The Tumor Microenvironment Is a Double-Edged Sword and Exerts Yin-Yang Activities

Cancer biologists’ presentations dealing with tumor progression often contain a slide showing a scale of proprogression and antiprogression factors. Tipping of the scale implies an imbalance toward one or the other group of factors.

This section will deal with specific microenvironmental factors that should appear on both sides of the scale because they play opposing roles in tumor progression by either promoting or alternatively antagonizing this process. Several variables such as the tumor type, the progression stage of the tumor, the status of certain receptors expressed by tumor cells, and other microenvironmental components determine if these factors will exert either a yin or a yang activity.

In the following discussion, we will review the most well-known cases in which microenvironmental factors either inhibit or promote tumor progression.

Transforming growth factor β (TGFβ), a multifunctional cytokine, controls many cellular functions including proliferation, differentiation, migration, apoptosis, adhesion, angiogenesis, immune surveillance, and cell survival. This cytokine can be considered as a prototype for factors playing promalignancy and antimalignancy roles in tumor progression (4). TGFβ is a potent inhibitor of several cell types, primarily epithelial cells, and it may induce apoptosis of various cell types (5). The signaling system responsible for this growth control mechanism includes the type I or type II TGFβ receptors and intracellular Smad-mediated transcriptional activation as well as non–Smad-associated mechanisms (6).

The growth-inhibitory and apoptotic activities of TGFβ characterize its role as a tumor suppressor gene (4, 6). The suppressor function of TGFβ is impaired by perturbations in its signaling pathways. This can be brought about by different mechanisms, the main ones being loss-of-function mutations in genes encoding TGFβ receptors and Smads (7) or by down-regulation of responsiveness to TGFβ-mediated suppressor effects (6).

Tumor cells at advanced progression stages not only lose responsiveness to the tumor suppressor functions of TGFβ but may also overexpress and release TGFβ and respond to this cytokine by enhanced progression (5). The molecular mechanism leading to the transition from antimalignancy to promalignancy activities is still not fully explained and probably differs from tumor to tumor. TGFβ enhances invasion and metastasis by multiple mechanisms. Among others, it mediates epithelial-to-mesenchymal transition (8), promotes angiogenesis (9), and suppresses antitumor immune responses of the host (10). Various cells in the tumor microenvironment, primarily fibroblasts but also macrophages and neutrophils, respond to TGFβ and secrete it. The TGFβ derived from these microenvironmental cells may further amplify and promote tumor progression by the direct or indirect mechanisms mentioned above.

Requests for reprints: Isaac P. Witz, Department of Cell Research and Immunology, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel-Aviv 69978, Israel. Phone: 972-3-6406979; Fax: 972-3-6406974; E-mail: isaacw@tauex.tau.ac.il.

©2008 American Association for Cancer Research.
doi:10.1158/0008-5472.CAN-07-2917

www.aacrjournals.org 9 Cancer Res 2008; 68: (1). January 1, 2008

Perspectives in Cancer Research

Downloaded from cancerres.aacrjournals.org on July 20, 2017. © 2008 American Association for Cancer Research.
The interaction of immune components with tumor cells represents another case of microenvironmental components which could either restrain or promote tumor progression.

The concept of immune surveillance postulates that immunity, the primary function of which is to protect the organism against harmful invaders, may also function as an efficient antitumor mechanism. The logical conclusion of this concept was to strengthen the deficient immune system found in many cancer patients by various forms of immunotherapy (11–13). Challenging the immune surveillance theory, Prehn (14) showed that tumor cells may not only resist immune insults but their propagation may even depend on immune reactivity. As a result, the tumor cell population becomes more aggressive and more resistant to other antimalignancy factors present in the same milieu. Prehn’s ideas were not readily accepted. It was indeed hard to tolerate a notion that a system that should be protective turns into an enemy from within. This attitude has changed and most of us accept the fact that the immune system functions as a double-edged sword in tumorigenesis and tumor progression and that whereas protective antitumor immunity does indeed operate, immune components may also function as promalignancy factors. Moreover, tumor cells and their products have the capacity to convert antimalignancy immune functions to activities that promote tumor progression (e.g., by activating regulatory T cells; ref. 15). The dichotomy between the humoral and cellular arms of tumor immunity (16) and a Th1/Th2 imbalance occurring in tumor-bearing hosts (17) further support the notion that tumor immunity may not always result in favorable outcome for the cancer patient.

Rudolph Virchow’s paradigm that inflammation contributes to carcinogenesis and tumor progression (18) is another manifestation of the antimalignancy/promalignancy dichotomy of immune components.

It is now well established that inflammatory cells and molecules whose physiologic function is to constitute a firewall against infectious agents may be causally involved in the initiation of certain types of cancer (inflammation-linked cancers) and promote tumor progression in essentially all types of cancer (19, 20). Mononuclear myeloid cells have been implicated to play an pivotal role in the promalignancy function of inflammation (21, 22). The products of these and other inflammatory cells serve as growth and survival factors for tumor cells.

Table 1 provides details on some lymphocyte/myeloid-associated molecules that mediate both antimalignancy and promalignancy functions.

<table>
<thead>
<tr>
<th>Microenvironmental molecule</th>
<th>Antimalignancy effectors and activities</th>
<th>Promalignancy effectors and activities</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGFβ</td>
<td>Growth arrest; apoptosis</td>
<td>Induction of EMT; angiogenesis; suppression of tumor immunity; promotion of invasion and metastasis</td>
<td>(4–10)</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Induction of protective immunity; induction of apoptosis</td>
<td>Induction of inflammation; protection against apoptosis</td>
<td>(23–27)</td>
</tr>
<tr>
<td>TNFα</td>
<td>Apoptosis; necrosis</td>
<td>Inflammatory cytokine; promotion of invasion and metastasis</td>
<td>(28)</td>
</tr>
<tr>
<td>TLR ligands (external and tumor-derived)</td>
<td>Innate antitumor resistance</td>
<td>Contribution to chronic inflammation (activation of NF-κB)</td>
<td>(29)</td>
</tr>
<tr>
<td>DR-TRAIL</td>
<td>Induction of apoptosis (several DRs)</td>
<td>Activation of tumor cells (DR3)</td>
<td>(26, 30, 31)</td>
</tr>
<tr>
<td>CXCR3–CXCL10</td>
<td>Angiostasis; recruitment of immunocytes</td>
<td>Promotion of invasion and motility</td>
<td>(32, 33)</td>
</tr>
</tbody>
</table>

Abbreviations: EMT, epithelial-to-mesenchymal transition; TLR, Toll-like receptor; DR, death receptor; TRAIL, TNF-related apoptosis-inducing ligand.
The death receptor/TNF-related apoptosis-inducing ligand axis also plays antimalignancy or promalignancy roles. TNF-related apoptosis-inducing ligand, a member of the TNF superfamily, is a microenvironmental ligand of death receptor and induces apoptosis of tumor cells by engaging several death receptors (26, 30). A recent study showed that death receptor-3 is an E-selectin ligand expressed by colon cancer cells. Its engagement by E-selectin did not induce apoptosis in the colon cancer cells but rather triggered the activation of p38 and extracellular signal-regulated kinase and conferred survival advantages on the tumor cells (31).

Until recently, the CXCR3-CXCL10 axis was considered to antagonize the growth and progression of certain tumors (32). It now turns out that this axis may also engage in promalignancy activities. It was recently shown that the interaction of the CXCL10 chemokine with its CXCR3 receptor expressed by colorectal carcinoma cells promotes, rather than antagonizes, tumor progression (33).

Taken together, all these examples, as well as several others not summarized here, suggest that antimalignancy or promalignancy activities exerted by microenvironmental factors may be a general and typical characteristic of such factors.

Vogelstein and Kinzler (2) wrote, under a heading entitled "Same actors in different roles," that "one might have expected that a specific mutation of a widely expressed gene would have identical or at least similar effects in different mammalian cell types. But this is not in general what is observed. Different effects of the same mutation are not only found in distinct cell types; differences can even be observed in the same cell type, depending on when the mutation occurred during the tumorigenic process."

The examples cited above show that the same can be said for microenvironmental factors. A single microenvironmental molecule may exert an antimalignancy or a promalignancy function depending, most often, on the progression state of the tumor.

The number of clinical trials targeting interactions between tumor cells and microenvironmental factors involved in tumor progression increases steadily (34). However, due to the fact that certain (possibly many) tumor-microenvironment interactions exert opposing effects with respect to tumor progression, the possibility cannot be excluded that such therapies could hit tumor-restraining, rather than or in addition to tumor-promoting, interactions.

In constructing rational modes of targeting progression-promoting microenvironmental factors in cancer patients, it would be important to provide answers to the following questions:

1. Does the targeted factor have any tumor suppressor activity? If not, it would be safe to target it.
2. Is the promotion of tumor progression by a candidate microenvironmental target a reversible or an irreversible situation in a given cancer patient? If it is reversible, can we design strategies to achieve such a reversion?
3. Do pro- and anti-tumor progression activities mediated by a candidate microenvironmental target coexist? In other words, does the progression-promoting or progression-restraining activity of the target factor represent a net balance of these two functions operating simultaneously?

Based on and supported by experimental and clinical evidence, Foulds (35) postulated around the 1950s some general rules governing tumor progression. One of these rules, the independent progression of different tumors occurring in a single tumor-bearing individual, is relevant to the present discussion. The realization that single tumors are heterogeneous with respect to the metastatic potential of different variants in a single tumor supports the independent progression concept at the level of the single clone (36). In this case, a microenvironmental factor having the potential to exert antimalignancy or promalignancy functions in a particular tumor may suppress the progression of variant A whereas the same factor may promote the progression of variant B in the same tumor. In this case, could we selectively target variant B? In view of the heterogeneity of malignant cell populations (36), will we be able to target all cells of variant B?

The Tumor Microenvironment: An Assortment of Vicious Cycles

Normal cell growth and proliferation is controlled by several signaling cascades. The cross talk between these different pathways is tightly coordinated.

In cancer, many signaling cascades are deregulated. This is manifested by the excessive activation of downstream pathways, by signaling pathways that are not functional under nonpathologic conditions, and by alterations in gene expression patterns (1).

These situations may involve newly formed interactions between microenvironmental factors and tumor cells and between different microenvironmental factors (1). These interactions constitute a fertile ground for the establishment of circular chains of tumor progression-enhancing events. Such chains of events may be described as vicious cycles.

The most prominent example of a vicious cycle in tumor progression is bone remodeling (manifested both by bone destruction as well as by bone formation) by bone-infiltrating metastatic cells of breast and prostate carcinoma origin (37, 38). A complex interplay between bone-infiltrating cancer cells, osteoclasts, osteoblasts, bone matrix, endothelial cells, immune cells, and products derived from these cells, such as cytokines, chemokines, growth factors, and differentiation factors, creates a self-perpetuating vicious cycle that, on the one hand, drives tumor progression even more and, on the other hand, further promotes bone remodeling (37, 38).

A similar vicious cycle seems to operate in bone destruction in multiple myeloma (39) and in B-cell lymphomas of bone origin.

Chemokine-driven vicious cycles operate in the progression of mammary carcinomas in mice and in breast cancer in humans. In a study done with a mouse mammary carcinoma, we showed that tumor cells secreting high levels of CCL2 (MCP-1) known for its capacity to attract monocytes to the tumor microenvironment. Monocyte-derived TNFα up-regulated CCL2 secretion from the tumor cells, and CCL2 in turn promoted the secretion of TNFα from monocytes. In this vicious cycle, the tumor cells and the monocytes in the tumor microenvironment promoted each other's ability to express and secrete promalignancy factors (40). A similar situation exists in breast cancer in humans (41). Monocyte chemoattractants CCL5 and CCL2 secreted by breast tumor cells may induce monocyte infiltration to the microenvironment of breast tumors. The resulting tumor-associated macrophages may secrete TNFα, which induces or up-regulates the secretion of several promalignancy factors from the tumor cells such as matrix metalloproteinases. TNFα also further up-regulates the secretion of CCL5 and CCL2, which drive the merry-go-round for another cycle (41). It is not unlikely that similar cycles operate also in other types of cancer.
A recent study indicated that a vicious cycle involving the CXCR3-CXCL10 axis and IFN-γ operates in colorectal carcinoma progression (33). CXCL10 secreted from CXCR3-expressing colorectal carcinoma cells promotes, by an autocrine mechanism, some progression-promoting functions in these tumor cells. CXCL10, at the same time, attracts CXCR3-expressing Th1 cells to the tumor site. The infiltrating Th1 cells secrete IFNγ, which, in addition to its immune functions, promotes the release of CXCL10 from IFNγ receptor–expressing colorectal carcinoma cells while up-regulating CXCR3 expression. This further promotes the capacity of the colorectal carcinoma cells to respond to CXCL10-mediated promalignancy functions.

A state of hypoxia is a universal characteristic of the microenvironment of solid tumors. Growing evidence indicates that hypoxia plays a critical and fundamental role in metastasis formation (42). Hypoxia drives tumor progression by influencing both the tumor cells as well as the tumor microenvironment. It increases genomic instability and heterogeneity in tumor cells and selects resistant tumor variants. It also alters the expression of several genes, among them hypoxia-inducible factor 1, a transcription factor that regulates a large variety of key genes controlling cell survival, migration, and angiogenesis to name just a few (43, 44).

Hypoxia and hypoxia-inducible factor 1 mediate progression-promoting or progression-restraining effects on tumor cells and on the microenvironment. These activities involve, on the one hand, regulation of genes that drive tumor progression (43, 44) and, on the other hand, the induction of genes that may cause the opposite effect (e.g., cell death; ref. 45). By surviving and propagating under hypoxia, resistant tumor cells further aggravate the state of tumor hypoxia. This, in turn, increases genomic instability and further stabilizes and activates hypoxia-inducible factor 1. This vicious cycle drives, as mentioned above, alterations of gene expression patterns in tumor cells and thereby enhances tumor progression.

Vicious cycles involve multiple participants, each of which may serve as target for specific adjuvant treatment of metastasis. For example, the vicious cycle leading to bone metastasis initiated the development of a variety of new agents for the treatment and prevention of such metastasis. These include small molecules and peptides that could interrupt these cycles (37, 38).

However, cancer cells are endowed with the capacity to bypass regulatory roadblocks or pathways by variety of mechanisms (46, 47). Every vicious cycle described above (and most others) involves numerous cellular interactions. Because the blocking of each interaction may be subject to a bypass strategy, we need to use multiple therapy modalities targeting most, if not all, components of such vicious cycles.

Conclusions: Quo Vadis Cancer Therapy?

Until recently, cancer therapy trials targeted exclusively the tumor cells. Realizing that the tumor microenvironment plays pivotal roles in tumor progression, this situation is changing. Attempts are being made to block tumor-microenvironment interactions that boost tumor progression and enhance interactions that counteract malignancy.

However, and by and large, tumor-microenvironment interactions are still terra incognita. To develop rational and effective cancer therapy modalities, we need to define the circumstances in which a certain microenvironmental factor acts like Dr. Jekyll or alternatively like Mr. Hyde; to elucidate the molecular mechanisms driving the various vicious cycles in the microenvironment; and to determine the net balance between promalignancy and antimalignant interactions in the microenvironment. Moreover, because the phenotype of nontumor cells in the microenvironment is not always normal (1, 48), it would be important to establish if the particular microenvironmental molecule or cell, whose interaction with tumor cells we wish to target, has a normal or an altered phenotype. Complying with all these requirements is definitely not a simple task, requiring a drastic change of attitude on our part. We should minimize reductionism, adopt combinatorial approaches used in the analysis of hypercomplex systems (49), and gain further biochemical and molecular insights into the communication between different microenvironmental factors.

Acknowledgments

Received 8/7/2007; revised 8/26/2007; accepted 9/10/2007.

Grant support: The Jacqueline Seroussi Memorial Foundation for Cancer Research; The Ela Kodesz Institute for Research on Cancer Development and Prevention, Tel Aviv University; The Finnbarg Family Fund (Orange County, CA); Bonnie and Steven Stern (New York, NY); The Fred August and Adele Wolpers Charitable Fund (Clifton, NJ); Natan Blutinger (West Orange, NJ); Arnold and Ruth Feuerstein (Orange County, CA); The Pikovsky Fund (Jerusalem, Israel); and James J. Leibman and Rita S. Leibman Endowment Fund for Cancer Research.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

I thank the former and present members of my team for their talent, creativity, and diligence.

References

18. Balkwill F, Charles KA, Mantovani A, Smolders and

www.aacrjournals.org 13 Cancer Res 2008; 68: (1). January 1, 2008 Downloaded from cancerres.aacrjournals.org on July 20, 2017. © 2008 American Association for Cancer Research.
Yin-Yang Activities and Vicious Cycles in the Tumor Microenvironment

Isaac P. Witz


Updated version

Access the most recent version of this article at:

http://cancerres.aacrjournals.org/content/68/1/9

Cited articles

This article cites 49 articles, 10 of which you can access for free at:

http://cancerres.aacrjournals.org/content/68/1/9.full#ref-list-1

Citing articles

This article has been cited by 12 HighWire-hosted articles. Access the articles at:

http://cancerres.aacrjournals.org/content/68/1/9.full#related-urls

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.