COMMENTARY

The Use of Inflammation by Tumor Cells

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Cancer is malignant, because tumor cells invade neighboring tissues and survive in these ectopic sites. This invasion permits them to enter into the circulation, from which they can reach distant organs and, eventually, form secondary tumors, called metastases.[1]

The classical metastatic cascade encompasses intravasation by tumor cells, circulation of these cells in lymph and blood vascular systems, arrest in distant organs, extravasation, and growth into metastatic foci.[1,2] However, the tumor cells can adopt a great variety of phenotypes; and, due to this plasticity of the malignant cells; it has been proposed that a more dynamic view is needed for the metastatic cascade.[2,3]

Invasion and metastases are not unique for cancer, because they also occur during embryonic development, in adult tissue maintenance, and in many noncancerous diseases, such as in repair processes.[1,2] In relation to the latter, tumor cells have been described as wounds that do not heal.[4]

Both tissue repair, a beneficial process, and tumor formation, a harmful process, share some molecular mechanisms that can be ascribed to inflammation.[1,2,5] Therefore, in one sense, it is possible that inflammation is shared by both processes: tissue repair and tumor formation.

The Possible Trophic Significance of the Inflammatory Response in Tissue Repair

To integrate the different alterations that are produced after injury by mechanical energy (posttraumatic inflammation), we consider that a response based on the successive functional predominance of the nervous, immune, and endocrine systems would be produced. This hypothesis implies that the final and prevalent functions of these systems may represent the consecutive phases of the response to stress, all of which may have trophic significance.[6–8]

In the nervous phase, ischemia-reperfusion, which causes interstitial and cellular edema, is produced. Both types of edema may represent an ancestral mechanism to feed the cells by diffusion. During the immune phase, the tissues are infiltrated by inflammatory cells and bacteria. Hence, extracellular digestion, by enzyme release

Supported by grant GE-EJS01-04 from the Principado de Asturias, Education and Culture Council.

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Received October 31, 2004; revision received February 14, 2005; accepted March 3, 2005.

DOI 10.1002/cncr.21165
Published online 3 June 2005 in Wiley InterScience (www.interscience.wiley.com).

TABLE 1
Inflammatory Response and Tumor Evolution

	Inflammatory response		
Tumor cell	**Nervous phase**	**Immune phase**	**Endocrine phase**
Benign Induces inflammatory response or host reaction	-Ischemia-reperfusion	-Infiltration by inflammatory cells	-Extracellular matrix -Angiogenesis -Cellular proliferation
		Desmoplasia	
Malignant Adopts an inflammatory phenotype	-Hypoxic tumoral cells -Anaerobic glycolytic metabolism -Revascularization -Reperfusion injury -Oxidative stress -Nutrition by diffusion	-Leukocyte tumoral phenotype -Anaerobic glycolysis -Proinflammatory gene expression -Migration and invasion -Lymph node metastasis -Micrometastasis (preangiogenic or "dormant") -Nutrition by digestion, (extracellular and intracellular)	-Vascularized malignant primitive tumor -Oxidative phosphorylation -Vasculogenic mimicry -Angiogenic metastasis -Cachectic syndrome

(fermentation) and intracellular digestion by phagocytosis may be associated with a hypothetical trophic capacity for the neighboring cells. Finally, in the late or endocrine phase, nutrition mediated by the blood capillaries is established.[7] In these three successive phases, the inflammatory response progresses from an anaerobic metabolism (ischemia), through a metabolism characterized by defective oxygen use (reperfusion, oxidative burst, and heat hyperproduction), and, finally, to an oxidative metabolism (oxidative phosphorylation) with correct use of oxygen to produce usable energy. This type of metabolism is characterized by a large production of adenosine triphosphate (ATP), which is used to drive specialized multiple cellular processes.[7,9,10]

Because the nervous, immune, and endocrine phases of the inflammatory response progress from ischemia to the development of an oxidative metabolism, it also is tempting to speculate on whether the body reproduces the successive stages by which life passes from its origin without oxygen until it develops an effective, although costly, system for the use of oxygen every time we suffer posttraumatic acute inflammation.[9,10] Likewise, the successive expression of these three functional systems during embryonic development and also during the evolutionary development of our species may explain why the inflammatory response is a ubiquitous mechanism that is common to multiple diseases, because it is an integrator of the ontogeny and phylogeny.[7]

Inflammatory Response and Tumors

Tumors can be noninvasive or benign, because they are cured easily by simple removal, and invasive—also called malignant or cancers that invariably kill their host if untreated.[1] The invasive capacity of cancers is reflected in the classic metastatic cascade, which is staged according to the volume of the primary tumor and its depth of invasion (T stage), the number and the volume of occupied lymph nodes as well as invasion through their capsule (N stage), and the presence of distant metastases (M stage).[1] However, if the previously described functional concept of inflammatory response is applied to tumor evolution, then this may help us to better understand the mechanisms that govern their invasive capacity and to obtain a more dynamic view of the metastatic cascade.

The tumor benign cells seem to be able to induce an inflammatory response in the host. Therefore, it is possible that the host may participate in establishment of the tumor by a process called desmoplasia, consisting of fibroblastic cells and extracellular matrix as inflammation and immune response, represented by lymphocytes, macrophages, and dendritic cells, and as angiogenesis, evidenced by newly formed blood and lymph vessels.[1] Essentially, all of the elements that constitute the inflammatory response participate in this "host reaction" that, thus, may have a trophic purpose for the tumor cells[7,9] (Table 1).

The nutritional importance of this host cell reaction for tumor cells, manifested by leukocytes, blood vessels, and stroma, would explain why these host elements, although more abundant in some types of cancer than in others, are omnipresent.[1] However, when tumor cells reach higher grades of malignancy, their invasive capacity seems to be more of a reflection of the new capacity to express the inflammatory response than to induce it in the host. In this hypothet-

ical circumstance, the successive phases that have been described in the posttraumatic inflammatory response would be expressed by tumor cells and would express their evolution with invasion and metastases (Table 1).

Thus, the first evolutive or nervous phase would be characterized by the ischemia-reperfusion phenomenon. In this sense, the tumor cell seems to adopt an ischemic phenotype (hypoxic),[11,12] which, when it comes into contact with oxygen, undergoes a process of revascularization. The transcriptional response to hypoxia relies on multiprotein complexes to regulate several transcription factors, the most well studied of which is hypoxia inducible factor-1 (HIF-1), which that enhances the expression of hypoxia-responsive genes and, thus, allows improved cell survival in conditions of limited oxygen availability.[11,12]

Hypoxic tumor cells change to an anaerobic glycolytic metabolism as the main source of ATP, become resistant to apoptosis (programmed cell death), present inhibition of differentiation, and become more likely to migrate to less hypoxic areas.[12] Moreover, during these initial avascular stages of tumor growth (tumor mass $<$ 0.5 cm), nutrition can be achieved by diffusion[13] (Table 1).

Tumor cells also can have an endothelial cell-like function and form channels that allow fluid flow and, thus, nutrition by diffusion. This vasculogenic mimicry is the ability of aggressive tumor cells to form the novo vessel-like networks in vitro in the absence of endothelial cells.[2,3] A defective vascular network also ensures an increased metastatic potential, because the newly formed intratumoral vessels, simulating venular-like spaces, easily are permeable to tumor cells, facilitating metastases.[14]

Hypoxic cells also produce proangiogenic factors, such as vascular endothelial growth factor (VEGF), that stimulate new blood vessel formation from existing vasculature. This makes hypoxic tumors the most proangiogenic type, with a highly aggressive phenotype.[12,15] Because all solid tumors, including micrometastases, have areas of hypoxia at the edges of the tumor in addition to the hypoxic areas found inside larger tumors that measure $>$ 1–2 mm in greatest dimension,[12] it is possible that, in these areas, induction of angiogenesis by VEGF may facilitate the revascularization process of hypoxic tumor cells and, thus, the acquisition of an aggressive phenotype.

Revascularization of hypoxic tumor cells may cause oxidative stress (reperfusion injury), like what occurs in the inflammatory response by the generation of reactive oxygen species (ROS).[16] In most inflammatory responses, the actions of ROS are mediated by the IκB/nuclear factor (NF)-κB system; and, in turn, this system can be regulated by hypoxia and/or reoxygenation.[11] More specifically, the expression of inducible genes leading to the synthesis of cytokines, chemokines, adhesion molecules, and autacoids relies on transcription factors; and, among the primary transcription factors, NF-κB plays a central role in the regulation of inflammatory mediators.[17]

Activation of the general stress-responsive transcription factors, such as NF-κB, in the tumor cells[11] may imply their transition to a hypothetical phase called an immune phase, because this may be associated with proinflammatory gene expression. Hence, tumor cells may usurp key mechanisms by which inflammation interfaces with cancer to further their colonization of the host.[18]

The association between inflammation and cancer can be established by studying the influence of inflammatory cells in tumoral progression. Currently, the tumor microenvironment, which is orchestrated largely by inflammatory cells, is considered an important participant in the neoplastic process, because it may foster the spread of tumors.[18] In addition, solid tumors are infiltrated by a heterogeneous population of leukocytes in which macrophages represent a major component. A role also has been suggested for infiltrated macrophages in the progression to malignancy.[19]

However, the interactions between the tumor and the host immune system have been a subject of much controversy, because the tumor also can induce immunosuppression.[20] More specifically, tumors have the ability to disable or even eliminate immune effector cells.[21,22]

Independent of the action of host leukocytes, however, and due to the great plasticity of malignant cells, we suspect that, among the wide variety of phenotypes they may express, they also may adopt a leukocytic phenotype. Hence, it has been shown that tumor cells can co-opt some of the signaling molecules of the innate immune system, such as chemokines, selectins, and their receptors, for invasion, migration, and metastases.[18]

Chemokines are a family of low-molecular-weight, proinflammatory cytokines. Their primary function is chemoattraction and activation of specific leukocytes in different immunoinflammatory responses.[5] However, chemokine biology extends to all cell types, including most human neoplastic cells; and, in particular, the chemokine-receptor system can be altered dramatically at the invasive edges of neoplastic tissue.[18]

The hypothetical activation by chemokines of the leukocytic phenotype in tumor cells would permit these cells to fulfill functions characteristic of activated inflammatory cells, e.g., functions associated

with neutrophils, such as hyperproduction of extracellular proteases like matrix metalloproteinases and other protease enzymes, that carry out true extracellular digestion of the basement membrane and the extracellular matrix and, thus, also aid invasiveness in the early stages of the disease.[23] The basement membrane of the extracellular matrix is a reservoir for many molecules, including growth factors and cytokines, which are released only upon its dissolution.[24] Therefore, these released mediators may play a role in inducing the immune phenotype in tumor cells during these earlier and invasive stages. In addition, tumor cells can present pseudopodia formation and directional migration.[25]

Other functions seem to correspond to a monocyte-macrophage phenotype, in the sense that tumor cells migrate to the regional lymph nodes through lymphatic capillaries.[26,27] In addition, lymphangiogenesis collaborates in lymphatic metastases.[3] VEGF-C and/or VEGF-D expression in tumor cells has been linked to lymphangiogenesis associated with tumors, invasion of malignant cells into the lymphatic vessels, and lymph node metastases.[1,3,27,28] It has been suggested that malignant cells may adopt normal mechanisms of lymph node homing during metastases[27] (Table 1).

The hypothetical adoption of an immune phenotype by the tumor cells also would imply the adoption of a similar metabolism. In this situation, like the activated phagocytes (granulocytes, monocytes), their functions would require anaerobic glycolysis as the main source of ATP.[29] It has been demonstrated that neutrophils and macrophages are highly dependent on the anaerobic glycolytic pathway for the generation of ATP,[30] suggesting that tumor cells also are able to adapt metabolically to the hypoxic environment in this evolutive stage. In this sense, it has been shown that HIF-1α is essential for the up-regulation of enzymes of the glycolytic pathway to supply phagocytes with sufficient levels of ATP.[29] This metabolic characteristic of the tumor cells in this stage explains why tumors, regardless of their angiogenic ability, grow in lymph nodes.[31]

During the immune phase of tumoral progression, soluble factors, such as colony-stimulating factor (CSF-1), may push tumor cells toward a monocyte-like phenotype and induce their premature migration to peripheral tissues. This explains why, in human breast carcinomas, overexpression of the macrophage CSF-1 and its receptor (CSF-1R) leads to a significant increase in pulmonary metastases and correlates with a poor prognosis.[19] In addition, tumor spread would be premature. According to the current view, metastases mark the end of a sequence of genomic changes underlying the progression of an epithelial cell to a lethal malignancy. However, it was demonstrated recently that human breast carcinoma cells disseminate much earlier in genomic development than expected from a sequential model of cancer progression. Therefore, seed cells of distant metastases can spread before surgery and even before the first diagnosis.[32]

In 1889, Paget[33] described the concept of "seed" (tumor cell) and "soil" (specific organ) for the nonrandom metastases of breast carcinoma to specific organs. This theory states that different organs provide growth conditions optimized for specific malignancies.[5,33] Hence, the monocyte phenotype of the tumor cells would favor the homing of metastatic tumor cells to specific organs, especially those in which populations of resident macrophages are abundant, i.e., lung (alveolar macrophages), liver (Kupffer cells), and bone (osteoclasts).

Tumor cells that arrive at a second site by blood do not necessarily proliferate immediately. Some cells may remain "dormant" for extended periods or until conditions become favorable for proliferation.[32,34] It has been proposed that tumor dormancy may be due to preangiogenic micrometastases that subsequently acquire the ability to become vascularized[2,34,35] (Table 1).

The adoption of a leukocytic phenotype by tumor cells also would force them to adopt a leukocytic metabolism, i.e., one based on glycolytic pathways; thus, their functions would require anaerobic glycolysis as the main source of ATP.[29,36] In turn, nutrition of tumor cells during the immune evolutive phase is based on extracellular (proteolytic enzymes) and intracellular (phagocytic functions) digestion.[7,9]

Therefore, tumors cells may assume the phenotypic characteristics of immune cells, and this would favor their migration and spread. Conversely, the tumor also induces immunosuppression by, among other mechanisms, apoptosis of the immune cells responsible for tumor cell elimination.[21,22] Thus, coopting by the tumor of the host immune system to its own advantage may be another characteristic of this immune phase.

Finally, the endocrine phase in the evolution of cancer is characterized by the ability of the tumor cells to use oxygen in the oxidative metabolism, which would explain the appearance of both local angiogenesis (tumor or T stage) and systemic angiogenesis (metastasis or M stage). This type of metabolism is characterized by a large production of ATP, which is used mainly for proliferation. Therefore, it is during this evolutive phase that the tumor can be considered a disease of growth.[1]

Angiogenesis (the formation of new blood vessels)

is critical to survival of the tumor and the metastatic cells at the new site.[24] In particular, once the tumor cells arrive at the secondary site, they must proliferate to form metastases. Both factors associated with the tumors themselves and environmental factors favor proliferation of angiogenic metastasis. Differential expression of genes by tumor cells influence angiogenesis.[2] In addition, the extracellular matrix at the secondary site serves as a reservoir for many molecules, including cytokines, growth factors, and angiogenic factors.[2,24] Moreover, tumor-associated macrophages play an important role in metastatic development, because they can induce angiogenesis by proteinases, cytokines, and growth factor secretion.[18,34,37] Metastatic cells, due to their previous leukocytic phenotype, also may develop functions similar to those described for tumor-associated macrophages. Thus, metastatic tumor cells can modify the host environment, so that tumor cells can be nourished by capillaries that are present due to angiogenesis (Table 1).

Angiogenesis, possibly induced by the new metabolic requirements of tumor cells, would provide the oxygen necessary to achieve effective oxidative metabolism (oxidative phosphorylation) with an increase in ATP synthesis, which is used to drive multiple cellular processes, especially those derived from intense tumor cell proliferation. This increase in metabolic requirements of the tumor cells may constitute one of the main causes of tissue catabolism that the host suffers in this late evolutive phase of the disease.[38,39] Therefore, the cancer cachexia syndrome, characterized by anorexia, weight loss with muscle wasting, and increased energy expenditure,[38–40] may be the result of an effective metabolic functional ability that the cancer cell develops to use the only available store of substrates: those that belong to the host. This may be the reason that tumor-related cachexia, which implies a hypermetabolic stage and host consumption, has been observed mainly in advanced stages of the cancerous disease,[41] because this is when the tumor cell acquires its ability to manipulate the host metabolically.

Therefore, it is possible to consider that the successive phases of tumoral evolution may have a trophic meaning, although the physiopathologic mechanisms involved would increase in complexity (Table 1). This hypothetical view of the mechanisms that govern metastatic progression along an axis from the primary tumor, to regional lymph nodes, to distant organ sites (an "axis of evil"[2]) also would be compatible with the classic concept that the most important, essential prognostic factor has always been the anatomic spread of the disease (TNM).[42]

Because the phases of tumoral evolution, like the phases described for posttraumatic inflammation,[7,9] go from ischemia to development of an oxidative metabolism, it also is tempting to speculate about whether the tumor cell reproduces the successive stages by which life passes from its origin without oxygen until it develops an effective, although costly, system for the use of oxygen.[43,44]

If so, then the succession of progressively more complex trophic mechanisms by the tumor cell may represent the successive evolutive phases of life on earth. Therefore, the plasticity of tumor cells, especially malignant cells, would facilitate the adoption of successive trophic phenotypes that also clearly have shown their effectiveness in the oxygenated environment of the earth over the last 1.5–2.0 billion years.[43,44]

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