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CANCER MECHANISMS

Why Cancer and Inflammation?

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Central to the development of cancer are genetic changes that endow these "cancer cells" with many of the hallmarks of cancer, such as self-sufficient growth and resistance to anti-growth and pro-death signals. However, while the genetic changes that occur within cancer cells themselves, such as activated oncogenes or dysfunctional tumor suppressors, are responsible for many aspects of cancer development, they are not sufficient. Tumor promotion and progression are dependent on ancillary processes provided by cells of the tumor environment but that are not necessarily cancerous themselves. Inflammation has long been associated with the development of cancer. This review will discuss the reflexive relationship between cancer and inflammation with particular focus on how considering the role of inflammation in physiologic processes such as the maintenance of tissue homeostasis and repair may provide a logical framework for understanding the connection between the inflammatory response and cancer.

INTRODUCTION

Basics of cancer development

Cancer results from the outgrowth of a clonal population of cells from tissue. The development of cancer, referred to as carcinogenesis, can be modeled and characterized in a number of ways. One way to describe this process is to illustrate the essential features of both cancer cells and tumors: the "hallmarks" of cancer [1]. Cancer development requires the acquisition of six fundamental properties: self-sufficient proliferation, insensitivity to anti-proliferative signals, evasion of apoptosis, unlimited replicative potential, the maintenance of vascularization, and, for malignancy, tissue invasion and metastasis [1]. Cancer can also be considered with regard to a step-wise development functionally grouped into three phases: initiation, promotion, and progression [2]. Initiation is characterized by genomic changes within the "cancer cell," such as point mutations, gene deletion and amplification, and chromosomal rearrangements leading to irreversible cellular changes. Tumor development is promoted by the survival and clonal expansion of these "initiated" cells. Progression encompasses a substantial growth in tumor size and either growth-related or mutually exclusive metastasis.

Essential to the development of cancer is the accumulation of genetic lesions in

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†Abbreviations: NSAID, non-steroidal anti-inflammatory drug; FAP, familial adenomatous polyposis; ROI, reactive oxygen intermediated; RNI, reactive nitrogen intermediates; RSV, Rous sarcoma virus; FGF, fibroblast growth factors; CAC, colitis associated cancer; AOM, azoxymethane; DSS, dextran sulfate sodium; DEN, diethylnitroseamine.

cells. Such events are obviously required for initiation but may also be involved in the promotion or progression of tumor development [2]. These genome-level events include the activation of cellular proto-oncogenes or inactivation of tumor suppressor genes, which act in a "cancer-cell intrinsic" manner bestowing these cells with certain properties. However, while these cell autonomous properties are necessary for tumorigenesis, they are not sufficient. Research over the last two decades has solidified the concept that tumor development and malignancy is the result of processes involving both the cancer cells themselves and non-cancer cells, many of which compose the heterocellular tumor. A clear example of this is illustrated by the requirement of neo-angiogenesis for tumor growth and thus the contribution of the vascular endothelial cells [3].

Cancer and inflammation

An association between the development of cancer and inflammation has longbeen appreciated [4,5]. The inflammatory response orchestrates host defenses to microbial infection and mediates tissue repair and regeneration, which may occur due to infectious or non-infectious tissue damage. Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer, i.e. long-term inflammation leads to the development of dysplasia. Epidemiologic studies estimate that nearly 15 percent of the worldwide cancer incidence is associated with microbial infection [6]. Chronic infection in immunocompetent hosts such as human papilloma virus or hepatitis B and C virus infection leads to cervical and hepatocellular carcinoma, respectively. In other cases, microbes may cause cancer due to opportunistic infection such as in Kaposi's sarcoma (a result of human herpes virus (HHV)-8 infection) or inappropriate immune responses to microbes in certain individuals, which may occur in gastric cancer secondary to *Helicobacter pylori* colonization or colon cancer because of long-standing inflammatory bowel disease precipitated by the intestinal microflora [4,5]. In many other cases, conditions associated with chronic irritation and subsequent inflammation predispose to cancer, such as the long-term exposure to cigarette smoke, asbestos, and silica [4,5].

Observing signs of inflammation, such as leukocyte infiltration, at tumors infected with microbes or sites of chronic irritation is expected. However, as first observed by Virchow in the middle of the 19th century, many tumors for which infection or irritation are not necessarily a predisposing factor, such as mammory adenocarcinoma, show a "lymphoreticular infiltrate." Many tumors of this type contain activated fibroblasts and macrophages, in addition to a gene expression profile with an inflammatory signature. Quantitative aspects of wound repair or inflammatory gene expression often correlate negatively with cancer stage and prognosis [7-9]. Further evidence for the role of inflammation has come from the use of nonsteroidal anti-inflammatory drugs (NSAIDs)† in the prevention of spontaneous tumor formation in people with familial adenomatous polyposis (FAP) [10]. Thus, cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles, and the efficacy of anti-inflammatory drugs in prophylaxis. These observations have provided impetus for investigation and hypothesis on the mechanisms and semantics of the relationship between cancer and inflammation.

There is evidence to suggest the inflammatory and immune systems may inhibit the development of cancer. This may occur by two cancer-associated recognition events. In tumor immunosurveillance, the host may have a dedicated mechanism to perceive and eliminate transformed cells. Adaptive immune recognition of tumor-associated and specific antigens also may be an important means by which the immune system controls the development of cancer [11]. Such topics will not be covered here. However, it seems the net effect of the inflammatory system is to positively affect tumor development. The relationship between cancer and inflammation is not simple and cannot be reduced to one grand theory. Previous reviews have focused on various aspects of the relationship

between cancer and inflammation, such as the role of various inflammatory cells [4,12,13], mediators [4,14-16], or signaling pathways [17] in cancer. The focus of this essay will be to discuss the relationship between cancer and inflammation along the organizing principle that the inflammatory response maintains physiological processes such as tissue homeostasis and repair after injury and that in this role, inflammation may be an ancillary, or perhaps inseparable, aspect of tumor development.

INFLAMMATION CAN CAUSE CANCER

As stated, long-standing inflammation secondary to chronic infection or irritation predisposes to cancer. How might such conditions lead to the emergence of initiated cells? In the case of some types of viral infection, it is clear that virally encoded genes can contribute to cellular transformation. An example of this are the transformative abilities of high risk HPV mediated by the oncoproteins E6 and E7 [18]. However, many microbes associated with cancer cannot transform cells. For example, while certain strains of *H. pylori* contain factors that affect host cell signaling, they are not classical oncogenes [19].

The chronic inflammatory states associated with infection and irritation may lead to environments that foster genomic lesions and tumor initiation. One effector mechanism by which the host fights microbial infection is the production of free radicals such as reactive oxygen intermediated (ROI), hydroxyl radical (OH•) and superoxide (O_2-•) and reactive nitrogen intermediates (RNI), nitric oxide (NO•) and peroxynitrite (ONOO-). Primarily thought to be anti-microbial, these molecules form due to the activities of host enzymes such as myeloperoxidase, NADPH oxidase, and nitric oxide, which are regulated by inflammatory signaling pathways. Importantly, ROI and RNI lead to oxidative damage and nitration of DNA bases which increases the risk of DNA mutations [20].

Cells have intrinsic mechanisms by which to prevent unregulated proliferation or the accumulation of DNA mutations. These include tumor suppressor pathways that mediate DNA repair, cell cycle arrest, apoptosis and senescence. In the face of DNA damage or oncogenic activation, cells will either repair their DNA and prevent mutations or initiated cells will undergo cell death.

In the face of massive cell death as occurs in infection or non-infectious tissue injury, lost cells must be repopulated by the expansion of other cells, often undifferentiated precursor cells such as tissue stem cells. There are two requisites for this: Some cells must survive the injury, and cells must expand to maintain cell numbers for a proper functioning tissue. Many inflammatory pathways function to mediate these two prerequisites of tissue repair [21,22]. In an extension of its physiologic role in mediating tissue repair or as a strategy in host defense to infection, the inflammatory response may play a role in providing survival and proliferative signals to initiated cells, thereby leading to tumor promotion.

Direct evidence for a link between tumorigenesis and either host defense and tissue repair has come from a number of observations. Many molecules and pathways double-up, playing roles in homeostasis, tissue repair, and tumorigenesis. The Wnt/β-catenin pathway plays a critical role in both the maintenance of the steady-state proliferative compartment and tumorigenesis of tissues [23]. Molecules such as COX-1 and -2, involved in the synthesis of prostaglandins that mediate the tissue repair process in the alimentary tract [24-26], play critical roles in tumor development at these sites [27,28]. For the most part, these observations are only associations, based on an entity's (enzyme or transcription factor) involvement in tissue repair and tumorigenesis. However, key supportive evidence to connect these processes has come from studies showing that dedicated tissue injury and wounding supports tumor growth and neoplastic progression. Injection of Rous sarcoma virus (RSV) into chickens leads to the growth of a sarcoma at the site of injection. Work over the years by the Bissell labora-

tory has shown that sarcomas may form at other sites of the chicken if that site is wounded [29]. The promotion of these wound-related tumors can be inhibited by glucocorticoids and may be mediated by the actions of transforming growth factor-β (TGF-β) and fibroblast growth factors (FGFs) [30-32]. In a B16 melanoma adoptive transfer study, tumor growth is enhanced in wounded limbs by the induction of paracrine factors such as TGF-β and bFGF in wound fluid [33].

Recent studies investigating the role of NF-κB (a family of transcription factors central to the induction of inflammation) in tumorigenesis has provided some more detailed insights into the role of inflammation in tumor promotion. Greten et al. used a model of colitis associated cancer (CAC) induced by the intraperitoneal injection of the carcinogen azoxymethane (AOM), followed by multiple rounds of inflammation and leukocyte infiltration caused by administration of the colonic epithelial cell toxin, dextran sulfate sodium (DSS) [34]. In this system, it is clear that chronic inflammation augments tumorigenesis, as when one dose of AOM is given without DSS cycling, no tumors arise. How then does the inflammatory response affect tumorigenesis in this model? Inactivation of the classical NF-κB pathway in colonic epithelial cells by conditional deletion of the IκB kinase β (IKKβ) protein resulted in a substantial decrease in the frequency of visible tumors [34]. Importantly, NF-κB signaling in epithelial cells was required for inhibition of apoptosis shortly after administration of one round of AOM and DSS, perhaps by the induction of anti-apoptotic factors such as Bcl-X_L. Thus upon intestinal epithelial injury and the addition of a mutagen, NF-κB provides a survival signal to initiated cells. Importantly, IKKβ in the colonic epithelium is responsible for mediating epithelial cell survival in protection from both infectious and non-infectious injury [22,35,36] and host defense pathways in intestinal epithelium [37]. A similar role for NF-κB in survival of initiated cells was demonstrated in a chronic inflammation model of hepatocellular carcinoma, which develops spontaneously in Mdr2-deficient mice [38]. In this model, when NF-κB activation was inhibited by use of a super-repressor of degradation of IκB selectively expressed in hepatic epithelial cells, there was an increased number of apoptotic hepatocytes, a finding which correlated with a decreased frequency of tumors compared to Mdr2-/- mice with degradable IκB [38].

Tumor promotion requires not only the survival of initiated cells, but also their expansion. Many inflammatory mediators such as cytokines, chemokines, and eicanosoids are capable of stimulating the proliferation of both untransformed and tumor cell proliferation [4]. Mice deficient in TNF have fewer skin tumors upon administration of the phorbol ester TPA and the mutagen DMBA [39]. Investigation into how TNF regulates tumor progression in this model suggested that this inflammatory mediator acts as a tumor promotor, since soon after application of TPA/DMBA, the characteristic hyperproliferation of keratinocytes was shown to be dependent on TNF [39]. What induces this production of inflammatory mediators, such as TNF, which leads to expansion of tumor initiated cells? NF-κB activation in myeloid cells recently was shown to play a critical role in the production of inflammatory mediator in both the AOM/DSS model of CAC [34] and mutagen-induced hepatocellular carcinoma upon administration of diethylnitroseamine (DEN) [40]. In both of these models, when myeloid cells were defective in activating NF-κB via the classical pathway, there was impaired production of inflammatory mediators, proliferation of dysplastic epithelium, and a decrease in both the frequency and size of tumors compared to WT mice [40]. Many of these factors, such as IL-6, are required for hepatic regeneration after injury [41]. An important finding of the DEN study was that when NF-κB was impaired in hepatocytes, there was increased epithelial cell death, yet a increased tumor burden [40]. This finding suggests that myeloid cells may lead to proliferation of initiated cells by detecting epithelial cell death [42]. Thus, in the

presence of initiation and both tissue injury and massive cellular death, activation of an inflammation dependent tissue repair/compensatory proliferative response leads to tumor promotion.

CANCER CAN CAUSE INFLAMMATION

Pre-malignant tumors are "wound-like" [43]. Such tumors are similar to healing or desmoplastic tissue in many ways, such as the presence of activated platelets [44,45]. As described by Coussens and Hanahan, tumor growth may be "biphasic" [43]. In the first phase, the body treats early tumors as wounds. This phase is characterized by tumor growth mediated by the actions of the stroma "indirect control" as occurs in physiologic tissue repair. For example, in murine models of skin and pancreatic carcinogenesis, bone-marrow derived cells, including mast cells, are responsible for providing matrix metalloproteases which convert VEGF into a biological active form to stimulate the pro-tumorigenic angiogenic switch [43,46,47]. However, during later tumor growth, it appears pro-inflammatory factors, such as MMPs, come under direct control by the tumors themselves [43]. A similar transition in the regulation of inflammation by early vs. late tumors may be at hand in spontaneous intestinal tumorigenesis in both mice and humans. COX-2 is expressed by stromal cells in early tumors [48,49], perhaps as part of a response to early tumor associated wounding; in larger tumors, COX-2 is expressed by the dysplastic epithelium itself [50]. One intriguing hypothesis as to why this phenomenon occurs is that there are intact regulatory mechanisms present in tumor associated stromal cells, limiting their expression of tissue repair factors. This may lead to the selective emergence of tumor cells that autonomously can maintain these ancillary processes and are not dependent on the "wound-like stroma." Eventually, however, the tumor associated stroma may undergo selective pressure, as there have been recent reports of genetic changes in tumor associated stroma [51] and even loss of p53 in tumor-associated fibroblasts [52].

In addition to playing a critical role in tumor growth, such as by mediating angiogenesis, the inflammatory response may have a role in other aspects of progression, such as tissue invasion and metastasis. Angiogenesis itself augments vascular invasion of migrating cells. Matrix metalloproteases and their inhibitors (TIMPs) are critical for angiogenesis and also in remodeling of extracellular matrix [14]. Infiltrating leukocytes may further aid tumor progression by blazing a trail through the ECM, the countercurrent invasion theory [53].

PROSPECTUS

As delineated above, the cell death and tissue injury that may occur right after initiation may induce tissue repair and homeostatic responses leading to tumor progression. In addition, signals derived from microbes also might activate innate microbial recognition pathways enhancing the development of tumors. In this manner, the inflammatory response plays a causative role in early tumor development via regulation of initiation and promotion.

Mutagens lead to DNA damage, and DNA damage may activate NF-κB via cell death or by DNA damage itself [54]. While such cell death is likely to be below the threshold required for compensatory proliferation and tumor promotion, repeated exposure to mutagens may cause enough cell death to warrant the survival of some initiated cells and their expansion. Repeated exposure of mice to mutagens alone (such as AOM) can induce tumorigenesis. Given that the life history of mammals is rife with both temporary (infection or burns) and constant environmental insults (ingested or airborne irritants), exposure to mutagens is likely to be coupled with some form of low level irritation or injurous agent. Thus, mutagens and irritants/infection may be at work in carcinogenesis in more cases and ways than previously estimated.

As cancers grow, tissues change in many ways. Much of these changes may resemble tissue injury and induce homeostatic mechanisms to maintain tissue function. For

example, the ischemia at the core of a solid tumor may initiate a physiologic response to hypoxia, such as activation of the HIF1 pathway and subsequent angiogenesis. Growing tumors also might degrade epithelial barriers, the cellular architecture of tissues, or disrupt the extracellular matrix. All of these processes are likely to stimulate homeostatic processes of tissue repair, including the recruitment of inflammatory leukocytes. These responses lead to tumor growth itself, thus promoting a positive feedback loop [44].

The next step in understanding the relationship between homeostatic processes, such as compensatory proliferation, tissue repair, and host defense, and tumorigenesis will be to determine whether pattern recognition of disturbances in homeostasis are involved in tumorigenesis. Are these pathways involved in intitiating tumor associated inflammation? Recognition of microbes or endogenous ligands by toll-like receptors is critical for tissue repair and regeneration at various organs [55-59]. Besides the TLRs, there are many microbial pattern recognition receptors for detection of virus and bacteria [60]. In addition, it has been purported that certain receptors may be involved in sensation of tissue injury and cell death, such as those that recognize extracellular matrix fragments (such as hyaluronan or fibronectin) or necrotic debris (including S100 and heat shock proteins and HMGB1). Any role for these recognition pathways in tumorigenesis is ripe for investigation.

An open question is what role innate pattern recognition pathways have in carcinogenesis secondary to microbial colonization, such as in *H. pylori*-induced gastric carcinoma. It will be important to determine the relative contributions of *microbe*-derived factors critical for microbial colonization and survival in the host (such as "virulence" or "adaptation" factors) and *host*-determined responses (such as inflammation) in tumor development as well as to determine synergy between these factors. Such investigations may identify important information regarding why certain forms of chronic inflammation do or do not predispose to tumor development.

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