Cell Host & Microbe
Review

Host Immune Response to Infection and Cancer: Unexpected Commonalities

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Both microbes and tumors activate innate resistance, tissue repair, and adaptive immunity. Unlike acute infection, tumor growth is initially unapparent; however, inflammation and immunity affect all phases of tumor growth from initiation to progression and dissemination. Here, we discuss the shared features involved in the immune response to infection and cancer including modulation by commensal microbiota, reactive hematopoiesis, chronic immune responses and regulatory mechanisms to prevent collateral tissue damage. This comparative analysis of immunity to infection and cancer furthers our understanding of the basic mechanisms underlying innate resistance and adaptive immunity and their translational application to the design of new therapeutic approaches.

Introduction

Organisms resist infections by establishing barriers and activating different classes of innate resistance and adaptive immunity. The tissue in which the infection occurs regulates the strength, quality, and type of the immune response for efficient pathogen eradication and tissue repair while limiting collateral tissue damage (Matzinger and Kamala, 2011). However, some microbes have evolved evasion mechanisms that thwart these host responses, resulting in uncontrolled or chronic infection associated with pathologic damage.

Unlike the traditional view of immunity as a response to foreign microbes and molecules, the primary trigger for innate resistance, which is followed by adaptive immunity in higher organisms, may be the sensing of altered self, such as changes in tissue homeostasis or integrity (Matzinger, 2002; Medzhitov, 2008). Innate receptors respond to microbe-associated molecular patterns (MAMPs) and also endogenous mediators of inflammation released by damaged tissues (damage-associated molecular patterns [DAMPs]). These tissue-intrinsic inflammatory responses are amplified by the recruitment of hematopoietic cells that express innate receptors for exogenous and endogenous ligands present in the inflamed tissue and set the stage, via antigen presentation and activation of T and B cells, for adaptive immunity.

Tumors may originate at sites of chronic inflammation that are either caused by infectious pathogens or often aseptic. Nevertheless, tumors eventually establish an almost symbiotic relationship with their host that mimics chronic infections or cohabitation with commensal microorganisms and maintain their presence by suppressing excessive inflammation and antitumor immune responses. The molecular alterations in the transformed cells or the surrounding epithelial and stromal cells are associated with a proinflammatory wound-healing microenvironment that, in addition to providing tumor growth and angiogenic factors, affects tissue remodeling and decreases the expression of molecules involved in cell-to-cell adhesion, initiating the epithelial-mesenchimal progression, which can lead to tumor cell invasion and progression (Edme et al., 2002; Salcedo et al., 2013). Nucleic acids and other products released upon cell stress or death in more advanced tumors or, following cytotoxic therapy, are recognized by innate sensors, resulting in the inflammation and activation of antigen-presenting cells (APCs) (Ma et al., 2013b). Thus, like infection, tumors influence and are affected by inflammation and immunity from their early initiation to progression, dissemination, and eventually death of the host. Cancer-associated inflammation not only affects local tumor growth and dissemination but is also responsible for severe cancer-associated comorbidities, such as anorexia, cachexia, and immunosuppression, making cancer a systemic, rather than localized, disease (Trinchieri, 2012). Malignant growth originates within differentiated tissues and maintains some of the functional, morphologic, and immune traits of the tissue of origin, representing a "caricature" of the original tissue (Pierce and Speers, 1988). The immune response elicited by the tumor will be, in most cases, unable to eradicate it and will establish a Darwinian environment that selects the genetically fittest cancer cells (tumor editing and escape) that evolve into aggressive malignant tumors or, in some cases, remain temporarily in equilibrium with nonmalignant host cells (Schreiber et al., 2011).

Given the parallels between immunity to infection and cancer, this review focuses on the similarities and differences in these processes and how these two fields can help each other in advancing our understanding of innate resistance and immunity.

Inflammation and Cancer

Inflammation and immunity are inherent characteristics of cancer, and avoiding immune destruction and tumor-promoting inflammation are now among the hallmarks of cancer (Hanahan and Weinberg, 2011). Up to a quarter of human cancers are related to infection or infection-associated chronic inflammation. *Helicobacter pylori*, human papillomaviruses (HPVs), Epstein-Barr virus (EBV), and hepatitis B and C viruses are the most common etiopathogenic factors (Parkin, 2006). Some oncogenic pathogens directly transform the tumor-forming cells (e.g., EBV or HPV), whereas others (e.g., *H. pylori*) establish an

inflammatory milieu favoring tumor generation. Other cancers initiate in tissues chronically inflamed for causes other than infection; e.g., tissue injury by physical or chemical insults or genetic diseases. Altered composition (dysbiosis) of the intestinal microbiota or its physical interaction with hematopoietic cells also regulate inflammation and has been shown to be a cause of cancer (Goldszmid and Trinchieri, 2012; Jobin, 2012; Rao et al., 2006). The class of inflammatory and immune response observed in tumors is determined by the characteristics of the originating tissue, the proinflammatory mediators released by the tumor cells or their stroma, and the nature of tissue damage, pathogens, or commensals associated with carcinogenesis. Although most proinflammatory cytokines may have pleiotropic pro- or antitumor effects, the classes of immune response with a predominant role in tissue repair and angiogenesis (e.g., the Th-2 response or the alternatively activated M2 macrophages) are most likely tumor promoting, whereas tissue and tumor damaging responses (e.g., Th1 or classically activated M1 macrophages) are generally associated with antitumor effects.

Chronic inflammation promotes cancer through multiple mechanisms. Genomic instability and DNA damage, mediated in part by reactive oxygen species (ROS), may cause genetic and epigenetic mutations that initiate cell transformation and cancer (Schetter et al., 2010). Inflammation also promotes tumor progression by inducing tissue remodeling, supporting angiogenesis, and providing growth factors (Schetter et al., 2010). In all tumors, regardless of their etiopathogenesis, cancer-associated inflammation is present and maintains a tumor-promoting milieu as well as an immunosuppressive environment, allowing the tumor to escape immunity (Grivennikov et al., 2010).

Hematopoietic Response in Infection and Cancer

Hematopoietic stem cell (HSC) proliferation, the formation of monocytes and granulocytes, extramedullary hematopoiesis, and reactive increase of circulating neutrophils and inflammatory monocytes are well-known responses to acute and chronic infections. The regulation of bone marrow (BM) HSCs is an integral part of the first response to inflammation or stress. HSCs express innate receptors as well as chemokine and cytokine receptors, and their mobilization, proliferation, and renewal is regulated by cytokines released during infection (King and Goodell, 2011). Leukocytosis, or an increase in white blood cells, has also been frequently associated with cancer and attributed to tumor cell production of colony-stimulating factors, which induce HSC activation and differentiation (Ascensao et al., 1987). Additionally, the contribution of myeloid cells to tumor pathogenesis by promoting angiogenesis, tissue invasion, and metastasis formation has been recently established (Shojaei et al., 2007; Yan et al., 2010). Also, both the tumor microenvironment and inflammation associated with infections endow some mobilized myeloid cells with immunosuppressive activity (Gabrilovich et al., 2012).

HSCs are present in BM-specialized endosteal arteriolar niches as quiescent or self-renewing cells (Kunisaki et al., 2013). The large majority of HSCs are dormant and divide a couple of times per year, whereas 5%–10% of HSCs are active, divide once a month, and participate in their self-renewal while generating a continuous output of all the hematopoietic lineages in order to maintain homeostasis (Pietras et al., 2011). In response to injury observed in both infections and cancer, quiescent HSCs are detached from their endosteal niche and induced into cell cycle and differentiation in vascular niches (Figure 1).

The factors regulating reactive hematopoiesis include early-acting cytokines such as interleukin 3 (IL-3), IL-6, and Fms-like tyrosine kinase 3 ligand as well as myeloid differentiating factors such as granulocyte colony-stimulating factor (G-CSF), macrophage (M) CSF, and granulocyte (G)-M CSF (King and Goodell, 2011). Acute exposure to either type I interferons (IFNs) or IFN-γ triggers activation and cycling of HSCs and, together with tumor necrosis factor (TNF), induces and skews the differentiation of monocytic lineages (Baldridge et al., 2011; de Bruin et al., 2012; Essers et al., 2009). However, chronic exposure to these factors induces a loss of HSC repopulation ability, possibly contributing to the hematopoietic defects observed in chronic infections or cancer (Baldridge et al., 2011). Other factors include neutrophil proteases that mobilize the HSCs from the endosteal niches and ATP, which acts on purinergic receptors on HSCs to induce cell cycling (Rossi et al., 2012). Ligands for the innate immune Toll-like receptors (TLRs), such as endotoxin, DNA, and endogenous ligands, directly activate HSCs or act indirectly on mesenchimal and inflammatory cells (Boettcher et al., 2012; Boiko and Borghesi, 2012).

Tumor cells can affect hematopoiesis by producing some of these factors, such as IL-6, G-CSF, or GM-CSF, or activating stromal cells to produce these cytokines. GM-CSF produced by pancreatic cancer cells regulates myeloid inflammation and is controlled by signaling through oncogenic Kras (Bayne et al., 2012). Similarly, GM-CSF is induced by oncogenic Hras in skin carcinogenesis in an IL-1-dependent manner (Salcedo et al., 2013). Low levels of type I IFN present in tumors are important for antitumor immunity and also centrally affect hematopoiesis (Fuertes et al., 2013). Additionally, damaged tumor cells release DAMPs involved in HSC mobilization. For example, mitochondrial damage releases DNA and formylpeptides, ligands for TLR9, and the chemoattractant formyl peptide receptors, respectively, and ATP is released by tumor cells damaged by anthracyclines, a class of anticancer chemotherapeutics (Ma et al., 2013a; Zhang et al., 2010).

The small number of HSCs normally present in circulation is dramatically increased in response to inflammation, and their homing to peripheral organs such as the liver, lung, and, in experimental animals, spleen establishes foci of extra medullary hematopoiesis. BM emargination of neutrophils depends on the expression of ligands for the chemokine receptor CXCR2 (Köhler et al., 2011), whereas signaling through TLRs induces the secretion of the chemokine ligand CCL2, which stimulates the egression of monocytes expressing the cognate chemokine receptor CCR2 into the peripheral blood (Serbina and Pamer, 2006). Then, $CCR2^+$ inflammatory monocytes migrate in a mostly CCR2-independent way to inflamed tissues or tumors, where they can differentiate into distinct subsets of activated myeloid cells sharing characteristics with macrophages and dendritic cells (DCs) (Serbina and Pamer, 2006).

Myeloid Cells in Infection and Cancer

Myeloid-derived cells in cancer, infection, or other stress conditions have been identified with different names, including reactive neutrophils, inflammatory monocytes, macrophages,