

Innate Immune Cells in Inflammation and Cancer

Roni Nowarski¹, Nicola Gagliani¹, Samuel Huber², and Richard A. Flavell^{1,3}

Abstract

The innate immune system has evolved in multicellular organisms to detect and respond to situations that compromise tissue homeostasis. It comprises a set of tissue-resident and circulating leukocytes primarily designed to sense pathogens and tissue damage through hardwired receptors and eliminate noxious sources by mediating inflammatory processes. While indispensable to immunity, the inflammatory mediators produced *in situ* by activated innate cells during injury or infection are also associated with increased cancer risk and tumorigenesis. Here, we outline basic principles of innate immune cell functions in inflammation and discuss how these functions converge upon cancer development. *Cancer Immunol Res*; 1(2); 77–84. ©2013 AACR.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflict of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should understand the functions of the innate immune system, the basic principles of inflammation as host defense against perturbed tissue homeostasis, and how persistent inflammasome signaling may promote tumorigenesis.

Introduction

In the context of defense against infectious pathogens, innate immunity entails preexisting defense mechanisms that have specialized to specifically recognize microbes and eliminate infection (1). Innate immunity is coordinated by epithelial barriers that block entry of microbes, protective plasma proteins, and tissue-resident or circulating leukocytes that are mostly phagocytic macrophages and neutrophils, dendritic cells (DC), natural killer (NK) cells, and innate lymphoid cells (ILC). The main purpose of the innate immune system is to mediate inflammation, the process in which blood cells and plasma components are delivered to sites of perturbed tissue homeostasis, as in the case of infection or injury (2, 3). Inflammation is triggered mainly by the recognition of microbes or other "danger" signals by receptors expressed by innate immune cells (4, 5). During the onset of an acute inflammatory response, tissue-resident macrophages, DCs,

and mast cells produce a variety of chemotactic molecules, cytokines, and inflammatory mediators that recruit neutrophils and monocytes to the affected tissue. Through the release of antimicrobial substances, extensive phagocytosis, extracellular matrix remodeling, and possibly activation of adaptive immune responses, innate immune cells act to eliminate the noxious source and regain tissue homeostasis.

The first wave of blood cell production in mammals occurs in extraembryonic yolk sac blood islands from where primitive hematopoietic and endothelial progenitors emerge (6). Definitive hematopoietic stem cells (HSC) originate subsequently in the midgestation embryo from hemogenic endothelium cells in the aortic-gonad mesonephros region (7). Following extramedullary hematopoiesis in the fetal liver, HSCs home to the bone marrow where their self-renewal and multilineage hematopoietic differentiation are supported throughout adulthood. The development of immune cells follows a hierarchy of differentiation of common lineage-committed progenitor cells in the bone marrow (8). In contrast with adaptive immune cells, innate immune cells are mostly postmitotic and need to be replenished from the pool of bone marrow stem and progenitor cells (9). Increases in peripheral demand for innate immune effector cells are therefore controlled mostly at the level of proliferation of the hematopoietic stem and progeny cells and mobilization via the blood stream to the affected sites. Nevertheless, *in situ* expansion of resident innate immune cells may be fundamental in certain inflammatory processes (10). Furthermore, mature innate immune cells show remarkable plasticity towards diverse cellular functions and fates in response to environmental signals (11). While this is an

Authors' Affiliations: ¹Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut; ²I. Medizinische Klinik und Poliklinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; and ³Howard Hughes Medical Institute, Chevy Chase, Maryland

Note: R. Nowarski, N. Gagliani, and S. Huber contributed equally to this work.

Corresponding Author: Richard A. Flavell, Department of Immunobiology, Yale University School of Medicine, 300 Cedar Street, TAC S-569, New Haven, CT 06520. Phone: 203-737-2216; Fax: 203-737-2958; E-mail: richard.flavell@yale.edu

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important attribute in the regulation of immune response to infection or injury, it may also be instrumental in the process of tumorigenesis, as discussed below.

Cells of the innate immune system

Macrophages, monocytes, and neutrophils. Macrophages are tissue-resident phagocytes initially described as end products of circulating monocytes that originate in the bone marrow. Along with this classical scheme of the mononuclear phagocytic system, it is also becoming apparent that the adult tissue macrophage population consists of distinct and diverse cell types with different developmental origins (12–14). Macrophages constitute 10% to 15% of most tissues and are required for homeostatic clearance of apoptotic cells, control of epithelial cell turnover, and assisting the adaptation of tissues to stress conditions (2, 15). The ability to phagocytose microorganisms and cell debris is shared by neutrophils, which are polymorphonuclear granulocytes that produce highly potent, albeit less specific and potentially cytotoxic, antimicrobial substances and abundant inflammatory mediators (16, 17). Neutrophils are short-lived leukocytes generated in great number in the bone marrow during steady state; they circulate in the blood stream for no more than a few hours and they are tightly regulated in tissues to avoid collateral damage. It is the interactive combined functions of these cells that allow not only for direct killing of pathogens, but also for the regulation and resolution of the inflammatory process (18).

The inflammatory response to infection follows 4 general consecutive phases: pathogen recognition, recruitment of immune cells to the site of infection, pathogen elimination, and resolution of inflammation (1). This sequence of events is initiated by resident macrophages or DCs as they sense pathogens or tissue damage (Fig. 1). In addition, a subset of "resident" (or nonclassical) monocytes has been shown to mediate early immune responses; they patrol the luminal endothelial surface in healthy tissues and can rapidly invade damaged or infected sites, where they differentiate into macrophages (19). Damage- or pathogen-associated molecular patterns (DAMP/PAMP) released by necrotic cell death are recognized by pattern recognition receptors (PRR) expressed by innate immune cells, leading to their activation and secretion of proinflammatory mediators (see below). The initial role of innate immune cell activation is to condition the vasculature of affected tissues for leukocyte infiltration, a process mediated by factors that induce vasodilation (histamine, prostaglandins, nitric oxide) and vascular permeability (histamine, leukotrienes), and the expression of leukocyte adhesion molecules on endothelial cells [TNF- α , interleukin (IL)-1; ref. 20]. The sensing of tissue damage signals such as reactive oxygen species or necrosis-associated proteins and other DAMPs induces the production of neutrophil-attracting chemokines and matrix metalloproteinases (MMP) by activated macrophages and monocytes that act mainly through the neutrophil chemokine receptor CXCR2 (18). Activated neutrophils extravasating across postcapillary venules and entering the interstitial space, release secretory vesicles containing proteins (e.g., azurocidin, CAP18) that activate endothelial cells, and increase vessel permeability

(16). Discharge of the neutrophil granular cargo of antimicrobial proteins and proteases further increases the recruitment of inflammatory monocytes by various mechanisms (21). Monocytes at the affected site act in concert with the recruited neutrophils and macrophages to eliminate the damage-inflicting source. Finally, a switch in lipid signaling from proinflammatory prostaglandins and leukotrienes to anti-inflammatory prostaglandins and lipoxins blocks further recruitment of neutrophils and induces their apoptosis and clearance by macrophages, thus enabling the resolution of inflammation and the reestablishment of tissue homeostasis (22, 23).

Dendritic cells. Appropriate immune responses result from a tightly coordinated interaction between the innate and the adaptive immune system. Cells of the innate immune system translate danger signals captured from the environment to the adaptive immune system, which, through antigen-specific immune responses, controls the invasion of pathogens. Several types of innate immune cells have the ability to process and present antigens, and among them, DCs, known as professional antigen-presenting cell (APC), have also the unique characteristic to prime naïve T cells and therefore efficiently initiate the adaptive immune response (24, 25). APCs originate in the bone marrow and migrate to and seed all tissues. The primary role of DCs is to capture self- and non-self-antigens, process, and present them in the form of peptide-MHC to cells of the adaptive immune system (CD4⁺ and CD8⁺ T cells; ref. 26). DCs actively ingest antigens by phagocytosis, using complement, Fc, and c-type lectin receptors. The ingestion of antigens in conjunction with the engagement of PRRs induces DC maturation, expression of chemokine receptors, and migration to lymphoid organs. At this stage, DCs have acquired the license to prime T cells and in turn initiate the adaptive immune response (25). Depending on the type of pathogens encountered, DCs present antigens through two types of MHC, namely class I or class II (27–29). CD4⁺ T cells are primed through MHC class II, whereas CD8⁺ T cells are primed through MHC class I (27). For example, antigens derived from viruses are presented in complex with MHC class I to CD8⁺ T cells. In general extracellular antigens are presented through MHC class II, although they can also be presented through MHC class I to CD8⁺ T cells in a process known as cross-presentation (29–31).

Innate lymphoid cells. ILCs are characterized by the absence of recombination activating genes (RAG-1 or RAG-2)-dependent rearranged antigen receptors and lack of phenotypic markers of myeloid and DCs. ILCs are divided into three major groups based on phenotypic and functional characteristics. ILC1 produce the signature cytokine and master transcriptional regulator of T helper 1 (T_H1) cells, namely IFN- γ and Tbet, but not the signature cytokines of T helper 2 (T_H2) and T helper 17 (T_H17) cells. NK cells are the prototypical members of this group. ILC2 produce IL-5, IL-13, and express Gata3, the signature cytokines and master transcriptional regulator of T_H2 cells. ILC3 express IL-17a, IL-22, and ROR γ t, the signature cytokines and master transcriptional regulator of T_H17 cells (32). In general, ILCs are a source for cytokines very early after infection and tissue damage and therefore have a critical role in cytokine-mediated activation of the immune

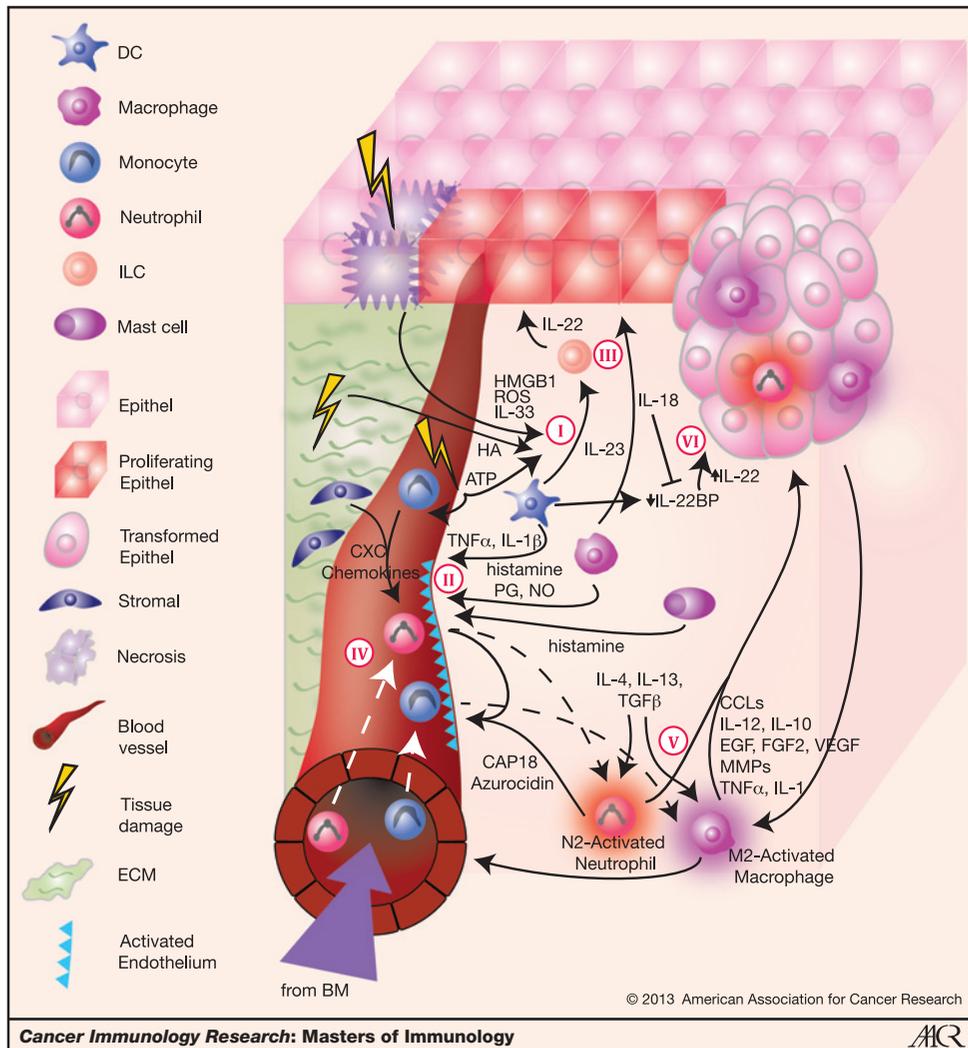


Figure 1. Innate immune response to tissue damage. I, DAMPs released from necrotic cells and damaged tissue activate PRRs in resident DCs, macrophages and mast cells, and in patrolling blood monocytes, leading to the secretion of inflammatory mediators and vasodilators [TNF- α , IL-1 β , prostaglandin (PG), histamine, and nitric oxide (NO)]. II, activation of endothelial cells and the production of CXC chemokines by innate and stromal cells recruit neutrophils. III, in parallel, inflammasome activation leads to the regulated secretion of IL-18 that induces IL-23 production in DCs and in turn IL-22 in ILC, thereby promoting regeneration of the epithelium. IV, recruited neutrophils migrating to the affected tissue mediate recruitment of inflammatory monocytes, which differentiate into tissue macrophages and promote further monocyte recruitment. V, type II polarization by TGF- β and IL-4 supports production of protumorigenic mediators such as EGF, FGF-2, and VEGF. VI, persistent inflammasome signaling may promote tumorigenesis by loss of epithelial barrier integrity and in part by sustained/unopposed IL-22 production. BM, bone marrow; ECM, extracellular matrix; HA, hyaluronic acid; ROS, reactive oxygen species; MMP, matrix metalloproteinase.

system and promotion of epithelial cell barrier integrity (33). In addition, ILC3 express MHC class II as well as process and present antigens to CD4⁺ T cells, thereby limiting commensal-specific CD4 T-cell responses in the intestine (34).

In contrast with the protective properties observed during infection and tissue damage, ILCs, in particular ILC3, have been linked to inflammatory bowel disease (IBD; refs. 35, 36). Results from human genetic studies have correlated the mutations in IL-23R with IBD (37); as the production of IL-22 by ILC3 can be induced efficiently by IL-23, a pathogenic role of IL-22/ILC3 has been suggested (38). However, IL-22 is not the only downstream target of IL-23 and results from murine studies indicated both context-dependent beneficial and path-

ogenic effects of IL-22 during colitis (39–41). Therefore, the functions of ILC3 and IL-22 in patients with IBD need to be clarified in future studies. Likewise, ILC3 have been implicated in colorectal cancer (42), as discussed below.

Pattern recognition receptors

Toll-like receptor signaling. TLRs are a family of trans-membrane receptors that recognize conserved molecular patterns of microbial origin; they play a crucial role upon tissue damage by regulating tissue repair and inflammation. Ligands of TLRs can be either exogenous [microbial, such as pathogen-associated molecular patterns (PAMP)] or endogenous (such as HSPs and uric acid crystals). Different microbial ligands are

recognized by different TLRs; for example, lipopolysaccharide is recognized by TLR-4, and bacterial flagellin by TLR-5 (for review, see ref. 43). TLRs are localized in different subcellular compartments. TLRs that recognize lipid or protein ligands are expressed on the plasma membrane (TLR-1, -2, -4, -5, -6), whereas those that respond to viral nucleic acids are in the endolysosomal compartment (TLR-3, -7, -9). Upon binding of the ligand, one or more adapter proteins transmit the intracellular signal. The most important adapter proteins are MyD88 and TICAM1 (TRIF; ref. 43; Fig. 2).

TLRs play an important role during host defense against infections. They regulate antimicrobial responses by epithelial cells at mucosal sites (44), enhance phagocytosis of microorganisms (45), promote leukocyte recruitment (46), and control activation of the adaptive immune response (47). TLR signaling also promotes tissue repair and regeneration by providing prosurvival signals and inhibiting apoptosis of epithelial cells (48). Polymorphisms in TLRs have been associated with human breast, stomach, and colon cancers, indicating a potential role for TLRs during carcinogenesis (49–52). However, further studies have indicated both negative and positive regulatory properties of TLRs during tumorigenesis. Anticancer effects have been shown both in humans and mice after injection of purified TLR ligands (53–55). These results are due to increased apoptosis of tumor cells, recruitment of NK and cytotoxic T cells, and stimulation of the adaptive immune

response thereby breaking tolerance to tumor self-antigens (53, 54, 56). Furthermore, TLRs are important for the recognition of viral pathogens that can promote the development of cancer, such as Epstein–Barr virus, hepatitis B and C viruses, human papillomavirus, and *Helicobacter pylori* (57–61). TLR signaling has also been reported to promote the growth and survival of tumor cells (62–64). MyD88 signaling has been shown to play a role during the development of colitis and colitis-associated colon cancer in murine models (65, 66). These pleiotropic functions of TLR signaling during tissue repair and tumorigenesis might be dependent on the respective milieu, cell type, and specific TLRs. Further studies are required to dissect the complex effects of TLRs during tumorigenesis.

Inflammasomes. The inflammasome is a large complex of proteins, which has the capacity to sense various PAMP and DAMP (67, 68), and is expressed in DCs, macrophages, and epithelial cells. Upon activation, inflammasomes are able to initiate immune responses toward the invading pathogens or tissue damage. The sensory components of the inflammasome are NOD-like receptors (NLR), which constitute a large family of cytosolic PRRs composed of a C-terminal leucine-rich repeat domain (LRR), a central nucleotide-binding domain (NBD), and an N-terminal pyrin domain (PYD). It has been proposed that the LRR and NBD modules are involved in ligand sensing and autoregulation, respectively. PYD is usually involved in the

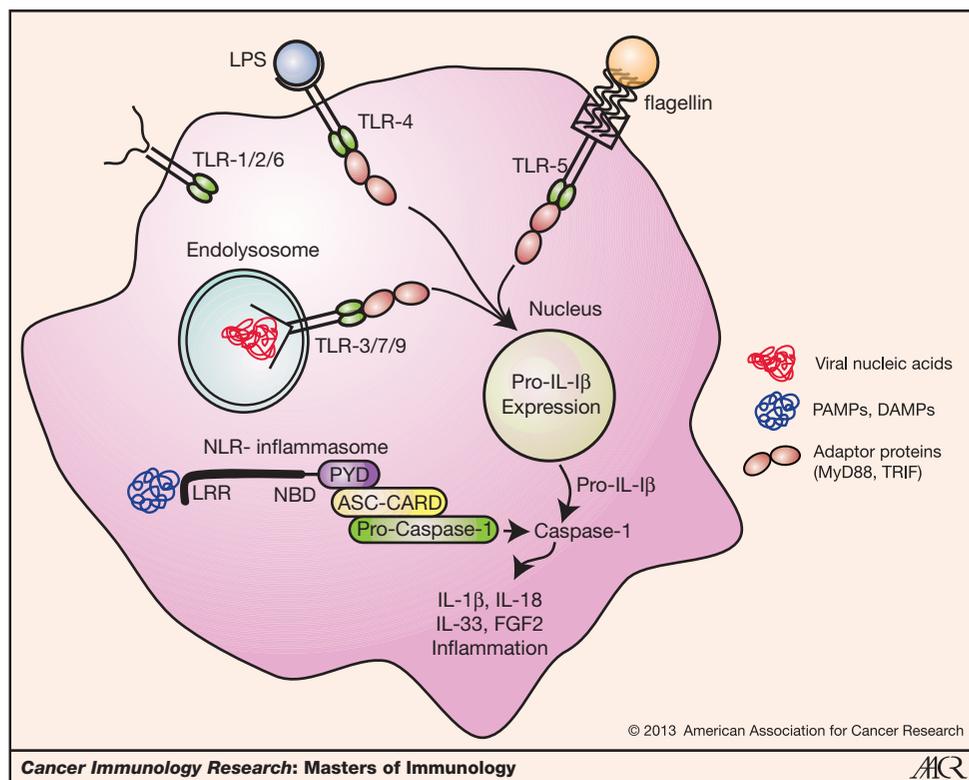


Figure 2. Innate immune response in inflammation. TLRs and NLRs are two forms of PRRs expressed by innate immune cells to sense and capture danger signals. Cell surface TLRs (TLR-1/2/4/5/6) sense exogenous pathogens and endolysosomal TLRs (TLR-3/7/9) recognize endogenous ligands. NLRs are cytosolic PRRs and the sensory components of the inflammasome. Both TLRs and NLRs are hardwired receptors that mediate inflammatory process to eliminate noxious sources that compromise tissue homeostasis.

recruitment of the adaptor protein ASC [apoptosis-associated speck-like protein containing a caspase-associated and recruitment domain (CARD)], which in turn is associated with pro-caspase-1. The ternary protein complex formed by NLRs, ASC (if required, as some NLRs contain CARD), and caspase-1 is referred to as an inflammasome.

Activation of the inflammasome complex leads to auto-cleavage and activation of pro-caspase-1, which in turn is responsible for the processing and secretion of the mature forms of proinflammatory cytokines IL-1 β and IL-18, and the secretion of IL-33 and FGF-2. The activity of these cytokines has been linked to several types of cancer (69). The activation of inflammasomes in certain cases can be followed by a lethal process called "pyroptosis". Contrary to classical apoptosis, pyroptosis promotes local inflammation associated with the release of IL-1 β and IL-18, and this mechanism of cell death is important to promote both the suicide of engulfed macrophages and cell-autonomous tumor suppression. Overall, inflammasomes sense the environment and modulate two key aspects of inflammation: proinflammatory cytokine activation and cell death, both of which are critical to tumor growth.

Paradigms for the role of innate immune cells in cancer

Innate cell polarization. Macrophages and neutrophils exist in a range of activation states that reflect their environment, and they can be polarized towards functional subclasses depending on the nature of the stress afflicting the tissue. One polarizing extreme is induced by IFN- γ -producing T_H1 cells and the engagement of TLRs by bacterial products, as in the case of bacterial or viral infection, generating conventionally activated macrophages (M1), neutrophils (N1), and myeloid progenitor cells. In contrast, responses to parasitic infections and wound healing involve the production of type II cytokines such as IL-4, IL-13, and TGF- β , which drive "alternative" (M2/N2) cell activation (15, 17, 70). These polarized activation states are contrasting driving forces in tumorigenesis, whereas M1/N1 cells are tumoricidal and destructive to the tissue (71, 72), M2/N2 cells account for the production of growth factors (e.g., EGF, FGF-2), angiogenic factors (e.g., VEGF, MMP-9), and inflammatory cytokines (e.g., TNF- α , IL-1), which collectively promote tumor initiation, progression, and metastasis (73–75). Extreme stress conditions such as hypoxia, necrosis, and injury are hallmarks of the tumor microenvironment and are exploited by the tumor to recruit and polarize inflammatory myeloid cells towards the tumor-promoting state (76–79).

Control of tissue regeneration and integrity. There is a network between different cells of the innate immune system that controls not only the adaptive immune response, but also the microflora, tissue regeneration, and carcinogenesis, particularly in the intestine. One example for such a complex regulatory mechanism is the control of IL-22 by DCs in the intestine. IL-22, a member of the IL-10 cytokine family can be produced by ILC3 and T_H17 cells. IL-22 has a protective function during the early phase of tissue damage (39, 80), whereby it promotes the activation of intestinal stem cells and in turn the wound healing of the intestine (81). However, a

high concentration of free IL-22 over a long period of time can be detrimental. IL-22 has been shown to promote colitis, which is associated with mucosal hyperplasia (41). Furthermore, results from several recent articles have shown that IL-22 can also promote tumorigenesis in the intestine (42, 82–85). Accordingly, IL-22 needs to be carefully controlled, and this regulation can be exerted by DCs in the intestine by at least two mechanisms. First, DCs have the capacity to promote the expression of IL-22 through the production of IL-23. DCs in the intestine participate in immune surveillance for possible pathogenic invasion. For example, microbial penetration and the presence of flagellin promote the activation of a particular subset of DCs, which are present in the lamina propria and which coexpress CD11b and CD103. Upon activation via TLR-5, these DCs produce a large amount of IL-23, which in turn boosts the production of IL-22 (38).

DCs can also control IL-22 via the production of a soluble IL-22 receptor [IL-22 binding protein (IL22BP, IL22Ra2)]. IL-22BP is produced by DCs in steady-state conditions (82, 86). Upon sensing tissue damage, the inflammasome shuts down the expression of IL-22BP via IL-18 activation, thereby allowing IL-22 to exert its protective effect. This is one example for a complex mechanism by which DCs regulate the availability and production of one cytokine to control homeostasis in the intestine. Perturbation of this coordinated crosstalk between microflora, DCs, and ILC3 at any stage may alter the balance in the intestine and result in increased tumorigenesis.

Immunosurveillance and immunoediting. The capacity of DCs to prime CD8⁺ T cells and trigger their cytotoxic activity against neoplastic cells is considered to be one of the key mechanisms by which the immune system can monitor and control the growth of tumor. In 1957, Sir Macfarlane Brunet and Lewis Thomas proposed for the first time the hypothesis of "cancer immunosurveillance" (87). The hypothesis, initially vague, has been validated by recent data, which clearly show that the immune system can interact with neoplastic cells and DCs are one of the pivotal components in this immunosurveillance. DCs can present tumor antigens to the adaptive immune system, which in turn is instructed to control the growth of transformed cells. Mice that lack RAG-1 or RAG-2 cannot produce lymphocytes and they have higher susceptibility to develop tumors (88). One of the most convincing lines of evidence supporting the hypothesis of tumor immunosurveillance is provided by humans afflicted by paraneoplastic syndromes, which are neurologic disorders that arise as a consequence of an antitumor immune response. The same antigens, which are normally expressed in neurons, can be expressed in breast cancer cells and some other carcinomas. Some patients with paraneoplastic syndromes develop a strong antigen-specific CD8⁺ T-cell-mediated response that efficiently controls tumor expansion, but that concomitantly results in autoimmune cerebellar degeneration (30). Immunosurveillance may be defined as the first stage of a continual "immunoediting" process in which tumor cells circumvent antitumor T-cell activity by the emergence of less immunogenic cells within the tumor (89, 90). Moreover, the tumor microenvironment can block tumor-specific T-cell responses

by converting myeloid cells into potent immunosuppressive cells (91, 92).

Concluding Remarks

Innate immunity is mediated by a network of tissue-resident, circulating, and recruited immune cells equipped with sensors for tissue damage and infection. Recent studies have highlighted the intricate interactions among the components involved in a successful inflammatory response. What enables the neutralization of a damage-inflicting source is the balance between activating and inhibitory signals that shape the nature and intensity of effector molecules production. Malfunction in components of this system can lead to a breakdown of tissue homeostasis. This is best exemplified by clinical studies and

animal models indicating that chronic inflammation may promote tumorigenesis. While much has been learned about acute inflammatory responses to injury and infection, our knowledge of chronic inflammatory processes is still at an early stage. Further studies are required to delineate these processes in greater detail to specifically manipulate innate immune cells for effective cancer therapy.

Authors' Contributions

Conception and design: N. Gagliani, R. Nowarski, S. Huber
Writing, review, and/or revision of the manuscript: N. Gagliani, R. Nowarski, S. Huber
Study supervision: R.A. Flavell

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