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REVIEW

Cooperativity of adaptive and innate immunity: implications for cancer therapy

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Abstract The dichotomy of immunology into innate and adaptive immunity has created conceptual barriers in appreciating the intrinsic two-way interaction between immune cells. An emerging body of evidence in various models of immune rejection, including cancer, indicates an indispensable regulation of innate effector functions by adaptive immune cells. This bidirectional cooperativity in innate and adaptive immune functions has broad implications for immune responses in general and for regulating the tumor-associated inflammation that overrides the protective antitumor immunity. Mechanistic understanding of this two-way immune cross-talk could provide insights into novel strategies for designing better immunotherapy approaches against cancer and other diseases that normally defy immune control.

Keywords Innate immunity · Adaptive T cells · Natural killer cells · Effector function · Immune regulation · Cancer immunotherapy

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Evolution of immune defense

Host immunity is well integrated with cancer development, progression, and rejection. Since the earliest reported observation of an enlarged supra-clavicular node due to leukoreticular infiltrates in gastrointestinal malignancy by Virchow in 1854, the immune system's protective surveillance and tumor-promoting nature have perplexed investigators. The innate and adaptive systems of immunity evolved to impart host fitness under a variety of selection pressures that included genomic and metabolic pressures as well as those from co-evolving parasitic and commensal microbes [1, 2]. Innate immunity came into existence with the appearance of the first single-celled microorganisms on earth over 3.5 billion years ago. The immunological function present among unicellular microorganisms such as amoebae was that of phagocytosis, which was primarily used to acquire nutrients, and played only a secondary role in microbial degradation. However, more sophisticated mechanisms of immunity were required following the great oxidation event about 600 million years ago, when the rise in atmospheric oxygen and development of aerobic metabolism fostered the evolution of multicellular organisms. Diversity in metazoans forced diversification of the innate recognition receptors. This included germline-encoded transmembrane pattern recognition receptors for pathogens or damaged self-components, such as the Toll-like receptors (TLR) and C-type lectin receptors (CLR), and the cytosolic nucleotide-binding domain and leucine-rich repeat-containing receptors (NLR) and retinoic acid-inducible gene I-like receptors (RLR) [3]. Invertebrates and early chordates relied on these receptors for the detection of infectious microbes. They used phagocytes as the primary immune effector cell and a variety of defense mechanisms including inducible antimicrobial peptides,

phenoloxidase cascade, nitric oxide synthase, clotting reactions, and serine protease inhibitors [4]. Long-lasting functional immune adaptation of the innate immunity, which provides protection against rechallenge by pathogens, has been known in insects [5–9]. Strain-specific immunity that passes from a mother to her offspring has been observed in various arthropods [10, 11]. Invertebrate allorecognition system has been observed in taxa as primitive as sponges [12]. Multiple examples showing adaptive characteristics of specificity and memory within innate immune systems have been reviewed by Kurtz [13]. As discussed later, these adaptive features of innate immunity may have important implications in the design of therapeutic strategies against cancer.

The specificities of the innate immune receptors, however, remained limited in the absence of mechanisms for the generation of somatic diversity. Ecological and metabolic cost requirements for a homologous recombination system necessary for the generation of receptor diversity as observed in vertebrates would far exceed the potential of the primitive nature of invertebrate body plans [14]. The earliest signs of limited somatic diversification of a set of highly variable immunoglobulin superfamily genes have been detected in echinoderms [15] and molluscs [16]. More efficient mechanisms for the somatic diversification of lymphocyte receptors evolved in the jawless vertebrates, the sea lampreys [17], and in the jawed vertebrates, the teleost fishes [18], to generate a virtually unlimited repertoire of antigen receptors capable of recognizing almost any molecular pattern. Somatic diversification may have become necessary with the changed lifestyle following the appearance of jaw and to meet the challenge of an enormous foreign antigenic burden presented by the co-evolving parasitic and commensal microbiota in the gastrointestinal tract of these vertebrates. About 540 million years ago, a major taxon of vertebrate gut endo-parasites, platyhelminthes, evolved with a new body layer of mesoderm. The resulting three-layered body surface in these flatworms enabled efficient nutrient intake and conferred greater resistance to host immunity [19]. The increasing diversity of endoparasitic and commensal microbiota in the nutrient-rich gut of vertebrates may have provided the evolutionary force for somatic diversification of immune receptors. Once a somatic diversifying mechanism was in place, such as the genomic invasion of a retroposon leading to the development of site-specific recombination activating genes (RAG), the evolution of complex immune surveillance mechanisms could have been accelerated.

However, self-reactivity is an inevitable consequence of somatically assembled receptors. Thus, somatic quality control mechanisms were needed to regulate self-reactivity of adaptive immune receptors. This could have led to the evolution of a host of subsets of the helper and regulatory T (Treg) cells along with the gastrointestinal effector $\gamma\delta$ T cells of mesodermal origin [20, 21]. Recently, it has become clear that multiple populations of gastrointestinal immune cells require the microbiota for their development and function [21]. Thus, the evolution of lymphocytes became feasible in vertebrates due to extensive gene duplications and added another powerful defense mechanism with the unique features of variable lymphocyte receptors and somatically assembled, clonally diverse, limitless array of anticipatory antigen receptors [1, 22–24]. In addition, the increased genome size of vertebrates gave rise to a higher propensity of genetic aberrations and instability. Genetic mutation rates may have been enhanced by oxidative damage to the nucleic acid chains as a result of the higher metabolic rate in vertebrates [25]. Moreover, following gene duplication, acquisition of new functions by a gene involves epigenetic silencing via methylation [26]. In this process, hypermethylation of some tumor suppressor genes must have initiated oncogenesis [27]. As a consequence, the vertebrate immune system had to engage in the surveillance of genetically altered cells and the associated neoplastic diseases which are predominantly unique to vertebrates, with some rudimentary presence in molluscs [28].

The evolution of the natural killer group 2, member D (NKG2D) receptor expressed on immune effector cells including natural killer (NK) cells, macrophages, $\gamma\delta$ T cells, and $CD8^+$ T cells [29], may have been an early step in the direction of immune surveillance against cancer. Cellular stresses such as infections, nucleic acid damage, malignant transformation, or heat shock have been known to induce the expression of NKG2D ligands [30]. While NKG2D seems to be expressed only in mammals, similar novel immune-type receptors have been reported in bony fish [31].

The evolutionary conditions that contributed to the evolution of immune systems are illustrated in Fig. 1. The combination of selection pressures ranging from the external (pathogens and commensals) and internal (cancerous and damaged cells) sources led to the evolution of immune surveillance and effector mechanisms.

Bidirectional immune cooperativity

The apparent dichotomy of the immune system into innate and adaptive immunity has undermined its appreciation as a bidirectionally interactive system. The conventional view of the differentiation of immune effector function emphasizes a unidirectional innate instruction of the adaptive immune system. Interactive feedback between $CD8^+$ T cells and dendritic cells (DC) has long been known in the clearance of antigen-loaded DCs in antiviral and antitumor immunity [32–34], as well as in the activation of DCs and

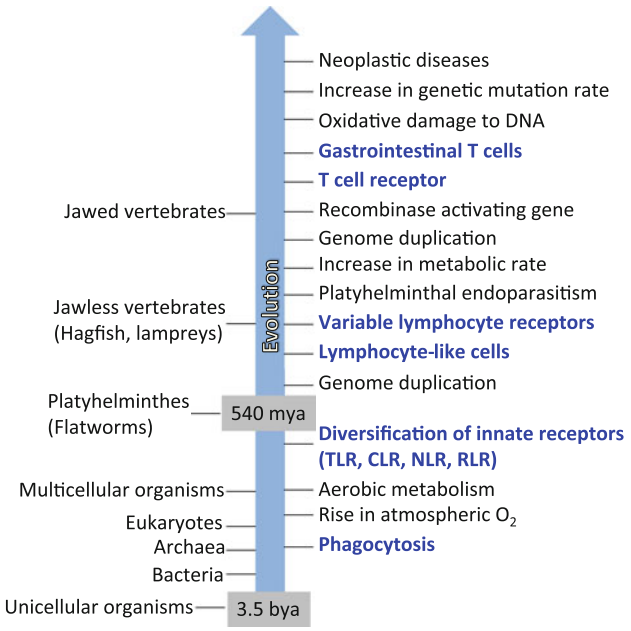

Fig. 1 The evolution of the immune system in the earth's history. The schematic illustration depicts evolutionary conditions that contributed to the evolution of the immune system. Atmospheric oxidation, increase in aerobic metabolic rates, host endoparasitism, and genome duplication in the earth's biota promoted the development of the immune system. *mya* million years ago, *bya* billion years ago, *TLR* Toll-like receptors, *CLR* C-type lectin receptors, *NLR* nucleotide-binding domain and leucine-rich repeat-containing receptors, *RLR* retinoic acid–inducible gene I-like receptors

IL-12 production [35–38]. Recent studies in various models of immune rejection ranging from cancer to peritonitis, infectious viruses and bacteria, commensal microbiota, lung emphysema, obesity, and atherosclerosis suggest a much broader bidirectional cooperativity of adaptive and innate immune regulation. It thus becomes worthwhile to focus on understanding the mechanisms of cross-talk between the two systems of innate and adaptive immunity. This may yield insights into novel strategies that can be harnessed to fight cancer and other diseases that have so far defied immune control. What follows in this review are examples of cross-talk in cytokine signaling and cooperativity of adaptive and innate effector responses in various contexts including the control of intestinal microbiota, acute and chronic inflammation, and memory responses that may be applicable to cancer immunity. We also discuss the convergence of immune effector mechanisms into a unified theory of the "immunologic constant of rejection".

Immune signaling cross-talk

Immune cells are exposed to more than one stimulus at any given time and need to be selectively stimulated to respond to infected or cancerous targets. This stimulation relies on appropriate signals generated from signaling cross-talk between cytokine receptor-mediated cellular communication and engagement of other cell surface receptors. This results in unique cell type–specific effector responses. Cytokines, upon binding with their respective receptors, follow a signaling pathway that consists of two components: four protein tyrosine Janus kinases (Jaks) and seven signal transducers and activators of transcription (STATs), inducing distinct activation programs specified by each particular member of the STAT family [39]. Cytokine receptors form multimers and are classified on the basis of their structures. The presence of the extracellular sequence motif WSXWS characterizes type I receptors, whereas the absence of this motif defines type II receptors. Both of these receptors follow the Jak-STAT-dependent signal transduction pathways. Other non-Jak-STAT cytokine receptors belong to the immunoglobulin, tumor necrosis factor (TNF), and transforming growth factor (TGF)-β superfamilies, which share either a common signaling adaptor, myeloid differentiation primary response gene 88 (MyD88) protein, or transducers, nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) or mitogen-activated protein kinases (MAPK).

In the steady state, multimeric cytokine receptors exist as individual subunits in the plasma membrane. They lack intrinsic tyrosine kinase activity despite their constitutive association with Jak kinases [40]. The Jak1, Jak2, and Tyk2 kinases are expressed ubiquitously, whereas Jak3 is restricted to hematopoietic cells. Upon cytokine binding at the plasma membrane, Jaks transactivate each other and phosphorylate their associated receptor. This facilitates the binding of STATs containing Src homology type 2 (SH2) domains to the receptor. Consequently, by means of reciprocal SH-2–phosphotyrosine interactions, they dimerize and translocate to the nucleus to initiate unique transcriptional programs leading to the expression of activating or inhibitory heterologous receptors. This forms the classical pathway of Jak-STAT-dependent cytokine-mediated regulation of cellular functions as illustrated in Fig. 2. Common cytokines that use this type of signaling are the T-cell fate-determining cytokines: interleukin (IL)-2, IL-4, interferon (IFN)-γ, IL-6, and IL-15. IFN-γ induces the expression of other receptors such as various Toll-like receptors [41] and Fas [42, 43]. IL-15 induces the expression of the NK cell activating receptor NKG2D and signaling adaptor protein DAP10 [44].

Alternatively, cytokine signaling can be coupled to other signaling pathways used by heterologous cellular receptors involving protein tyrosine kinase Fyn, pyruvate kinase Pyk2, GRB2-associated-binding protein 2 (Gab2), guanine nucleotide exchange factor Vav, phosphatidylinositol 3-kinases (PI3K), extracellular-signal-regulated kinases (Erk), and serine/threonine protein kinase Akt, some of

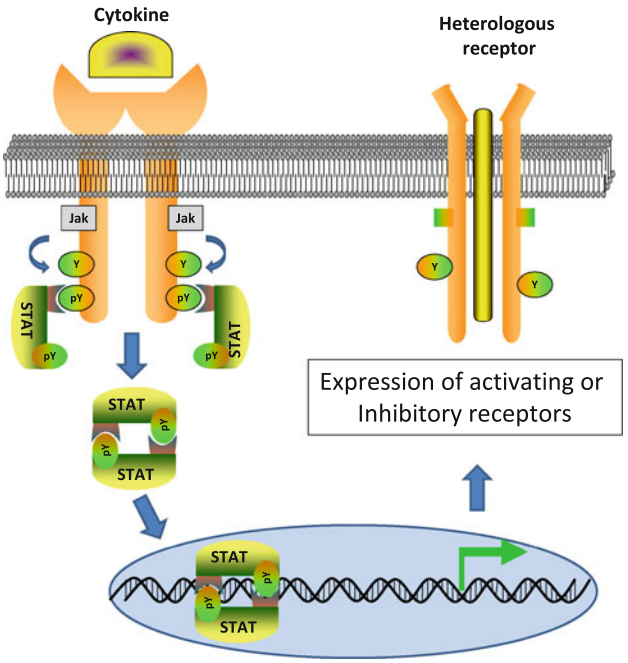

Fig. 2 The classical STAT-dependent pathway of cytokine receptor cross-talk. The schematic illustration depicts the classical pathway of Jak-STAT-dependent cytokine-mediated regulation of heterologous receptor functions. Cytokine signaling initiates a unique transcriptional program leading to the cellular expression of activating or inhibitory heterologous receptors

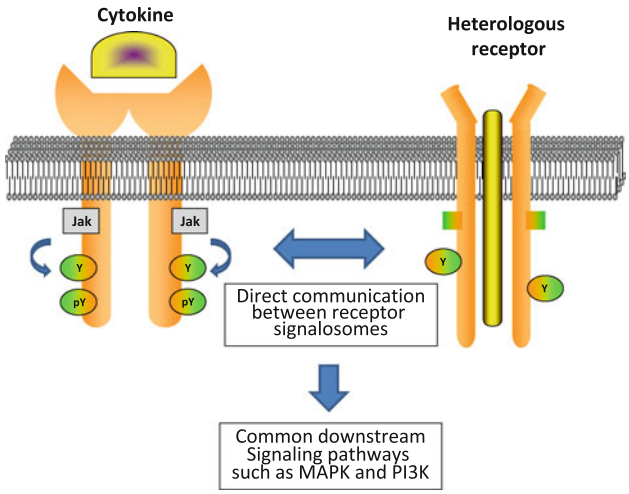

Fig. 3 The alternative STAT-independent pathway of cytokine receptor cross-talk. The schematic illustration depicts the alternative pathway of STAT-independent cytokine-mediated regulation of the expression of activating or inhibitory heterologous receptors. Cytokine receptors may directly communicate with other cellular receptor signalosomes within plasma membrane microdomains to initiate common downstream signaling pathways

them in a STAT-independent manner. Emerging models of cross-communication between cytokine receptors and heterologous receptors have been described recently [45]. For example, the IL-15 receptor in lymphocytes, which express all three (α, β, and γ) IL-15 receptor chains, triggers the kinases Lck, Fyn, Lyn, and Syk as well as NFκB, PI3K, Akt, and the Ras-Raf-MEK-MAPK pathways [46]. In addition, cytokine receptors may directly communicate with other cellular receptor signalosomes within plasma membrane microdomains (Fig. 3). Receptors with immunoreceptor tyrosine-based activation motif (ITAM) or inhibitory motif (ITIM) or ITAM-like motifs are examples of such receptors, which recruit cytosolic tyrosine kinases as opposed to receptor tyrosine kinases. A noteworthy example of heterologous receptor coupling particularly relevant for cancer immunotherapy is the activation of the NKG2D receptor.

Cooperativity of adaptive and innate effector responses in tumor rejection

Cancer immunotherapy has been a field of intensive investigation. Major efforts have focused on T-cell-based immunotherapy. However, adaptive T-cell effectors alone have shown limited clinical efficacy. In addition, it has been established that adaptive immunity, in at least highly immunogenic tumors, plays a role in the development of tumor escape variants and in the maintenance of the "occult" cancer in the equilibrium state [47]. On the other hand, tumor-infiltrating innate immune cell effectors such as NK cells, neutrophils, and even macrophages have been found to cause elimination of tumor cells in a spontaneous regression/complete-resistance mouse model [48–50] and in a xenograft tumor model following oncolytic viral therapy [51]. These studies predict that both arms of immunity, when appropriately stimulated, should be capable of rejecting tumors. Cytotoxic T cells do exert a direct cytolytic effect against tumors even under conditions when the tumor cells present low levels of tumor antigens [43]. In fact, T cells are also crucial for activating dormant innate immunity against tumors. Activated $CD8^+$ T cells specific to the self-tumor antigen P1A, which is expressed on mastocytoma cells [52], provide a necessary "help" to dormant NK cells in eliciting their effector function against mastocytoma tumors [53, 54]. The cooperativity of innate and adaptive effector mechanisms leads to complete rejection of tumors, including antigen-deficient tumor escape variants when they are present along with antigen-expressing tumor cells. No role for bystander lysis by T cells was found in this study. Rather, tumor regression required NK cell activity that was observed only if activated $CD8^+$ T cells were present in close vicinity. Thus, under appropriate conditions, $CD8^+$ T cells can activate dormant NK cells into becoming killer effectors at the tumor site.

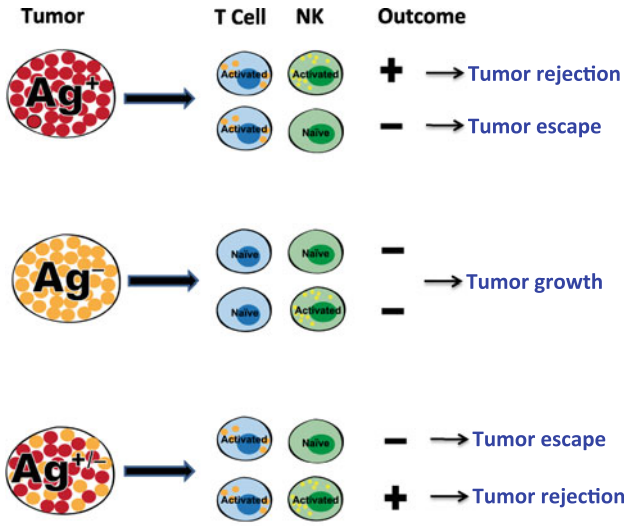

Fig. 4 T cell–NK cell cooperativity restricts tumor escape. Among various conditions in tumor microenvironment, depending on the presence or absence of the relevant antigen, tumor regression requires NK cell activity that is observed only if activated T cells are present locally in the vicinity of NK cells. Complete tumor rejection becomes possible only when there is a timely cooperative interaction between the T cells and NK cells

The necessity of NK cells in tumor rejection also becomes evident under conditions of restricted T-cell receptor diversity in mice [55]. The ability of mice to reject tumors is directly proportional to precursor frequencies of both tumor-specific $CD8^+$ T cell and NK cell effectors and is partially dependent on NKG2D-mediated mechanisms. Combined T-cell and NK cell effector function is also observed in the control of EMT6 mammary tumors following photodynamic therapy [56] and in the control of MB49 bladder carcinoma [57] and intraperitoneal mesenchymal tumors [58]. Complete tumor regression thus becomes possible only when there is a productive interaction between the activated $CD4^+$ or $CD8^+$ T cells and NK cells (Fig. 4). The provision of promoting innate effector mechanisms, in addition to T-cell effectors, may be helpful in an immunosuppressive tumor microenvironment. This may also be helpful during systemic Th2/Th17-oriented chronic inflammation that overrides protective adaptive immunity against tumors, for example, as reported recently in an induced melanoma model [59]. Thus, to improve cellular immunotherapy efforts against cancer, one needs to focus on strategies to promote the cooperative action of innate and adaptive immune effectors.

Gut microbial manipulation of immune receptor cross-talk and cancer

All metazoans harbor in their gastrointestinal tract commensal microorganisms that out-number the body's own cells by ten to one [60]. Emerging evidence supports a pivotal role of gut microbiota in the development of many gastrointestinal diseases, from inflammatory bowel disease to cancer [61, 62]. Gut microorganisms are capable of shaping host immunity by influencing the balance between pro-inflammatory and regulatory immune responses. To maintain an equilibrium of these enteric microorganisms, the immune system evolved a fine continuum of adaptive and innate effector mechanisms. Intestinal cells of epithelial lineage such as enterocytes, goblet cells, and $\gamma\delta$ intraepithelial lymphocytes control enteric bacteria by expressing antimicrobial proteins following MyD88-dependent TLR activation [63]. DC sample bacteria at the mucosal surface, traffic to mucosal lymphoid tissue, and induce B cells to secrete bacteria-specific immunoglobulin A [64]. Mice deficient in innate mechanisms such as TLR and IL-1/IL-18 receptor signaling ($Myd88^{-/-}Ticam1^{-/-}$) or phagocyte oxidative burst ($Nos2^{-/-}Cybb^{-/-}$) mount a robust $CD4^+$ T-cell-dependent antibody response following intragastric exposure to *Escherichia coli* bacteria [65]. Similar immune compensatory defense mechanisms have been noted in some IL-1 receptor-associated kinase 4-deficient ($IRAK\text{-}4^{-/-}$) children unable to signal following TLR stimulation [66, 67]. Thus, under innate immune deficiency conditions, adaptive immune cells possess the ability to compensate for innate clearance of bacteria, to provide host protection without a cognate antigenic response. Rapid non-cognate activation of IFN-γ-producing $CD8^+$ T cells is observed in response to cytokines such as IL-12 and IL-18 secreted by phagocytic cells following intracellular bacterial infection with *Burkholderia pseudomallei* or *Listeria monocytogenes* [68]. These studies suggest that innate and adaptive immune mechanisms collaborate to control commensal microbiota and intracellular pathogens. Microbes have, however, also evolved strategies to undermine host immunity by subverting the molecular signaling cross-talk between immune receptors [69]. Understanding these strategies will help design therapeutic approaches to redirect the host immune response and promote protective antitumor immunity.

Adaptive immune regulation of inflammation and cancer

Inflammation plays a dominant role at all stages of tumor development: initiation, progression, and metastasis [70]. Tumor-associated inflammation causes a decline in immune function and overrides tumor immunosurveillance and immunotherapy [59]. Understanding the immune regulatory mechanisms of inflammation and balancing them in favor of tumor immunity will help improve cancer immunotherapy approaches. Studies in various immunopathological

conditions highlight adaptive control of inflammation that need to be promoted in cancer.

The need for an adaptive control of inflammation becomes apparent as early as in neonatal mice and human newborns. As the embryonic development of the innate immune system precedes that of the adaptive system [71], exposure to various forms of TLR stimulation following infection in neonatal mice causes a cytokine storm, which leads to high mortality [72]. Similarly, in human newborns of small gestational age, excessive levels of TNF-α, IL-1, and IL-6 have been detected following infections [73–76]. This is primarily due to a lack of control of the innate inflammatory response by the type I IFN- and IL-10-producing B cells [77] and Tregs [78], both of which are present at insufficient number in neonatal stage [79, 80]. Tregs also coordinate the timing of entry of the innate immune cells into the infected tissue. Ablation of Treg cells delays the arrival of NK cells, DCs, and effector T cells to the site of herpes simplex virus infection in mice [81]. Non-Treg resting T cells have also been shown to temper the production of IFN-γ and TNF during initial innate inflammation in a hepatitis viral infection model. This is accomplished in an antigen-independent manner by direct contact inhibition, requiring the major histocompatibility complex molecule [82]. These examples show that adaptive immune cells are indispensable for controlling inflammation.

Direct evidence of adaptive suppression of intracellular complexes called inflammasomes that process IL-1β, a major pro-inflammatory cytokine [83], came from a study in a murine peritonitis model [84]. Activated T cells suppressed potentially damaging innate inflammation through inhibition of inflammasomes, including intracellular inflammation sensing proteins of the NLR family, NLRP1 and NLRP3. This blocked the caspase-1 axis and thereby decreased neutrophil recruitment. The T-cell-mediated contact-dependent blockade of macrophage caspase-1 activation, IL-1β release, and IL-18 secretion in a cognate manner left the beneficial release of inflammatory mediators, such as chemokine (C-X-C motif) ligand 2 (CXCL2), IL-6, IL-12, and TNF (crucial for tissue healing) intact. TNF family ligands expressed by T cells were implicated in turning off the inflammasome. This is consistent with the established role of the TNF family in coordinating immune signaling networks [85]. In addition, IFN-γ produced by T cells in response to influenza infection has been shown to inhibit alveolar macrophages [86]. Thus, T cells edit excessive innate inflammation by direct contact and secretion of cytokines, while maintaining their competence in antigen-specific recognition and stimulation. Induction of inflammatory response against *Plasmodium falciparum*-infected erythrocytes and vaccine-induced cellular responses to rabies virus were also shown to involve cross-talk between T cells and NK cells [87, 88]. In these studies, activation of NK cells and their IFN-γ production and degranulation were crucially dependent on IL-2-mediated signals from $CD4^+$ T cells.

Chronic inflammation, which supports carcinogenesis, has also been found under the control of adaptive immune regulation. This has been particularly evident in adipose obesity, a physiological condition of chronic inflammation, that is initiated by alterations in the composition of T cells, B cells, and macrophages [89–92]. Infiltration of large numbers of effector $CD8^+$ T cells into epididymal adipose tissue, concomitant with a decrease in the numbers of $CD4^+$ T helper and Treg cells, is an early event during the development of mouse obesity [93–95]. In lean mice, Treg and Th2 cells dominate in the adipose tissue. These cells secrete IL-4 and IL-10, restricting inflammation in the resident adipose tissue macrophages. However, in obese mice, the accumulation of $CD8^+$ T cells and T_H1 cells in the adipose tissue signals the recruitment of inflammatory macrophages via chemokine (C–C motif) ligand (CCL) 2. Activated $CD8^+$ T cells secrete humoral factors known to induce macrophage migration, differentiation, and activation, including IFN-inducible protein-10, monocyte chemoattractant protein (MCP)-1, MCP-3, and RANTES (regulation upon activation, normal T cell expressed and secreted protein).

Thus, T cells contribute to the initiation and propagation of inflammation by directly affecting the production of inflammatory mediators such as IL-1, IL-6, TNF-α, and serum amyloid A-3, as well as intercellular adhesion molecule-1 and matrix metalloproteinases (MMP) 2 and 3, leading to systemic insulin resistance and metabolic disorder [93, 95]. In non-obese diabetic mice, $CD8^+$ T cells trigger nitric oxide production by macrophages, while macrophages trigger IFN-γ production by $CD8^+$ T cells to cause islet destruction [96]. T cells, largely via IFN-γ, have also been shown to regulate the magnitude of the atherogenic proinflammatory response of macrophages [97]. Deposited underneath the endothelium of arteries, the lipid-laden macrophages lead to the formation of inflammatory atherosclerotic plaques [98]. Lipid-laden myeloid cells may play similar roles in causing inflammation, contributing to carcinogenesis. In a mouse model of human papilloma virus-driven squamous epithelium carcinogenesis, with the help of $CD4^+$ T cells, B cells have been shown to orchestrate macrophage-driven, tumor-promoting inflammation by producing antibodies that interact with and activate Fcγ receptors on both tumor-resident and tumor-recruited myeloid cells at the tumor site [99]. B cells can also drive M2-like polarization of macrophages and promote the growth of B16 melanomas [100]. $CD4^+$ T cells can also regulate pulmonary metastasis of mammary tumors by enhancing pro-tumor properties of macrophages [101]. Depending on the context, the cross-talk between B

cells, T cells, and macrophages can mediate tumor-promoting inflammation or provide antitumor activity [102]. Further identification of various cellular and molecular pathways that participate in cancer inflammation and the mechanistic correlation of T-cell activity with other leukocytes that may influence chronic inflammation, such as NK cells, Th17 cells, and B cells, or antigen presentation will be required to design strategies to check pro-tumor inflammation.

Increased numbers of T cells are also observed in the lungs of patients with chronic obstructive pulmonary disease. In a cigarette smoke-induced murine model of emphysema, a $CD8^+$ T-cell product, IFNγ-inducible protein-10, was shown to induce the production of macrophage elastase (MMP-12) that degrades elastin and generates elastin fragments to serve as monocyte chemokines, augmenting macrophage-mediated lung destruction [103]. The precise factors that cause the accumulation of activated $CD8^+$ T cells or Th1 cells in obese tissue or lungs are not known. Most likely, these factors are endogenous antigens and stimuli such as cholesterol crystals that develop in atherosclerotic plaques [104] or smoke particles that accumulate in lungs. It is important to identify similar antigens expressed in early developing nascent tumors to strengthen tumor immunity.

These examples demonstrate that interdependent cooperative cross-talk between adaptive and innate immunity has the potential to minimize immunopathology and maximize host defense. Identification of the underlying signaling mechanisms responsible for the cross-talk between innate cells and the various populations of resting, effector, and regulatory T cells, as well as B cells, will help decipher new networks of immune regulation. This will reveal new intervention targets applicable for cancer therapy and prevention.

Adaptive and innate cooperativity in immune memory responses

In order to provide a long-lasting protective immunity against cancer, it is necessary to strengthen antitumor immune memory. Antibacterial and antiviral memory responses are dependent on the cooperativity between innate and adaptive effector mechanisms. Activation of innate mononuclear phagocytic cells (MPCs) is required by memory $CD8^+$ T cells for the clearance of secondary bacterial infections [105]. Following re-infection with the bacteria, existing memory T cells release CCL3 chemokine to mobilize MPCs, which in turn release TNF-α to cause neutrophils and other MPCs to produce radical oxygen intermediates (ROI) for the clearance of bacteria. During secondary responses, activated innate effector cells can also clear unrelated ROI-sensitive pathogens. Thus, memory $CD8^+$ T cells, following an antigen-dependent phase of reactivation, control the activation of innate effector mechanisms. In a similar fashion, following influenza re-infection, memory $CD4^+$ T cells recruit innate effector cells at early phases of secondary responses and markedly enhance the early expression of innate inflammatory cytokines and chemokines in a pathogen-independent, but antigen-dependent, manner [106].

Furthermore, it is important to realize that immune memory is not a feature of adaptive immune cells alone. As discussed earlier, multiple examples showing adaptive characteristics of specificity and memory exist within innate immune systems of invertebrates [13]. It has been assumed that innate immune systems are not adaptive and respond identically to rechallenges. Recent evidence has proved this wrong. NK cells exhibit characteristics of immune memory. Mice deficient in T and B cells demonstrate contact hypersensitivity responses to haptens. The NK cell population expressing Ly49C-I receptors from sensitized mouse livers can transfer hapten-specific memory [107]. In addition, NK cells bearing virus-specific Ly49H receptors persist in lymphoid and non-lymphoid organs for several months after viral infection. These NK cells, upon adoptive transfer into naïve animals, confer protective immunity by a secondary expansion following viral challenge [108], though one report suggests that the activation of $Ly49H^+$ NK cells can be detrimental to the long-term antiviral T-cell responses [109]. Similarly, macrophages also undergo a differentiation program with features of memory by selective modification of their histone proteins that package genes activated in response to pathogens, to adapt to repeated exposure [110, 111]. Phagocytic cells in *Drosophila melanogaster* can remember previous infections with certain bacteria [112]. Moreover, initial type-2 immunity to gastrointestinal helminths is mediated by newly described innate immune cells, nuocytes [113], and multipotent innate helper cells [114] that mimic the role of T cells, albeit more promptly and less specifically.

Clearly, various features of adaptive immunity manifest in the evolutionarily ancient innate immune systems. Further understanding of innate memory responses is of particular interest since tumors are frequently associated with the suppression of adaptive effector mechanisms. Promotion of innate memory responses against tumors would provide a novel therapeutic opportunity against cancer. So far, in cancers where viruses play a causal role, vaccines against these viruses have proved to be successful cancer-preventive agents, for example, in human papillomavirus-positive cervical cancer [115]. Recently, IL-10-producing $CD5^+$ regulatory B cells have been described to dampen immune responses to adjuvants and vaccines by controlling

Table 1 The converging immune pathways determining tissue-specific destruction

	Stat-1 IRF-1 T-bet^{+} IFN-γ IL-15	GNLY GZM TIA	CXCL-9 CXCL-10 CXCL-11 CXCR3	CCL5 CCR5	References
Cancer prognosis					
Colorectal *hu* CA	+	+			[128, 129]
Lung *hu* CA	+	+			[130]
Melanoma *hu* Xeno	n.t.	n.t.	+	+	[131]
Ovarian *hu* CA Xeno	+	+	+	+	[132]
Tumor rejection					
Mastocytoma *mus*	+	+		+	[53]
Breast *hu* CA Xeno	+	+	+	+	[51]
BCC *hu* CA	+	+	+	+	[133]
Allo-transplant rejection					
Kidney *hu*	+	+	+	+	[134–136]
Heart *hu*	n.t.	n.t.	+	n.t.	[137]
Islet *pig*	n.t.	+	+	+	[138]
GVHD	+	+	+	n.t.	[139]
HCV viral clearance					
Chimp	+	+	+		[140, 141]
Hu	+		+		[142, 143]
Acute cardiovascular events (*hu*)	+		+		[144]
COPD			+		[145]

This table summarizes gene activation or protein expression profiles in tissues undergoing immune-mediated tissue-specific rejection under various pathological conditions described in the studies reported

GNLY granulysin, *GZM* granzymes, *TIA* cytotoxic granule-associated RNA binding protein, *hu* human, *CA* carcinoembryonic antigen, *n.t.* not tested, *Xeno* xenograft, *mus* mouse, *BCC* basal cell carcinoma, *GVHD* graft-versus-host disease, *HCV* hepatitis C virus, *chimp* chimpanzee, *COPD* chronic obstructive pulmonary disease

innate inflammation and DC functions [116]. This imposes the necessity to understand the complexities of the interplay between innate and adaptive immune cells in achieving short-term effector and long-term memory responses. In effect, the collective priming of adaptive and innate immune cells should be attempted to generate effective memory responses against tumors. This will have significant implications in the design of cancer vaccines and the evaluation of their efficacies.

Unified view of immune effector functions

Immune-mediated tissue-specific responses can be triggered by distinct mechanisms during allograft or tumor rejection, autoimmunity, and pathogen clearance. However, the effector mechanisms converge into common pathways that can be synthesized into a unified theory of the "immunologic constant of rejection" [117]. This immunologic constant comprises a combination of factors necessary to convert an indolent chronic inflammatory response into an acute inflammatory reaction. Based on the global gene and protein expression profiling of tissues in mammals, including humans, from cancer and other pathological conditions, the convergent characteristics of immune pathways determining tissue-specific destruction are summarized in Table 1. In various types of immune-responsive and non-responsive human xenograft tumors, tumor rejection was associated with the activation of two distinct set of genes encompassing IFN-stimulated genes and effector molecules of the innate and adaptive immune mechanisms [51]. A similar signature of genes in tumor-infiltrating immune cells emerges in breast cancer patients [118]. These gene signatures mimic those observed in humans during allograft rejection, graft-versus-host disease, autoimmunity, pathogen clearance, and acute cardiovascular and chronic obstructive pulmonary diseases. IL-32 gene, which encodes an IL-2- and IL-18-inducible inflammatory factor and amplifies cytokine production [119, 120], is expressed preferentially in metastatic melanoma compared with other less immune-responsive cancers [121]. IL-32 is expressed by all NK cells and activated

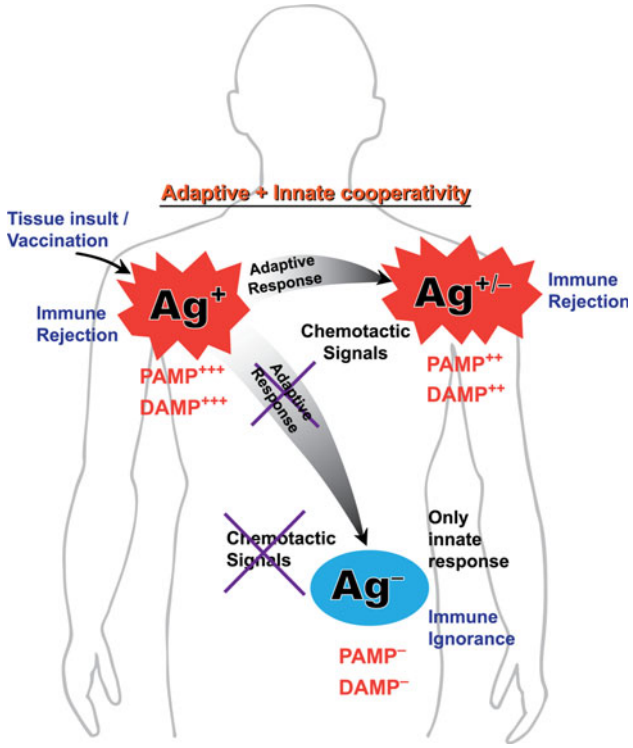

Fig. 5 The cooperativity between adaptive and innate immune rejection. Adaptive immune responses are necessary to mediate tissue specificity in a cognate manner by directing chemokine-promoted innate effector activation and mobilization to the site of infection or disease. The concentration of pathogen-associated molecular patterns (PAMPs) and/or danger-associated molecular patterns (DAMPs) and other alarmin-like signals may be critical for this immune interaction. Cooperativity between adaptive and innate responses optimizes a successful host immune rejection via a balance of immune regulatory networks. Absence of adaptive response at the site of insult due to lack of sufficient antigen (Ag) may often lead to immune ignorance

$CD8^+$ T cells [122]. Thus, we require a baseline cluster of IFN-stimulated genes, which are necessary for immune activation, but are insufficient to cause tumor rejection. Additionally, a signature comprising cytotoxic effector genes is also required for tumor elimination. Disruption of lymphocyte IFN signaling appears to be a common feature of immune dysfunction, at least in the immunopathologies examined so far. Indeed, in peripheral blood lymphocytes from breast cancer, melanoma, and gastrointestinal cancer patients, IFN-α-induced signaling was reduced in T and B cells, and IFN-γ-induced signaling was reduced in B cells [123].

Vaccines specific to tumor antigens have been successful in the activation of T cells [124] but tumor antigen exposure alone is not sufficient to maintain antitumor cytotoxic activity of $CD8^+$ T cells. As costimulatory signals are often lacking at the site of most tumors, tumor-specific T cells remain quiescent on their encounter with tumor cells at the target site as observed in melanoma patients [122, 125]. Thus, tumor-specific T cells co-exist in the host alongside their target cells. Similar observations have been observed in the context of chronic infections, well-controlled allo-transplant reactions and autoimmunity [117]. Depending on an assortment of genetic factors related to host background, or the evolving phenotypes of the heterogenous tissue and its environment, as is the case in cancer, immune responses may not always result in tissue destruction and may lead to equilibrium of the immune cells and the target cells. Adaptive immune cells are, however, necessary to provide tissue specificity by guiding the chemokine-promoted innate effector cells to the site of tumor. In this context, a timely cooperative action of adaptive and innate immune effector cells becomes highly relevant to mediate efficient tumor elimination. The magnitude of this immune collaboration may be regulated by the concentration of antigens and the disease/pathogen-associated molecular patterns and/or danger-associated molecular patterns [126] and alarmin-like signals [127]. The cooperativity between adaptive and innate responses to optimize a successful host immune rejection via a balance of immune regulatory networks is illustrated in Fig. 5. Absence of an appropriate adaptive immune response at the site of insult to support innate effector responses may often lead to immune ignorance.

Conclusions and future directions

The observations from different immunological conditions discussed in this review compel us to revisit the current approach in designing immune therapies against cancer and other defiant diseases. The co-evolution of innate and adaptive immunity has culminated in codependence and cooperativity. The success of an immune effector response depends on a fine productive balance between the innate and adaptive components of immunity. Besides providing an effector response, cognate adaptive immune cells are necessary to mediate tissue specificity in the chemokine-promoted recruitment of innate immune cells to the site of cancer or other lesions following a pathological insult and to generate their effector responses in a controlled fashion. Although the exact triggers and magnitude controls that regulate this adaptive/innate immune cooperativity during cancer or other diseases need to be dissected, it is clear that the immune system has evolved in its capacity to generate a powerful immunological "orchestra". The dynamics of this immune orchestra will become evident as the intricacies of immune interactions and their regulatory networks are further revealed. Future advances in cancer therapy will require an integrative immunological approach to inform on the finer details of the immune signaling networks that

will be directly applicable for designing novel anticancer strategies.

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