Leading Edge
Review

Cell

The Basis of Oncoimmunology

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http://dx.doi.org/10.1016/j.cell.2016.01.049

Cancer heterogeneity, a hallmark enabling clonal survival and therapy resistance, is shaped by active immune responses. Antigen-specific T cells can control cancer, as revealed clinically by immunotherapeutics such as adoptive T-cell transfer and checkpoint blockade. The host immune system is thus a powerful tool that, if better harnessed, could significantly enhance the efficacy of cytotoxic therapy and improve outcomes for cancer sufferers. To realize this vision, however, a number of research frontiers must be tackled. These include developing strategies for neutralizing tumor-promoting inflammation, broadening T-cell repertoires (via vaccination), and elucidating the mechanisms by which immune cells organize tumor microenvironments to regulate T-cell activity. Such efforts will pave the way for identifying new targets for combination therapies that overcome resistance to current treatments and promote long-term cancer control.

Introduction

Cancer is an insidious disease traditionally classified by cell and tissue type of origin. Cancer has historically been treated according to a "one size fits all" approach based on broad pathologic criteria and involving various regimens of cytotoxic therapy. With the advent of modern sequencing methodologies, however, we now appreciate that significant genomic, transcriptomic, and epigenetic heterogeneity exists within individual tumor types; this recognition has enabled subclassification of tumors of common origin. This, in turn, has led to improved outcomes for some cancer types, as response rates to targeted and cytotoxic therapies increase when patients are stratified based on the molecular characteristics of their tumors. Examples include imatinib in chronic myelogenous leukemia (Druker et al., 2006), HER2-targeted therapies for HER2-positive breast cancer (Shepard et al., 1991), and estrogen antagonists for estrogen-receptor-positive breast cancers (Heiser et al., 2012). These molecular advances helped to usher in a new era of precision medicine that is reshaping clinical treatment across the cancer spectrum. However, there remain significant fractions of patients that do not respond to "designer" therapies even when their tumors are classified based on molecular and pathologic criteria. Additional tumor or systemic characteristic(s) are thus unaccounted for that not only impact neoplastic growth and dissemination, but also impact response to therapy.

Recent seminal in vivo studies revealed that neoplastic cells rely on the diversity of normal resident and recruited accessory cells to support their evolution (Hanahan and Coussens, 2012). Accessory cells are now recognized as "neoplastic cell-extrinsic hallmarks of cancer" and include those forming the hematogenous and lymphatic vasculature, tissue-specific mesenchymal support cells, and myeloid and lymphoid-lineage immune cells. Accessory cells integrate with the dynamic soluble and insoluble matrices constituting the "tumor stroma"; collectively, they fuel neoplastic evolution (Hanahan and Coussens, 2012). In other words, reciprocal interactions between accessory cells, their mediators, structural components of the extracellular matrix (ECM), and genetically altered neoplastic cells regulate all aspects of tumorigenicity. These realizations fueled the development of anti-cancer agents targeting the vasculature (Kerbel, 2011) and, more recently, propelled clinical investigations into the efficacy of immune therapeutic approaches that neutralize tumor-promoting chronic inflammation and/or embolden or unleash cytotoxic activities of antigen-specific T cells (Coussens et al., 2013; Pardoll, 2012).

Indeed, cancer is visible to the immune system, i.e., immunogenic, during early neoplasia. Classic studies from Schreiber and colleagues in mice with carcinogen-initiated sarcomas revealed that the immune system could recognize and reject cancerous cells (Dunn et al., 2004). Elimination can be explained by cytotoxic antigen-specific T cells responding to relatively high mutational burdens induced by carcinogens and thus providing neo-antigens for T-cell priming; these findings established the principles of elimination, equilibrium, and eventually escape when neoplastic cells become invisible to the immune system (Dunn et al., 2004). Neoplastic cells in part escape when tumor arises out of chronically inflamed tissues—there, chronic infiltration of tissue by leukocytes (e.g., type 2 cytokine-activated myeloid cells and immune-suppressive B, T, and myeloid subsets) subvert T-cell-directed elimination and thus aid tissue-based programs, e.g., angiogenesis, lymphangiogenesis, matrix remodeling, etc., supporting neoplastic progression (Coussens et al., 2013).

Mounting observations in humans support the concept that cancer initiation and progression are significantly impacted by altered or misled immune responses (Figure 1). Individuals suffering from chronic inflammatory conditions are at increased

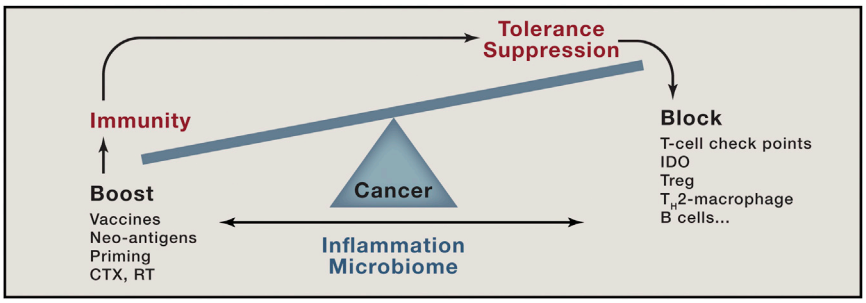

Figure 1. The Makings of Tumor Immunity

The communication between cancer and the immune system is a dynamic process, reminiscent of a balance. When immunity to cancer is "up" and the suppressive processes are "down," cancer is under control. However, a strong anti-tumor immune response will trigger largely physiological processes designed to dampen effector T cells to prevent tissue damage and maintain tissue homeostasis. Given that the immunity might have evolved mainly to maintain self, to establish coexistence with environment, and to occasionally protect self from external threats, the suppression prevails. Multiple pathways of suppression are at play in tumor microenvironments, including cells such as T_H2-polarized macrophages, immature and suppressive monocytes, regulatory B cells, and regulatory T cells, as well as molecules such as checkpoints that control T-cell differentiation (for example, CTLA-4 and IDO) and effector function (such as PD-1). Pharmacological blockade of these inhibitory pathways can tip the balance toward anti-cancer effector T cells. The latter ones can be primed or boosted by antigen-presenting cells (DCs) and/or by co-stimulatory signals (for example, CD137 ligands). Recent studies demonstrate that thymus-independent neo-antigens generated in adult life by somatic mutation or post-translational regulation (for example, phosphorylation) might be more immunogenic (or perhaps linked with less suppression) than shared tumor antigens. Neo-antigens can occur as random results of somatic mutation, as well as a by-product of anticancer treatments, e.g., chemotherapy (CTX) or radiation therapy (RT), or by targeting epigenetic control mechanisms or drugs intervening with DNA repair pathways. They can be presented to T cells in exogenous vaccines, as well as endogenously via DCs that captured dying neoplastic cells. When T cells specific to defined antigens kill neoplastic cells, such a process can enable generation of responses to other antigens, so called epitope spreading. A critical factor in the balance between immunogenicity and suppression is inflammation (which, in turn, is impacted by the microbiome); indeed, the type of inflammation (tumor-destructing T_H1 or tumor-promoting T_H2 and T_H17) should become a part of TNM grading, along with pathology, microbiome phenotype, and immune infiltrate assessment.

risk for developing cancer (Thun et al., 2004). Incidence of viral (DNA tumor virus) and carcinogen-associated cancers is increased in immune-compromised individuals, even as the relative risk of cancer types lacking viral or carcinogen etiology is diminished (reviewed in de Visser et al., 2006). Age-related immunosenescence likely plays a role in increased incidence of malignancy in aged individuals (Campisi et al., 2011). The advent of some biologic therapies impacting how tissues activate and resolve inflammation, e.g., tumor necrosis factor (TNF) blockade (Bongartz et al., 2006), also skews cancer incidence metrics. However, the role(s) that immune pathways play in driving malignancy remains to be clarified. How does the immune system recognize tissue-specific mediators triggering and maintaining chronic inflammatory responses? What oncogenic events and altered metabolic states lead to the generation of neo-antigens that in turn induce T-cell responses? What physiological mechanisms regulate immune homeostasis such that (acute) inflammation can be resolved as rapidly as it is activated (a critical control program to thwart autoimmunity)? What is the role of the host microbiota in regulating systemic immune responses to neoplasia? How do neoplastic cells survive immune attack by T cells? These questions are in need of answering to effectively move cancer research and cancer medicine forward.

A common feature of all cancers, regardless of origin, is prominent presence of diverse assemblages of immune cells (Coussens et al., 2013). The consequences of such infiltrates on the fate of cancerous cells are diverse (Figure 2). For example, under continual immune pressure, i.e., antigen presentation to T cells, neoplastic cells become "immune-edited" to escape immune surveillance (Dunn et al., 2004) and instead co-opt immune cells to favor their sustained proliferation (Balkwill et al., 2005). Nonetheless, recent studies demonstrate that the presence of lymphoid aggregates is linked with improved responses to cancer therapies—for example, standard cytotoxic therapies, vaccine-based treatments, or immune checkpoint blockade (Topalian et al., 2015). Such "hot" tumors are thus more amenable to control than "cold" tumors, i.e., tumors with diminished T-cell infiltrates, thus driving modern cancer medicine to investigate how to reprogram the tumor microenvironment (TME) to attract the right type of immune infiltrate. This topic, along with other open questions in the field of oncoimmunology, are discussed here.

The Makings of the Immune Response to Cancer

Tumors are organized tissues with numerous reciprocal local and systemic connections with immune cell populations of both the myeloid and lymphoid lineages. Here, we summarize the key myeloid and lymphoid populations regulating the immune response to cancer and how the fundamental physiological processes that they govern are harnessed for neoplastic progression and tumor formation.

The Myeloid Compartment

Myeloid cells have multiple homeostatic functions that are co-opted by evolving neoplasms; these can be roughly summarized as: (1) antigen capture for degradation (macrophages) or presentation (dendritic cells [DCs]); (2) tissue repair (macrophages), and (3) effector functions (mast cells, monocytes, and granulocytes). Neoplastic cells can alter the steady-state activity of all myeloid cells present in the TME, including tissue-resident and blood-derived cells, by secreting factors such as interleukin (IL)-6 or granulocyte-macrophage colony-stimulating factor (GM-CSF), that increase recruitment and proliferation of immature myeloid cells atypical under physiological conditions (Gabrilovich et al., 2012).

An important feature of myeloid cells is their functional plasticity in response to environmental signals. This property can dictate such opposite outcomes as antigen degradation or antigen presentation when macrophages acquire DC capabilities (Banchereau et al., 2000), tissue repair rather than inflammation when macrophages are polarized toward type 2 states, and protective or non-protective T-cell immunity when programmed by cancer-derived factors (Balkwill et al., 2005). Thus, plasticity