Basics of Immunity

Brian T. Edelson

Abstract This chapter will serve as a brief review of immunology for oncologists. No single chapter can fully describe the complexity of the immune system and so the goal here will be to simply serve as a refresher. Innate and adaptive immunity will be concisely reviewed, with a brief description of the cells of each system. Focus will then be paid to the how T cells are activated and function. Finally, basic principles of T cell-mediated immunity to tumors will be presented. These foundational concepts will be useful for understanding later chapters which largely deal with the purposeful engineering of immune cells for adoptive cellular therapies. An attempt has been made to highlight recent review articles for further reading, with an emphasis on those that involve tumor immunology.

Keywords Innate immunity · Adaptive immunity · B cells · T cells · Natural killer (NK) · Natural killer T (NKT) cells · CD4+ cells · CD8+ cells · T helper (Th1, Th2, Th17) · T follicular helper (Tfh) · T regulatory cells (Treg) · Mucosal-associated invariant T (MAIT) cells · γδ T cells · Myeloid-derived suppressor cells (MDSCs) · Innate lymphoid cells (ILCs) · Cytotoxic T lymphocytes (CTLs) · B cell receptor (BCR) · T cell receptor (TCR) · Dendritic cells (DCs) · Antigen presenting cells (APCs) · Major histocompatibility (MHC) class I and class II molecules · Pathogen-associated molecular patterns (PAMPs) · Pathogen recognition receptors (PRRs) · Toll-like receptors (TLRs) · Tumor microenvironment (TME)

Innate Vs. Adaptive Immunity

The responses of the immune system to injury or infection that occur within the first minutes to hours are collectively called the innate immune response. These systems are evolutionarily old, and mainly serve the functions of pathogen recognition and

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rapid pathogen attack. Components of innate immunity exist in all human cell types, although a specialized set of immune cells, both tissue-resident and blood-circulating, also contributes in important ways. Components of innate immunity alert other cells to the presence of a pathogen, such that they can be mobilized to the site of invasion, or their cell-intrinsic defenses can be strengthened in preparation for an upcoming encounter with the pathogen. Aspects of the innate immune system are also active in processes that don't involve pathogen invasion per se, including normal growth and organ development, responses to sterile wounding, physiologic interactions with the microbiome, and autoimmune responses. In the setting of tumor development, growth, and metastasis, cellular and soluble components of the innate immune system play important roles in both tumor promotion and restriction.

Adaptive immunity refers to the processes whereby lymphocytes of both the B cell and T cell lineages engage with antigens and carry out effector functions, again typically aimed at pathogen clearance. Unlike innate immune cells, which are typically more promiscuous in their recognition of common pathogen components or damaged cells, B and T cells are exquisitely antigen-specific and are called to duty only in the very special circumstance when their cognate antigen is involved. B and T cell development takes place in the bone marrow and thymus, respectively, in orchestrated processes whereby each cell is endowed with a single antigen-specific receptor [a B cell receptor (BCR) or T cell receptor (TCR)] in an anticipatory manner, such that the collection of B and T cells provides an immense repertoire of specificities for recognition of the universe of pathogens. By anticipatory, here, I mean that the instruction for which unique antigen-receptor a particular B or T cell comes to express developmentally is not instructed by any encounter with cognate antigen itself. B and T cell development occurs in a manner whereby self-reactive cells are eliminated. This "central" tolerance system is not always complete, however, and so mechanisms of "peripheral" tolerance are also in place to assure that, in most cases, self-reactive lymphocytes are held in check.

One other important concept in understanding adaptive immunity is that the process is clonal. A single B or T cell retains its unique BCR or TCR throughout its lifespan, and this antigen-receptor specificity is retained by progeny of the cell that arise through cell division. This is termed clonal expansion. For T cells, the TCR expressed by a single T cell clone is completely immutable, even upon T cell proliferation. B cells, however, can make limited changes to the sequence of their BCR upon activation through a process called somatic hypermutation, in which amino acid changed arise in specific regions of the BCR. These changes are subtle, and ideally result in B cell progeny with BCRs that display heightened affinity for cognate antigen, a process called affinity maturation.

The Stereotypical Immune Response to a Pathogen

Here, I will describe a stereotypical immune response to an invading pathogen, as it illustrates many of the concepts important to understanding how immune responses occur more broadly. In general, the innate and adaptive immune systems

work together, which each feeding information to the other through soluble components and cellular interactions. Upon initial encounter with a pathogen, innate immune cells and soluble pathogen recognition systems like the complement proteins serve as initial sentinels to warn and prepare other host cells, but also make attempts to initially contain the pathogen and limit its spread. Effector systems of the innate response include molecules directly toxic to the pathogen, phagocytosis of the invading organisms, and mobilization of cell-autonomous defenses like the type I interferon (IFN) system. These systems also alert B and T cells that a pathogen has been encountered and create a set of conditions for optimal priming of naïve B and T cell responses. Priming typically occurs in the lymph nodes draining a breached tissue, or in the spleen, in the case of blood-borne pathogens. Intact pathogens, or components of the pathogen, reach lymph nodes via afferent lymphatic vessels, sometimes carried by migratory innate immune cells. In an amazingly efficient process, rare B and T cells with specificities for antigens of the invading pathogen engage these antigens, are activated through cell signaling cascades, proliferate, and take on effector phenotypes as directed by signals they receive from innate immune cells.

Priming of antigen-specific, naïve T cells requires specialized antigen presentation by dendritic cells (DCs, a specialized innate immune cell type). Antigen presentation is a process whereby antigen presenting cells (APCs) partially catabolize protein antigens and display short peptide fragments of these antigens on their surface in complexes with major histocompatibility (MHC) molecules (Fig. 1). Pathogen recognition by innate immune cells can sense the type of pathogen encountered via recognition of pathogen-associated molecular patterns (PAMPs). PAMPs are recognized at the cell surface, within endosomal compartments, and within the cytosol by an array of pathogen recognition receptors (PRRs), including multiple Toll-like receptors (TLRs) and a diverse set of cytosolic sensors. Distinct cytokine signals arising from antigen-presenting DCs based on the PAMPs detected drive specialized T cell responses, such that distinct effector T cell "subsets" develop.

In the cortex of lymph nodes, antigen-activated B and T cells also communicate with each other through soluble proteins called cytokines and through cell-cell interactions within the lymph node to orchestrate effects on the proliferating B cells, including adaptation to antibody secretion, optimization of antibody affinity (somatic hypermutation/affinity maturation) and isotype (a process called isotype switching), and the development of antigen-specific long-lived memory B cells and plasma cells. The complexities of B cell responses to antigens will not be covered further here.

Following T cell activation in lymph nodes, a process which usually takes 5–7 days, effector T cells are recruited to sites of infection by chemokine signals created by innate immune cells. Here, effector T cells orchestrate an inflammatory reaction which ideally can eliminate the pathogen with minimal tissue damage. This reaction includes both recruitment of more innate immune cells, signals to the non-immune cells that make up the tissue, direct cytotoxicity of infected cells, and eventually signals that restore homeostasis and promote healing. While this T cell-mediated reaction is occurring, memory T cells are also forming to provide a

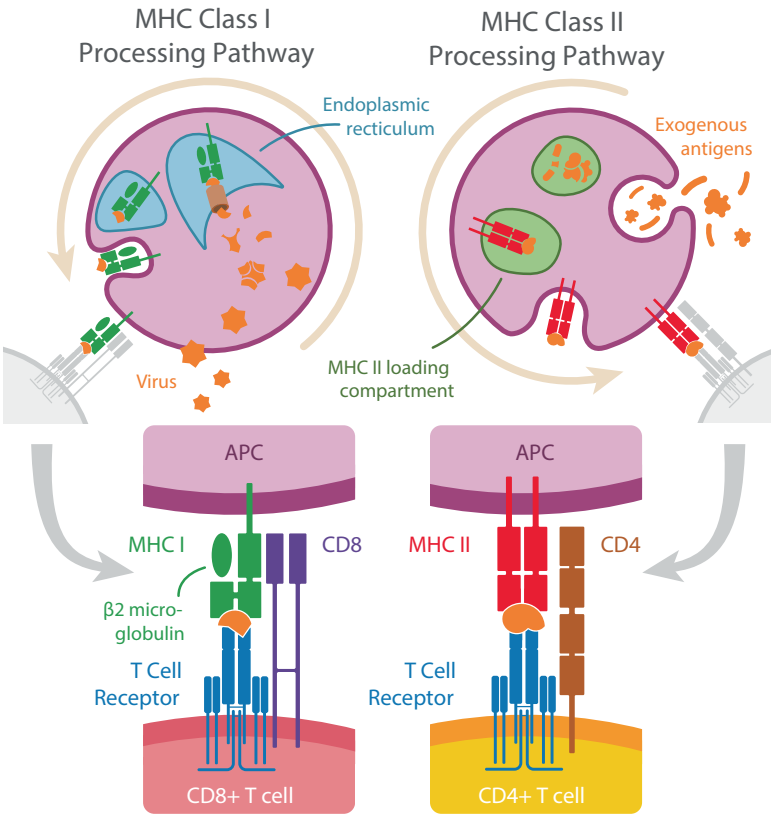

Fig. 1 Antigen presentation pathways. The MHC class I processing pathway (left) involves limited catabolism of cytosolic proteins into peptides which are then transported into the endoplasmic reticulum for loading onto MHC class I molecules. These MHC class I-peptide complexes traffic to the cell surface for presentation to TCRs on CD8+ T cells. The MHC class II processing pathway (right) involves limited catabolism of exogenous protein antigens within vesicular compartments. Peptides are loaded onto MHC class II molecules in the MHC II loading compartment. MHC class II-peptide complexes traffic to the cell surface for presentation to TCRs on CD4+ T cells

reservoir of antigen-specific T cells which have the properties of longevity and more rapid and robust activation for future encounters with the same pathogen. Following elimination of antigen, the large population of antigen-specific effector T cells that has formed through clonal expansion is markedly reduced, leaving behind a more modest but still important population of memory T cells. Notably, in chronic infections where antigen cannot be fully eliminated, T cell activation persists through repeated encounters with peptide-presenting APCs. T cells in this situation take on an "exhausted" phenotype, becoming recalcitrant to repeated stimulation and less robust in their cytokine secretion and cytotoxic activity.

Cells of the Innate Immune System

Here, I will briefly describe the major cell types of the innate immune system. Note that some effector arms of the innate immune system, including complement, will not be covered.

Granulocytes. These can be divided into neutrophils, basophils, and eosinophils. They are myeloid cells that produced in the bone marrow and traffic via the blood to sites of inflammation. Each of these has specialized granules which can be deployed upon cell signaling and which contain compounds toxic to microbes. There are examples of these cells playing roles in the immune response to cancer as regulators of the tumor microenvironment (TME), sometimes in a manner that promotes tumor growth or immune evasion, and at other times playing tumoricidal roles [1, 2]. Different tumor types may have different interactions with these cells. Neutrophils, in particular, have been associated with establishment of the pre-metastatic niche [3]. Furthermore, neutrophil-like myeloid-derived suppressor cells (MDSCs), sometimes called granulocytic or polymorphonuclear MDSCs, have been described that also can suppress anti-tumor adaptive immune responses [4].

Cells of the mononuclear phagocyte system. This collection of mononuclear cells encompasses monocytes, macrophages, and DCs. Monocytes are blood-circulating myeloid cells that form in the bone marrow and possess the properties of cell migration, phagocytosis, pathogen recognition, cytokine production, and antigen presentation [5]. Upon pathogen encounter and/or activation by inflammatory cytokines, these cells can differentiate into various forms of cells that morphologically resemble the other cells of this lineage, creating significant nomenclature issues in the field (e.g. so-called inflammatory macrophages or monocyte-derived DCs) [6]. Monocyte responses to tumors, like granulocytes, can probably be both pro- and anti-tumoral, and monocyte-like MDSCs also have been identified and characterized [4].

Macrophages refer to a set of tissue-resident large phagocytes present in all organs in the steady state. Organs are seeded during embryogenesis with macrophage progenitors from either the yolk-sac or fetal liver, and in most organs mature macrophages are self-renewing [7]. In different organs, macrophages take on distinct features in response to environmental cues, such that historically these cells have been given diverse names (e.g. microglia, alveolar macrophages, red pulp macrophages of the spleen, Kupffer cells of the liver) and have been appreciated for their morphologic differences. Tissue-resident macrophages are important in tissue homeostasis and can respond to pathogens by enhanced phagocytosis, microbicidal activity, and cytokine production. These cells can also present antigenic peptides via surface MHC molecules to T cells. To different degrees in different organs, tissue-resident macrophages are replaced with age by blood-monocyte derived cells in the steady state. Monocytes respond to environmental cues and adopt the phenotype of embryonically derived macrophages, such that in adults, tissue-resident macrophages represent a mixture of cells derived from embryonic precursors and monocytes [8]. Tumors contain a complex array of macrophages, including some derived from their organ's originally resident macrophage population, and others derived from blood monocytes that have entered the tumor [9]. It is common for

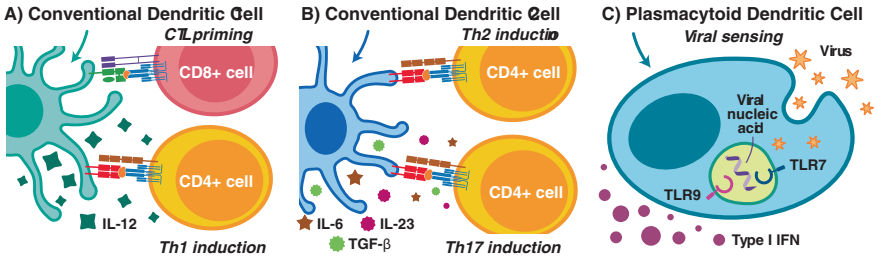

Fig. 2 Dendritic cell subsets and functions. Three subsets of DCs, (A) cDC1s, (B) cDC2s, and (C) pDCs, are shown performing their classic functions. cDC1s prime CTL responses and provide the cytokine signals needed for the instruction of Th1 cell responses. cDC2s provide the cytokine signals needed for the instruction of Th2 cell and Th17 cell responses. pDCs recognize viral nucleic acids and are rapid producers of type I IFNs

macrophages in tumors to be designated "tumor-associated macrophages", typically referring to cells with tumor-supporting characteristics, although this is an oversimplification that does not appreciate their heterogeneity [10].

DCs are bone-marrow derived cells present in all tissues and exist in three basic subsets, conventional DC1s (cDC1s), cDC2s, and plasmacytoid DCs (pDCs) [11] (Fig. 2). These subsets also exist in lymphoid organs. The two cDC subsets are premier APCs and, based on their collection of ligands for T cell-expressed costimulatory receptors and their cytokine production, are especially capable of priming naïve T cells. cDC1s are important in the priming of CD8+ T cells [12], with cDC2s having been thought to have a stronger role in priming CD4+ T cells [13, 14]. cDC1s possess a specialized antigen presentation pathway called cross presentation, in which exogenous protein antigens captured through pinocytosis or phagocytosis can be catabolized to peptides presented on MHC class I molecules, the group of MHC molecules that presents peptide to CD8+ T cells [15]. In all other cell types, including non-hematopoietic cells, MHC class I-presented peptides derive from cytosolic protein antigens. cDCs of both subsets also perform typical antigen processing of exogenous protein antigens to present peptides on MHC class II molecules to CD4+ T cells. cDC presentation of tumor antigens is exceptionally important in the context of T cell immunity to tumors, with recognition that in some cases cDC1s are uniquely required for CD8+ T cell priming and T cell-mediated clearance of model immunogenic tumors [12]. Newer data also suggests cDC1s play an important role in priming CD4+ T cell responses to tumor antigens, with CD4+ T cells subsequently "licensing" cDC1s to optimally prime anti-tumor CD8+ T cell responses [16]. pDCs are specialized cells with a unique collection of pathogen recognition receptors and which produce large amounts of type I IFNs upon receptor signaling. This response is thought to be a means of rapidly responding to viruses. A role for pDCs in tumor immunity is unclear. Several attempts have been made to harness the power of DCs as cell-based therapeutics for the induction of a T cell response to tumor antigens [17]. In most cases, the cells used were dendritic in nature, but not *bona fide* cDCs. Rather, they were cells derived from blood monocytes following in vitro treatment with hematopoietic growth factors. Such monocyte-derived DCs may retain some of the antigen-presenting properties and T

cell priming abilities of *bona fide* cDCs, and therefore could be useful therapeutics. There continues to be interest in harnessing the power of cDCs to initiate or augment anti-tumor T cell responses.

Mast cells. These myeloid cells are rich in connective and mucosal tissues and are heavily loaded with secretory granules. They are best recognized for their role in allergic responses following triggering by Fc epsilon receptor-bound IgE in response to allergens. They can also respond to other diverse ligands including complement components and PAMPs. Their granules contain heparin, histamine, and proteases but they also release lipid mediators and cytokines that altogether can initiate a rapid and robust inflammatory response. Mast cells have been identified as a component of certain human tumors, and in different cases have been suggested to be pro- or anti-tumoral [18].

Innate and innate-like lymphocytes. Several types of innate and innate-like lymphocyte lineages have been identified with diverse functions. In general, many of these cell types are tissue-resident and some express a characteristic semi-invariant BCR or TCR for recognition of non-peptide ligands. These cells have homeostatic functions in tissues, but also are fast-acting and are important in the early phases of immune encounters with pathogens. This broad topic is beyond the scope of this chapter, but a few cell types deserve mention. Innate B cells, including B-1 cells and marginal zone B cells, secrete natural IgM important in the earliest phases of a primary immune response and may have immunoregulatory properties [19]. Innate-like lymphocytes (also called unconventional T cells) include natural killer T (NKT) cells, mucosal-associated invariant T (MAIT) cells, and γδ T cells [20]. These cell types secrete cytokines and/or display cytotoxic function in response to activation of their semi-invariant TCRs by specific ligands which are often derived from the microbiota [21]. Whether they play roles in immune responses to tumors remains unclear [22]. Finally, classical natural killer (NK) cells and innate lymphoid cells (ILCs) are non-TCR-expressing lymphocytes which share properties of cytotoxicity and cytokine production with T cells. NK cells utilize an array of activating and inhibitory ligands to sense cells experiencing various forms of cell stress and can be potent cytotoxic cells. NK cells are thought to be a component of tumor immunosurveillance [23]. ILCs exist as three tissue-resident subsets (ILC1, ILC2, and ILC3) that secrete distinct cytokines and have roles in tissue homeostasis [24]. Their roles in cancer are less clear. Importantly, and related to the chapters that follow, attempts are being made to harness the therapeutic potential of innate lymphocytes, especially NK cells, for the treatment of cancer [25].

Cells of the Adaptive Immune System

B cells. These lymphocytes develop in the bone marrow through a process of antigen receptor gene rearrangement of the immunoglobulin heavy and light chain genes, a process called V(D)J rearrangement [26, 27]. Developing B cells proceed through a series of defined stages in which their rearranged immunoglobulin genes are tested for function, but also for self-reactivity. Naïve, mature B cells emerge

from this process that are selective for non-self antigens with each B cell expressing a unique BCR that contains 2 identical antigen-binding regions. In naïve B cells these BCR molecules utilize specific constant regions determined by gene rearrangements of the heavy chain locus, such that these cells express BCRs of the IgD and IgM isotype. Transmembrane BCR proteins associate with short transmembrane proteins that contain cytosolic tails which can be phosphorylated upon BCR engagement by antigen. Naïve B cells circulate through the blood and lymphoid tissues scanning for their cognate antigen. Upon antigen binding, cell signaling pathways are triggered, largely involving phosphorylation events, leading to complex changes in transcription, metabolism, and cytoskeletal structure [28]. This process is called B cell activation. Antigen-activated B cells proliferate clonally and take on various phenotypes including forms that secrete immunoglobulin. Secreted immunoglobulin maintains the antigen specificity and basic structure of the transmembrane BCR, but instead does not express a transmembrane portion, allowing the protein to traffic intracellularly for glycosylation and ultimately secretion. B cells that receive T cell help in the form of cytokines and cell-cell interactions in the lymph node undergo complex phenotypic changes to result in clonal production of memory B cells and long-lived plasma cells, a process termed the germinal center reaction [29, 30]. This topic is beyond the scope of this chapter.

T cells. These lymphocytes develop from dedicated progenitors that leave the bone marrow and travel to the thymus for completion of development. Here, T cell precursors undergo v(D)J recombination to ultimately express a mature TCR and the associated transmembrane signaling molecules (generally referred to as the CD3 complex). During this process selection occurs such that T cells with high reactivity for self-peptides presented by MHC molecules on thymic APCs are eliminated (negative selection). Further, only T cells with low affinity recognition for self-peptide with MHC molecules receive survival signals (positive selection). T cells with TCRs that are ignorant (i.e. have no recognition) of self-peptide/MHC are eliminated by apoptosis.

During this education process in the thymus, TCRs with low affinity for self-peptide and MHC class I molecules take on the phenotype of "cytotoxic T lymphocytes' (CTLs) and express the surface protein CD8. Likewise, other TCRs with low affinity for self-peptide and MHC class II molecules direct cells to become CD4-expressing "helper" T cells. As reviewed earlier, each naïve T cell that develops expresses a single TCR specificity that has a unique reactivity with a foreign (but not yet "seen") peptide in the context of one self MHC molecule (this is referred to as MHC restriction).

T Cell Activation and Effector Functions

CD8+ T cells are recognized for their ability to rapidly kill target cells through a process that involves perforin and granzyme secretion in response to TCR recognition of cognate antigenic peptide presented by an MHC class I molecule. TCR

signaling and costimulation, most notably through CD28 binding to B7 molecules during priming by DCs, results in a phenotypic change in CD8+ T cells to become effector cells with increased perforin- and granzyme- containing granules and heightened cytokine secretion. CD8+ T cell proliferation is rapid, such that antigen-specific clones expand by several logs over the first week of an immune response to a pathogen. Many of these effector CD8+ T cells will eventually die by apoptosis after pathogen clearance, although some responding CD8+ T cells will phenotypically change during an immune response to become a heterogenous set of long-lived memory cell types. CD8+ T cells responding to chronic stimulation, in the form of non-resolving chronic infections or tumor antigens, however, undergo further phenotypic changes to become "exhausted" [31]. This phenotype is characterized by metabolic alterations, lower cytotoxicity, and lower cytokine secretion (particularly IL-2, TNFα, and IFNγ). Exhausted T cells express a collection of negative costimulatory molecules, the most recognized of which is PD-1. Enhanced negative costimulation and chronic cytokine stimulation by IL-10 and TGFβ contribute to T cell exhaustion.

CD4+ T cells orchestrate immune responses through their elaboration of cytokines and their direct interaction with antigen presenting B cells. They play important roles in the establishment of CD8+ T cell memory, as well. Upon activation through TCR signaling and costimulation, CD4+ T cells expand clonally (Fig. 3). During priming by DCs, instructive cytokines determine the gene expression profile of activated CD4+ T cells, such that they take on stereotypical "T helper subset" phenotypes through the actions of specific transcription factors. Activated CD4+ T cells have been divided into five basic subsets (Th1, Th2, Th17, Tfh, and Treg). Th1, Th2, and Th17 cells are marked by the production of their hallmark cytokines IFNγ, IL-4, and IL-17A, respectively [32, 33]. Each of these subsets is tailored to the response to a specific pathogen type (intracellular pathogens for Th1 cells,

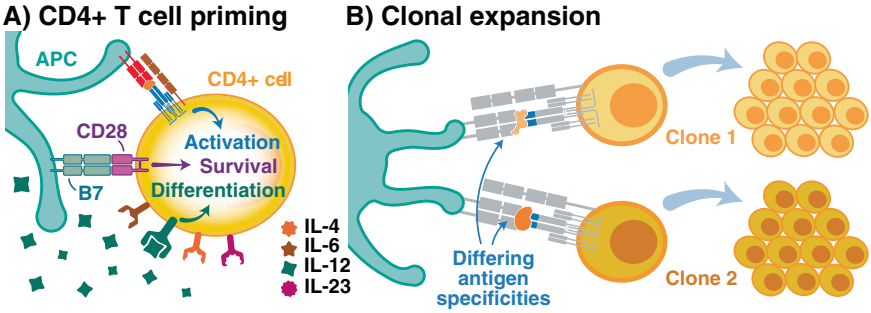

Fig. 3 Activation and expansion of CD4+ T cells. (A) CD4+ T cell priming requires three signals. The TCR recognizes cognate MHC class II peptide complexes on the surface of the APC. Costimulatory molecules like CD28 signal in response to binding of their ligands. Cytokine receptors signal in response to secreted cytokines. Together these signals lead to activation, survival, and differentiation of the CD4+ T cell. (B) Different CD4+ T cells, each with specificity for a distinct peptide ligand, will proliferate in response to these activating signals to generate expanded clones

helminths for Th2 cells, and extracellular bacteria and fungi for Th17 cells). T follicular helper (Tfh) cells play a specific role in the germinal center response by providing signals to activated B cells to instruct their somatic hypermutation and isotype switching. T regulatory cells (Tregs) play an immunoregulatory role in suppressing autoreactive cells through a variety of mechanisms including elaboration of immunosuppressive cytokines. Beyond these five basic subsets, other T helper cell subsets have been recognized based on their production of specific inflammatory cytokines, but these, in general, are not as well characterized. Each of the T helper cell subsets can play important roles in tumors in different contexts and can recognize tumor antigens [34].

Basics Principles of T Cell-Mediated Immunity to Cancer and Immune Evasion

Immunosurveillance is the process whereby the immune system can recognize cancer cells and eliminate them before they progress to tumor formation or effects on health. This is understood to be the domain of classical T cells and requires functioning antigen presenting cells and the action of innate immune cells to allow effective T cell priming and effector function. There are also roles for innate-like lymphocytes and ILCs in the recognition of tumor cells through changes in tumor cell expression of MHC molecules and stress ligands which serve to activate NK cells, NKT cells, and γδ T cells [35–37]. A three-phase process encompassing an elimination phase, an equilibrium phase, and an escape phase has been described to explain the interaction of lymphocytes with tumor cells ultimately tumor growth. The initial phase involves successful elimination of malignant cells upon first recognition, a second phase in which malignant cells develop alterations to become partially resistant to lymphocyte cytotoxicity, and ultimately a phase in which variant malignant cells have the ability to completely resist the action of lymphocytes and grow unchecked. This sculpting of the biology of tumor cells by the immune system to select for those that can escape immune pressure is termed immunoediting [38–40]. The avoidance of immune recognition includes genetic and epigenetic changes such that tumor cells can reduce their expression of MHC molecules, alter their expression tumor antigens, express soluble factors or membrane proteins that negatively regulate T cells, or change the tumor microenvironment to include immune cells that result in T cell suppression, including Tregs and MDSCs.

CD4+ and CD8+ T cells recognize peptides derived from tumor antigens in the same way they would recognize foreign peptides, and DCs are critical for priming of these T cell responses. Tumor antigens can be divided into three basic types that are important to recognize when designing or utilizing adoptive cell therapy. Tumor-associated antigens are overexpressed normal proteins that either play a role in oncogenesis or represent a protein expressed at high levels by both tumor cells and normal cells of the same origin (“differentiation” antigens). T cells are normally tolerant to these antigens, but they can be useful targets of certain forms of

immunotherapy. Tumor-restricted antigens, also referred to as "cancer-testes" antigens, are proteins which are normally only expressed on germ cells but become aberrantly expressed on tumor cells. These can be immunogenic and can be recognized by T cells. Tumor-specific antigens are either viral proteins expressed in tumor cells by oncogenic viruses or mutated self-proteins. This latter group, termed neoantigens, encompass either peptides derived from oncogenic proteins or "passenger" mutations to non-oncogenic proteins such that the amino acid changes result in a peptide that can be presented by MHC molecules and recognized as foreign by T cells. Neoantigenic peptides presented by MHC class I molecules to CD8+ T cells have garnered the most attention, but similar peptides exist that are presented by MHC class II molecules to CD4+ T cells. Optimal anti-tumor T cell responses require the priming of both types of T cells, and tumors with a higher mutational burden possess more neoantigens. Neoantigen-based cancer vaccines offer the promise of identifying neoantigens in a personalized fashion and delivering a vaccine that could prime or boost T cells specific to these peptides [41].

Finally, a few words on the three most prominent forms of cancer immunotherapy, immune checkpoint blockade, T/NK cell engagers, and adoptive T cell therapy [42]. Immune checkpoint blockade refers to monoclonal antibody-based therapeutics which block negative costimulatory molecule signaling on T cells. The most prominent negative costimulatory molecules expressed on T cells to date are CTLA4 and PD-1, and agents targeting these have been remarkably successful at inducing profound anti-tumor responses in a subset of patients in a variety of cancer types. These work, in general, through enhanced activation of T cells and increased proliferation, effector function, and memory cell development. They may also have negative effects on Tregs such that the tumor microenvironment becomes more amenable to the action of effector T cells. Other negative costimulatory molecules on T cells are also of considerable interest as targets for novel checkpoint inhibitors.

T/NK cell engagers are engineered multi-functional antibody-like proteins with at least one antigen-binding site specific for a T cell or NK cell activating receptor and at least one antigen-binding site specific for a surface-expressed tumor-associated antigen. T/NK engagers coordinate an interaction between a lymphocyte and a tumor cell to promote direct tumor cell killing.

Adoptive T cell therapy refers broadly to the injection of patient-derived or allogenic T cells aimed at promoting an anti-tumor response. "Donor lymphocyte infusions" can be a component of allogeneic hematopoietic stem cell transplantation and mediate graft vs. tumor effects. Other forms of adoptive T cell therapy include the in vitro expansion and reinfusion of patient-derived tumor-infiltrating lymphocytes (TILs) that target tumor antigens, TCR gene-modified T cells (TCR-T), viral specific cytotoxic lymphocytes (viral CTLs), NK cells, and chimeric antigen receptor T cells (CAR-T cells). In particular, the last few years has seen an explosion in interest in CAR-T cells and related forms of engineered cells that are the subject of many of the subsequent chapters in this volume. These cells are being designed with specificity for new target antigens that may allow them to target solid tumors and are being modified to enhance their trafficking, function, and longevity. Challenges for both immune checkpoint blockade-based therapies, T/NK cell engagers, and

adoptive cell therapies include patient selection, serious immune-mediated adverse events, high cost, and treatment resistance. These challenges are being tackled by numerous basic, translational, and clinical studies, and the future is bright for cancer immunotherapy.

References

1. Duhan V, Smyth MJ. Innate myeloid cells in the tumor microenvironment. Curr Opin Immunol. 2021;69:18–28.
2. Mattei F, Andreone S, Marone G, et al. Eosinophils in the tumor microenvironment. Adv Exp Med Biol. 2020;1273:1–28.
3. Jablonska J, Lang S, Sionov RV, Granot Z. The regulation of pre-metastatic niche formation by neutrophils. Oncotarget. 2017;8:112132–44.
4. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol. 2021;1:1–14. (Epub ahead of print)
5. Guilliams M, Mildner A, Yona S. Developmental and functional heterogeneity of monocytes. Immunity. 2018;49:595–613.
6. Guilliams M, Ginhoux F, Jakubzick C, et al. Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol. 2014;14:571–8.
7. T'Jonck W, Guilliams M, Bonnardel J. Niche signals and transcription factors involved in tissue-resident macrophage development. Cell Immunol. 2018;330:43–53.
8. Liu Z, Gu Y, Chakarov S, Bleriot C, et al. Fate mapping via Ms4a3-expression history traces monocyte-derived cells. Cell. 2019;178:1509–25.
9. Zhu Y, Herndon JM, Sojka DK, et al. Tissue-resident macrophages in pancreatic ductal adenocarcinoma originate from embryonic hematopoiesis and promote tumor progression. Immunity. 2017;47:323–38.
10. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. Nat Rev Immunol. 2019;19:369–82.
11. Anderson DA 3rd, Dutertre CA, Ginhoux F, Murphy KM. Genetic models of human and mouse dendritic cell development and function. Nat Rev Immunol. 2021;21:101–15.
12. Hildner K, Edelson BT, Purtha WE, et al. Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity. Science. 2008;322:1097–100.
13. Dudziak D, Kamphorst AO, Heidkamp GF, et al. Differential antigen processing by dendritic cell subsets in vivo. Science. 2007;315:107–11.
14. Binnewies M, Mujal AM, Pollack JL, et al. Unleashing Type-2 dendritic cells to drive protective antitumor CD4+ T cell immunity. Cell. 2019;177:556–71.
15. Gros M, Amigorena S. Regulation of antigen export to the cytosol during cross-presentation. Front Immunol. 2019;10:41.
16. Ferris ST, Durai V, Wu R, et al. cDC1 prime and are licensed by CD4+ T cells to induce anti-tumour immunity. Nature. 2020;584:624–9.
17. Fu C, Zhou L, Mi QS, Jiang A. DC-based vaccines for cancer immunotherapy. Vaccines (Basel). 2020;8:706.
18. Aponte-López A, Muñoz-Cruz S. Mast cells in the tumor microenvironment. Adv Exp Med Biol. 2020;1273:159–73.
19. Grasseau A, Boudigou M, Le Pottier L, et al. Innate B cells: the archetype of protective immune cells. Clin Rev Allergy Immunol. 2020;58:92–106.
20. Pellicci DG, Koay HF, Berzins SP. Thymic development of unconventional T cells: how NKT cells, MAIT cells and γδ T cells emerge. Nat Rev Immunol. 2020;20:756–70.
21. Constantinides MG. Interactions between the microbiota and innate and innate-like lymphocytes. J Leukoc Biol. 2018;103:409–19.

22. Chou C, Li MO. Re(de)fining innate lymphocyte lineages in the face of cancer. Cancer Immunol Res. 2018;6:372–7.
23. Molgora M, Cortez VS, Colonna M. Killing the I\invaders: NK cell impact in tumors and anti-tumor therapy. Cancers (Basel). 2021;13:595.
24. Branzk N, Gronke K, Diefenbach A. Innate lymphoid cells, mediators of tissue homeostasis, adaptation and disease tolerance. Immunol Rev. 2018;286:86–101.
25. Cortés-Selva D, Dasgupta B, Singh S, Grewal IS. Innate and innate-like cells: the future of chimeric antigen receptor (CAR) cell therapy. Trends Pharmacol Sci. 2021;42:45–59.
26. Wang Y, Liu J, Burrows PD, Wang JY. B cell development and maturation. Adv Exp Med Biol. 2020;1254:1–22.
27. Chi X, Li Y, Qiu X. V(D)J recombination, somatic hypermutation and class switch recombination of immunoglobulins: mechanism and regulation. Immunology. 2020;160:233–47.
28. Tanaka S, Baba Y. B cell receptor signaling. Adv Exp Med Biol. 2020;1254:23–36.
29. Elsner RA, Shlomchik MJ. Germinal center and extrafollicular B cell responses in vaccination, immunity, and autoimmunity. Immunity. 2020;53:1136–50.
30. Ise W, Kurosaki T. Plasma cell differentiation during the germinal center reaction. Immunol Rev. 2019;288:64–74.
31. McLane LM, Abdel-Hakeem MS, Wherry EJ. CD8 T cell exhaustion during chronic viral infection and cancer. Annu Rev Immunol. 2019;37:457–95.
32. Zhu X, Zhu J. CD4 T helper cell subsets and related human immunological disorders. Int J Mol Sci. 2020;21:8011.
33. Dong C. Cytokine regulation and function in T cells. Annu Rev Immunol. 2021;11:51. (Epub ahead of print)
34. Alspach E, Lussier DM, Miceli AP, et al. MHC-II neoantigens shape tumour immunity and response to immunotherapy. Nature. 2019;574:696–701.
35. Guillerey C. NK cells in the tumor microenvironment. Adv Exp Med Biol. 2020;1273:69–90.
36. Fujii SI, Shimizu K. Immune networks and therapeutic targeting of iNKT cells in cancer. Trends Immunol. 2019;40:984–97.
37. Willcox CR, Mohammed F, Willcox BE. The distinct MHC-unrestricted immunobiology of innate-like and adaptive-like human γδ T cell subsets - nature's CAR-T cells. Immunol Rev. 2020;298:25–46.
38. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol. 2004;22:329–60.
39. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331:1565–70.
40. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. Curr Opin Immunol. 2014;27:16–25.
41. Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol. 2021;20:1–15. (Epub ahead of print)
42. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. 2020;20:651–68.