Overview

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Anatomy and Physiology of the Immune System

The immune system is a complex network of metabolic pathways and cells, which are designed to distinguish harmful insults from harmless changes or fluctuations in metabolism and to mount an appropriate response to these harmful insults without compromising the affected tissue. Therefore, it walks a fine line to combat pathogens and cellular transformation on the one hand and to tolerate commensals on mucosal surfaces (such as normal gut bacteria), and food components, on the other hand.

Moreover, it has evolved to specifically meet the challenges of its respective host species concerning pathogens encountered in the ecological niche that the host occupies and during the time of reproduction that has to be protected to guarantee propagation of the species. Therefore, the differences even between closely related mammalian species are considerable, placing the immune system in third position of the most divergent organs between mouse and man [1, 2].

These challenges are met by the immune system with stringent education of its components to ignore the physiological state (which happens in so-called primary lymphoid organs such as the thymus or bone marrow) and by integration of afferent information (which happens in immunological decision centers, the secondary and tertiary lymphoid tissues such as spleen or lymph nodes). Concomitantly, efferent responses (cellular and humoral) to target harmful insults are mounted.

All soluble factors directed at insults are called humoral immune responses. These include invariant molecules like antimicrobial peptides or the alternative pathway of complement system and molecules of the adaptive immune system, mainly antibodies. The complement activation is part of the innate immune system and establishes pores in targeted cells (cell lysis), enhances phagocytosis of antigens (opsonization), and attracts macrophages and neutrophils (chemotaxis).

Antibodies are selected from a large repertoire that is generated by (1) somatic DNA recombination and then further shaped to recognize the targeted antigen with higher affinity and (2) additional effector mechanisms such as somatic hypermutation and class switch recombination, producing different subtypes of immunoglobulins (Ig).

The cellular immune responses include activation of cytotoxic effector cells and phagocytes. Again these responses can be innate (including natural killer cells and pathogen recognition by phagocytes, such as macrophages, using scavenger receptors), or they can be adaptive (including cytotoxic T cells and

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T-cell activation of phagocytes). Therefore, the immune system has a large armamentarium to restore the healthy steady state.

Specific Pathways and Metabolic Processes of the Immune System and Its Cells

Primary Lymphoid Tissues

The main primary lymphoid tissues are the thymus and the bone marrow, where T cells and B cells (also known as T and B lymphocytes) are educated, respectively. T cells can detect changes (such as the presence of foreign proteins) inside cells, whereas B cells secrete effector molecules, mainly antibodies to target extracellular pathogens. Selectivity of T and B cells is achieved by somatic recombination of their respective antigen receptor genes, followed by a stringent selection process to ensure they carry functional receptors, which do not recognize self-structures, such as endogenous proteins or sugar moieties on the surface of host cells [3, 4].

B cells develop from hematopoietic precursors in the bone marrow and are deleted by apoptosis if they fail to generate a functional antibody on their surface (see below) and also if this antibody recognizes self-structures in the bone marrow.

T cells originate from precursors that also develop in the bone marrow, but then migrate to the thymus. There, only T cells continue to develop, whose T-cell receptors recognize major histocompatibility complex (MHC) molecules, which in humans are also called human leukocyte antigen (HLA) molecules. These scaffolding proteins display products of the protein and lipid catabolism of thymic epithelial cells to the T cells. After this positive selection, T cells are eliminated by negative selection if they strongly react to MHC molecules that present self-structures, thus generating a central tolerance. In general, both cluster of differentiation 4-positive ($CD4^+$) T-helper (T_h) cells and $CD8^+$ cytotoxic T cells develop that recognize foreign structures, in particular extracellular and intracellular peptides, on MHC class II and class I molecules, respectively.

Secondary Lymphoid Tissues

Once the mature and educated T and B cells emerge from primary lymphoid organs, they home to secondary lymphoid organs like spleen, lymph nodes, tonsils, and gut mucosa-associated lymphoid tissues via the blood stream. In the secondary lymphoid organs, they extravasate from the blood in specialized endothelia, called high endothelial venules, in response to gradients of chemokines, attractants for migration, such as chemokine (C-C motif) ligand (CCL) 19 and 21 (Fig. 1).

For activation of T cells, processed foreign structures (mostly peptides) are presented on MHC molecules by dendritic cells (DCs) that have picked up these antigens at various sites of the body in order to carry them to secondary lymphoid tissues via afferent lymphatic vessels (Fig. 1) [5]. This antigen transport occurs from all organs, and therefore a dense network of secondary lymphoid tissues weaves through the body to keep the antigen transport times short. Once a T cell detects a specific antigen, it proliferates and differentiates.

T cells differentiate into effector cells, e.g., T_h1, T_h2, or T_h17 cells, which secrete different sets of cytokines to communicate with other immune and somatic cells, or into memory cells, which will continue to migrate through secondary lymphoid tissues and promptly respond by proliferation and defense mechanisms, in case the antigen comes back (Fig. 1).

Upon activation by cognate antigen recognition, B cells enter germinal centers in secondary lymphoid tissues [6]. At these sites, they mature their antigen receptor by somatic hypermutation (called affinity maturation) in order to produce antibodies that bind foreign structures called antigens with higher avidity. At the same time, they switch their antibody molecule isotype, e.g., from IgM to IgG, allowing them to acquire additional effector functions, like binding to Fc receptors on phagocytes, follicular dendritic cells, or cytotoxic cells and complement fixation. Only if the altered antibody still recognizes the antigen (signal 1), e.g., presented bound to the complement or Fc receptors on follicular dendritic cells,

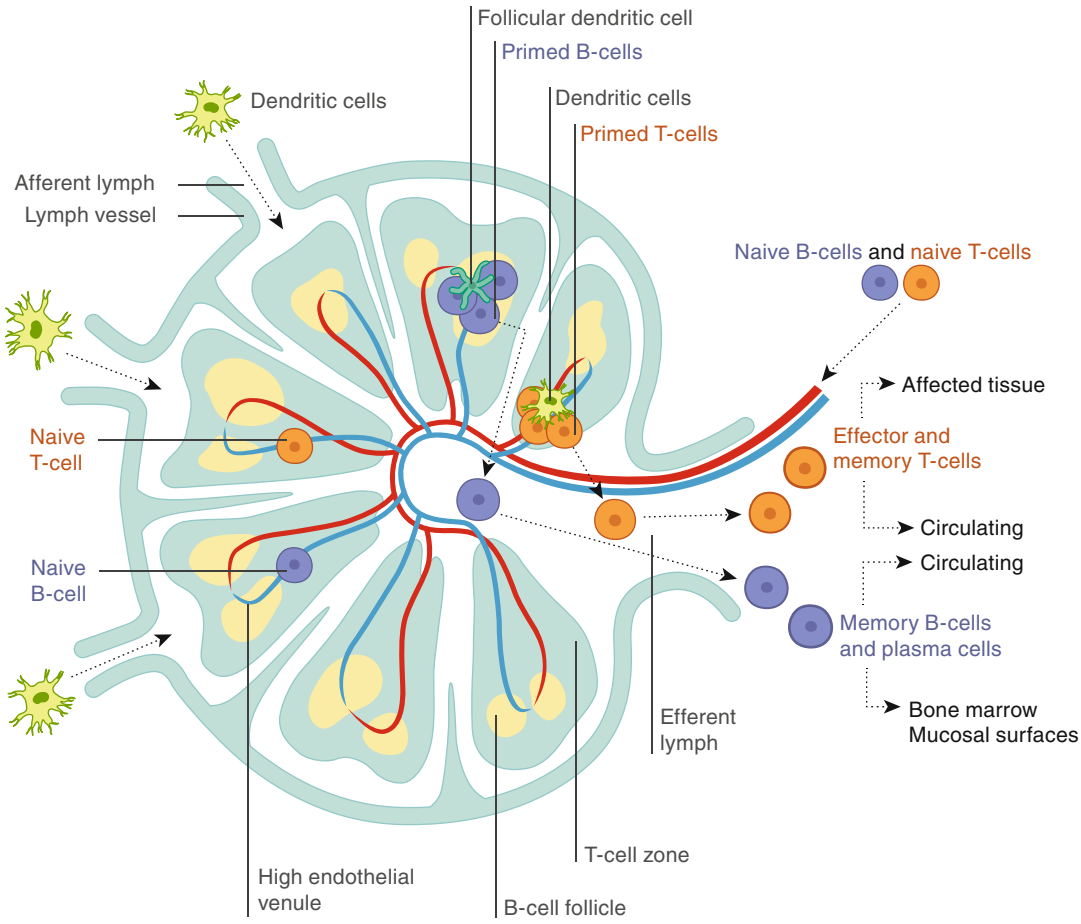

Fig. 1 Schematic section through a lymph node, a secondary lymphoid organ. Information on the health of peripheral tissues is continuously reported to the lymph nodes in the form of the degree and quality of dendritic cell (*DC*) activation. Processed peptide antigens are presented on the major histocompatibility complex (MHC) molecules of DCs. Naive and memory T cells circulate through these organs via extravasation at high endothelial venules and exit through efferent lymph vessels. T cells get activated when their T-cell receptors bind to antigens on activated DCs. T cells get primed (see text), proliferate, and differentiate into effector or memory T cells. Effector T cells then home back to the diseased tissue to fight the infection or assist B cells in the germinal center. There, antigen-stimulated B cells affinity mature their B-cell receptor, which will serve as blueprint for the antibody that will be later secreted by this B cell. The somatically mutated B-cell receptor has to still recognize the unprocessed, original antigen, bound on the surface of follicular DCs via complement or Fc receptors. The B cells still require T cell help (not shown). Only if these two checkpoints are passed, the activated B cell will go on to develop into a memory cell or an antibody producing plasma cell. These can also leave the lymph node via efferent lymph, and plasma cells often home to the bone marrow or mucosal surfaces. Note that the cells are displayed in higher magnification compared to the lymph node

and the B cell receives signals ("help") from a T cell (that in most cases has to recognize the same antigen but in a processed form preferential on MHC molecules, signal 2), the B cell survives this germinal center reaction and can go on to develop into a memory B cell or an antibody-secreting plasma cell.

T and B cells emigrate from secondary lymphoid tissues via the efferent lymphatics to the sites of the harmful insult guided by chemokine gradients, like the chemokine (C-X-C motif) ligand (CXCL) 9 and CXCL10 (Fig. 1). This process of immune response initiation is called priming.

Tertiary Lymphoid Tissues

In order to keep the distances for immune cell migration short and therefore the response time to a minimum, tertiary lymphoid tissues develop at sites of chronic immune cell infiltrates and inflammation [7]. These are similar in structure and function to secondary lymphoid tissues.

Outside-In: Communication of Stromal Cells with Immune Cells

The afferent arm of immune responses is mainly represented by DCs, which continuously report the immunological health of organs to secondary lymphoid tissues by transporting organ constituents and the conditions, under which they have acquired these as their surface molecule phenotype and cytokine secretion pattern. They can detect pathogens in all organs directly via receptors for pathogen-associated molecular patterns (PAMPs), such as bacterial cell wall components, viral unmethylated DNA, and viral RNA, which activate them. Alternatively, they can also detect organ or tissue destruction indicated by the release of danger-associated molecular pattern (DAMPs) [8, 9], like ureate crystals as well as extracellular high mobility group B1 protein and ATP release (Fig. 2). Some of these are recognized by inflammasomes, of which the NLRP3 containing protein complex is the best studied [8]. Their activation allows interleukin 1 (IL-1) production, which is the main mediator of inflammation causing heat, redness, pain, swelling, and loss of tissue function. Both, PAMPS and DAMPs, thus activate DC migration and immune response priming in secondary lymphoid organs. In addition, stromal cells can communicate with DCs via chemokines and cytokines. Therefore, the input by the organ environment is crucial for the afferent communication of the immune system with secondary lymphoid organs.

Inside-In: Communication Between Immune Cells

Chemokines (chemotactic cytokines), such as CXCL9 and CXCL10, are produced to build gradients in tissues to attract immune cells such as effector T cells. Immune cells (such as macrophages and T cells) communicate with each other and stromal cells through surface receptors that accumulate at membrane contact areas, so-called immunological synapses. Cytokines, e.g., interferon γ (IFNγ), are secreted into these synapses or to neighboring cells to further refine the communication between immune cells.

Three signals constitute the core of the communication between immune cells, which primarily happens in secondary lymphoid tissues between antigen carrying DCs and responding T cells (Fig. 2). The first signal is the presentation of catabolic products of antigens (mainly peptides) by DCs on MHC molecules to the T-cell receptor of T cells. These peptides originate from the two main proteolytic machineries of the cell, i.e., lysosomes and proteasomes [10]. Proteasomal products are presented on MHC class I molecules to cytotoxic $CD8^+$ T cells, whereas lysosomal products are presented on MHC class II molecules to helper $CD4^+$ T cells, which assist maintenance and differentiation of both primed $CD8^+$ T and B cells. This first signal induces proliferation of T cells, only if co-stimulatory signals (see below) are present. If these signals are absent, the antigen-specific T cells are eliminated after a few cell divisions, a process contributing to peripheral tolerance [11].

Thus, activated DCs save the proliferating T cells from dying by releasing cytokines and other co-stimulatory molecules, like IL-12 and IL-15, toward them, and shape their profile [12]. These cytokines imprint information about the conditions, under which DCs have been activated, onto the responding T cell. For example, IL-12 favors the development of T_h1 polarized T cell responses and is mainly secreted by DCs after virus encounter. A T_h1 response can trigger the destruction of virus-infected cells by cytotoxic T cells. Furthermore, this so-called polarization also gives $CD4^+$ T cells a certain profile of chemokine receptors that will direct them to the tissues, in which the DCs had been activated. For example, the C-C chemokine receptor type 9 is required for homing $CD4^+$ T cells to the gut [13], while $CD8^+$ T cells acquire a less variant chemokine receptor repertoire that will direct them to sites of inflammation. There, a tailored response is mounted, including the

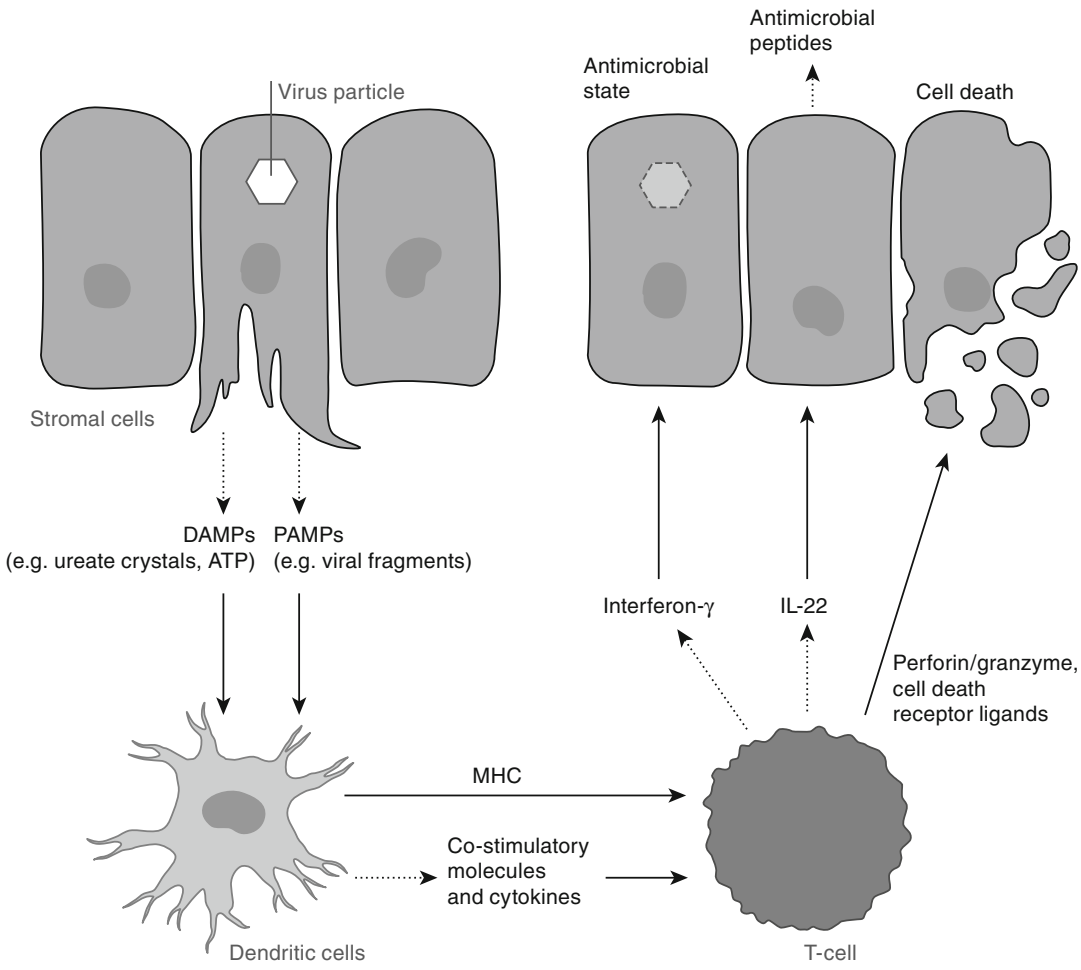

Fig. 2 Schematic pathway of dendritic cell and T-cell activation and subsequent cellular changes. The immune system receives cues from all organs. Stromal cells in an inflamed or infected tissue can activate dendritic cells through the release of danger- (*DAMPs*) and, if infected, pathogen-associated molecular patterns (*PAMPs*), which are, e.g., contained in necrotic cellular debris. Once activated, dendritic cells can prime T cells in secondary or tertiary lymphoid tissues. The T cells then home to the tissue to change its intracellular milieu and its secretome via interferon (*IFN*) and interleukin (*IL*) secretion, e.g., IL-22 and IFNγ. Primed T cells also influence the survival of the cells within an inflamed tissue via cell-contact-dependent cytotoxicity, e.g., via perforin/granzyme or apoptosis-inducing ligands

secretion of cytokines, acting on the infected or transformed tissue, e.g., IFNγ to inhibit viral replication, and the expression of cytotoxic molecules, e.g., perforin-1, to directly destroy the diseased cells.

Distinct metabolic pathways, such as macroautophagy [14], are required for T-cell proliferation [15], which also occurs locally in infected tissues, presumably to further amplify the T-cell response. Oxidative phosphorylation generates most ATP in resting T cells. However, activated T cells dramatically increase their rates of glycolysis and lactate production. Importantly, glucose is strictly required for T-cell proliferation and cytokine production, even when other metabolic substrates such as glutamine or fatty acids are present, likely due to the ability of glucose metabolism to consistently generate ATP and NADPH and stabilize antiapoptotic proteins [16]. Moreover, aerobic glycolysis is necessary for T-cell effector function, in particular for IFNγ production [17]. Finally, whereas most T cells rely on glycolysis, a subset of T cells (such as regulatory T cells, also called T_{reg}, or $CD8^+$

memory T cells) requires fatty acid oxidation, showing that energy metabolism influences immune responses [16].

Inside-Out: Communication of Immune Cells with Stromal Cells

The effector molecules from polarized T cells are then able to change tissue homeostasis in the inflamed and/or infected organs, from which the DCs carried the antigens to the secondary lymphoid organs. A wide variety of responses can be elicited, ranging from metabolic changes in target cells to release of antimicrobial peptides, or to induction of apoptosis. Metabolic changes aim to make cells less hospitable for infectious agents and reduce pathogen replication. For example, IFNs can induce an antiviral state in part by inhibiting anabolic pathways required for virus production [18]. Secretion of antimicrobial peptides by epithelial cells at mucosal surfaces is stimulated by IL-22, which is either secreted by innate lymphoid cells or T_h17 polarized $CD4^+$ T cells [19]. Cell death can be triggered by cytotoxic $CD8^+$ T cells via perforin-mediated granzyme injection into an infected target cell. During this process, at least one of the cell death initiating proteases of the granzyme family enters the target cell through pores that are formed by perforin. Alternatively, a cytotoxic T cell kills an infected or transformed cell by activation of its cell death receptors (Fig. 2) [20]. Thus, immune cells can dramatically change cellular physiology within an inflamed organ.

Miscommunication in the Immune System as the Basis of Disease

The borderline between hyporesponsiveness of the immune system resulting in susceptibility to disease [21] and hyperresponsiveness leading to immunopathology and autoimmunity [22] is not easily defended by the immune system and drawn by the genetic makeup of the individual. Any significant insult that releases DAMPs can change the organ environment and metabolism so that it is no longer recognized as self by the immune system. This is in part explained by the circumstance that the lymphocytes were educated toward a different steady state. Sometimes the resulting autoimmune responses are transient, just causing immunopathology during the infectious or traumatic insult. However, sometimes, but fortunately rarely, they result in self-perpetuating autoimmune disease [22], depending in part on the genetic variation of the affected individuals (see, e.g., chapters "Rheumatoid arthritis" and "Diabetes mellitus").

Final Remarks

The key physiological function of the immune system is to defend multicellular organisms against harmful "nonself" by transporting information from organs to secondary lymphoid tissues and mounting immune responses when this information indicates infection or tissue damage. Both overshooting (see chapter "Rheumatoid arthritis") and too cautious immune reactions (see chapter "Community-acquired pneumonia") lead to disease and are caused by the combination of the individual's genetic predisposition and the environmental conditions.

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