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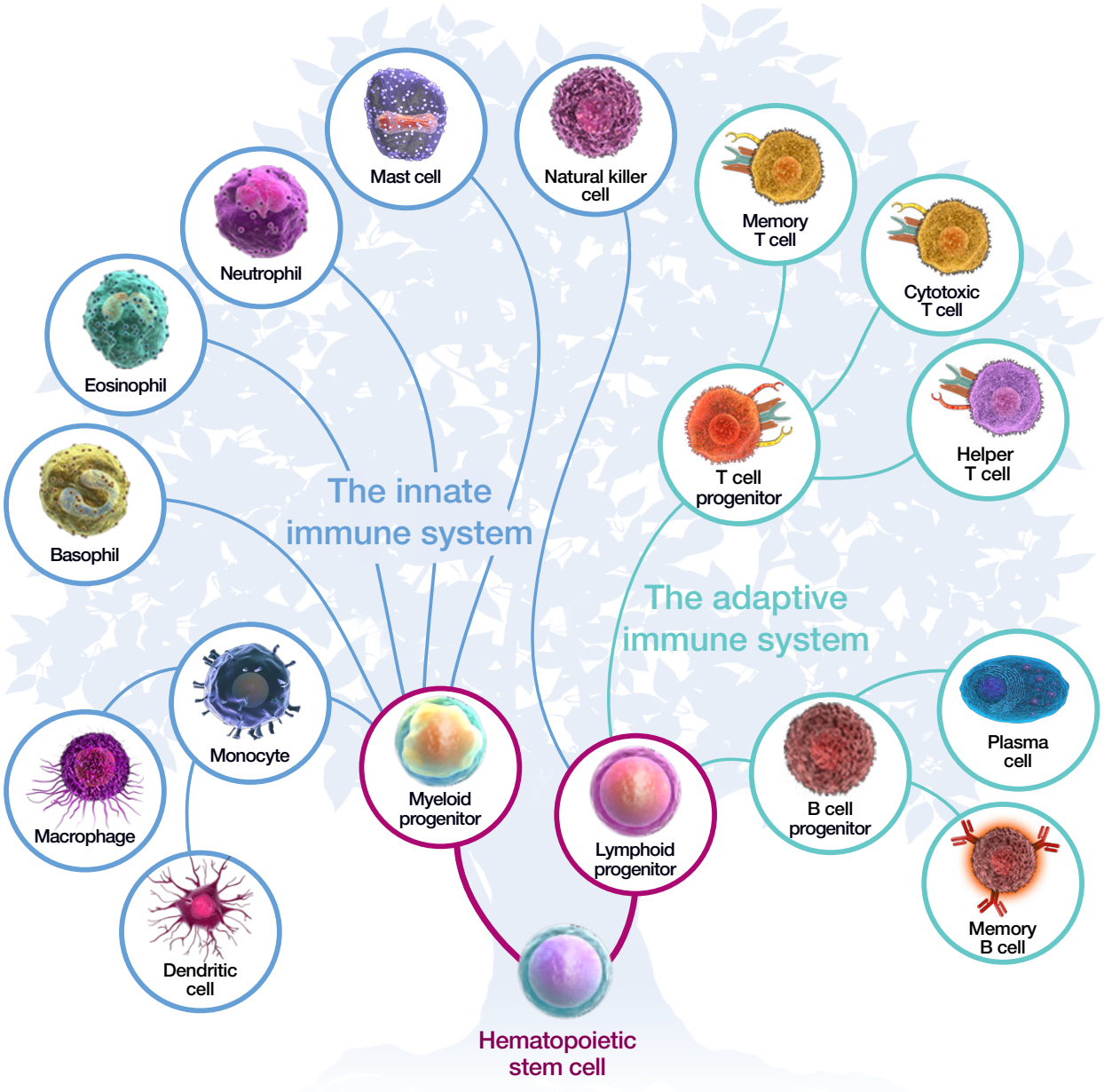
Cells of the immune system

The immune system is the body's defense against infections and diseases, and consists of two major arms—the innate immune system and the adaptive immune system. Both parts are composed of many cell types, each with its own specialty, that work together to fight off diseases and help maintain the body's health [1]. All cells of the immune system develop from hematopoietic stem cells located in bone marrow. The hematopoietic stem cells give rise to lymphoid and myeloid progenitors—each of which differentiates into a variety of cell types. The myeloid lineage consists mostly of innate immune system cells, whereas the lymphoid progenitors differentiate into three categories of cells: B cells, T cells, and natural killer (NK) cells [2-4].



Hematopoietic stem cell			
		Self-renewal cytokines	**Expansion cytokines**
	Hematopoietic stem cell	SCF; TPO	Flt3 ligand; SCF; TPO; IL-3; IL-6

The innate immune system				The adaptive immune system			
		Differentiating cytokines*	**Secreted cytokines***			**Differentiating cytokines***	**Secreted cytokines***
	Myeloid progenitor	IL-3; IL-6; EPO; GM-CSF; G-CSF			Lymphoid progenitor	IL-7	
	Monocyte	GM-CSF; G-CSF			B cell progenitor	IL-3; IL-4; IL-6; IL-7; SCF	
	Macrophage	IFN-γ; IL-6; IL-10; M-CSF	TGF-β; TNF-α; VEGF; IL-1β; IL-6; IL-10; IL-12		Plasma cell	IL-4; IL-5; IL-10; IL-21; TGF-β; IFN-γ	
	Dendritic cell	Flt3 ligand; GM-CSF; IFN-α; IL-4	IL-1α; IL-1β; IL-4; IL-6; IL-10; IL-12; TGF-β; IFN-α; IFN-γ		T cell progenitor	IL-2; IL-7; Notch	GM-CSF; TGF-β; TNF-α; IL-4; IL-6; IL-10; IL-12
	Eosinophil	IL-3; IL-5; GM-CSF	TGF-β; VEGF; PDGF-BB; TNF-α; IL-1α; IL-1β; IL-2; IL-4; IL-5; IL-6; IL-8; IL-12; IL-13		Helper T cell**	IL-2; IL-4; IL-6; IL-12; TGF-β; IFN-γ	IFN-γ; TNF-α; TGF-β; IL-4; IL-5; IL-6; IL-9; IL-10; IL-13; IL-17; IL-21; IL-22
	Basophil	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; IL-4; IL-6; IL-13		Cytotoxic T cell	IL-2; IL-5; IL-7; IL-12	IFN-γ; TNF-α; TNF-β; IL-2; sFas ligand
	Mast cell	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; GM-CSF; IL-3; IL-4; IL-5; IL-6; IL-8; IL-13				
	Neutrophil	IL-6; GM-CSF; G-CSF; SCF	APRIL; sRANK ligand; TNF-α; TGF-β; VEGF; IL-1α; IL-1β; IL-6; IL-12; IL-18; IL-21				
	NK cell	IL-15	GM-CSF; IFN-γ; TNF-α; MIP-1α; MIP-1β; IL-5; IL-10; IL-17; IL-22				

* The list of differentiating and secreted cytokines is partial.

** All of the secreted cytokines are secreted by different subsets of helper T cells.

The innate immune system

The innate immune system is the body's first line of defense and provides a quick-yet-general immune response, while the adaptive immune system works by detecting and eliminating specific pathogens that threaten the body. While both systems work to fight off infections, the adaptive immune system takes much longer to respond than the innate immune system. The activity of the cells of the innate system is based on pattern recognition receptors (PRRs)—special proteins that engage in detecting conserved antigens of groups of bacteria and viruses. There are two types of structures that are recognized by PRRs: pathogen-associated molecular patterns (PAMPs) that are involved in pathogen recognition, and damage-associated molecular patterns (DAMPs) that function in recognizing damaged cells [5, 6]. There are several families of PRRs that include:

toll-like receptors (TLRs) involved in microbial recognition, | **C-type lectin receptors (CLRs),** which are major fungi receptors, and | **retinoic acid–inducible gene I (RIG-I)–like receptors (RLRs)** that recognize RNA viruses.

Unlike PRRs, which are germline-encoded, fixed, and limited in number, antigen-specific T cell receptors (TCRs) and B cell immunoglobulin (Igs) of the adaptive immune system are the result of somatic gene rearrangements and can recognize practically any antigen [3].

Hematopoietic lineage of the innate immune system

Myeloid progenitors give rise to neutrophils, eosinophils, basophils (named after their staining characteristics), mast cells, and monocytes, which further differentiate into dendritic cells (DCs) and macrophages [2, 4].

Neutrophils, together with eosinophils and basophils, are granulocytes (cells containing granules) and belong to a family of leukocytes known to be polymorphonuclear (PMN) because of their multi-lobed nuclei. Neutrophils are the most common phagocytes, being the first to arrive at the site of tissue damage. They specialize in phagocytosis and digestion of pathogens, especially bacteria, throughout the body [2, 4].

Eosinophils possess kidney-shaped, lobed nuclei that release the content of their granules in order to extracellularly digest pathogens, especially parasites, as well as secrete a variety of cytokines and growth factors that affect other cells of the immune system.

Although they are the least common granulocytes, **basophils** are the largest of the granulocytes, exhibiting bi-lobed nuclei and histamine-rich granules. Basophils are involved in a variety of inflammatory reactions, including reactions associated with allergic symptoms and are an important source of IL-4, a cytokine responsible for inducing the differentiation of naïve to mature T helper (Th) cells [2, 4].

Mast cells are tissue-resident granulocytes that secrete histamine and heparin among other factors involved in the defense against parasites, wound healing, and angiogenesis [2, 4].

Monocytes, the largest of the white blood cells, give rise to the two other types of professional antigen-presenting cells (APCs), dendritic cells (DCs) and macrophages [2, 4].

DCs are present mostly in tissues that are in contact with the environment outside the body, such as the skin, lungs, and intestines. DCs are regarded as the most efficient APCs, and their main function is to process, present, and cross-present antigens to T and B cells. Upon activation, they are also able to secrete cytokines like IL-6, IL-10, and IL-12 [2, 4].

Macrophages (from Greek, "makrós" and "phagein" meaning "big eaters") are phagocytic scavengers that engulf and process a variety of unwanted materials that differ from healthy cells, such as cellular debris, pathogens, and cancer cells. They are tissue residents and have specific names according to their respective location. Activated macrophages are divided into two major groups, M1 and M2. M1 macrophages have pro-inflammatory activities, while the M2 macrophages are involved in wound healing and tissue regeneration as well as exhibiting anti-inflammatory properties [2, 4].

NK cells are cytotoxic cells, with small granules in their cytoplasm containing perforins and granzymes, which are used to kill their target cells. They are generated from the common lymphoid progenitor, which also produce B and T lymphocytes, but they belong to the innate immune system. NK cells destroy cancerous and infected cells by a rapid response, without the need for antigen-specific recognition and activation [2, 4].

The adaptive immune system

An important feature of the adaptive immune system is the ability to provide long-term memory. This allows for faster and more efficient immune response in future encounters with a specific pathogen [3, 4].

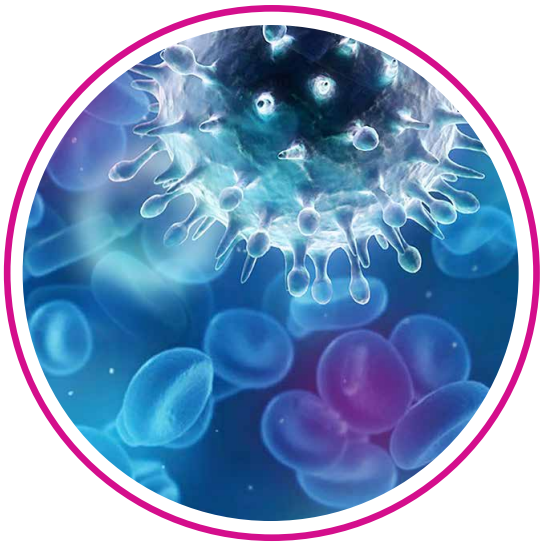
Hematopoietic lineage of the adaptive immune system

Mature **B cells**, when activated, differentiate into memory cells and plasma cells that secrete pathogen-specific antibodies, which play a central role in the protective immune response. B cells are one of three types of professional antigen-presenting cells (APCs) [3, 4]. Major histocompatibilty complex (MHC) class I proteins are expressed constitutively on the surfaces of all nucleated cells in the body, while MHC class II proteins are typically expressed on the surfaces of certain APCs, such as macrophages, B cells, and dendritic cells, along with a variety of co-stimulatory molecules. MHC class II cells are involved in the activation of T cells by displaying peptide fragments of processed antigens [7].

Many types of **T cells** arise from a common T cell progenitor. Of these cells, the most commonly known are memory T cells, $CD8^+$ cytotoxic T cells (Tc), and $CD4^+$ Th cells. Tc cells identify and destroy cells carrying pathogen-specific antigens. On the other hand, Th cells secrete cytokines that regulate the immune response upon being activated by antigen-presenting cells. This action is especially characteristic of the adaptive immune system, in which Th cells enhance or suppress the activity of other immune cells. The Th cells are further divided into several subsets, such as Th1, Th2, Th17, and Treg, each secreting a specific cytokine profile and having a particular regulatory function of the immune response. **B plasma cells** and various types of T cells are key elements of the adaptive immune system [3, 4].

Communication between the innate and the adaptive immune system

The adaptive immune system requires members of the innate system, such as DCs, to present antigens in order to launch and direct its responses. DCs, in particular, form a bridge between the innate and adaptive immune systems by conveying several signals that regulate and direct the adaptive immune response [8]. The interaction between the two systems is not one-sided, as phagocytes and other cells of the innate system recognize, through their Fc receptors, antibodies bound to pathogens that enable the phagocytes and other mature cells of myeloid progeny to identify and destroy pathogens more efficiently. As a result, these activated phagocytes support T cell responses [9].



Cellular crosstalk plays an important role in the adaptive-immune response, such as in the case of naïve B cells that require stimulation by $CD4^+$ Th cells in order to mount an effective response to antigens [10]. Such crosstalk also occurs in the innate immune system when activated cells, such as neutrophils, secrete chemokines and cytokines. This activity influences the recruitment and activation of DCs [2].

Thus, the two arms of the immune system work together using cellular crosstalk and chemical signals in the form of cytokines and other secreted molecules in order to provide the most efficient protection for the body [10].

References

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