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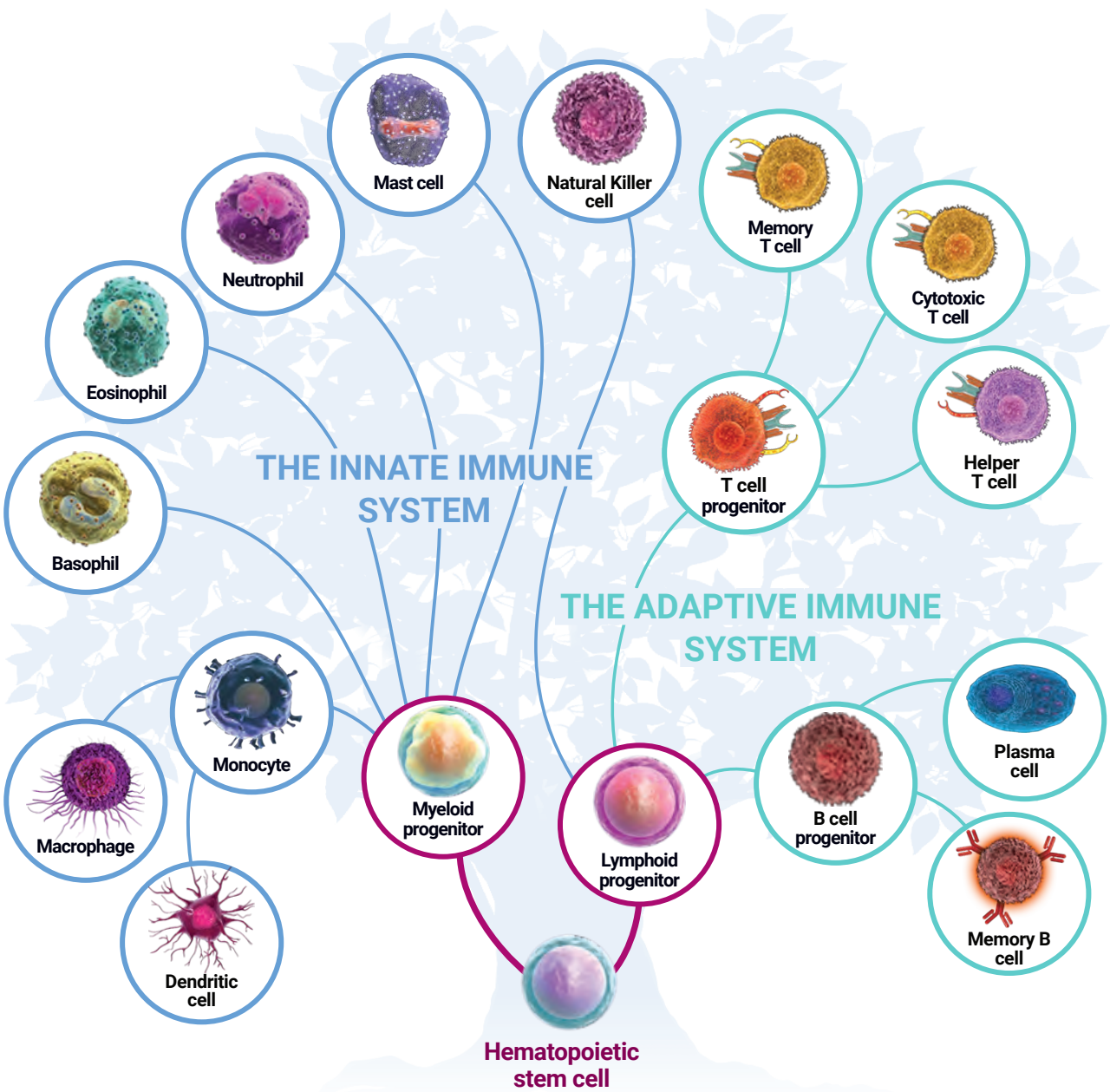
Cells of the Immune System

The immune system is the body's defense against infection and diseases, and consists of two major arms - the innate immune system and the adaptive immune system. Both parts are comprised of many cell types, each with its own specialty, that work together to fight off disease and help maintain the body's health.

All the 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 differentiate 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.



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		
	DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES
Myeloid progenitor	IL-3; IL-6; EPO; GM-CSF; G-CSF	
Monocyte	GM-CSF; G-CSF	
Macrophage	IFN-γ; IL-6; IL-10; M-CSF	TGF-β; TNF-α; VEGF; IL-1β; IL-6; IL-10; IL-12
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
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
Basophil	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; IL-4; IL-6; IL-13
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; RANKL; 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 ADAPTIVE IMMUNE SYSTEM		
	DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES
Lymphoid progenitor	IL-7	
B cell progenitor	IL-3; IL-4; IL-6; IL-7; SCF	
Plasma cell	IL-4; IL-5; IL-10; IL-21; TGF-β; IFN-γ	
T cell progenitor	IL-2; IL-7; Notch	GM-CSF; TGF-β; TNF-α; IL-4; IL-6; IL-10; IL-12
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
Cytotoxic T cell	IL-2; IL-5; IL-7; IL-12	IFN-γ; TNF-α; TNF-β; IL-2; sFas Ligand

Note - The list of the differentiating and secreted cytokines is partial.
***** - Secreted by different subsets of Th 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 infection, 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. 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

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 immunoglobulins (Igs) of the adaptive immune system are the result of somatic gene rearrangements and can recognize practically any antigen.

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.

Neutrophils, together with eosinophils and basophils, are granulocytes (cells containing granules), that belong to a family of leukocytes known as polymorphonuclear (PMN) due to 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.

Eosinophils possess kidney-shaped, lobed nuclei that release the content of their granules in order to extracellularly digest pathogens, especially parasites, as well as secreting 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.

Mast cells are tissue-resident granulocytes, secreting histamine and heparin, among other factors, which are involved in the defense against parasites but also in wound healing and angiogenesis.

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

DCs are present mostly in tissues that are in contact with the environment outside the body, such as the skin, lungs, and intestines. Regarded as the most efficient APCs, DCs' 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.

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.

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.

The Adaptive Immune System

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

HEMATOPOIETIC LINEAGE OF THE ADAPTIVE IMMUNE SYSTEM

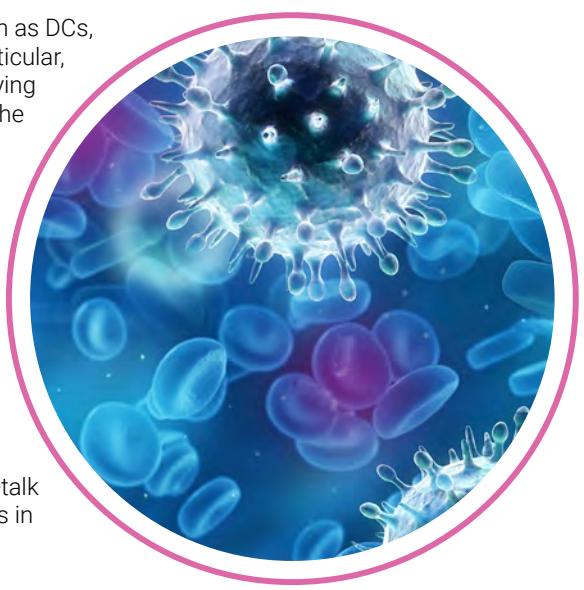
Mature **B cells**, when activated, differentiate into memory cells and plasma cells that secrete pathogen-specific antibodies, which play a central role in the protective immune response. B cells are one of three types of professional antigen-presenting cells (APCs). MHC class I proteins are expressed 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 (Major Histocompatibilty Complex) Class II cells are involved in the activation of T cells by displaying peptide fragments of processed antigens.

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. Th cells, on the other hand, 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.

Communication Between Innate and Adaptive Immune Systems

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 which regulate and direct the adaptive immune response. 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.



Cellular cross-talk 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. Such cross-talk 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.

Thus, the two arms of the immune system work together via cellular cross-talk and chemical signals in the form of cytokines and other secreted molecules in order to provide the most efficient protection for the body.

Characterization Antibodies

	HUMAN			MOUSE		
CELLS	MARKER	CLONE	CAT.#	MARKER	CLONE	CAT.#
Hematopoietic stem cells	CD34	4H11	06411	CD117 (c-Kit)	ACK2	19112
	CD59	OV9A2	11611	SCA-1 (Ly-6A/E)	D7	82912
	CD90/Thy1	5E10	03011	CD34	RAM34	06412
Monocytes	CD14	61D3	06211	CD11b	M1/70	03221
	CD16	CB16	08211	CD115 (CSF-1R)	AFS98	17212
	CD64	10.1	06711	Ly-6C	1A8	83112
Macrophages	CD11b	ICRF44	03211	CD45	30-F11	07512
	CD68	Y1/82A	10711	CD64	X54-5/7.1	06712
	CD163	GHI/61	15711	F4/80	BM8.1	02922
Dendritic cells	CD1c	L161	03131	CD11c	N418	03212
	CD11c	3.9	03231	CD24	M1/69	06312
	CD123	6H6	15311	MHC Class II	M5/114.15.2	86212
	HLA-DR	LN3	74111			
Eosinophils	CD11b	ICRF44	03211	CD11b	M1/70	03221
	CD193	5E8-G9-B4	16011	F4/80	BM8.1	02922
Basophils	CD123	6H6	15311	CD41	MWReg30	03512
	FcεRIα	AER-37 (CRA1)	84111	FcεRIα	MAR-1	84112
Mast cells	CD33	WM53	05411	CD117 (c-Kit)	ACK2	19112
	CD117 (c-Kit)	YB5.B8	19211	FcεRIα	MAR-1	84112
Neutrophils	CD11b	ICRF44	03211	CD11b	M1/70	03221
	CD15	HI98	07211	CD184 (CXCR4)	12G5	16911
	CD16	CB16	08211	Ly-6G (Gr-1)	RB6-8C5	83122
NK cells	CD16	CB16	08211	CD49b (Integrin α2)	DX5	11532
	CD56 (NCAM)	MY31	08631	CD161 (NK1.1)	PK136	83712
	CD335 (NKp46)	9E2	37411	CD335 (NKp46)	29A1.4	37412
B cells	CD19	HIB19	11211	CD19	1D3	11212
	CD20	2H7	02311	CD45R (B220)	RA3-6B2	07131
T cells	CD3	OKT3	05121	CD3	17A2	05112
	CD4	OKT4	06111	CD4	RM4-5	06122
	CD8a	Hit8a	10111	CD8a	53-6.7	10122
				CD8b	H35-17.2	10132

Additional reading:

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