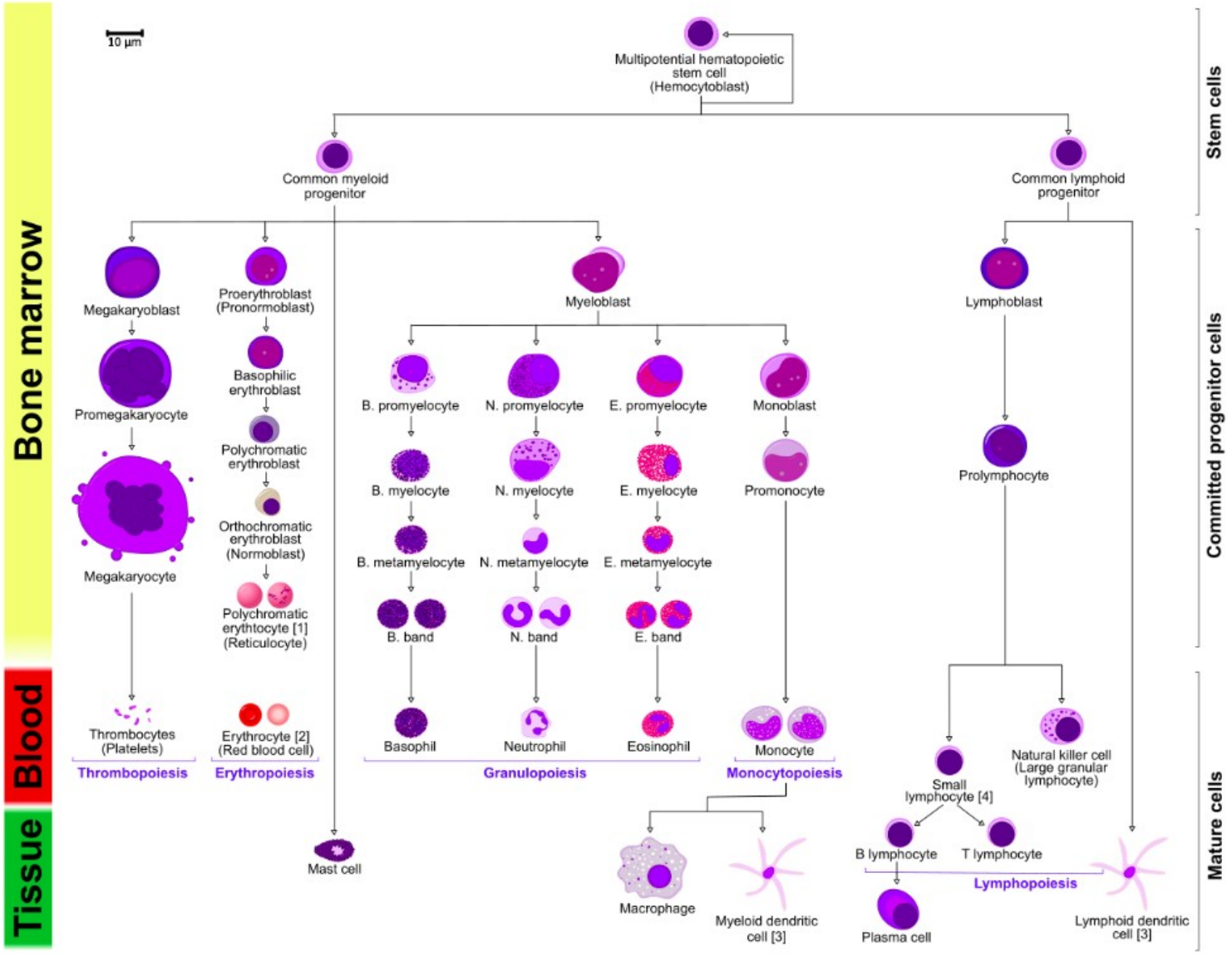
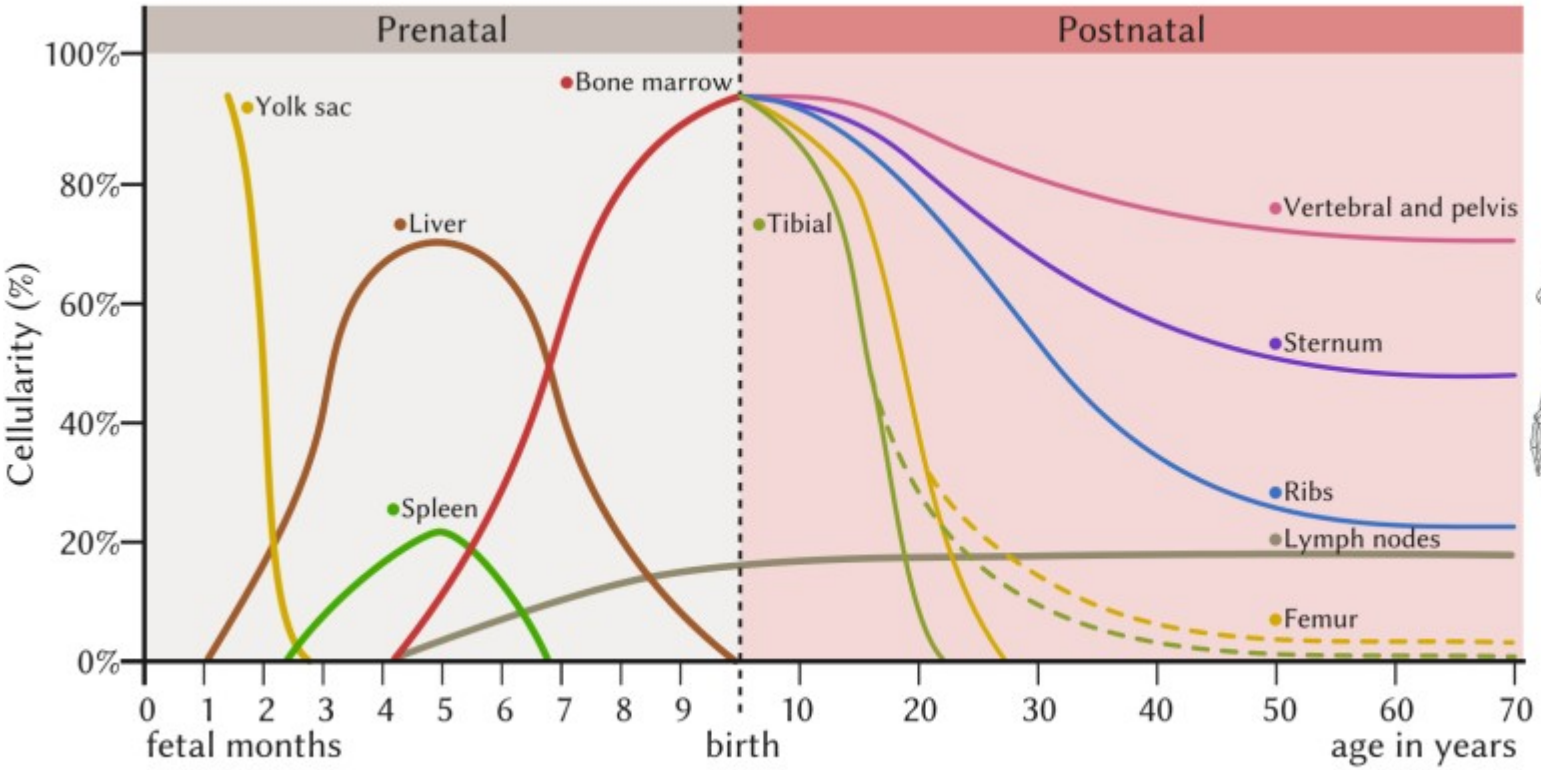
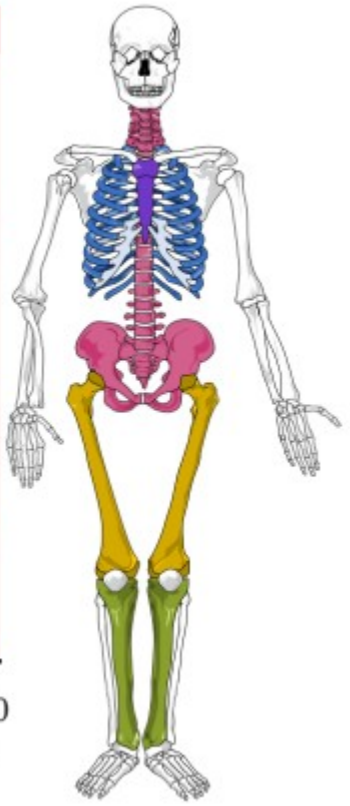
Bağışıklık sistemi organ, hücre ve mikroçevresi


Bone marrow
Blood
Tissue
10 µm
Multipotential hematopoietic stem cell (Hemocytoblast)
Common myeloid progenitor
Common lymphoid progenitor
Stem cells
Committed progenitor cells
Mature cells
Megakaryoblast
Promegakaryocyte
Megakaryocyte
Thrombocytes (Platelets)
Thrombopoiesis
Proerythroblast (Pronormoblast)
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast (Normoblast)
Polychromatic erythtocyte [1] (Reticulocyte)
Erythrocyte [2] (Red blood cell)
Erythropoiesis
Mast cell
Myeloblast
B. promyelocyte
B. myelocyte
B. metamyelocyte
B. band
Basophil
N. promyelocyte
N. myelocyte
N. metamyelocyte
N. band
Neutrophil
E. promyelocyte
E. myelocyte
E. metamyelocyte
E. band
Eosinophil
Granulopoiesis
Monoblast
Promonocyte
Monocyte
Monocytopoiesis
Macrophage
Myeloid dendritic cell [3]
Lymphoblast
Prolymphocyte
Small lymphocyte [4]
B lymphocyte
T lymphocyte
Lymphopoiesis
Plasma cell
Natural killer cell (Large granular lymphocyte)
Lymphoid dendritic cell [3]

HEMATOPOIESIS

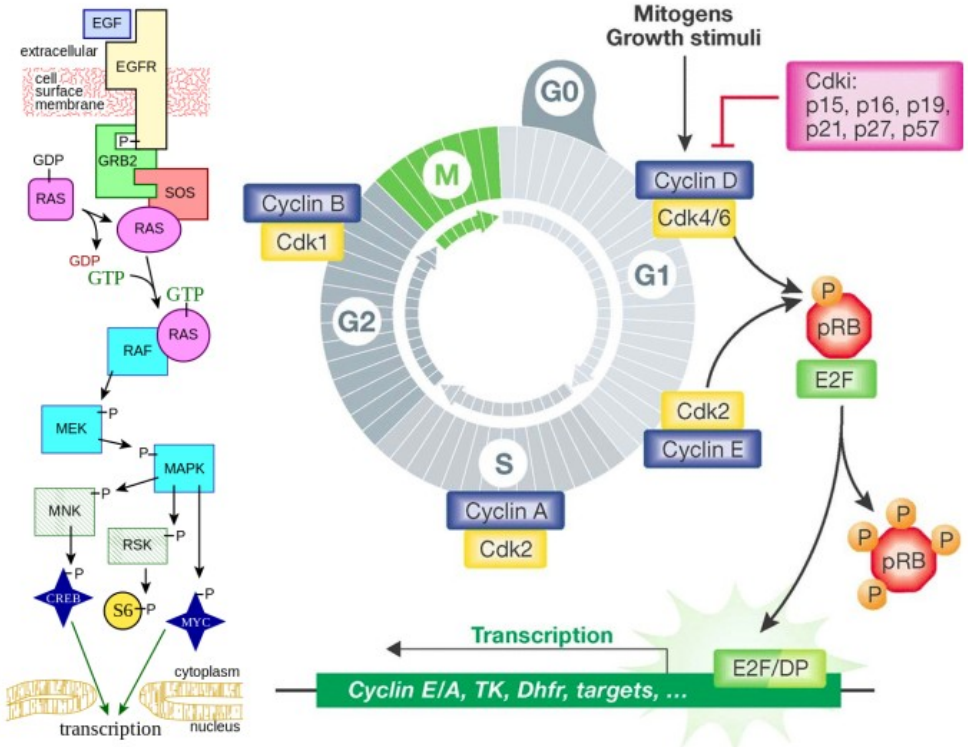




https://en.wikipedia.org/wiki/Haematopoiesis

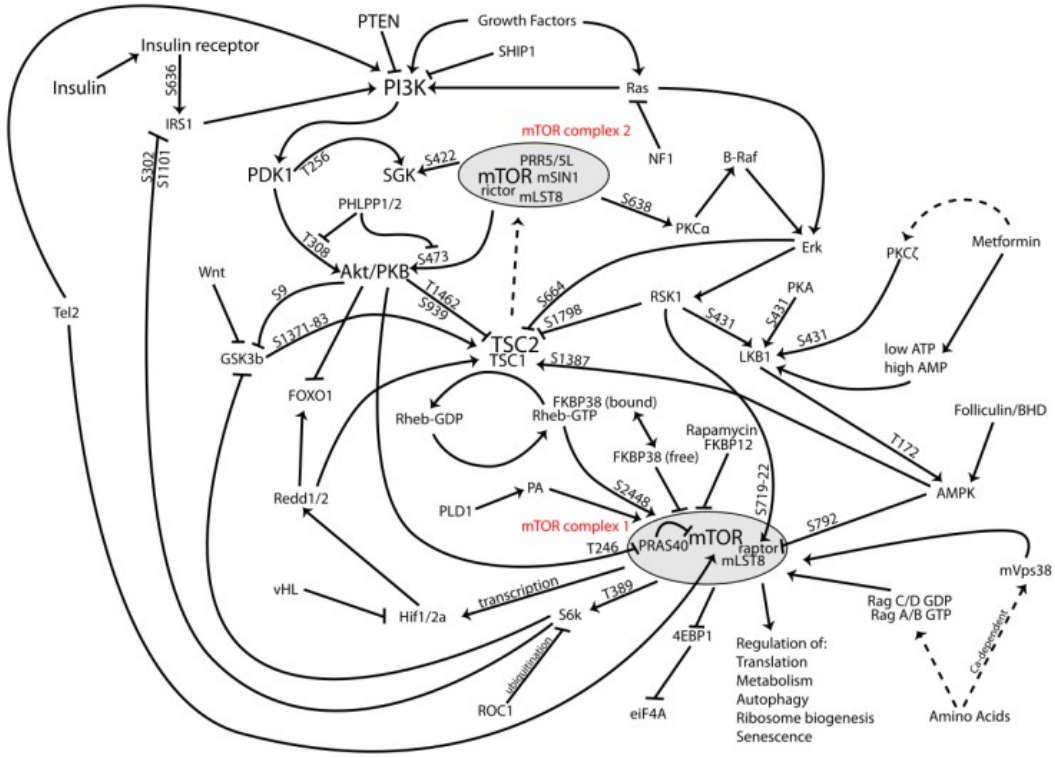
Quiescence - Reversible growth arrest

MAPK/ERK yolağı

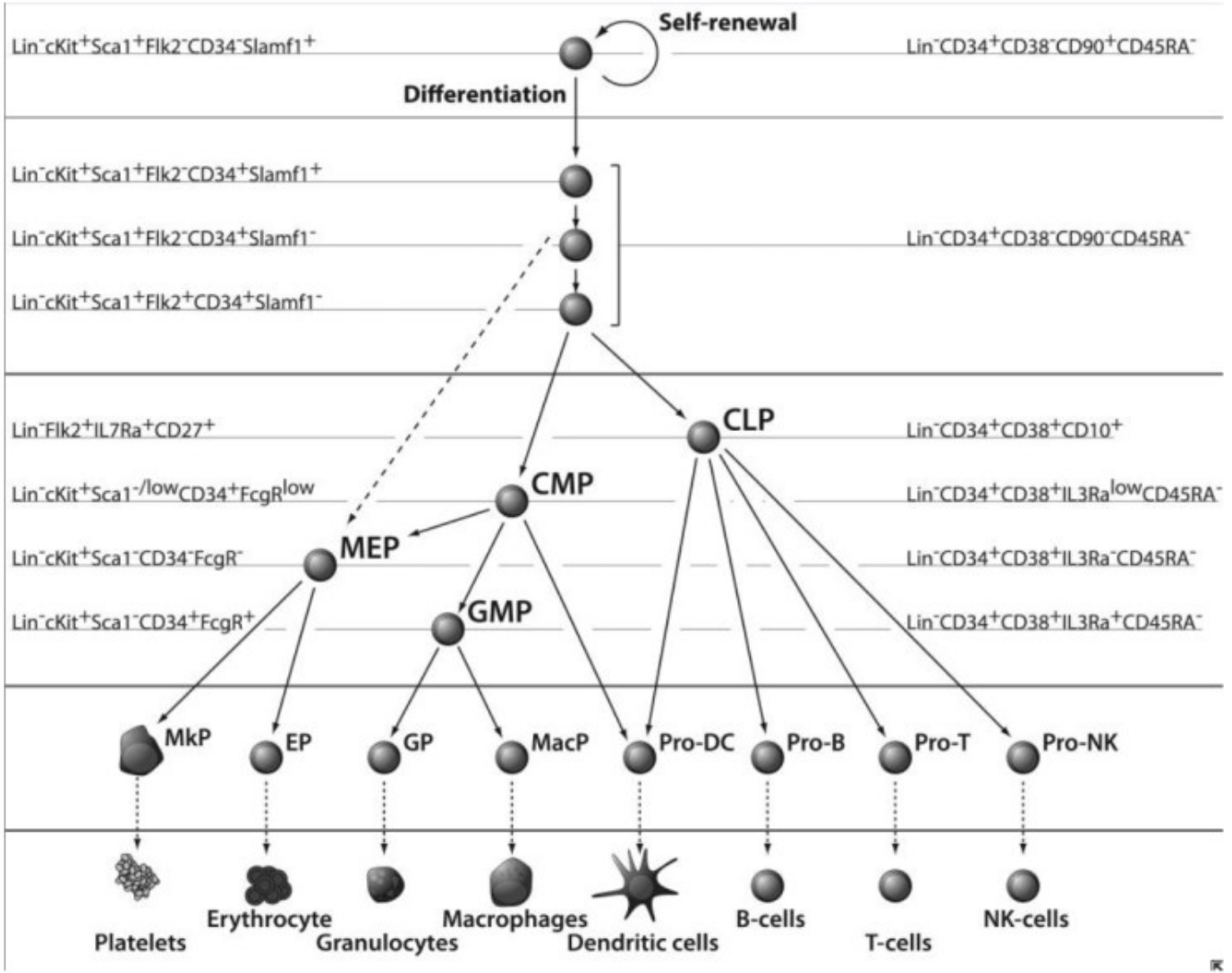


https://en.wikipedia.org/wiki/MAPK/ERK_pathway

PI3K/AKT/mTOR yolağı



https://en.wikipedia.org/wiki/PI3K/AKT/mTOR_pathway



Jun Seita and Irving L. Weissman. Hematopoietic Stem Cell: Self-renewal versus Differentiation. Wiley Interdiscip Rev Syst Biol Med. 2010 Nov-Dec; 2(6): 640–653. doi: 10.1002/wsbm.86

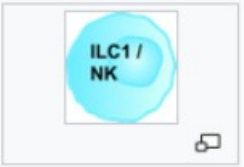
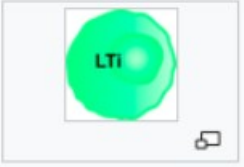
Designation	Differentiation potential implied by designation	Examples of Stem/Progenitors with these Properties
Toti-potent	All embryonic and extraembryonic tissues	zygote
Pluri-potent	All embryonic tissues	ICM, ES cell, iPS cell
Multi-potent	All lineages of a tissue/organ	HSC, NSC
Oligo-potent	Several but not all lineages of a tissue/organ	CMP, CLP
Uni-potent	Single lineage of a tissue/organ	Macrophage progenitor

Receptor	Fetal Development	Phenotype on Blood System in Adult	Number of HSC in Adult	Ref
c-Kit*	Lethal (postimplantation) ~ Normal	Macrocytic anemia	Decrease	See text
c-Mpl	Normal	Thrombocytopenia	Decrease	[136]
Tie-2	Lethal (E 10.5)	N/A	N/A	[137, 138]
Il3Ra	Normal	Normal	Normal	[139]
Csf2rb	Normal	Acidocytopenia	Normal	[140]
Il6st (gp130)	Lethal (E 12.5~term)	N/A	N/A	[141]
Il11Ra	Normal	Normal	Normal	[84]
Tgfbr1	Lethal (E 10.5)	N/A	See text	[142]
Tgfbr2	Lethal (E 10.5)	N/A	N/A	[143]

Cytokine	Receptor	Fetal Development	Phenotype on Blood System in Adult	Number of HSC in adult
SCF*	c-kit	Normal	Macrocytic anemia	Decrease
TPO	c-Mpl	Normal	Thrombocytopenia	Decrease
Ang-1	Tie-2	Lethal (E 12.5)	N/A	See text
IL-3	IL3Ra + Csf2rb	Normal	Lack of response to infection in Mast Cells	Normal
IL-6	IL6R + Il6st	Normal	Decrease of T-cells in peripheral blood	Normal
IL-11	Il11Ra + Il6st	No report of KO mice		
TGF-b1	TGFbr1 + TGFbr2	Lethal (E 10.5) ~ Normal	Significant increase of monocyte & neutrophil	
TGF-b2	TGFbr1 + TGFbr2	Born with multiple defects	Not evaluated	Not evaluated
TGF-b3	TGFbr1 + TGFbr2	Born with abnormal lung development and cleft palate	Not evaluated	Not evaluated

Jun Seita and Irving L. Weissman. Hematopoietic Stem Cell: Self-renewal versus Differentiation. Wiley Interdiscip Rev Syst Biol Med. 2010 Nov-Dec; 2(6): 640–653. doi: 10.1002/wsbm.86

Immune function of ILCs

Stimuli	Tissue Signals	Cell	Mediators	Immune Function
Tumours Intracellular microbes (virus, bacteria, parasite)	IL-12 IL-15 IL-1B		IFN-γ Granzymes Perforin	Type 1 immunity (Macrophage activation, cytotoxicity, oxygen radicals)
Large extracellular molecules (parasites and allergens)	IL-25 IL-33 TSLP		IL-4, IL-5, IL-13, IL-9 AREG	Type 2 immunity (Mucus production, alternative macrophage activation, extracellular matrix/tissue repair, vasodilation, thermoregulation)
Extracellular microbes (bacteria, fungi)	IL-1B IL-23		IL-22, IL-17 GM-CSF Lymphotoxin	Type 3 immunity (Phagocytosis, antimicrobial peptides, epithelium survival)
Mesenchymal organizer cells (retinoic acid, CXCL13, RANK-L)	IL-1B IL-23 IL-6		RANK, TNF, Lymphotoxin IL-17, IL-22	Formation of secondary lymphoid structures

https://en.wikipedia.org/wiki/Innate_lymphoid_cell

Table 1

Phenotype of human ILC

	Group 1 ILC [6,7,11**,12**,37*,117*,119,120]			Group 2 ILC [24,29,35,36*,121]	Group 3 ILC [37*,39–43,53,72**,110*,117*]	
	CD127⁻ ILC1	CD127⁺ ILC1	NK cells	ILC2	NKp44⁻ ILC3	NKp44⁺ ILC3
Markers						
CD127 (IL-7Rα)	–	+	lo/–	+	+	+
CD117 (c-Kit)	–	–	lo/–	+/–	+	+
CD25 (IL-2Rα)	ND	+/–	+/–	+	+/–	lo
IL-23R	ND	lo	+/–	lo	+	+
IL-17RB	ND	–	–	+	ND	–
ST2 (IL-33R)	ND	ND	–	+	ND	–
IL-1R1	ND	lo/–	+/–	lo	+	+
CD161	lo	+	+	+	+	+
CD56	+	–	+	–	+/–	+/–
CD94	+	–	+/–	–	–	–
CD16	–	–	+/–	–	–	–
NKp30	ND	ND	+	+	+/–	+
NKp44	+	–	+[a]	–	–	+
NKp46	+	–	+	–	+/–	+
KIR	–	–	+/–	–	–	–
CD103	+	ND	–	ND	ND	–
CCR6	–	+	–	+	+	+
RANKL	ND	ND	–	ND	+	+
CRTH2	ND	–	–	+	–	–
ICOS	ND	ND	–	+	ND	+
Perforin	+	–	+	–	–	–
Transcription factors						
T-bet	+	+	+	–	–	–
Eomes	+	–	+	–	–	–
RORγt	–	–	–	–	+	+
GATA3	ND	lo/–	lo/–	+	lo/–	lo/–
AhR	lo	lo	lo	+	+	+
Cytokines						
IFN-γ	+	+	+	–	–	–
TNF	ND	+	+	–	+	+
IL-22	–	–	–	lo	lo/–	+
IL-17	ND	–	–	–	+	–
IL-13	ND	lo	–	+	–	lo
IL-5	ND	–	–	+	–	–

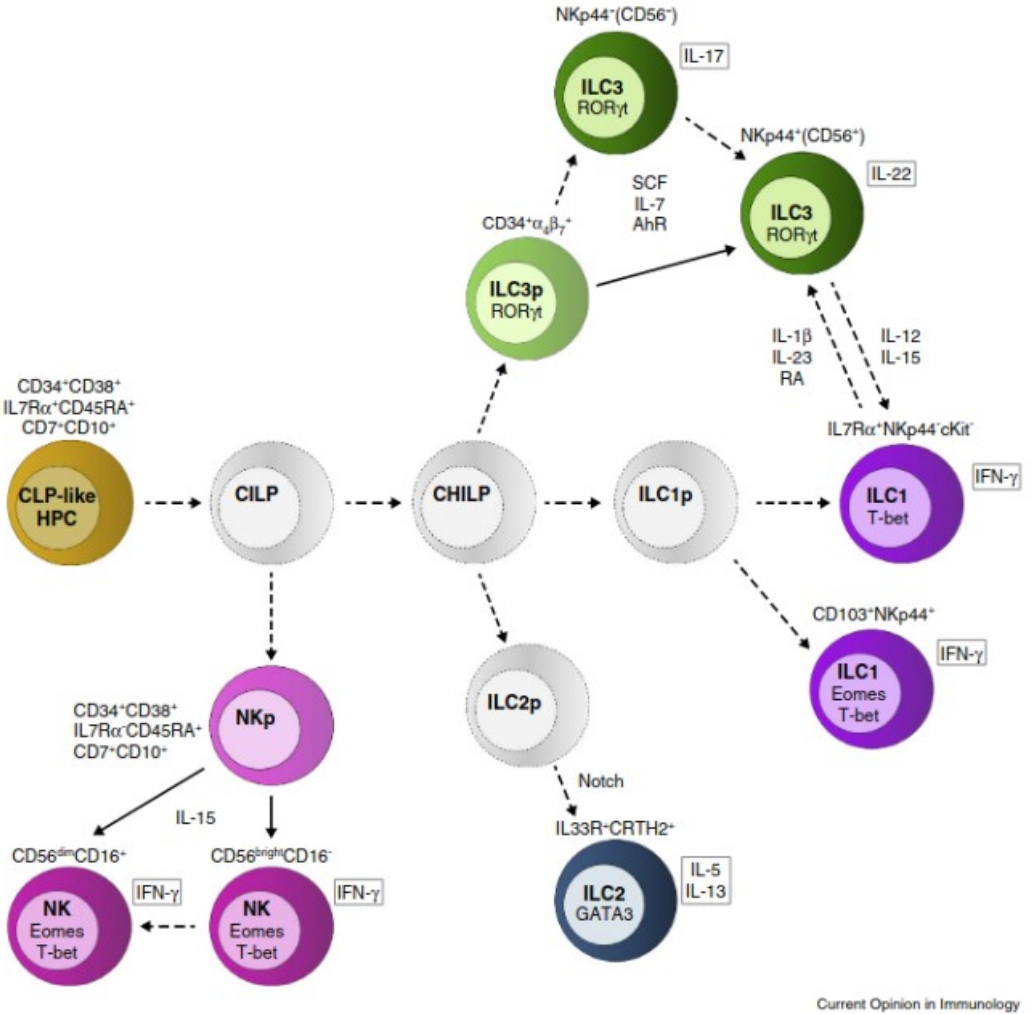
+ indicates high expression, – indicates no expression, +/– indicates bimodal expression, lo indicates low expression, a indicates expression on activated cells, ND indicates not determined according to published reports.

Table 2

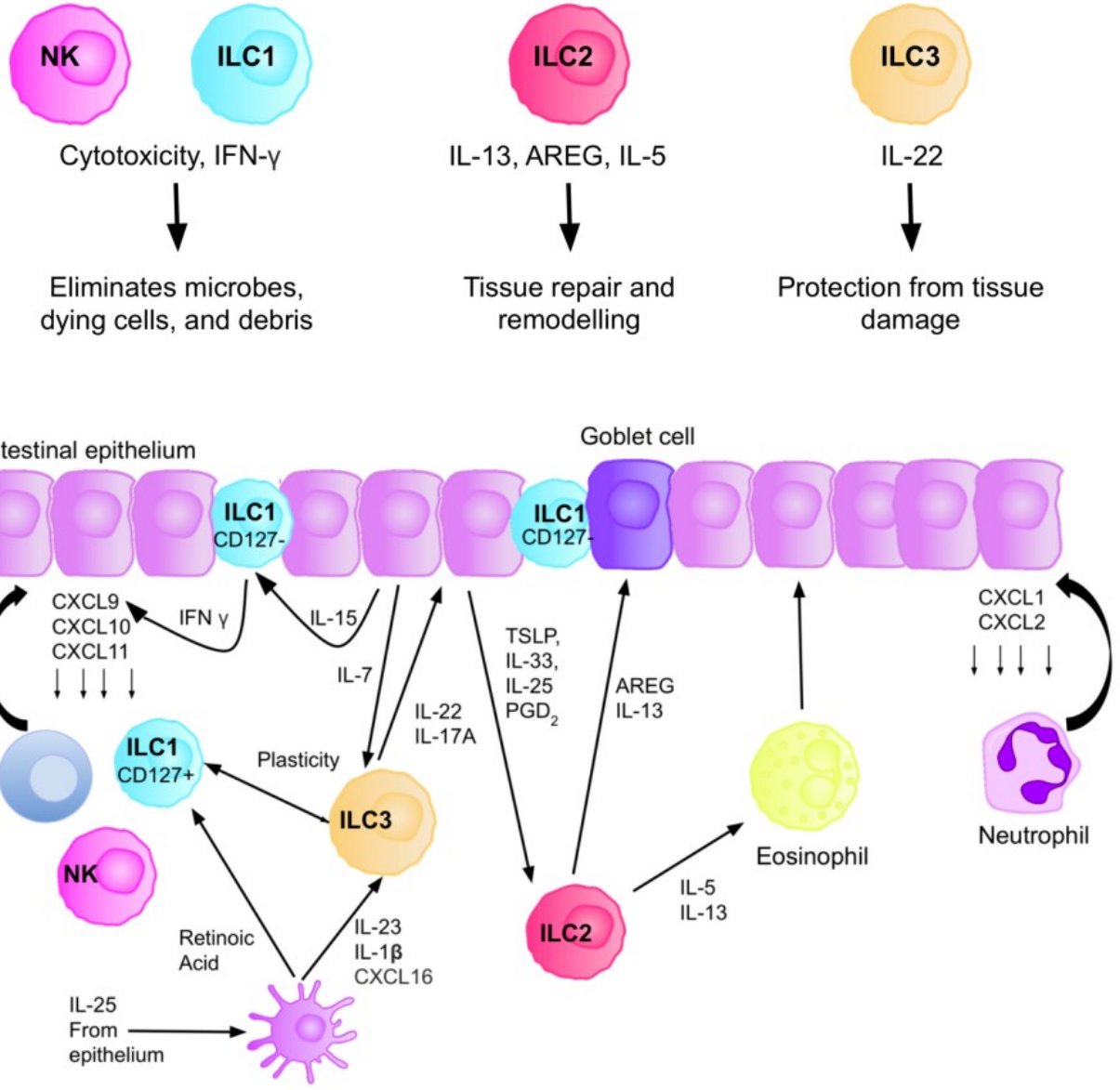
Tissue distribution of human ILC

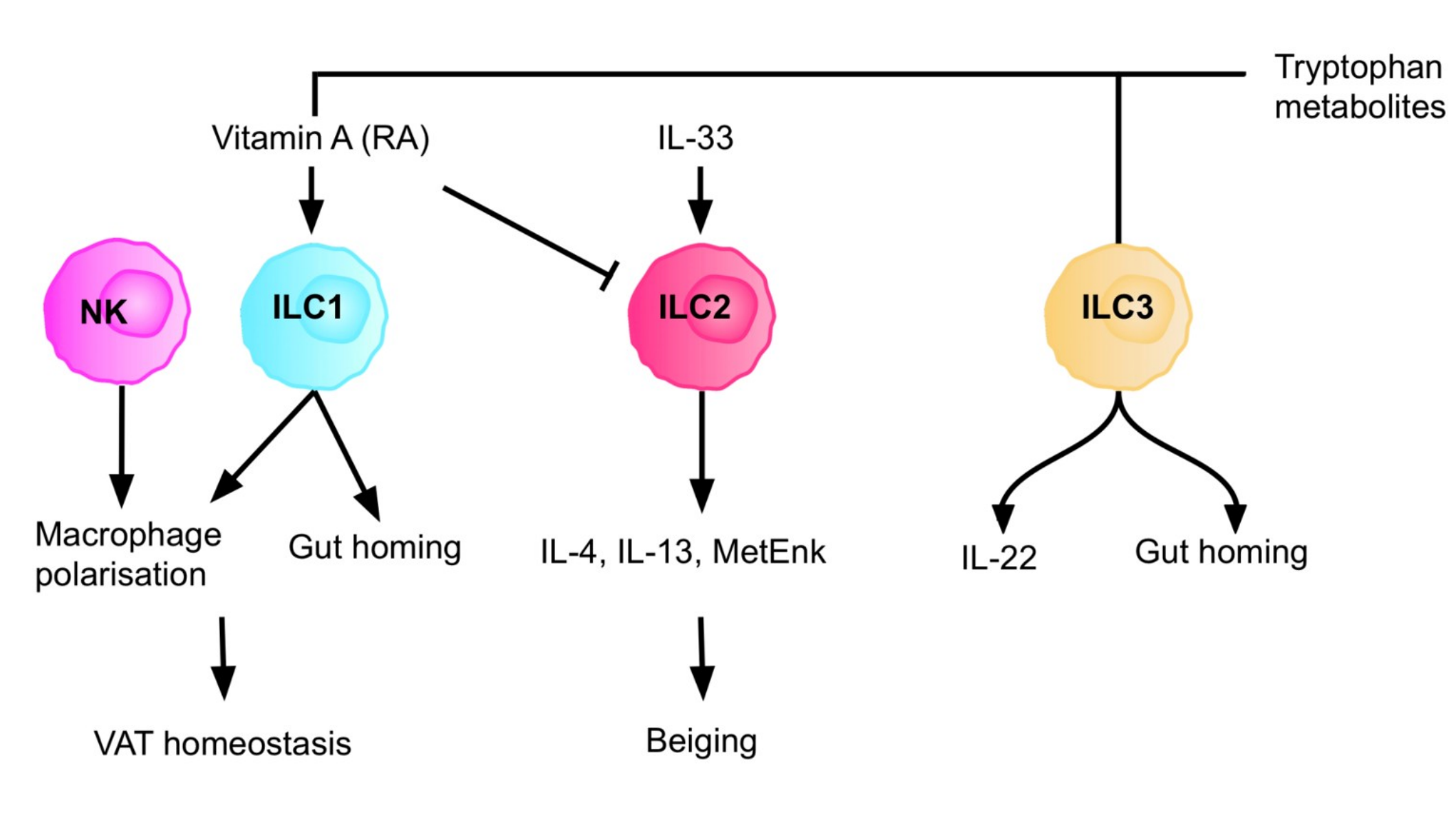
	Group 1 ILC			Group 2 ILC	Group 3 ILC	
	CD127⁻ ILC1	CD127⁺ ILC1	'NK cells'/ILC1?	ILC2	NKp44-ILC3	NKp44⁺ ILC3
Location						
Gut (adult)	+ [11**,117*]	+ [12**,117*]	+ [122]	lo [30]	+	+ [40,53]
Tonsil	+ [11**,117*]	+ [12**,117*]	+ [37*,72**]	+ [12**]	+ [12**,53,123]	+ [37*,39,40,53]
Skin		+ [15*]	+ [33*,124]	+ [15*,25*,29,36*]	+ [15*,25*,33*]	+ [15*,25*,33*]
Lung			+ [125]	+ [30–32]		+ [52*]
Spleen			+ [51*,119]			+ [51*]
Liver			+ [13*,126–128]			
Uterus	+ [14*]	+ [14*]	+ [14*,129,130]		+ [14*]	+ [14*,131]
AT			+ [132]	+ [34*]		
PB		+ [15*]	+	+ [15*,25*,30,32]	+ [15*,25*,123]	+˙ [15*,25*,123]

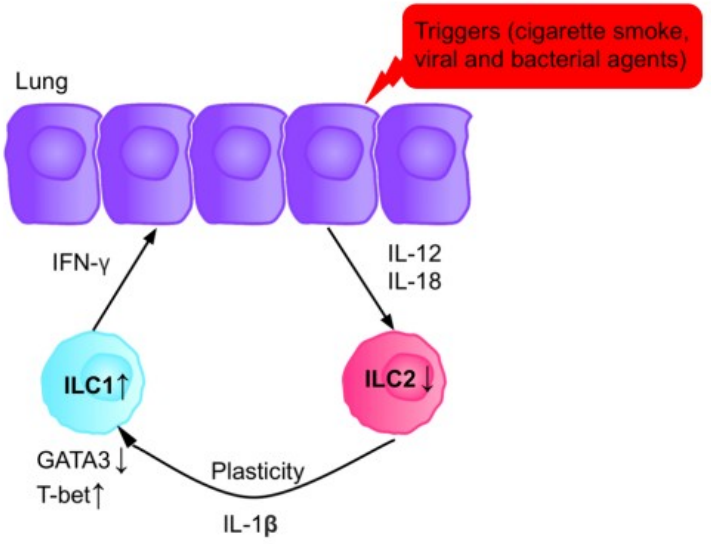
+ indicates presence, lo indicates low presence according to published reports.
˙ Absent in PB from healthy individuals but enriched in patients with Psoriasis or in acute leukemia patients both after induction chemotherapy and after allogeneic HSCT.

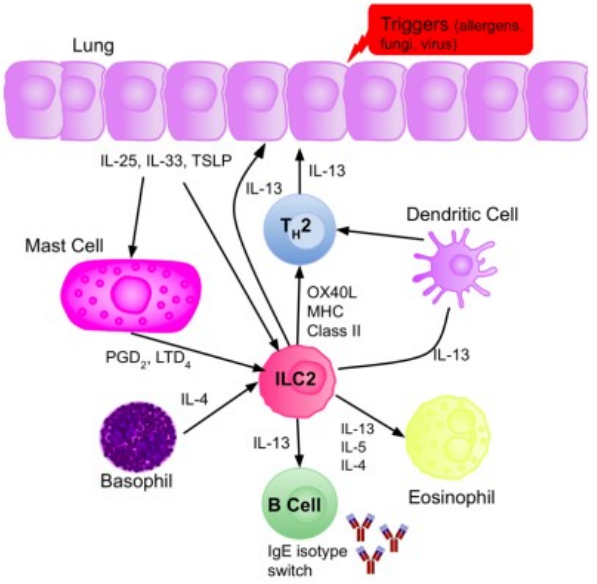


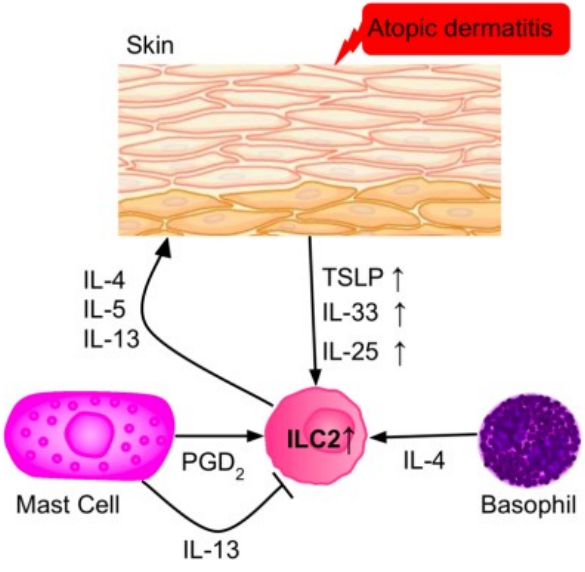
Kerstin Juelke and Chiara Romagnani
Differentiation of human innate lymphoid cells (ILCs)
Current Opinion in Immunology 2016,38:75–85

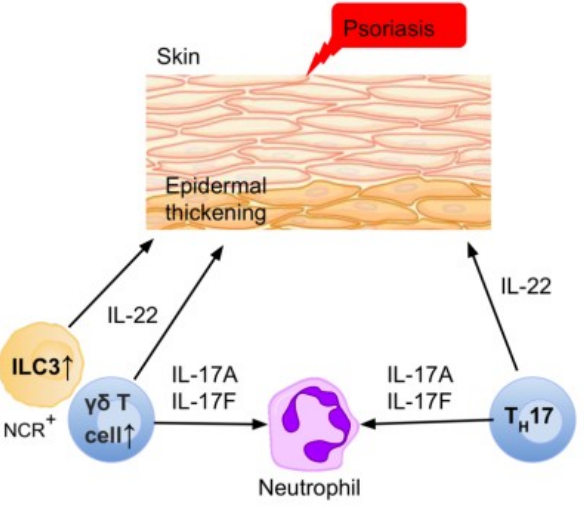

NK
ILC1
ILC2
ILC3
Cytotoxicity, IFN-γ
IL-13, AREG, IL-5
IL-22
Eliminates microbes, dying cells, and debris
Tissue repair and remodelling
Protection from tissue damage
Intestinal epithelium
Goblet cell
ILC1 CD127-
ILC1 CD127-
CXCL9 CXCL10 CXCL11
IFN γ
IL-15
IL-7
IL-22 IL-17A
TSLP, IL-33, IL-25 PGD2
AREG IL-13
CXCL1 CXCL2
ILC1 CD127+
Plasticity
ILC3
NK
Retinoic Acid
IL-23 IL-1β CXCL16
IL-25 From epithelium
ILC2
IL-5 IL-13
Eosinophil
Neutrophil

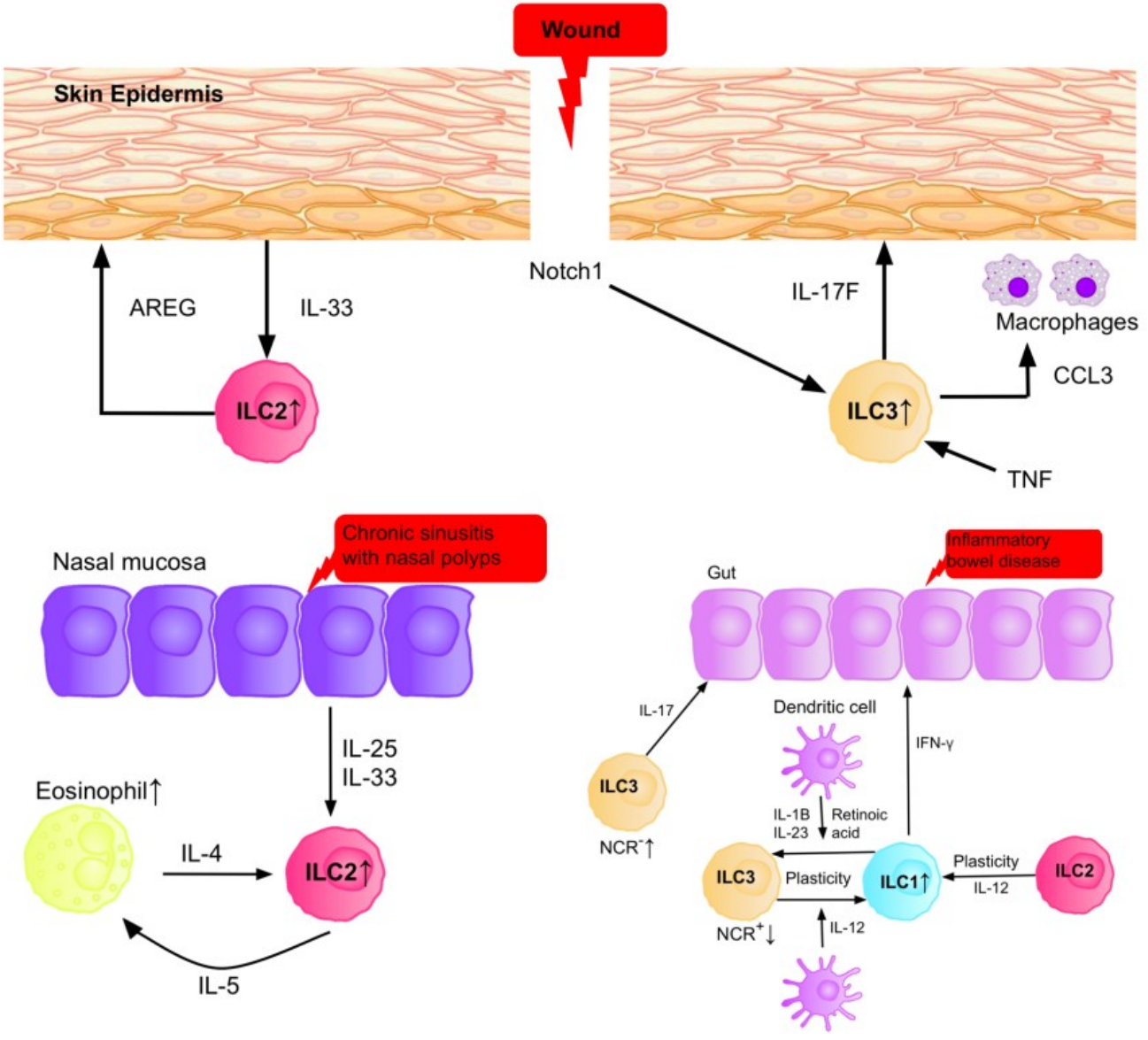

Tryptophan metabolites
Vitamin A (RA)
IL-33
NK
ILC1
ILC2
ILC3
Macrophage polarisation
Gut homing
IL-4, IL-13, MetEnk
IL-22
Gut homing
VAT homeostasis
Beiging

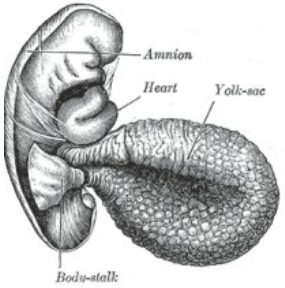

Triggers (cigarette smoke, viral and bacterial agents)
Lung
IFN-γ
IL-12
IL-18
ILC1↑
ILC2↓
GATA3↓
T-bet↑
Plasticity
IL-1β


Triggers (allergens, fungi, virus)
Lung
IL-25, IL-33, TSLP
IL-13
IL-13
T_H2
Dendritic Cell
Mast Cell
OX40L
MHC
Class II
PGD_2, LTD_4
ILC2
IL-13
IL-4
IL-13
IL-13
IL-5
IL-4
Basophil
Eosinophil
B Cell
IgE isotype switch


Atopic dermatitis
Skin
IL-4
IL-5
IL-13
TSLP ↑
IL-33 ↑
IL-25 ↑
ILC2↑
PGD_2
IL-4
Mast Cell
Basophil
IL-13


Psoriasis
Skin
Epidermal thickening
IL-22
IL-22
ILC3↑
NCR+
γδ T cell↑
IL-17A
IL-17F
IL-17A
IL-17F
T_H17
Neutrophil


Wound
Skin Epidermis
AREG
IL-33
ILC2↑
Notch1
IL-17F
Macrophages
CCL3
ILC3↑
TNF
Nasal mucosa
Chronic sinusitis with nasal polyps
IL-25
IL-33
Eosinophil↑
IL-4
ILC2↑
IL-5
Gut
Inflammatory bowel disease
IL-17
Dendritic cell
IFN-γ
ILC3
NCR⁻↑
IL-1B
IL-23
Retinoic acid
ILC3
Plasticity
ILC1↑
Plasticity
IL-12
ILC2
NCR⁺↓
IL-12



Nereden geliyorlar?

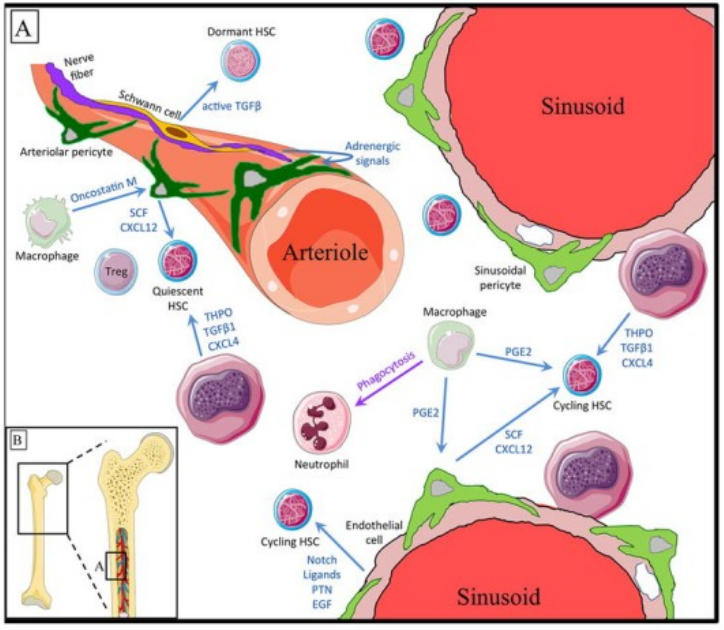
Yolk sac and the hemangioblast theory

Aorta-gonad-mesonephros region

Placenta and the fetal liver

Bone marrow Endoosteal
Perivasküler

Ann N Y Acad Sci. 2016 Apr; 1370(1): 82–96. doi: 10.1111/nyas.13016
PMCID: PMC4938003 Niche heterogeneity in the bone marrow
Alexander Birbrair and Paul S. Frenette

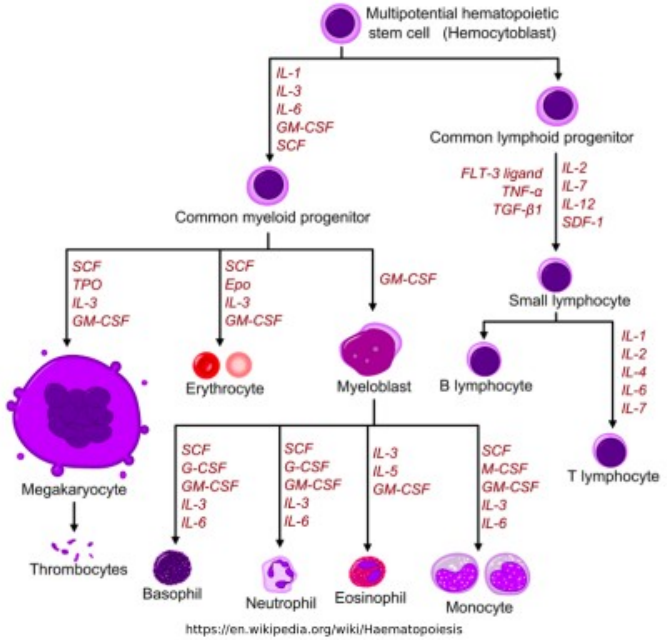


Osteoblastlar
Endotel hücreleri
Perisitler
Adipositler
Schwann hücreleri (sempatik sistem)
Sinir hücreleri

Makrofajlar
Megakaryositler
Lenfositler
Nötrofiller

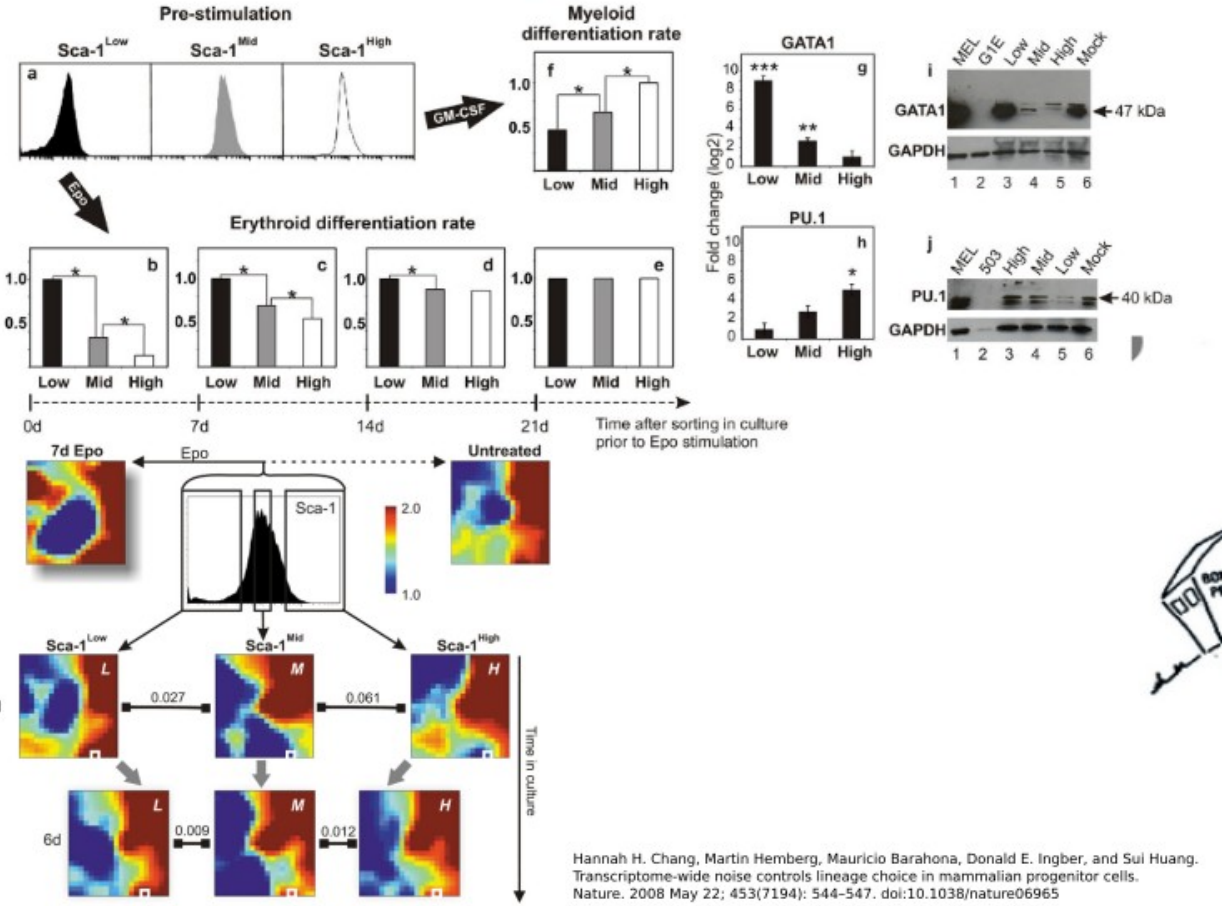
deteminizm vs stokastisite

Stimüle edici faktörler farklılaşmayı indükler



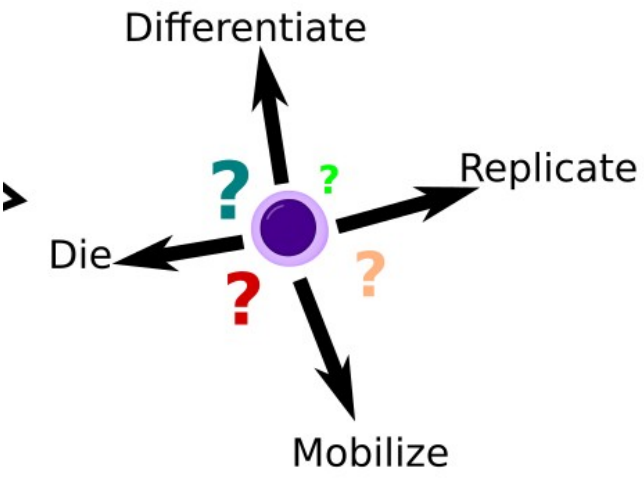
https://en.wikipedia.org/wiki/Haematopoiesis

non-genetical cell individuality

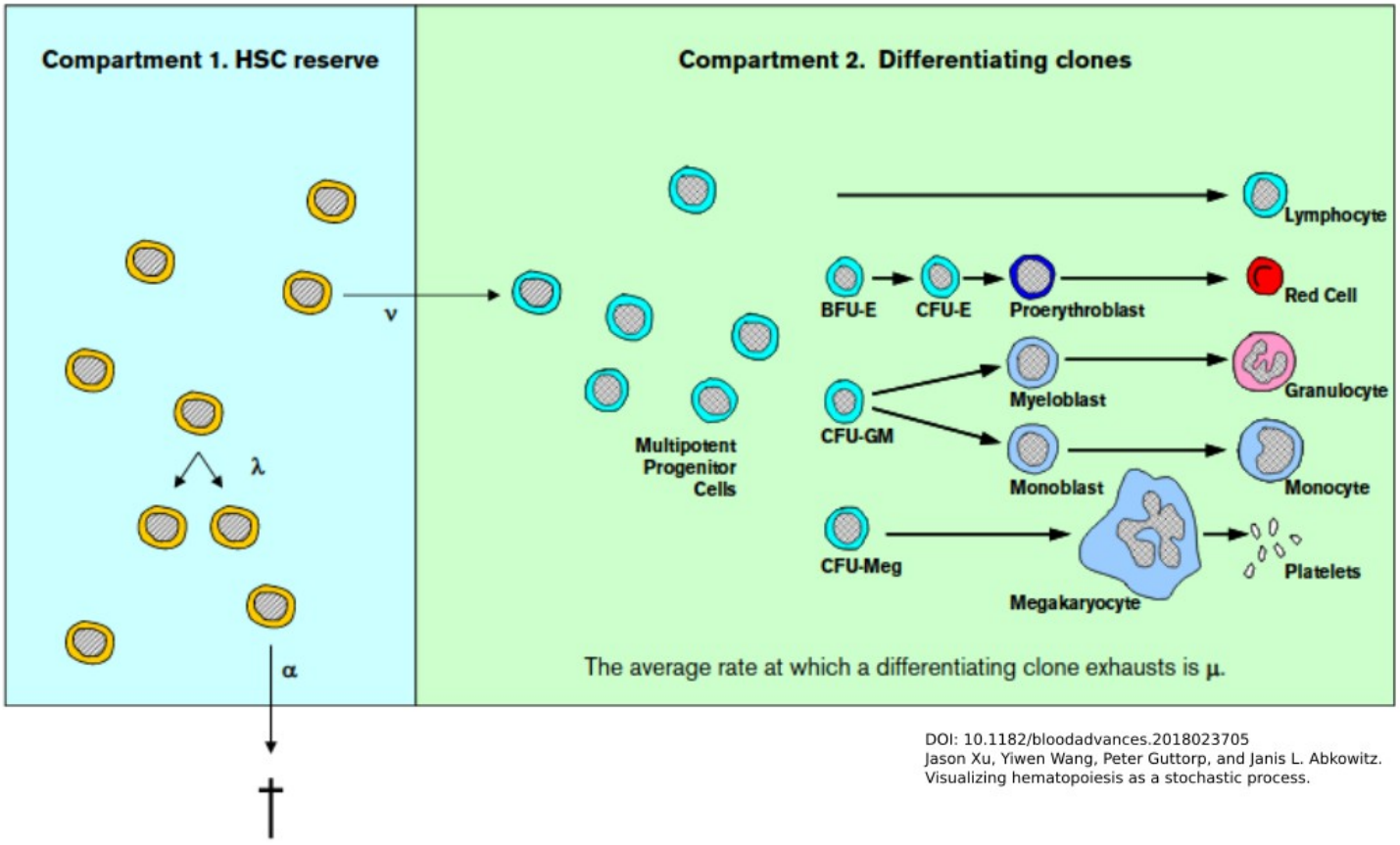


Hannah H. Chang, Martin Hemberg, Mauricio Barahona, Donald E. Ingber, and Sui Huang.
Transcriptome-wide noise controls lineage choice in mammalian progenitor cells.
Nature. 2008 May 22; 453(7194): 544–547. doi:10.1038/nature06965

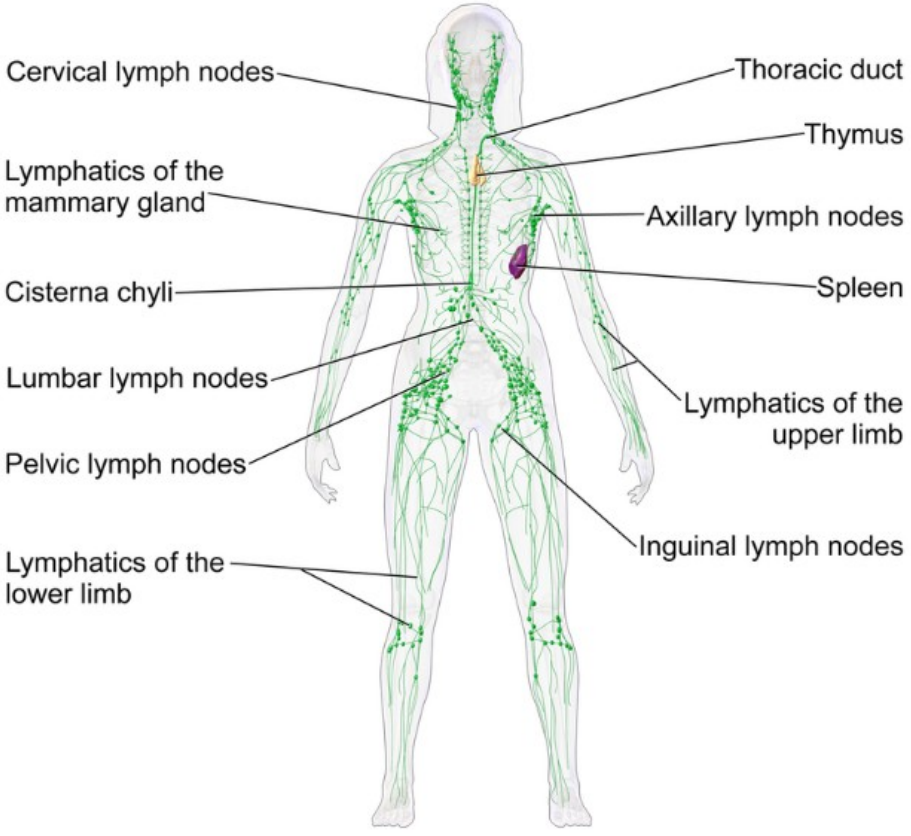
Hematopoietik Kök Hücreler: 1 / 10,000,000

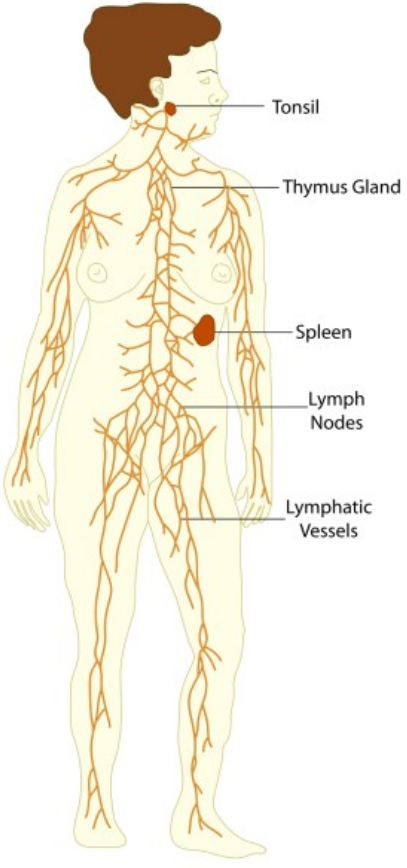


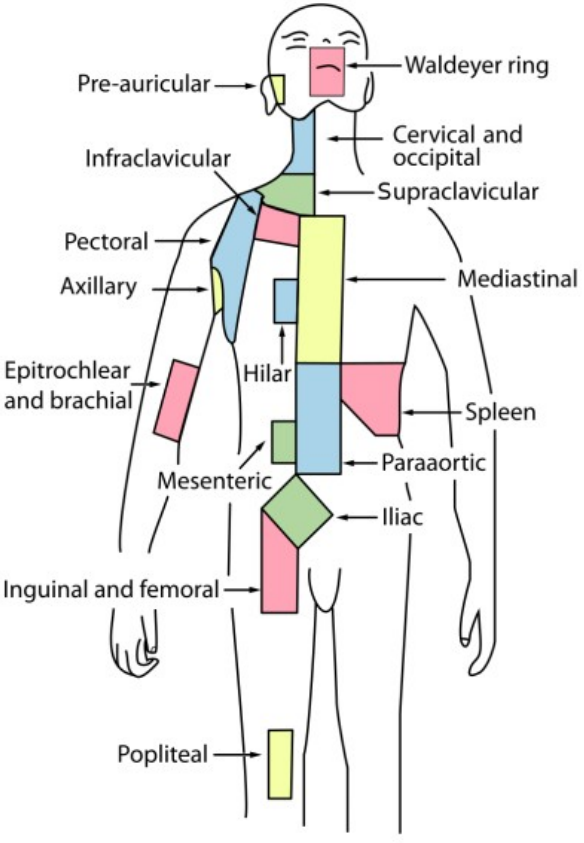
Parameters	
R0	Initial number of cells in reserve compartment (initial number of HSCs, compartment 1 cells)
C0	Initial number of cells in contributing compartment (initial number of differentiating clones, compartment 2 cells)
K_R	Upper limit for numbers of HSCs in the HSC reserve
λ	HSC replication (self-renewal) rate
α	HSC apoptosis (death) rate
ν	HSC differentiation rate (average rate at which an HSC gives rise to a differentiating clone)
μ	Differentiating clone exhaustion rate (thus, 1/μ is the average length of time a differentiating clone contributes to blood cell production)

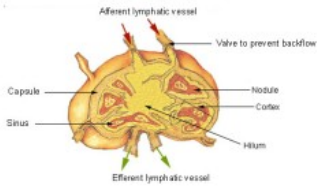


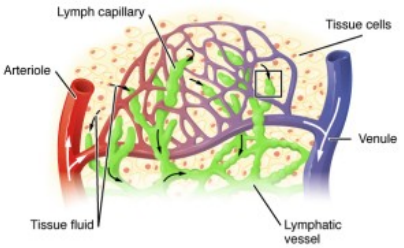
DOI: 10.1182/bloodadvances.2018023705
Jason Xu, Yiwen Wang, Peter Guttorp, and Janis L. Abkowitz.
Visualizing hematopoiesis as a stochastic process.

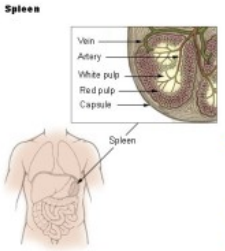

Cervical lymph nodes
Thoracic duct
Thymus
Lymphatics of the mammary gland
Axillary lymph nodes
Cisterna chyli
Spleen
Lumbar lymph nodes
Lymphatics of the upper limb
Pelvic lymph nodes
Inguinal lymph nodes
Lymphatics of the lower limb

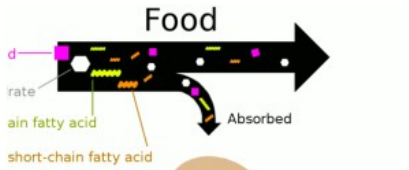

Tonsil
Thymus Gland
Spleen
Lymph Nodes
Lymphatic Vessels

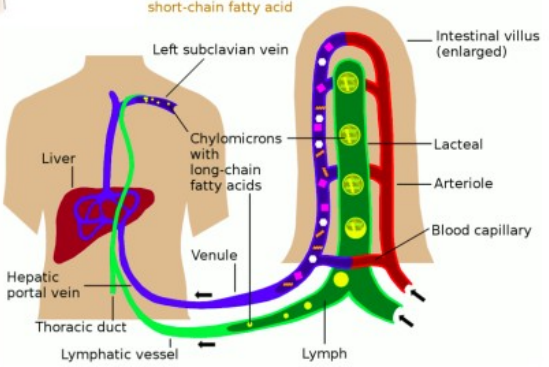

Waldeyer ring
Pre-auricular
Cervical and occipital
Infraclavicular
Supraclavicular
Pectoral
Axillary
Mediastinal
Hilar
Epitrochlear and brachial
Spleen
Paraaortic
Mesenteric
Iliac
Inguinal and femoral
Popliteal

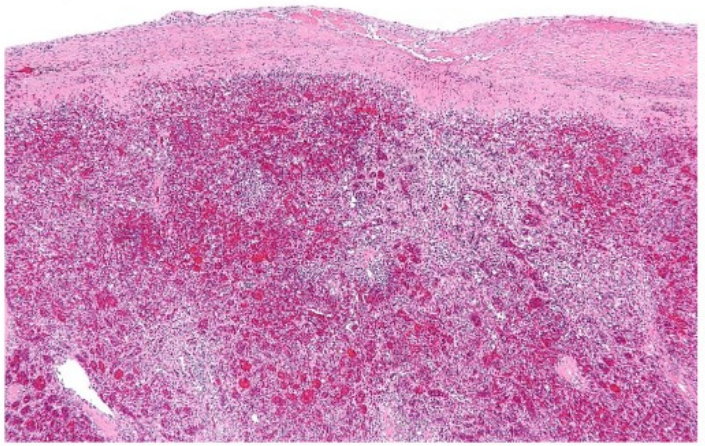












https://immunology.sciencemag.org/content/4/33/eaau6085/tab-figures-data

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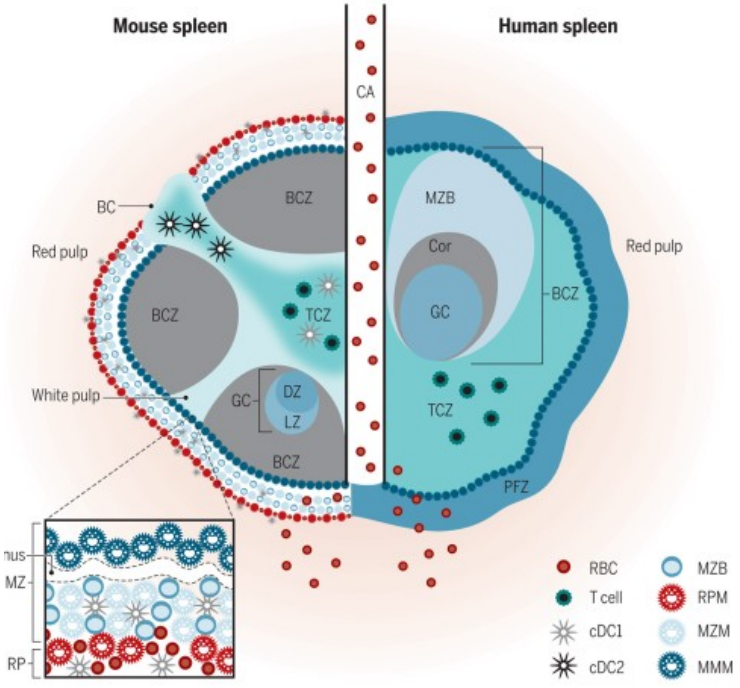

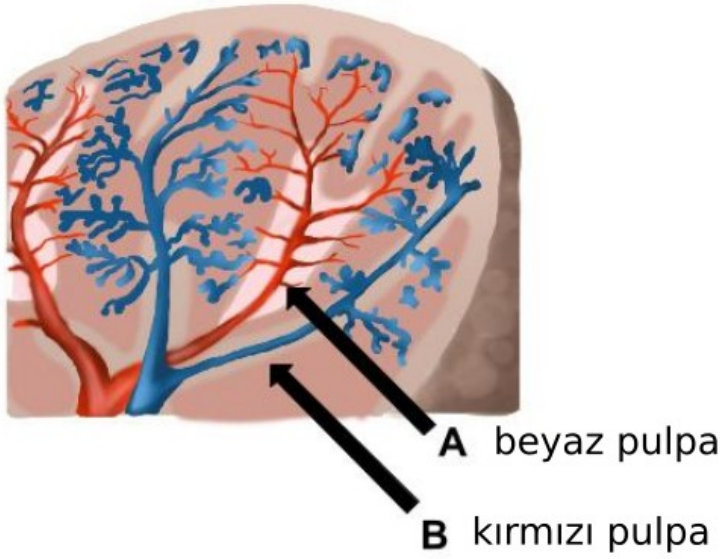

There are structural differences between the murine (left) and human (right) splenic immune system, most notably, the organization of T cell zone (TCZ, turquoise; also known as PALS) and B cell zone (BCZ) follicles (gray and shades of blue, shown with light zone, LZ, and dark zone, DZ, organization in mouse spleen) within the WP and the border between the WP and RP, the MZ (marginal zone) in mouse or perifollicular zone (PFZ) in human (dark blue outer ring). Because applications of advanced imaging techniques to the human spleen have been limited, the extent to which the mouse MZ and human PFZ are analogous remains unknown. For example, the precise layering and composition of macrophage subsets in the MZ is known for mice (see bottom left box)—CD169+ MMMs (dark blue) form a concentric ring around the WP with MZMs (light blue) and MZB cells (darker blue)—but not for humans. In humans, MZB cells surround activated B cells, containing a GC (light blue in the human spleen on the right) and Corona (gray, “Cor”). The homeostatic location of dendritic cell (DC) subsets in mice is shown (with cDC2s in the bridging channel, BC, and cDC1s in the TCZ, MZ and RP, red pulp). Release of blood into the MZ of the WP from a central arteriole (CA) is shown.