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ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
UNIVERSITY OF CRETE

Innate Immunity

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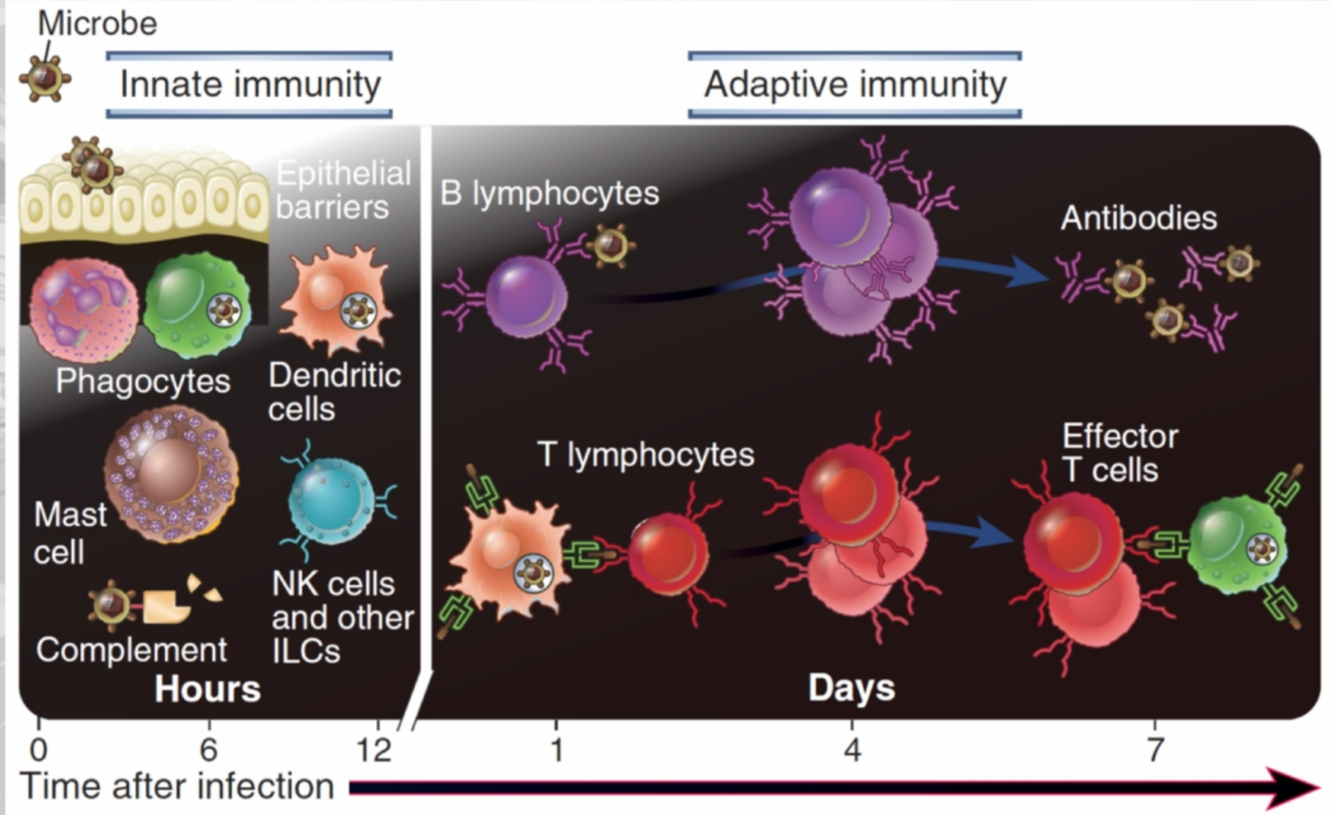
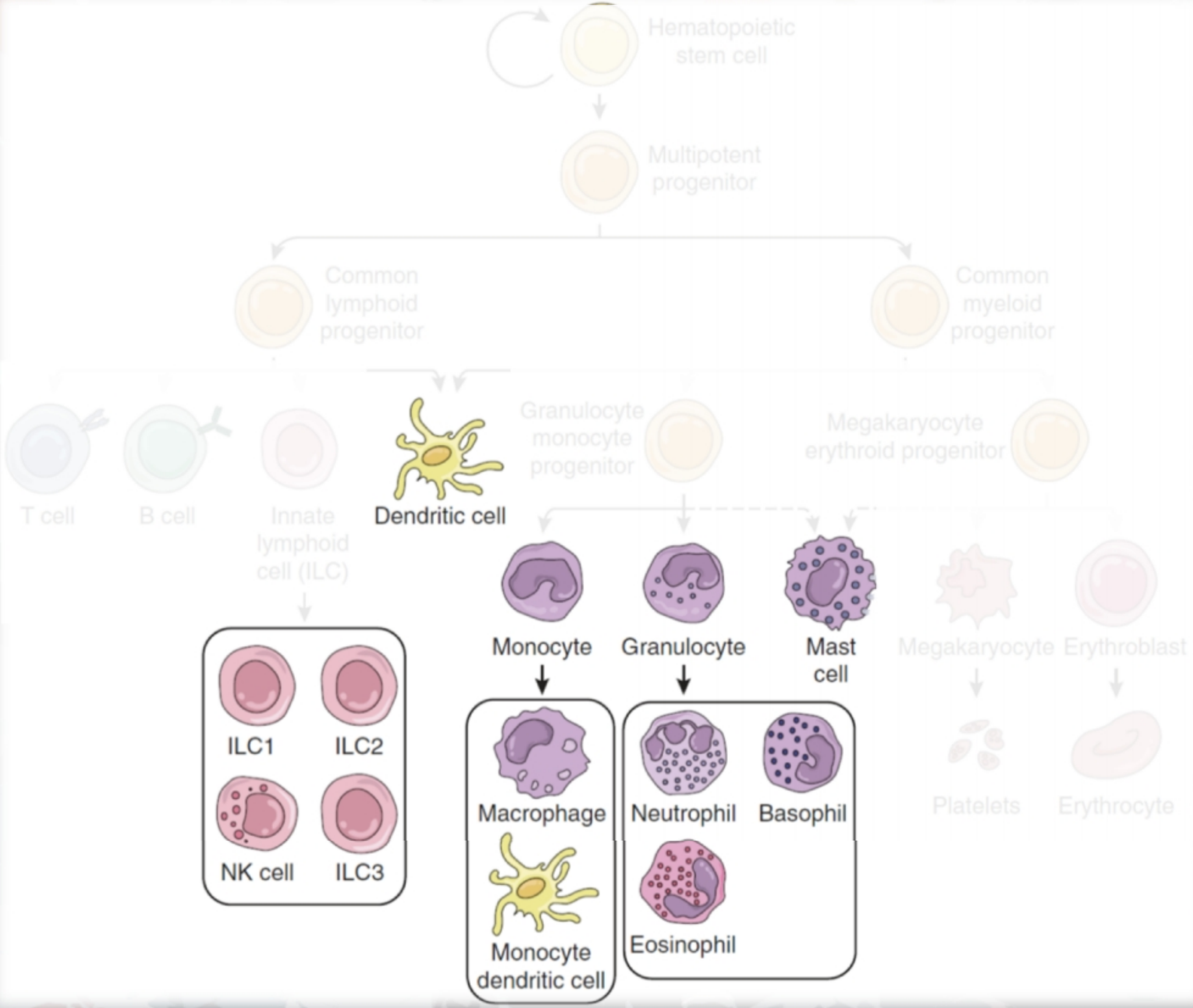
Properties of innate immunity

- ✓ First line of defense (mucosal surfaces, skin barriers)
- ✓ Tissue resident and patrolling cells
- ✓ Acute response to microbes or damage (within minutes)
- ✓ Stimulates and shapes adaptive immune responses
- ❑ No **antigen** specificity
- ❑ No immunological memory*



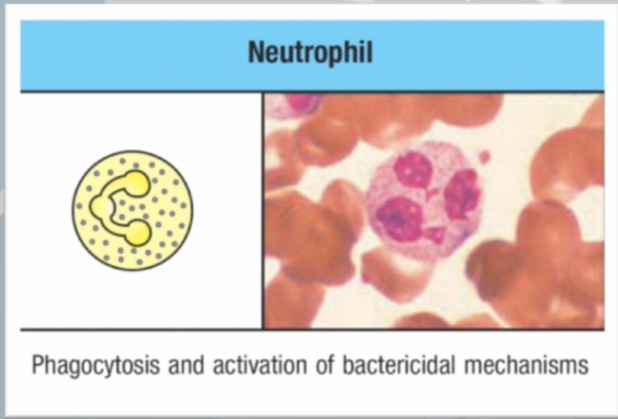
Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Cells of the immune system

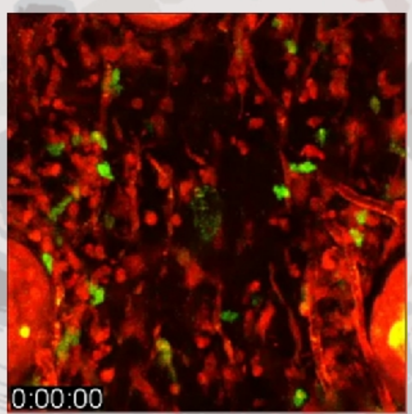


Krause P. J. et al. (eds.), Immunoepidemiology, 2019

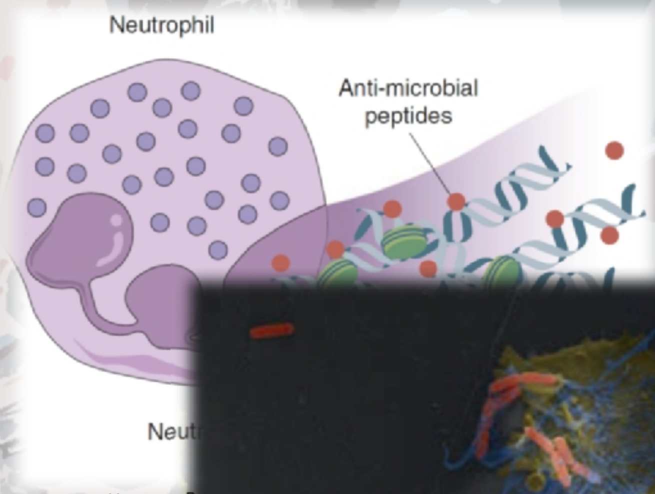
Cells of the innate immune system: Neutrophils



Janeway's Immunobiology, 9th edition, Garland Science 2017



Lämmermann T. et al. ***Nature***, 2013



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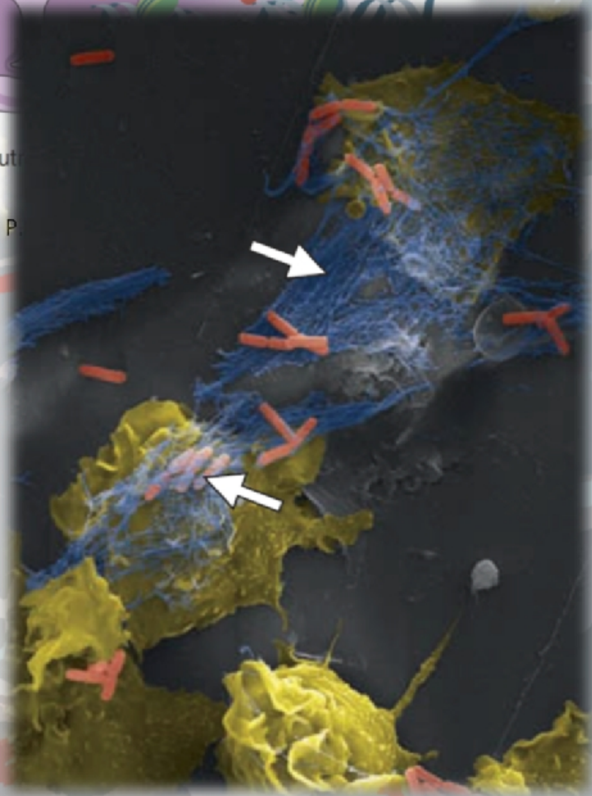
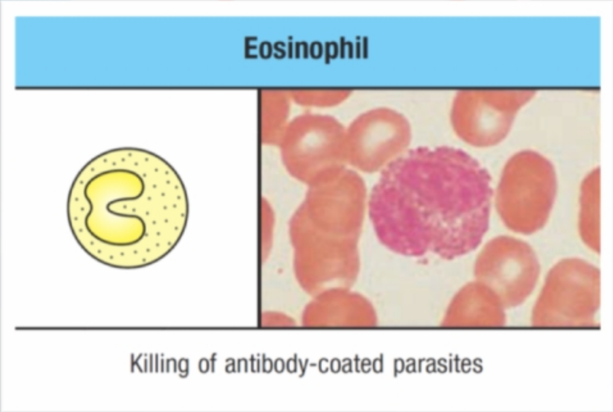
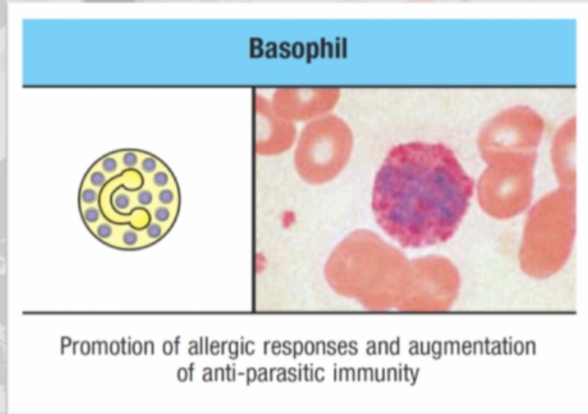


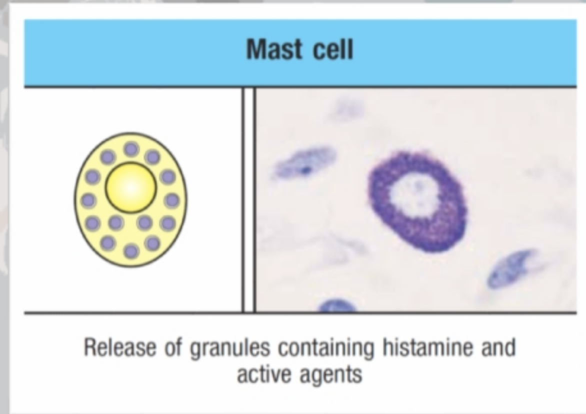
Cellular And Molecular Immunology, 9th edition, Elsevier 2018
Photo courtesy of Arturo Zychlisky

- ➢ 50-70% of all circulating leukocytes
- ➢ The first cell type to respond to a chemoattractant and arrive to the site of infection or injury
- ➢ Employ a range of mechanisms to destroy phagocytosed pathogens (e.g. lytic enzymes, ROS/NO)
- ➢ Trap and kill extracellular pathogens via the formation of Neutrophil Extracellular Traps (NET)
- ❑ Individuals with neutropenia are highly susceptible to deadly infection with a wide range of pathogens and commensal microbes

Cells of the innate immune system: Granulocytes



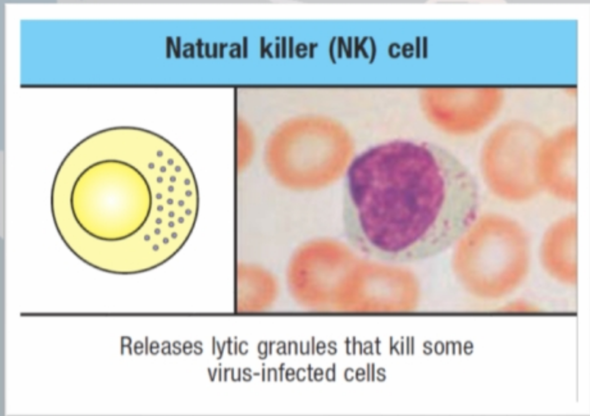




Janeway's Immunobiology, 9th edition, Garland Science 2017

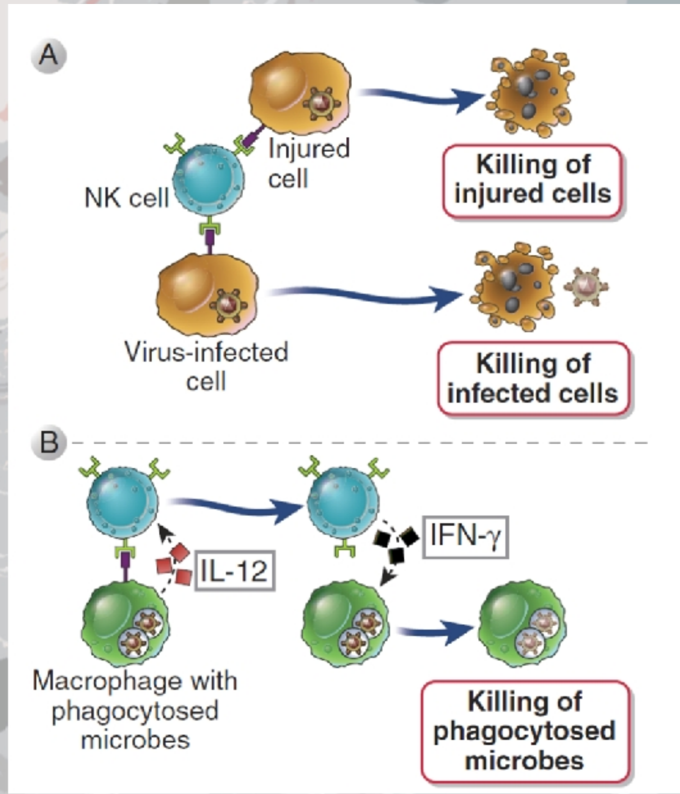
- Low phagocytic activity
- High content of granules containing lytic enzymes and inflammatory mediators
- Released compounds from granules aim to destroy parasites, bacteria and other pathogens
- Molecules released include toxins, histamine, proteases and other inflammatory factors
- Major role in allergic responses (e.g. basophils release Th2 cytokines, IL-5 participates in maturation and activation of eosinophils, IL-13 induces B cells to produce IgE)

Cells of the innate immune system: Natural Killer cells



Janeway's Immunobiology, 9th edition, Garland Science 2017

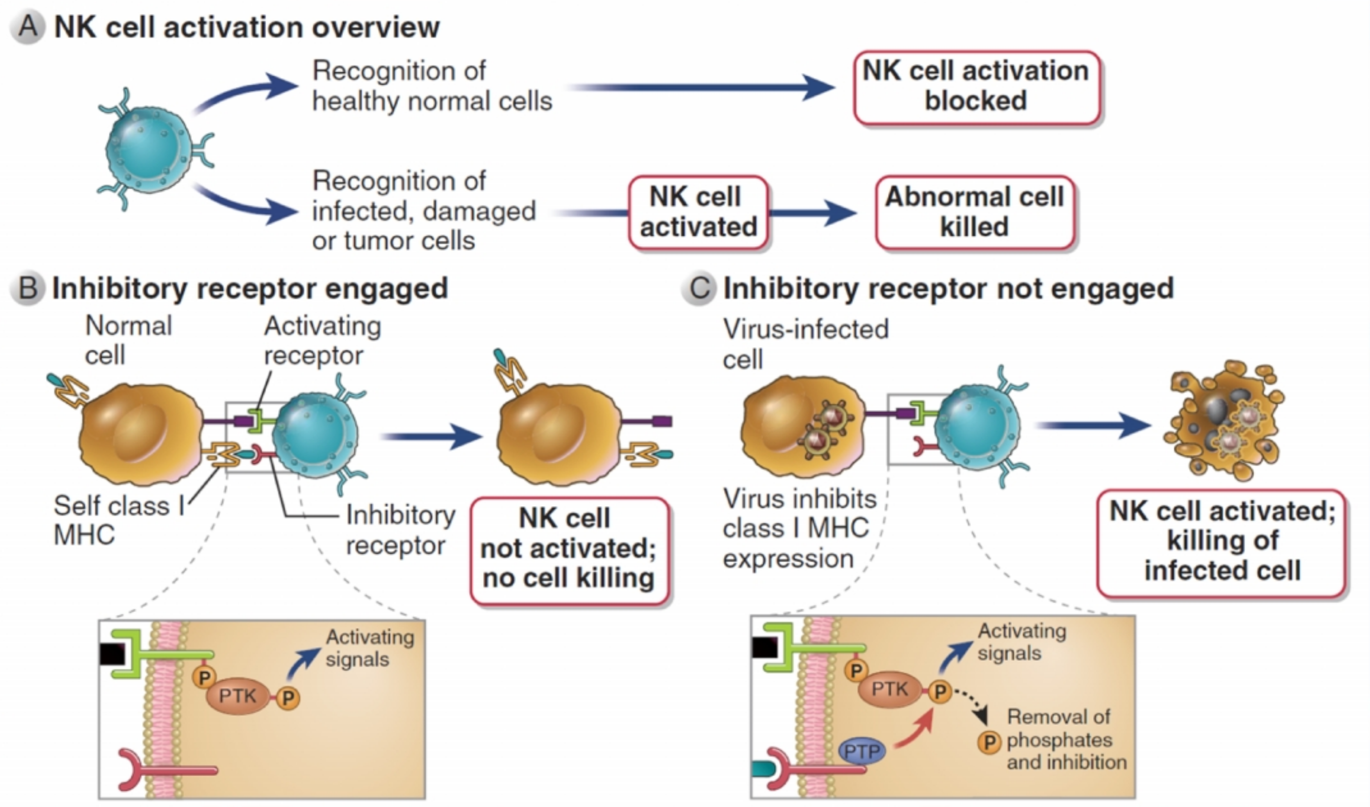
- Large granulated cells, compose 5-10% of blood lymphocytes
- Also found in skin, gut, liver, lung
- Important role in host defense → cytotoxic to tumour cells and virally infected cells
- Interaction with MΦs leads to elimination of phagocytosed pathogens
- Complex sets of activating and inhibitory receptors: balance of signals



Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Cells of the innate immune system: Natural Killer cells

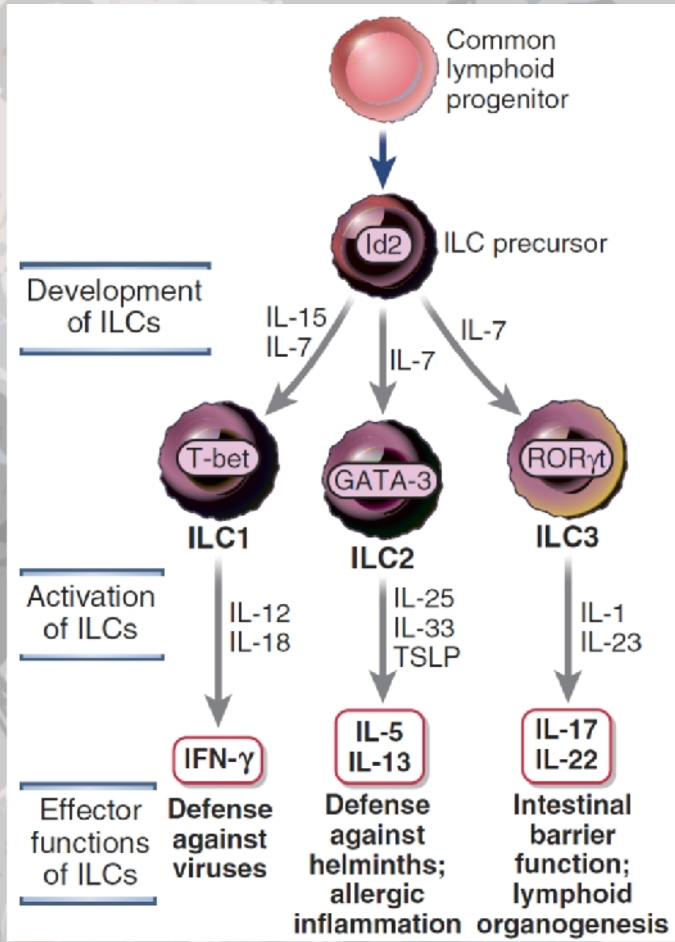
- NK cells express a combination of **activating** and **inhibitory** receptors
- Activating receptors recognize cell-surface proteins induced on target cells by infection, transformation or stress
- Inhibitory receptors on NK cells recognize surface molecules such as MHC Class I molecules
- If the MHC I molecules are missing or downregulated (tumor cells, virally-infected), activating signals prevail
- Stimulation of activating receptors leads to the release of cytokines and chemokines that enhance NK cell cytotoxic capacity



Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Cells of the innate immune system: Innate Lymphoid Cells

- In 2008 studies from 12 independent laboratories around the world discovered ILCs as the new players within the lymphocyte compartment
- Primarily tissue resident cells, found in both lymphoid and non-lymphoid tissues and rarely in the blood
- Categorized into three main groups (ILC1, ILC2, and ILC3) based on their cytokine profiles and roles
- ILC groups resemble Th cell types
- Play a role in the defense against viruses, bacteria and parasites and maintain tissue homeostasis
- Aberrant ILC-related immune responses can lead to autoimmunity (IBD) and allergic responses (asthma)

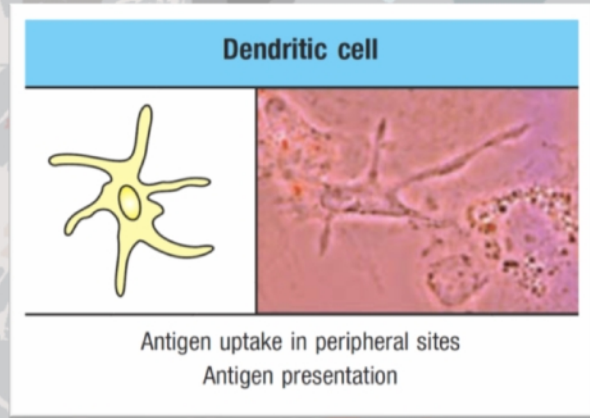


Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Cells of the innate immune system: Dendritic Cells

- Named after their 'tree-like' or dendritic shapes
- DCs are found in the skin, gastrointestinal tract, respiratory system, spleen and in circulation
- **Immature** DCs surveil and sample peripheral tissues for pathogens, dead/damaged cells and other non-self particles
- **Mature** DCs migrate to lymph nodes and present antigens to naïve T cells
- "Sentinels" of the immune system, recognize microbial pathogens, secrete cytokines, enhance/initiate innate and adaptive responses

The bridge between innate and adaptive immunity



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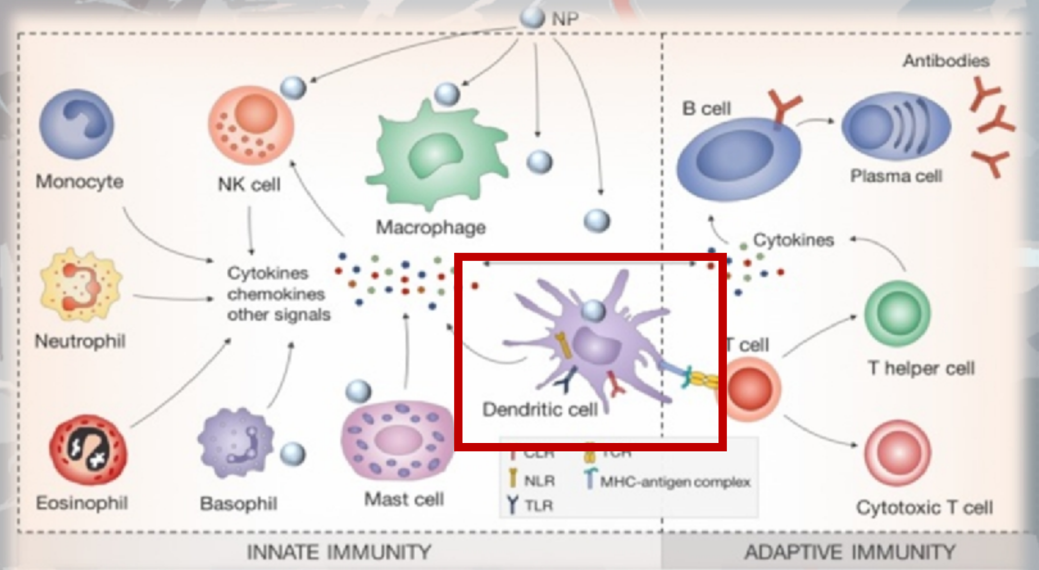
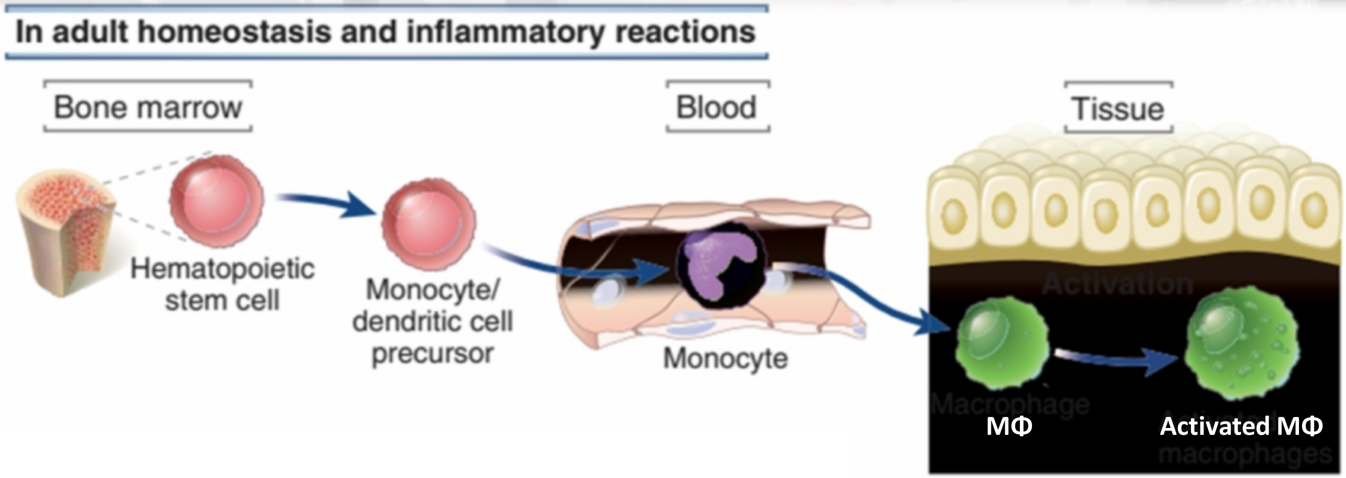
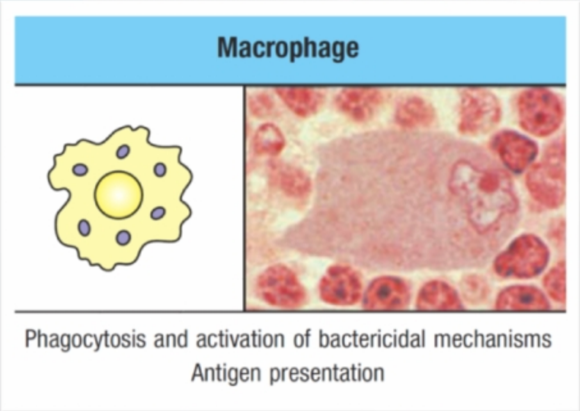


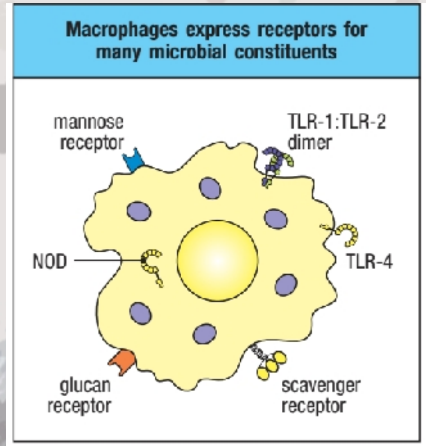
Cells of the innate immune system: Monocytes & Macrophages

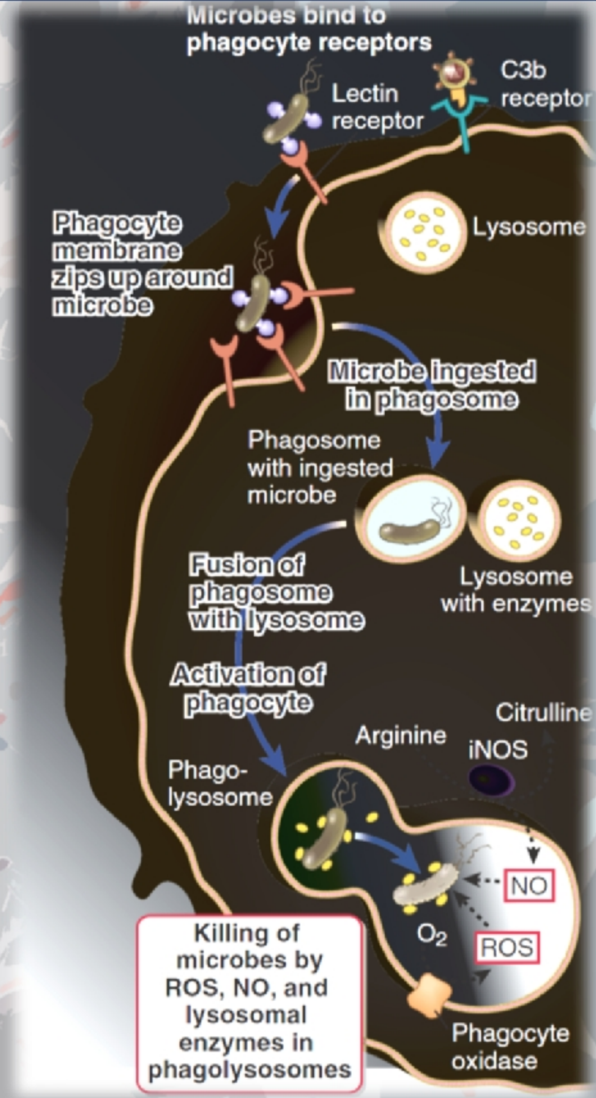


Cells of the innate immune system: Monocytes & Macrophages



Janeway's Immunobiology, 9th edition, Garland Science 2017





Cellular And Molecular Immunology, 9th edition, Elsevier 2018

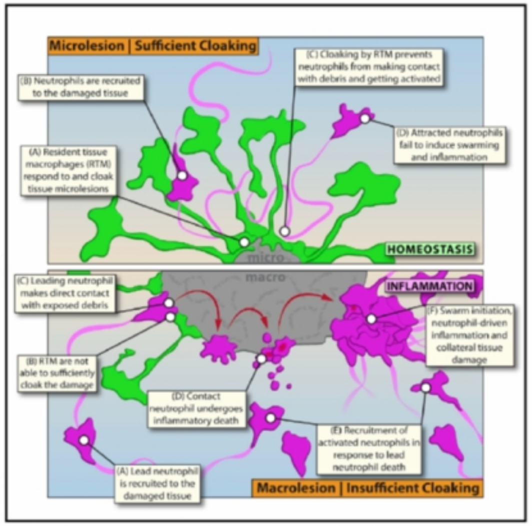
- Monocytes → patrolling cells
- Macrophages → tissue resident cells
- Both are professional phagocytes which sense and destroy a wide array of pathogens
- They exhibit antigen presentation activity
- They can initiate inflammatory responses or maintain tissue homeostasis via differential cytokine secretion

Macrophages and homeostasis maintenance

Cell | Article

Resident Macrophages Cloak Tissue Microlesions to Prevent Neutrophil-Driven Inflammatory Damage

Graphical Abstract



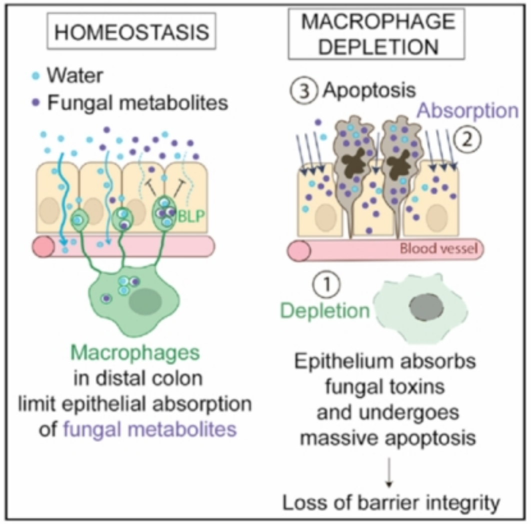
Authors

Stefan Uderhardt, Andrew J. Martins, John S. Tsang, Tim Lämmermann, Ronald N. Germain

Cell | Article

Macrophages Maintain Epithelium Integrity by Limiting Fungal Product Absorption

Graphical Abstract



Authors

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Correspondence

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In Brief

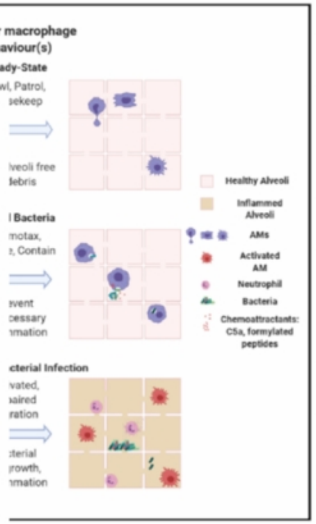
Protrusions on distal colonic macrophages orchestrate fluid sampling, which is critical to protect epithelial cells from absorbing fluids enriched in fungi toxins/metabolites.

Chikina et al., 2020, Cell

Cell | Article

Patrolling Alveolar Macrophages Conceal Bacteria from the Immune System to Maintain Homeostasis

Graphical Abstract



e alveolar spaces

ement toward inhaled bacteria

for bacterial clearance

d during viral infection

Authors

Arpan Sharma Neupane, Michelle Willson, Andrew Krzysztof Chojnacki, ..., Craig Jenne, Ajitha Thanabalasuriar, Paul Kubes

Correspondence

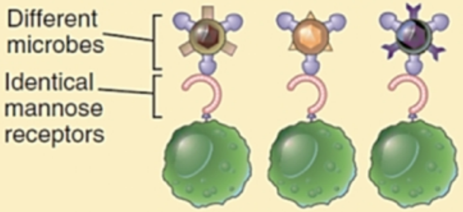
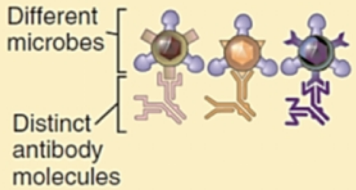
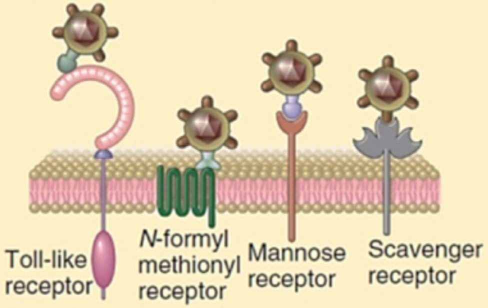
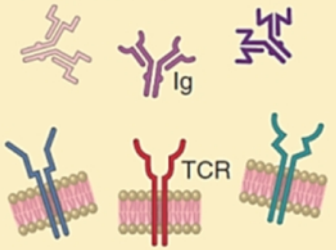
ajitha.thanabalasuriar@mcgill.ca (A.T.), pkubes@ucalgary.ca (P.K.)

In Brief

Neupane et al. develop an intravital method to image alveolar macrophages in the lung in real time, overcoming the challenge presented by the air-liquid-air barrier of the alveoli. They use this *in vivo* approach to show that alveolar macrophages move between alveoli to provide efficient immune surveillance of the airway and phagocytosis of inhaled bacteria before they can induce harmful lung inflammation. Furthermore, they show that respiratory virus infections can interfere with alveolar macrophage surveillance, leading to bacterial superinfection.

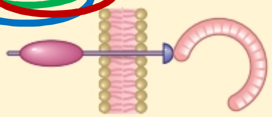
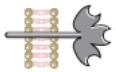
Neupane et al., 2020, Cell

Innate immune system: Type of specificity

	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns)  	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Number of microbial molecules recognized	About 1000 molecular patterns (estimated)	>10^7 antigens
Receptors	Encoded in germline; limited diversity (pattern recognition receptors)  	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Number and types of receptors	<100 different types of invariant receptors	Only 2 types of receptors (Ig and TCR), with millions of variations of each
Distribution of receptors	Nonclonal: Identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Genes encoding receptors	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Innate immune system: Pattern Recognition Receptors

Pattern Recognition Receptors	Location	Specific Examples	Ligands (PAMPs or DAMPs)
Cell-Associated			
TLRs 	Plasma membrane and endosomal membranes of DCs, phagocytes, B cells, endothelial cells, and many other cell types	TLRs 1–9	Various microbial molecules including bacterial LPS and peptidoglycans; viral nucleic acids
NLRs 	Cytosol of phagocytes, epithelial cells, and other cells	NOD1/2 NLRP family (inflammasomes)	Bacterial cell wall peptidoglycans Intracellular crystals (urate, silica); changes in cytosolic ATP and ion concentrations; lysosomal damage
RLRs 	Cytosol of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
CDSs 	Cytosol of many cell types	AIM2; STING-associated CDSs	Bacterial and viral DNA
CLRs 	Plasma membranes of phagocytes	Mannose receptor DC-sign Dectin-1, Dectin-2	Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal and bacterial cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides
N-Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing *N*-formylmethionyl residues

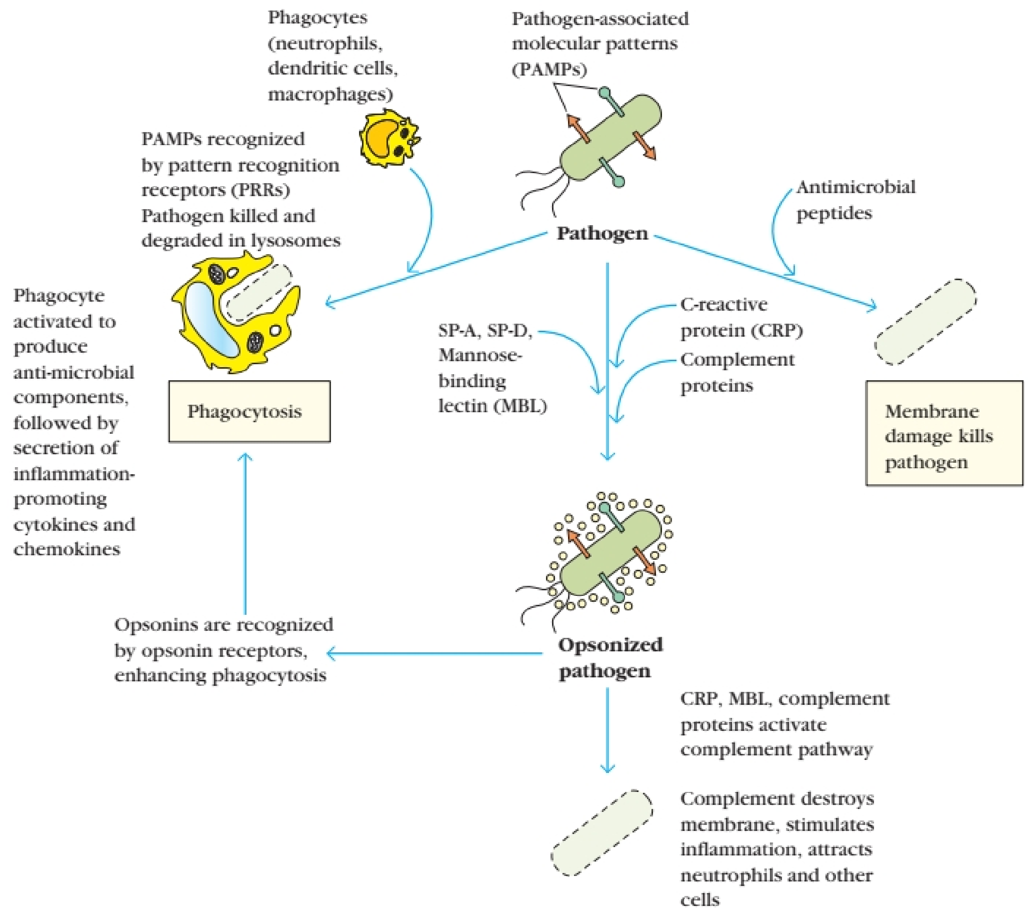
		Microbe Type
Pathogen-Associated Molecular Patterns		
Nucleic acids	ssRNA dsRNA CpG	Virus Virus Virus, bacteria
Proteins	Pilin Flagellin	Bacteria Bacteria
Cell wall lipids	LPS Lipoteichoic acid	Gram-negative bacteria Gram-positive bacteria
Carbohydrates	Mannan Glucans	Fungi, bacteria Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	—
Crystals	Monosodium urate	—
Proteolytically cleaved extracellular matrix	Proteoglycan peptides	—
Mitochondria and mitochondrial components	Formylated peptides and ATP	—
Nuclear proteins	HMGB1, histones	—

Cellular And Molecular Immunology, 9th edition, Elsevier 2018

Innate immune system: Soluble Pattern Recognition Receptors

Pattern Recognition Receptors	Location	Specific Examples	Ligands (PAMPs or DAMPs)
Soluble			
Pentraxins 	Plasma	C-reactive protein	Microbial phosphorylcholine and phosphatidylethanolamine
Collectins 	Plasma Alveoli	Mannose-binding lectin Surfactant proteins SP-A and SP-D	Carbohydrates with terminal mannose and fructose Various microbial structures
Ficolins 	Plasma	Ficolin	*N*-acetylglucosamine and lipoteichoic acid components of the cell walls of gram-positive bacteria
Complement 	Plasma	Various complement proteins	Microbial surfaces

Cellular And Molecular Immunology, 9th edition, Elsevier 2018



Kuby Immunology, 7th Edition, W.H. Freeman, 2013

Properties of innate immunity

- ✓ Innate immune cells have **specificity** for PAMPs and DAMPs via recognition from PRRs

- ❑ What about **memory**?

Innate immune system: the concept of Trained Immunity

Cell Host & Microbe
Perspective

Trained Immunity: A Memory for Innate Host Defense

Mihai G. Netea,[1,*] Jessica Quintin,[1] and Jos W.M. van der Meer[1]
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DOI 10.1016/j.chom.2011.04.006
Cell Host & Microbe 9, May 19, 2011 ©2011 Elsevier Inc.

Table 1. Selected Experimental Models in which Biological Activity Compatible with the Concept of Trained Innate Immunity Has Been Reported

Organism	Experimental Model	Biological Effect	Specificity	References
Plants—Systemic Acquired Resistance				
Large variety of plants	Viruses, bacteria, fungi	Protection against reinfection	Variable	Durrant and Dong, 2004; Sticher et al., 1997
Nonvertebrates				
Mealworm beetle	LPS, or bacterial prechallenge	Protection against secondary infection	No	Moret and Siva-Jothy, 2003
Drosophila	*S. pneumoniae* prechallenge	Protection against *S. pneumoniae*	Uncertain	Pham et al., 2007
Anopheles gambiae	*Plasmodium* prechallenge	Protection against *Plasmodium*	No	Rodrigues et al., 2010
Sponges	Transplantation	Rejection	Yes	Hildemann et al., 1979
Corals	Transplantation	Rejection	Yes	Hildemann et al., 1977
Vertebrates				
Mice	BCG	Protection against candidiasis	No	Van 't Wout et al., 1992
Mice	*Candida* vaccination	T/B cell-independent protection	No	Bistoni et al., 1986, 1988
Mice	Murine CMV infection	NK-dependent protection	No	Sun et al., 2009
Humans	BCG	Nonspecific protection to secondary infections	No	Garly et al., 2003

Innate immune system: the concept of Trained Immunity

mTOR- and HIF-1α–mediated aerobic glycolysis as metabolic basis for trained immunity

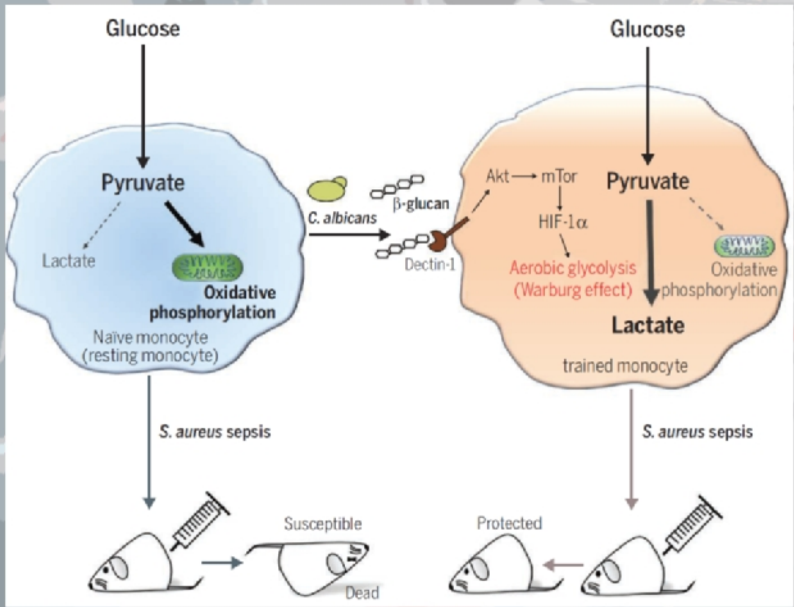
Shih-Chin Cheng, Jessica Quintin, Robert A. Cramer, Kelly M. Shepardson, Sadia Saeed, Vinod Kumar, Evangelos J. Giamarellos-Bourboulis, Joost H. A. Martens, Nagesha Appukudige Rao, Ali Aghajanirefah, Ganesh R. Manjeri, Yang Li, Daniela C. Ifrim, Rob J. W. Arts, Brian M. J. W. van der Meer, Peter M. T. Deen, Colin Logie, Luke A. O'Neill, Peter Willems, Frank L. van de Veerdonk, Jos W. M. van der Meer, Aylwin Ng, Leo A. B. Joosten, Cisca Wijmenga, Hendrik G. Stunnenberg, Ramnik J. Xavier, Mihai G. Netea*

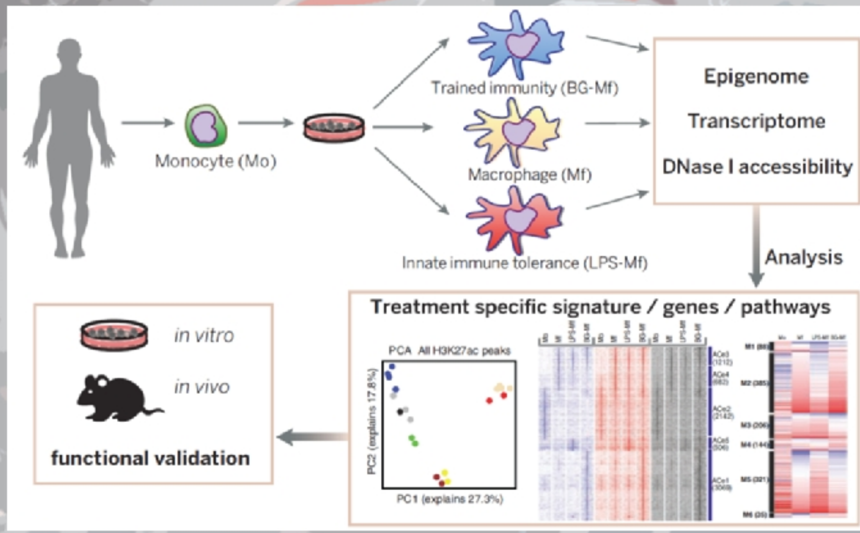
Cheng S-C. et al., **Science** 345, 2014

Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity

Sadia Saeed,[1*] Jessica Quintin,[2*] Hindrik H. D. Kerstens,[1*] Nagesha A. Rao,[1*] Ali Aghajanirefah,[1*] Filomena Matarese,[1] Shih-Chin Cheng,[2] Jacqueline Ratter,[2] Kim Berentsen,[1] Martijn A. van der Ent,[1] Nilofar Sharifi,[1] Eva M. Janssen-Megens,[1] Menno Ter Huurne,[1] Amit Mandoli,[1] Tom van Schaik,[1] Aylwin Ng,[3,4] Frances Burden,[5,6] Kate Downes,[5,6] Mattia Frontini,[5,6] Vinod Kumar,[7] Evangelos J. Giamarellos-Bourboulis,[8] Willem H. Ouwehand,[5,6] Jos W. M. van der Meer,[2] Leo A. B. Joosten,[2] Cisca Wijmenga,[7] Joost H. A. Martens,[1] Ramnik J. Xavier,[3,4] Colin Logie,[1]† Mihai G. Netea,[2]† Hendrik G. Stunnenberg[1]†

Saeed S. *et al.*, **Science** 345, 2014





Innate immune system: the concept of Trained Immunity

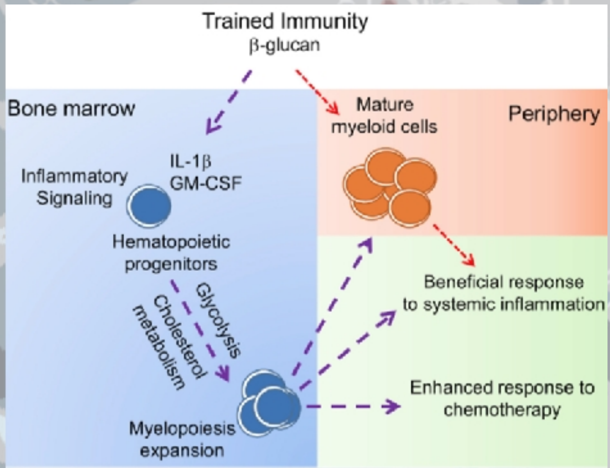
Cell 172, 135–146, January 11, 2018 © 2017 Elsevier Inc.

Article

Cell

Metabolic Induction of Trained Immunity through the Mevalonate Pathway

Siroon Bekkering,[1,2,10] Rob J.W. Arts,[1,10] Boris Novakovic,[3] Ioannis Kourtzelis,[4] Charlotte D.C.C. van der Heijden,[1] Yang Li,[8] Calin D. Popa,[5] Rob ter Horst,[1] Julia van Tuijl,[1] Romana T. Netea-Maier,[9] Frank L. van de Veerdonk,[1] Triantafyllos Chavakis,[4] Leo A.B. Joosten,[1,6] Jos W.M. van der Meer,[1] Henk Stunnenberg,[3] Niels P. Riksen,[1,11,*] and Mihai G. Netea[1,7,11,12,*]



Cell 172, 147–161, January 11, 2018 © 2017

Article

Cell

Modulation of Myelopoiesis Progenitors Is an Integral Component of Trained Immunity

Ioannis Mitroulis,[1,18,*] Klara Ruppova,[1,16] Baomei Wang,[2,16] Lan-Sun Chen,[1,16] Michal Grzybek,[3,4,16] Tatyana Grinenko,[1] Anne Eugster,[5] Maria Troullinaki,[1] Alessandra Palladini,[1,3,4] Ioannis Kourtzelis,[1] Antonios Chatzigeorgiou,[1] Andreas Schlitzer,[6] Marc Beyer,[7,8] Leo A.B. Joosten,[9] Berend Isermann,[10] Mathias Lesche,[11] Andreas Petzold,[11] Kai Simons,[12,13] Ian Henry,[12] Andreas Dahl,[11] Joachim L. Schultze,[7,14] Ben Wielockx,[1] Nicola Zamboni,[15] Peter Mirtschink,[1] Ünal Coskun,[3,4] George Hajishengallis,[2,17] Mihai G. Netea,[7,9,17] and Triantafyllos Chavakis[1,17,19,*]

Innate immune system: the concept of Trained Immunity

Cell

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Article

Innate Immune Training of Granulopoiesis Promotes Anti-tumor Activity

Lydia Kalafati,[1,2,14] Ioannis Kourtzelis,[1,2,3,14,*] Jonas Schulte-Schrepping,[4] Xiaofei Li,[5] Aikaterini Hatzioanno
Tatyana Grinenko,[1] Eman Hagag,[1] Anupam Sinha,[1,2] Canan Has,[1] Sevina Dietz,[7] Antonio Miguel de Jesus D
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Inducing trained immunity in pro-metastatic macrophages to control tumor metastasis

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Trained Immunity-Promoting Nanobiologic Therapy Suppresses Tumor Growth and Potentiates Checkpoint Inhibition

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Influenza-trained mucosal-resident alveolar macrophages confer long-term antitumor immunity in the lungs

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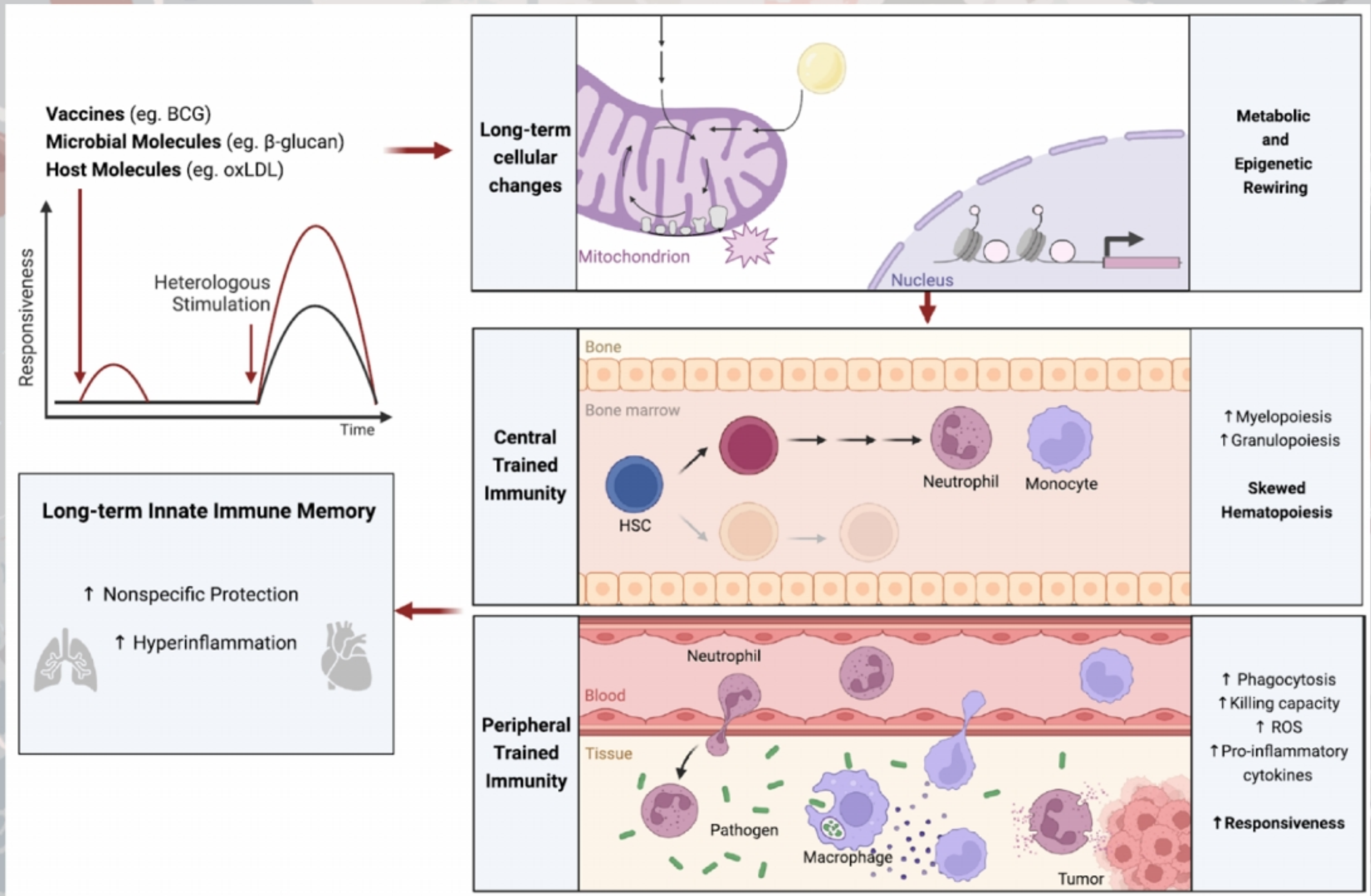
Innate immune system: the concept of Trained Immunity



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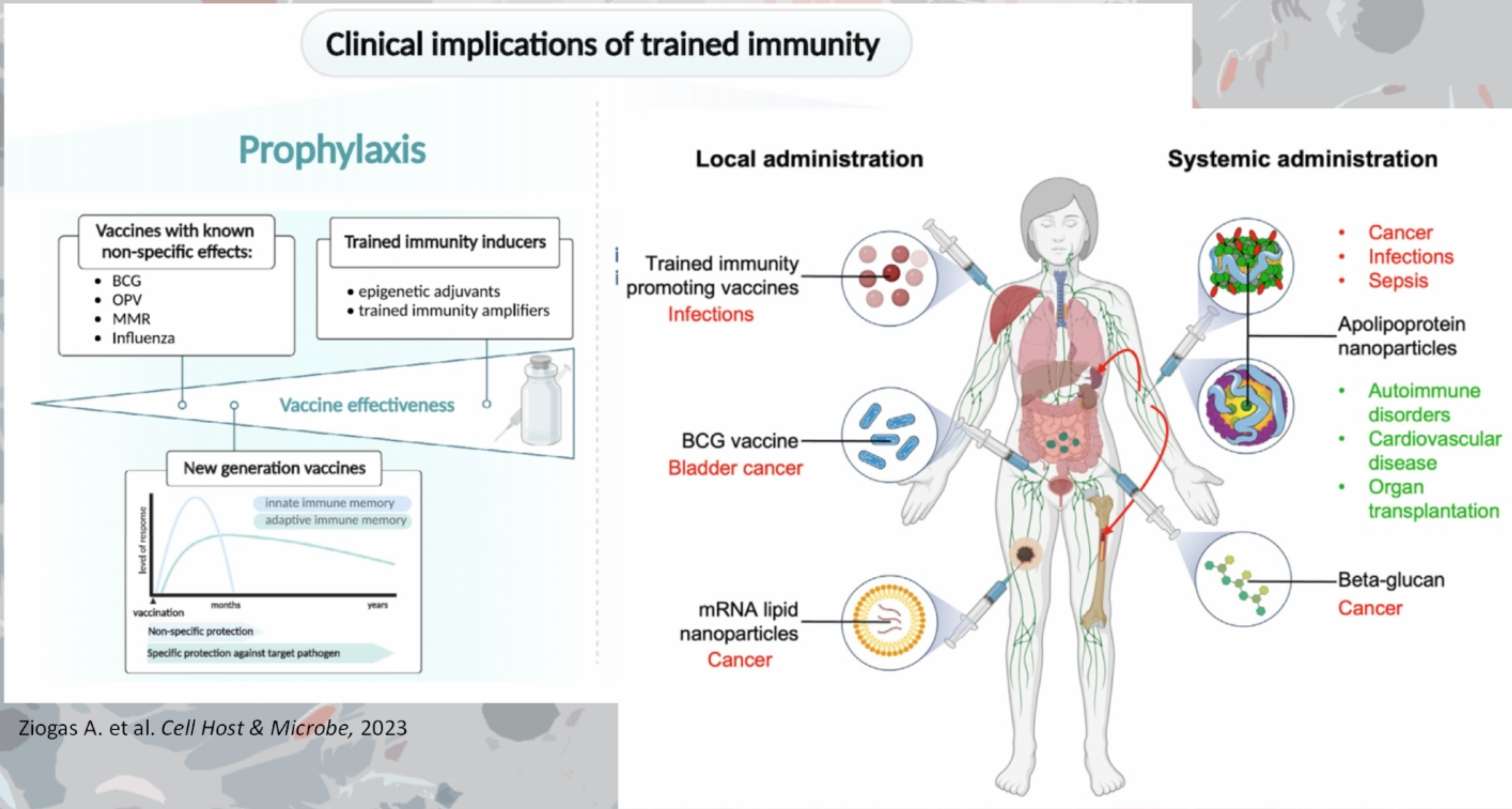
Innate immune system: the concept of Trained Immunity



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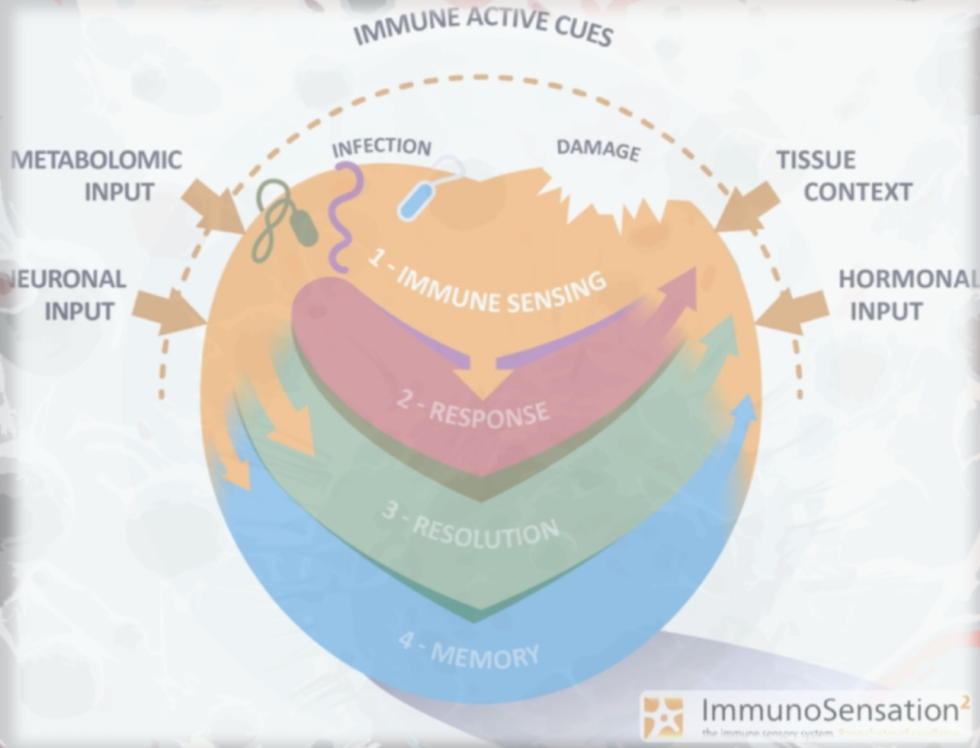
IMMUNE ACTIVE CUES
METABOLOMIC INPUT
INFECTION
DAMAGE
TISSUE CONTEXT
NEURONAL INPUT
HORMONAL INPUT
1 - IMMUNE SENSING
2 - RESPONSE
3 - RESOLUTION
4 - MEMORY
ImmunoSensation^2


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