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MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

The Link of Innate Immunity and Adaptive Immunity

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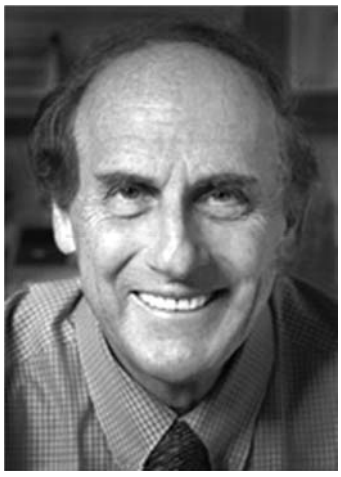
Introduction

2011 Nobel prize was awarded to 3 scientists who have studied innate immunity and adaptive immunity. Drs. Beutler and Hoffman discovered activation pathways of innate immunity and Dr. Steinman discovered dendritic cells. Dendritic cells linker cells between innate and adaptive immunity. Unfortunately, Dr. Steinman was dead before announcement of novel prize.

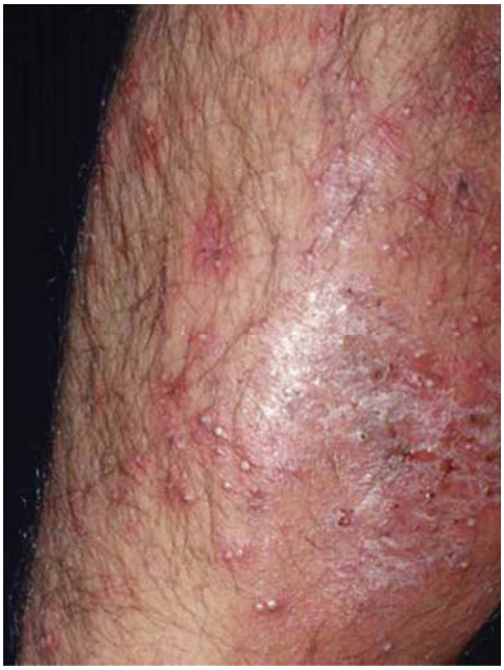
Bruce A. Beutler

Jules A. Hoffmann



Ralph M. Steinman

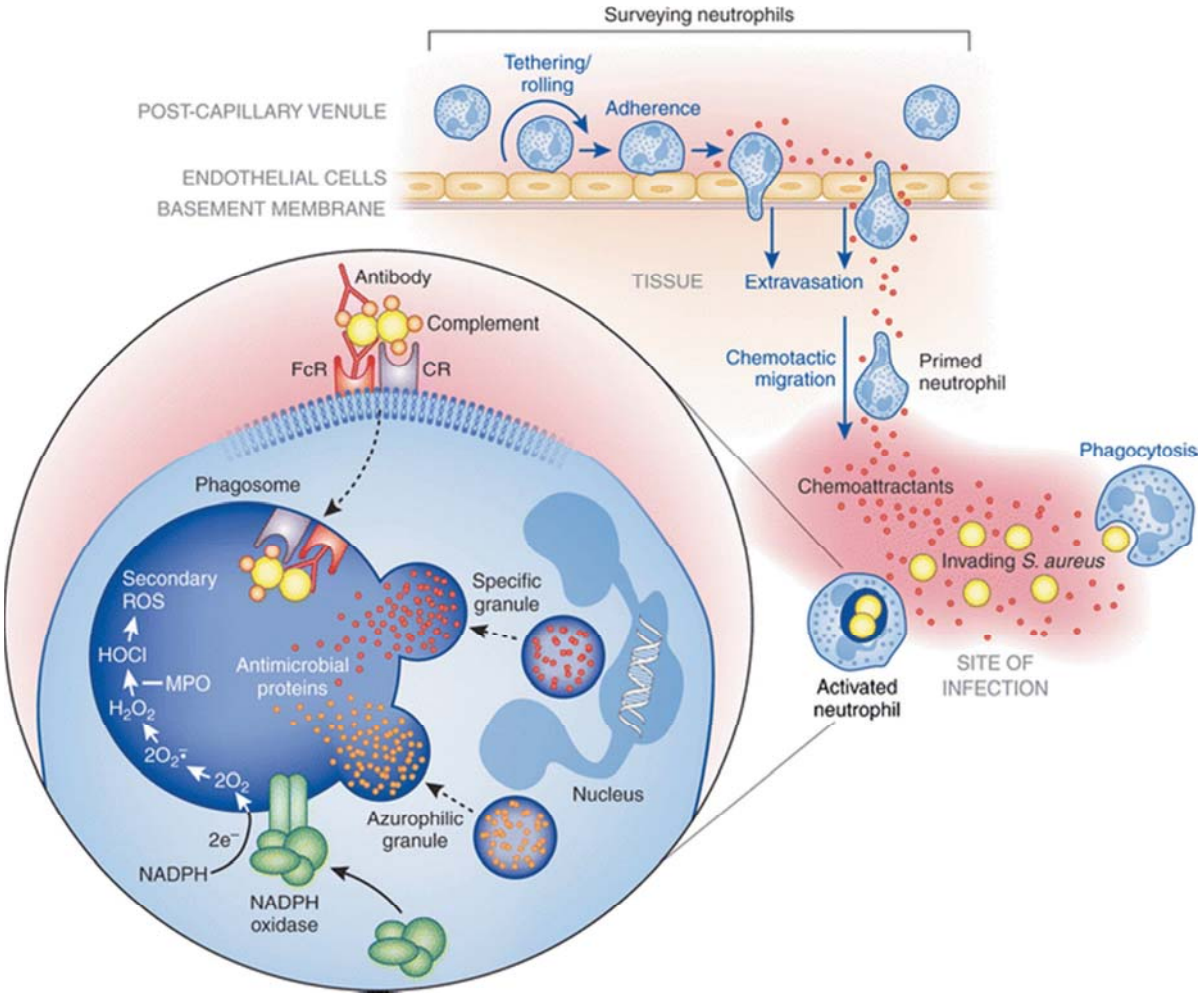
Let me tell one example of infectious diseases, skin infection.



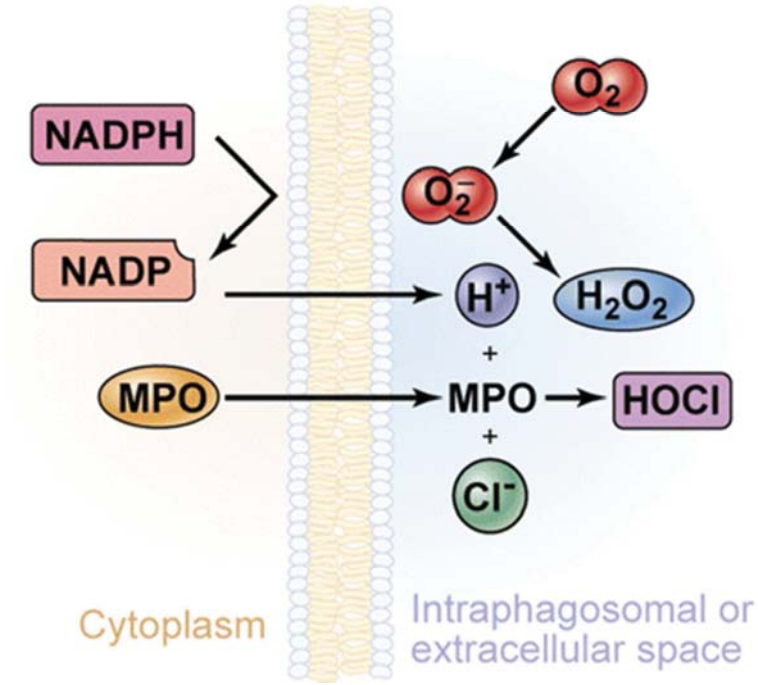
As shown in this picture, numerous infected hair follicles present as follicularly based erythematous, warm, edematous papules and pustules on this extremity. Most cells in this folliculitis lesion are neutrophils, polymorphonuclear leukocytes (PMNLs).

Neutrophils are the first line of innate immune defense against infectious diseases. Marginating neutrophils survey post-capillary venules for signs of inflammation or invading microorganisms, undergoing transient tethering interactions with endothelial cells that facilitate neutrophil rolling along the endothelial wall and allow neutrophils to search for host- and/or microbe-derived chemotactic signals. Chemotactic molecules diffusing from the site of infection and into the bloodstream bind specific receptors on the neutrophil surface, arresting the rolling process and inducing firm adherence to the endothelial wall.

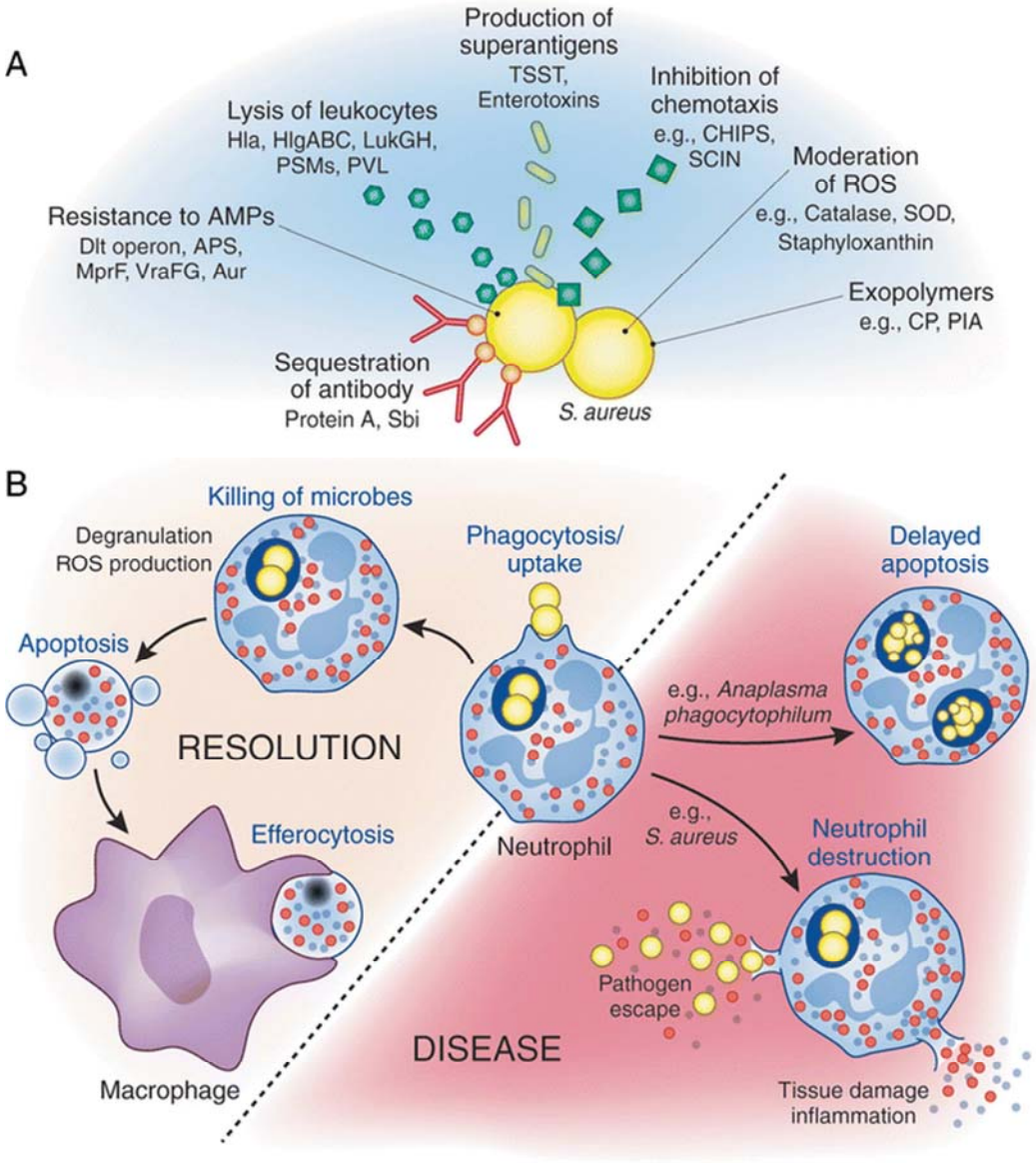
Firm adherence subsequently leads to neutrophil transmigration through the endothelial wall into the tissue, a process known as extravasation. Once in the tissue, primed neutrophils chemotactically migrate to the site of infection where they recognize and phagocytose invading microorganisms. Within the phagosome of the activated neutrophil, microbes are destroyed by NADPH oxidase-derived reactive oxygen species and antimicrobial proteins released upon granule fusion with the phagosome (degranulation).



Moreover, hydrogen peroxide interacted with myeloperoxidase and a halide, predominantly chloride, to generate the potent antibacterial substance, hypochlorous acid, within the phagosome.

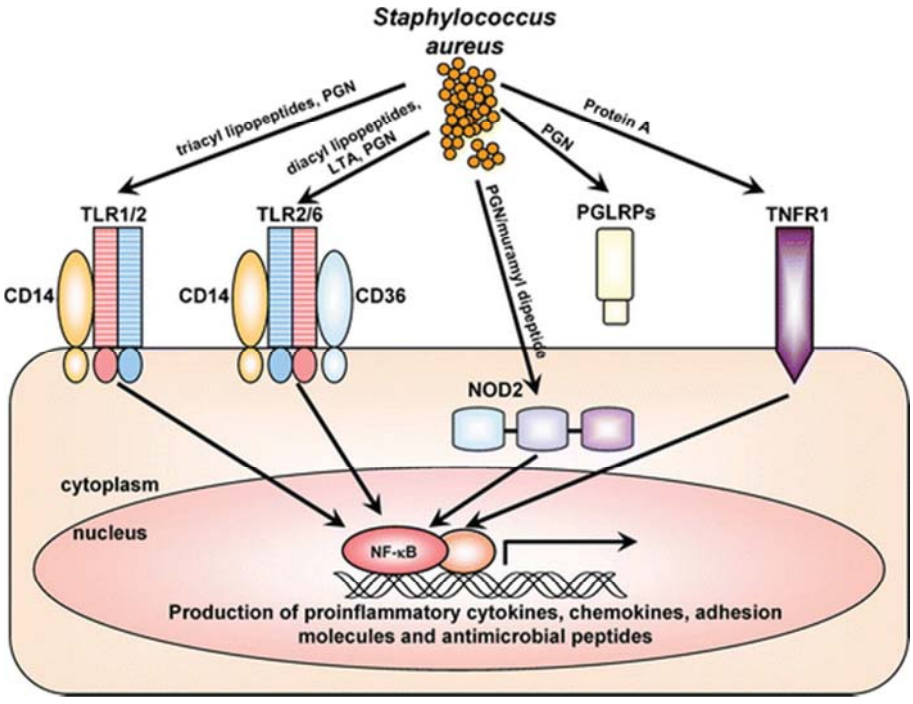


Immune evasion by S. aureus includes strategies that serve to prevent recognition, inhibit chemotaxis, moderate ROS, protect against AMPs, and directly damage immune cells. Phagocytic uptake of bacteria triggers production of ROS and degranulation, working collectively to kill ingested bacteria, after which neutrophils undergo apoptosis to be removed by macrophages and promote healthy resolution of infection. Alternatively, bacterial pathogens can alter normal neutrophil turnover, promoting either a delay in neutrophil apoptosis or an accelerated neutrophil lysis. Alteration of normal neutrophil turnover facilitates pathogen survival and promotion of disease.

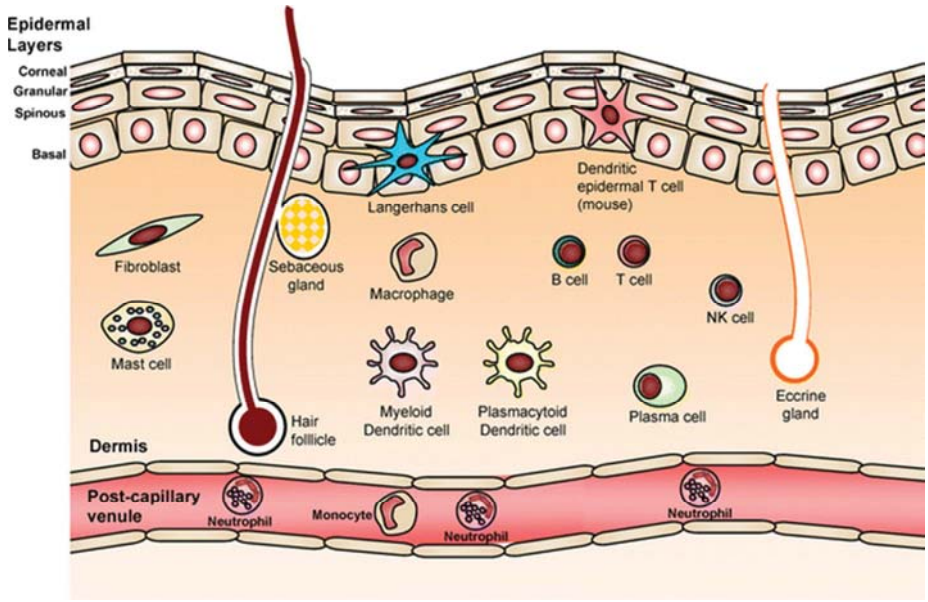


Neutrophils can impact several immune related functions from leukocyte recruitment and T-cell regulation to thrombosis and autoimmunity. Neutrophil effects are communicated by direct contact with other cells and/or the secretion of inflammatory mediators.

PRRs involved in recognizing components of *S. aureus* and cellular localization of these PRRs are shown. Toll-like receptor 2 (TLR2) recognize tri- and di-acyl lipopeptides, respectively (including *S. aureus* lipoteichoic acid [LTA], which is diacylated, *aureus* peptidoglycan (PGN). CD14 and CD36 act as TLR2 co-receptors. Nucleotide-binding oligomerization domain containing 2 (NOD2) is an intracellular cytoplasmic receptor that recognizes the *S. aureus* peptidoglycan breakdown product muramyl dipeptide. Peptidoglycan receptor proteins (PGRPs or PGLYRPs) are secreted proteins that recognize S. aureus PGN. TNFR1 is a cell surface receptor that is activated by TNF-α but has also been shown to recognize *S. aureus* protein A. In general, signaling from these PRRs promotes activation of NF-κB and other transcription factors that induce transcription of proinflammatory cytokines, chemokines, adhesion molecules, and antimicrobial peptides that are involved in cutaneous host defense against *S. aureus*.



TLR2 is expressed on the cell surface of numerous cell types in the skin, including keratinocytes, Langerhans cells, monocytes/macrophages, dendritic cells, mast cells, endothelial cells, fibroblasts, and adipocytes.



Neutrophils, macrophages, dendritic cells, natural killer (NK) cells, and NKT cells in conjunction with natural barriers (mostly skin, and gastrointestinal and respiratory mucosa), antimicrobial agents, opsonins (e.g., complement), and cytokines are critical innate components.

Effector cells of adaptive immunity, T cells need antigen presentation from specific cells, dendritis cells. Innate immune cells can elicit adaptive immune reaction through dendritic cells. In the picture, you can see antigen capture, processing and presentation by dendritic cells.

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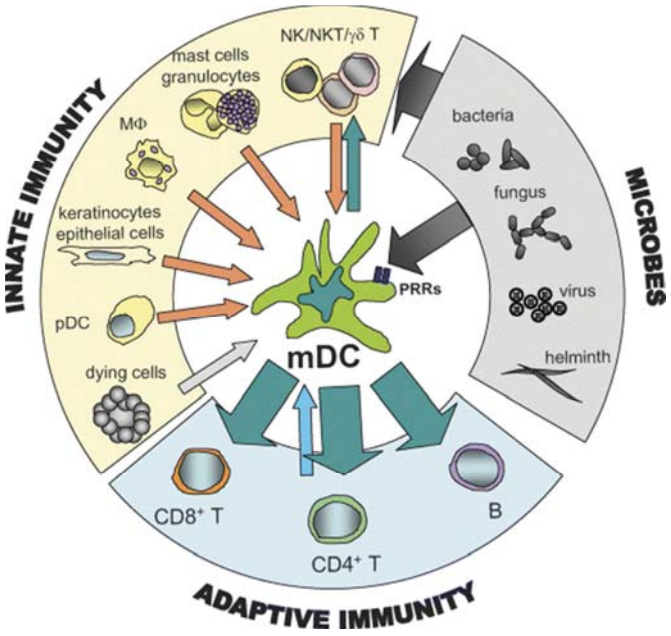
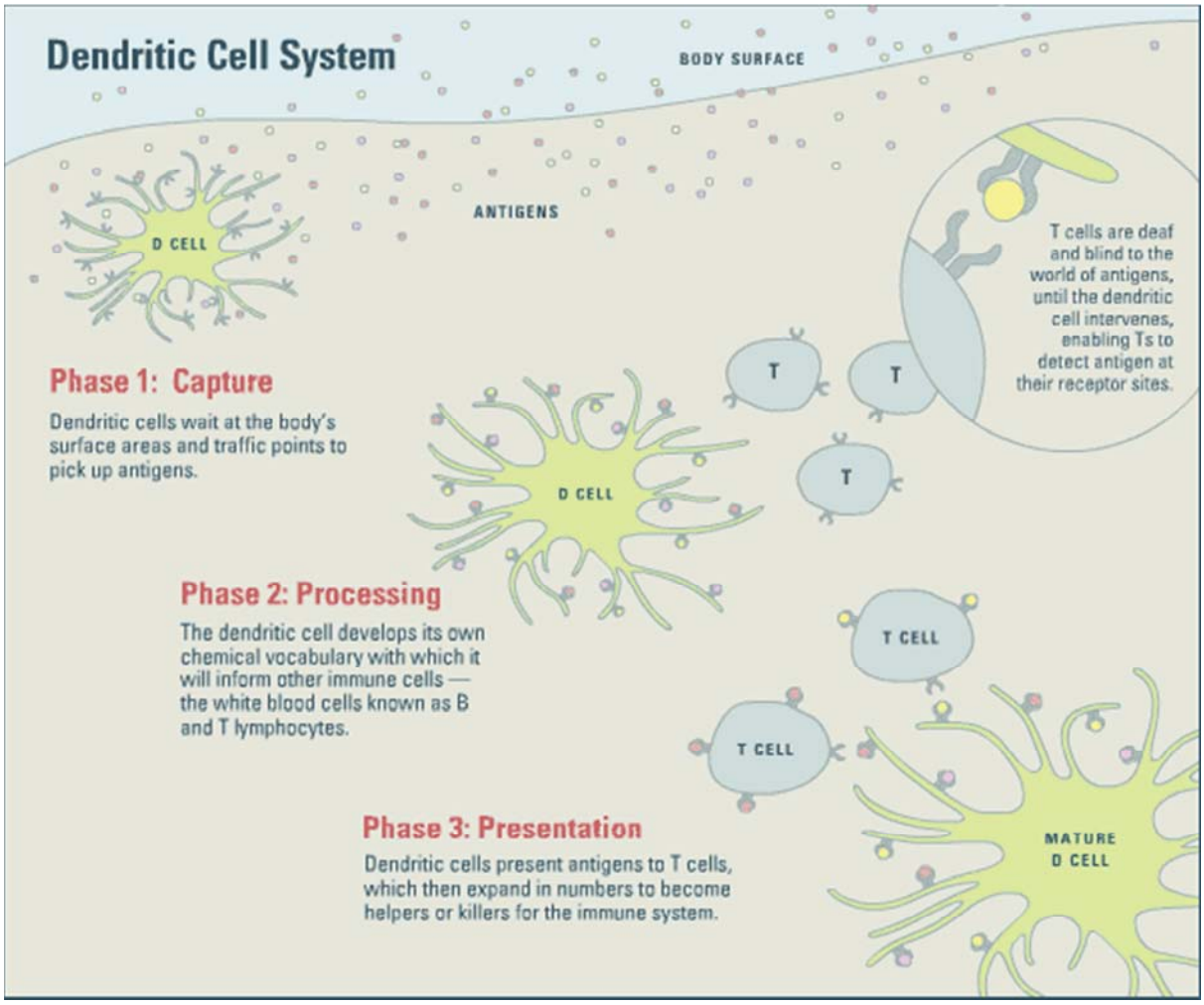
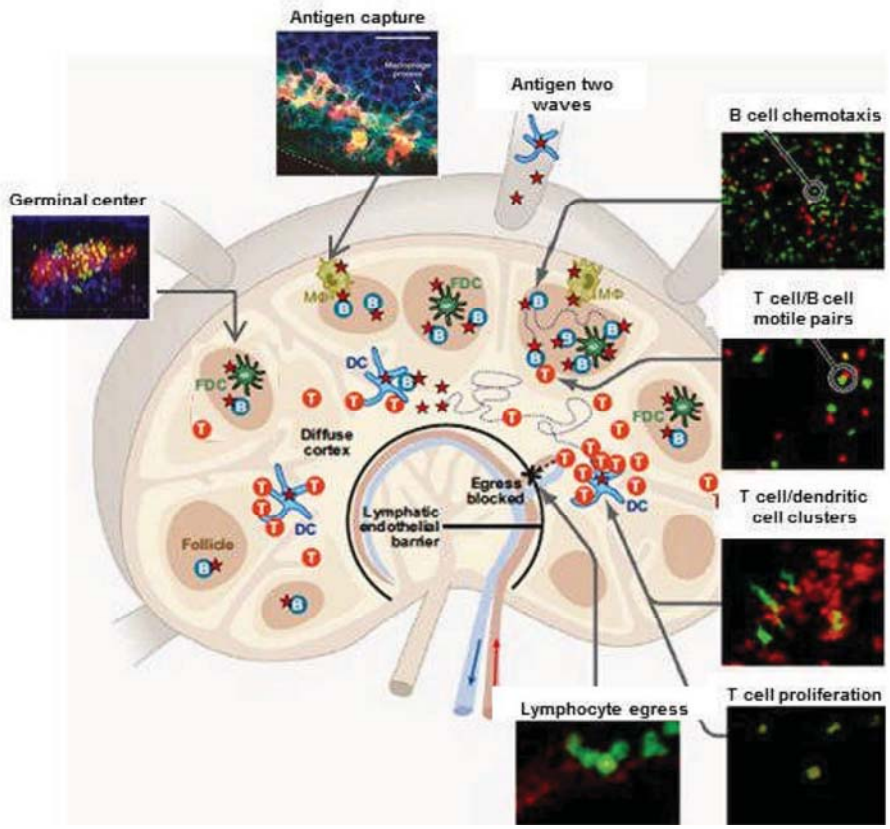
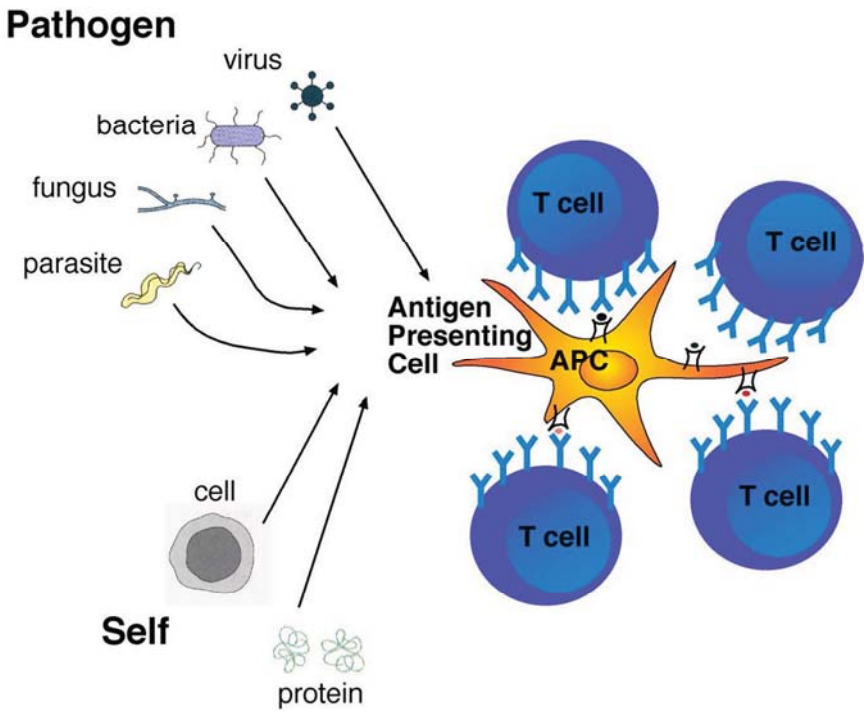




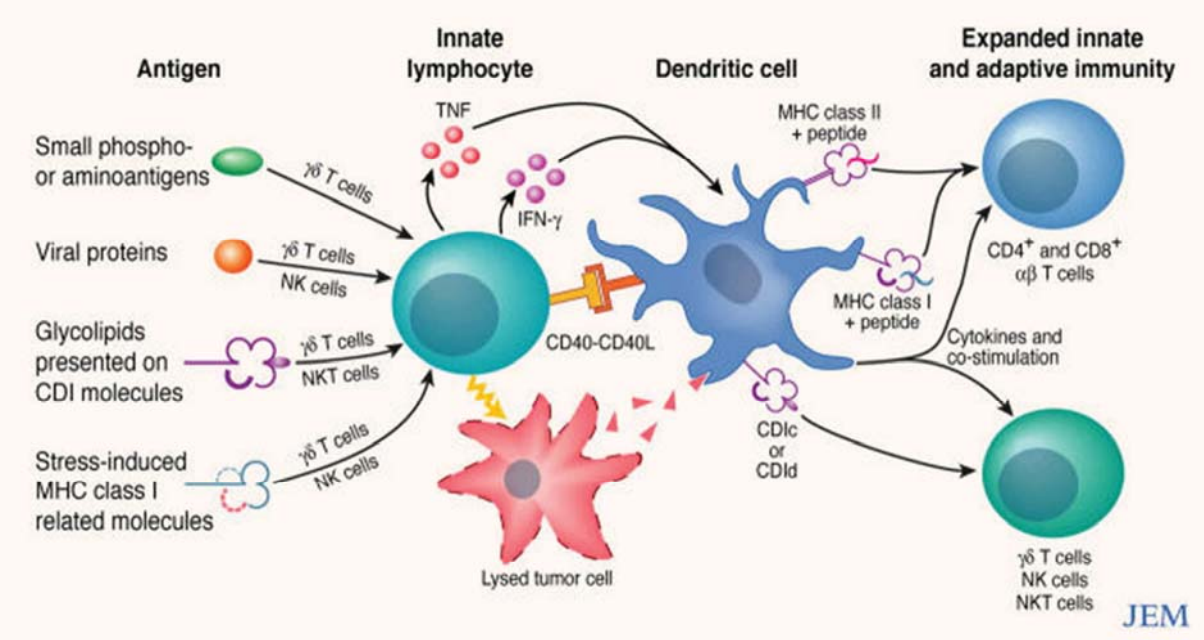
There are cellular interactions among T cells, B cells, dendritic cells, macrophages during the response to antigen in lymph organs. This diagram shows antigen capture, T cell-dendritic cell interactions, T cell proliferation, chemotaxis of B cells to the follicle edge, motile T cell-B cell conjugates, germinal center dynamics, and lymphocyte egress.



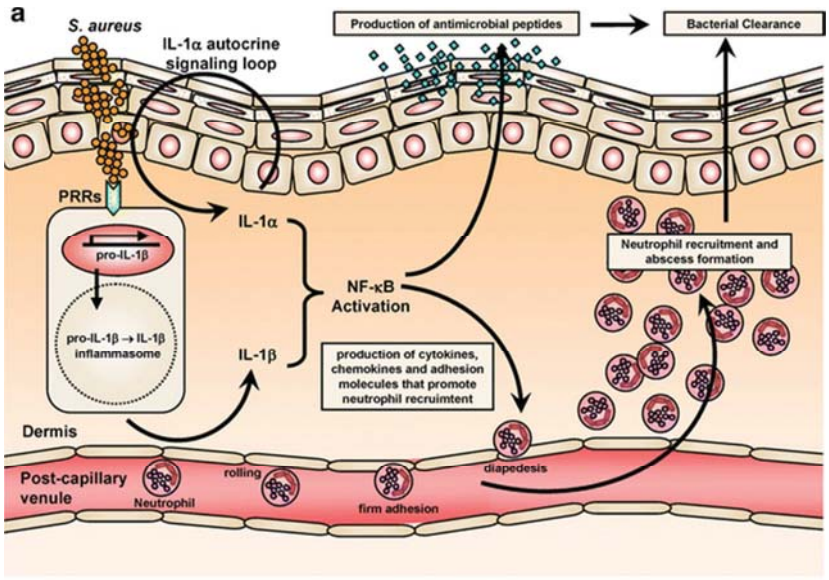
Dendritic cells engulf exogenous pathogens, such as bacteria, parasites or toxins in the tissues and then migrate, via chemotactic signals, to the T cell enriched lymph nodes. MHC:antigen complex is recognized by T-cells passing through the lymph node. Exogenous antigens are usually displayed on MHC class II molecules, which activate CD4+ helper T-cells. Endogenous antigens are typically displayed on MHC class I molecules, and activate CD8+ cytotoxic T-cells.

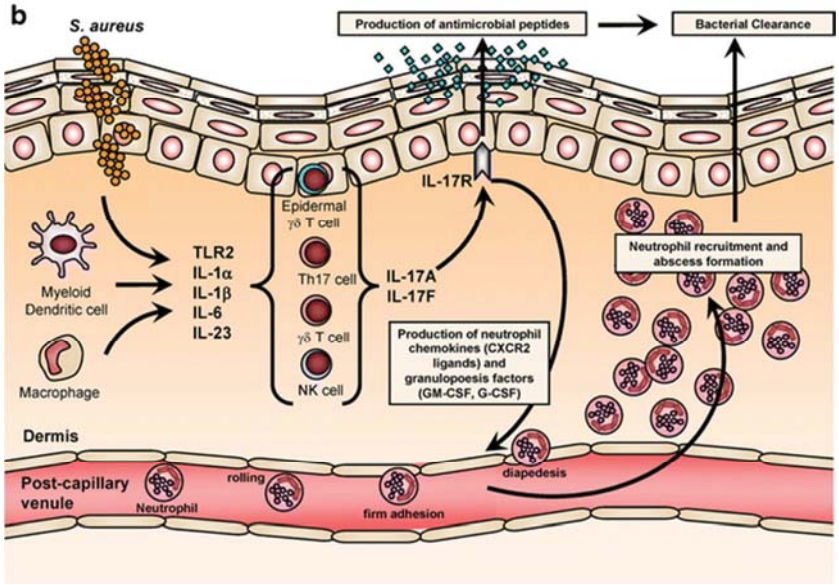


Innate lymphocytes, including γδ T, NKT, and NK cells recognize pathogen-derived and self-antigens on infected cells, tumors, and stressed self-tissues (left). Their activation leads to DC maturation, presumably under conditions where the DCs are also presenting ligands recognized by innate lymphocytes. The DCs thus expand the innate response (bottom right) and also elicit adaptive immunity to processed antigens (top right), including those derived from cells lysed by innate lymphocytes. Cytokines and cell contact–dependent molecules mediate DC activation by different types of innate lymphocytes, whereas DCs produce cytokines that expand and differentiate additional innate and adaptive lymphocytes.

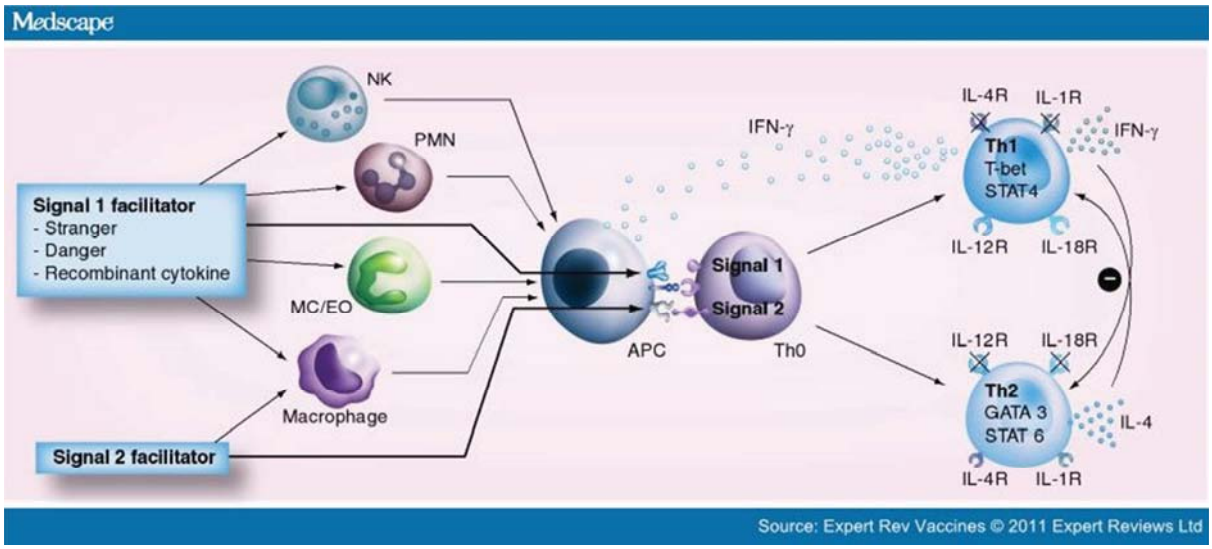


In response to *S. aureus*, IL-1α is produced and released by keratinocytes in an autocrine signaling loop. In addition, *S. aureus* skin infection results in activation of PRRs and the inflammasome by resident and recruited cells (such as macrophages and dendritic cells), which leads to production and secretion of active IL-1β. (B) IL-17 mediated response against *S. aureus*. IL-17 are produced by multiple different types of cells in the skin, including Th17 cells, γδ T cells, and NK cells (and perhaps mast cells and neutrophils) in response to different signals such as activation by TLR2, IL-1α/β, IL-6, and IL-23. IL-17 mediates immune responses by binding to the IL-17R, which is expressed primarily by keratinocytes. Both the IL-1 and IL-17 responses promote neutrophil recruitment and abscess formation and keratinocyte production of antimicrobial peptides (e.g., hBD2, hBD3, and LL-37) to help control *S. aureus* skin infections and mediate bacterial clearance.

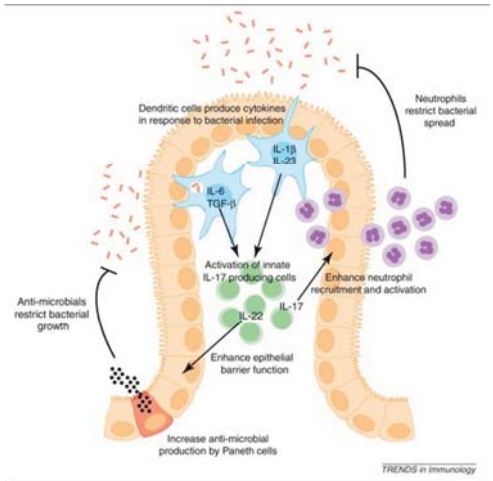

a
S. aureus
IL-1α autocrine signaling loop
Production of antimicrobial peptides
Bacterial Clearance
PRRs
pro-IL-1β
pro-IL-1β → IL-1β inflammasome
IL-1α
IL-1β
NF-κB Activation
production of cytokines, chemokines and adhesion molecules that promote neutrophil recruimtent
Neutrophil recruitment and abscess formation
Dermis
Post-capillary venule
Neutrophil
rolling
firm adhesion
diapedesis


b
S. aureus
Production of antimicrobial peptides
Bacterial Clearance
IL-17R
Epidermal γδ T cell
Th17 cell
γδ T cell
NK cell
TLR2
IL-1α
IL-1β
IL-6
IL-23
IL-17A
IL-17F
Myeloid Dendritic cell
Macrophage
Production of neutrophil chemokines (CXCR2 ligands) and granulopoesis factors (GM-CSF, G-CSF)
Neutrophil recruitment and abscess formation
Dermis
Post-capillary venule
Neutrophil
rolling
firm adhesion
diapedesis

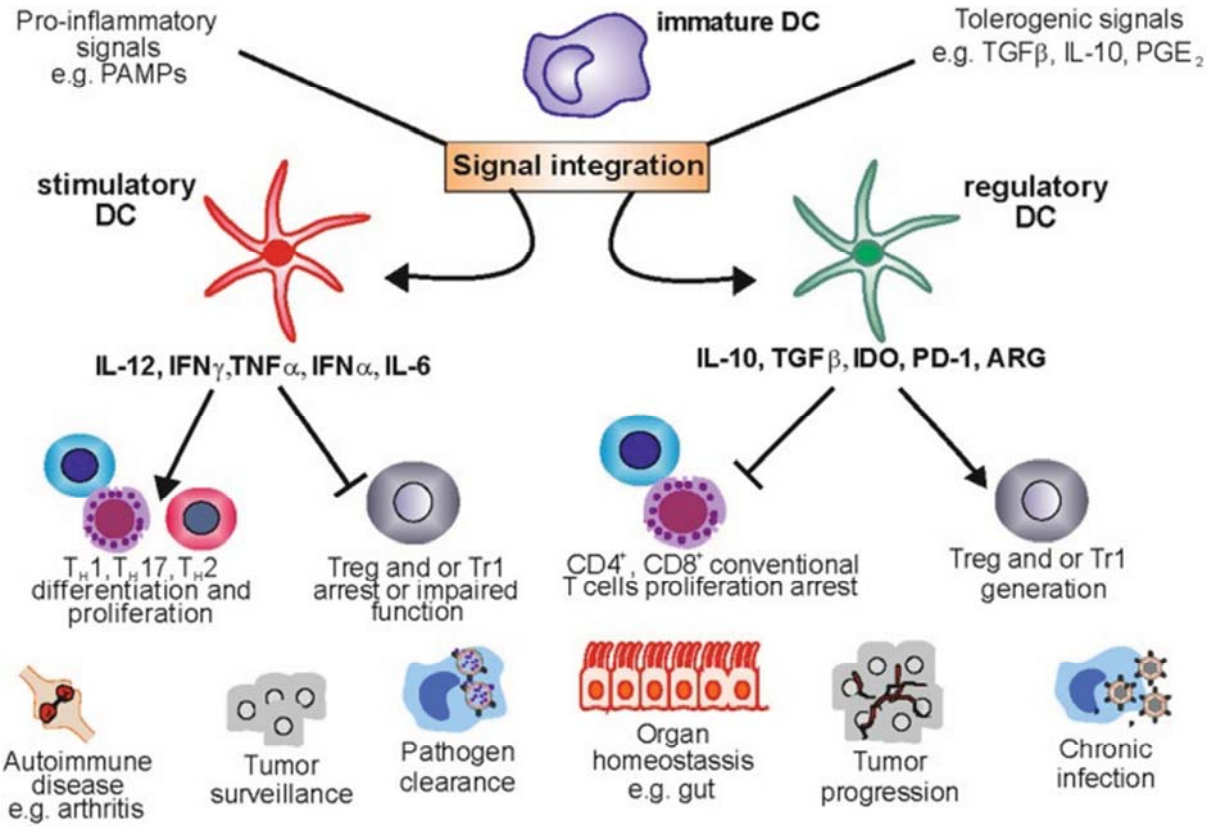
Cytokine production by dendritic cells affects the function of T cells. The progress is called signal 2. Signal 1 is the interaction between MHC on dendritic cells and T cell receptors.



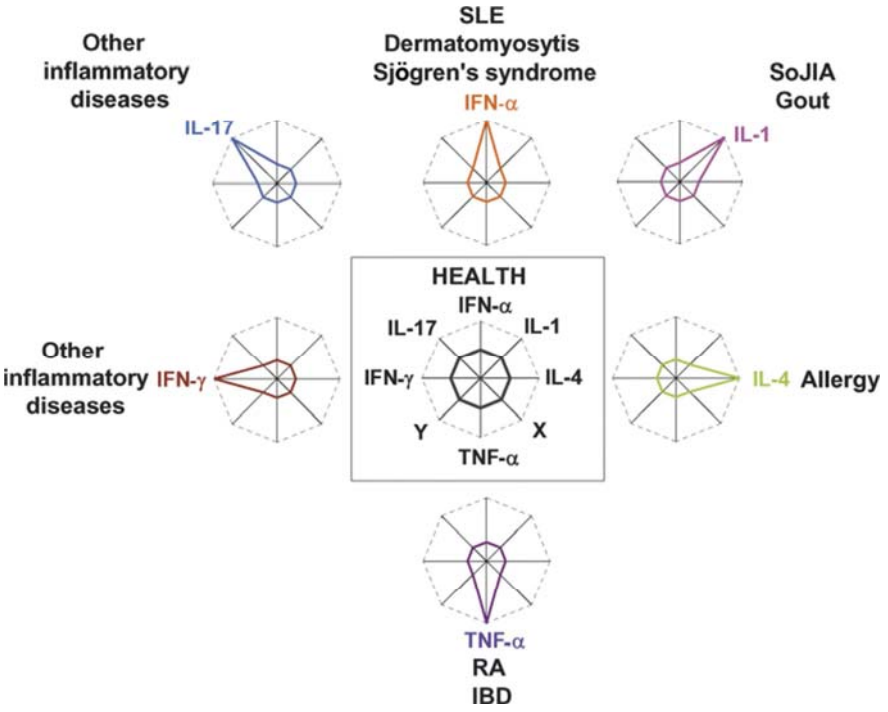
Extracellular pathogens (such as *C. rodentium*) and intracellular pathogens (such as *S.* Typhimurium) are detected via either direct or indirect mechanisms by DCs that produce cytokines (TGF-β, IL-6, IL-23 and IL-1 β) that drive IL-17 and IL-22 production by innate lymphocytes. IL-22 primarily acts on epithelial cells (such as Paneth cells) to promote barrier functions such as enhancing production of antimicrobial peptides that control bacterial growth, whereas IL-17 acts to promote recruitment and activation of neutrophils that prevent bacterial spread.



Immature DCs patrol via the blood systems throughout the body and can invade peripheral tissues to take up antigens from infected or dying cells via macropinocytosis, phagocytosis, and endocytosis. Several soluble factors such as TGFβ, IL-10, or PGE_2 known to play a role in immune inhibition have been linked to the induction of regulatory DCs.

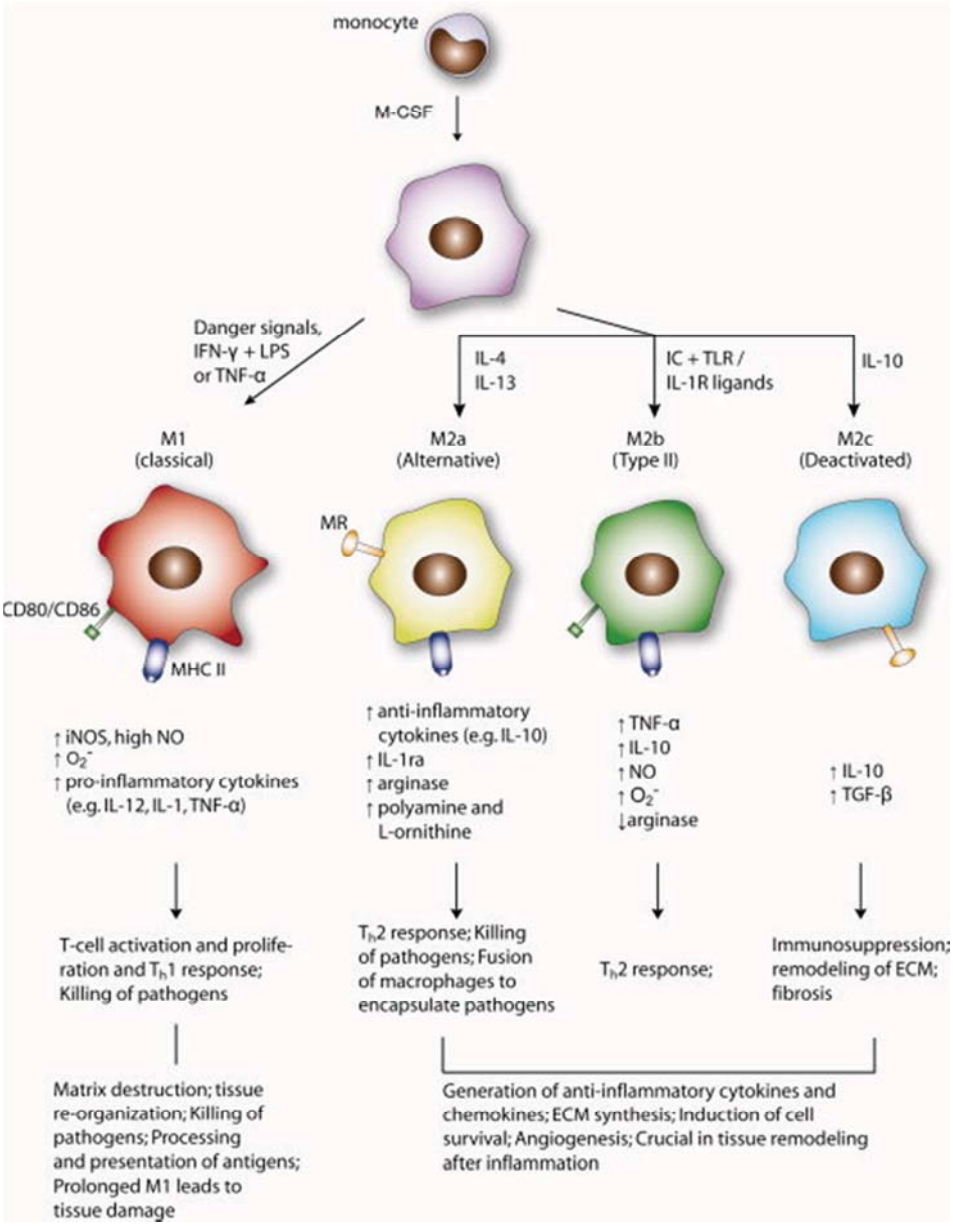


Therefore, alteration of cytokine production by dendritic cells and T cells is related to various immune diseases.

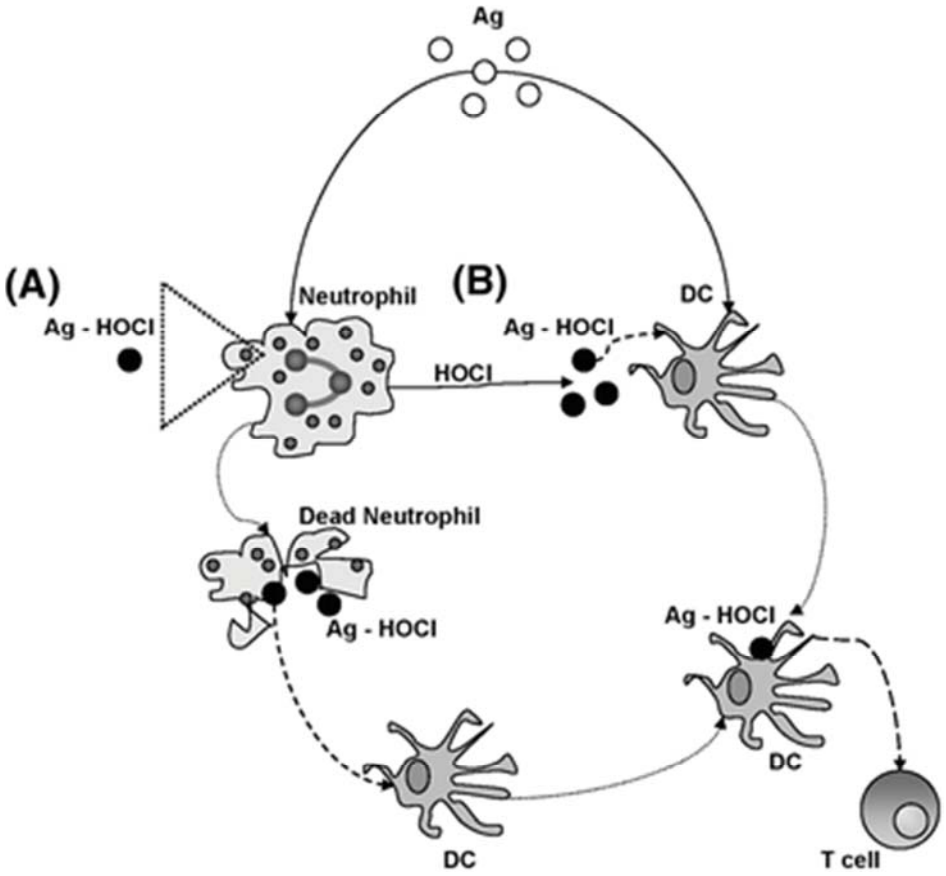


iDCs can be derived from monocytes in the presence of IL-4 and GM-CSF. Interestingly, IL-6 may maintain the differentiation of monocytes into Mϕ despite the presence of IL-4 and GM-CSF. Similar to Mϕs, DCs can acquire different phenotypes in response to stimuli. Danger signals and PAMPs can activate iDCs into classical mDCs. These mDCs express higher levels of costimulatory molecules (CD80/86 and CD40), MHC class II molecules, release proinflammatory cytokines, migrate to the lymph nodes, and stimulate naïve or memory T cells. This result show increased expression of surface markers on activated dendritic cells and morphological changes. During the steady state, tolerogenic DCs are naturally actively induced in response to apoptotic cells and self-antigens. These tolerogenic DCs release anti-inflammatory cytokines such as IL-10 and induce T-cell anergy, T-cell apoptosis and/or T_{reg} expansion. DCs can also be alternatively

activated by anti-inflammatory molecules such as dexamethosone and IL-10. These aaDCs have been shown to release anti-inflammatory cytokines, induce T_{reg} expansion, and promote angiogenesis.



Protein antigens are likely to be exposed to HOCl oxidation via two ways: (A) oxidation occurs within the neutrophil phagosome, dead neutrophil are then phagocytosed by antigen-presenting cells (DC dendritic cells) that are processing and presenting HOCl-oxidized antigens (Ag-HOCl); (B) oxidation occurs in the immediate vicinity of neutrophil infiltration, HOCl-oxidized antigens are directly taken up, processed and presented by DCs.



In conclusion, the link of innate immunity and adaptive immunity is very important in the development and treatment of various diseases.

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