Lecture 5 of Advanced Immunology
By Dr Alia Alubadi

During infection in the host, a nonspecific and immediate immune response is initiated to eliminate the pathogen, and this nonspecific response involves the recruitment of neutrophils, macrophages and dendritic cells, complement activation, and cytokine production.

This response can inhibit or limit microbial growth but also can cause host damage, and so it is necessary to keep this response under control by some strategies, including the production of cytokines, which play an essential role in intercellular communication and coordinate the innate and adaptive response.

The recognition of pathogens by the immune system involves 2 main class of PRRs:

1- Membrane-bound PRRs include

A) TLRs

B) C-type lectin receptors (CLRs)

2-Cytoplasmic PRRs include

A) Retinoic acid-inducible gene I (RIG-I) like receptors (RLRs)

B) Nucleotide-binding oligomerization domain-like (NOD-like) receptors (NLRs)

In microbial infections, the pattern-recognition receptors (PRRs) recognize several PAMPs, such as DNA, double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and 5′-triphosphate RNA, as well as lipoproteins, surface glycoproteins, membrane components peptidoglycans, lipoteichoic acid (LTA), lipopolysaccharide (LPS), and glycosyl-phosphatidyl-inositol.

The recognition of PAMPs by PRRs leads to the activation **of NF-κB and/or MAPK (are a proteins complex that controls transcription of DNA, cytokine production and cell survival)** to produce several cytokines.

1- Cytokine profile in bacterial infections

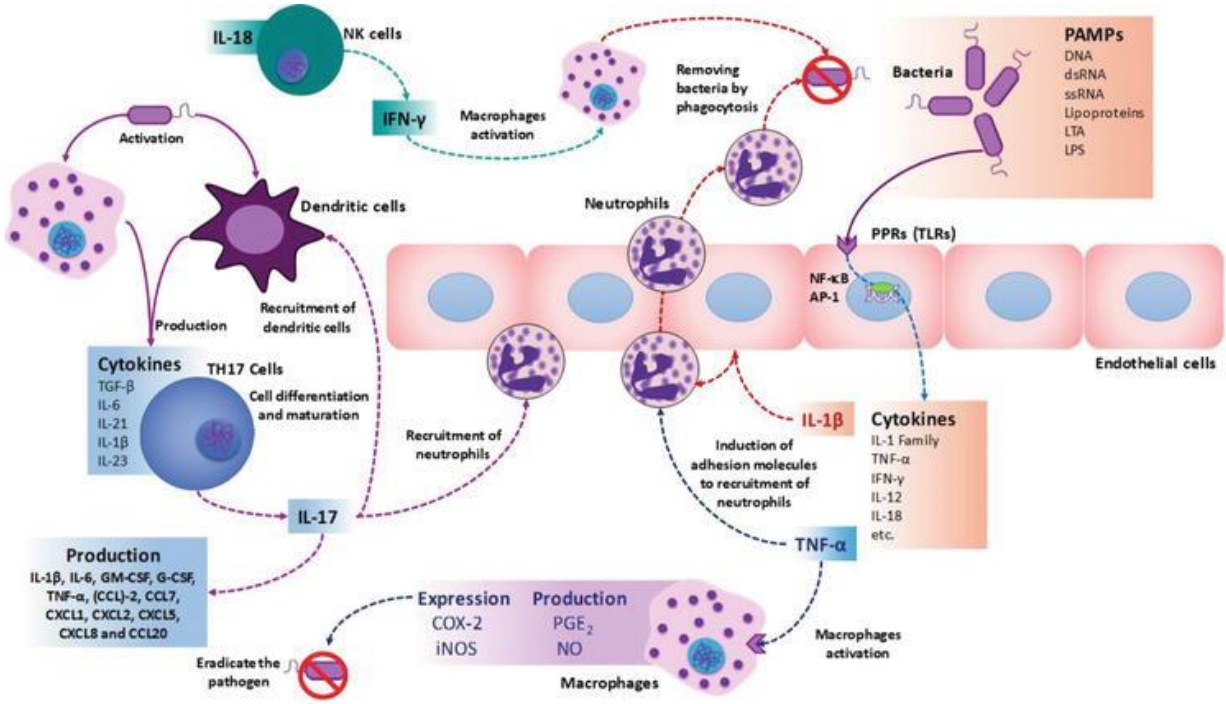
In response to bacterial infection, the IL-1 family cytokines with its receptors IL-1R induces the expression of adhesion molecules in the endothelial cells and promotes the recruitment of neutrophils to the site of inflammation. TNF-α plays an important role through the recruitment of neutrophils and macrophages, besides inducing the expression of proinflammatory mediators to the site of infection. Th17 cells produce IL-17A by a subpopulation of CD4 T-cells, which induces the production of inflammatory mediators such as IL-1β, IL-6, GM-CSF, G-CSF, and TNF-α, as well as adhesion molecules, IL-18 also promotes the secretion of other proinflammatory cytokines like TNF-α, IL-1β, IL-8, and GM-CSF and consequently enhancement, migration, and activation of neutrophils during infections.

The protective capacity of IL-17A against infectious agents can be mediated through several mechanisms,

1- IL-17A induces the production of inflammatory mediators, in the barrier surfaces, such as IL-1β, IL-6, GM-CSF, granulocyte colony-stimulating factor (G-CSF), and TNF-α, as well as adhesion molecules.

2- IL-17A also induces the production of chemotactic factors, such as chemokine-(C-C motif)-ligand (CCL)-2, CCL7, CXCL1, CXCL2, CXCL5, and CXCL8, responsible for recruiting neutrophils and monocytes, as well as the CCL20 that is involved in the recruitment of dendritic cells, with the aim of eliminating the extracellular pathogen.

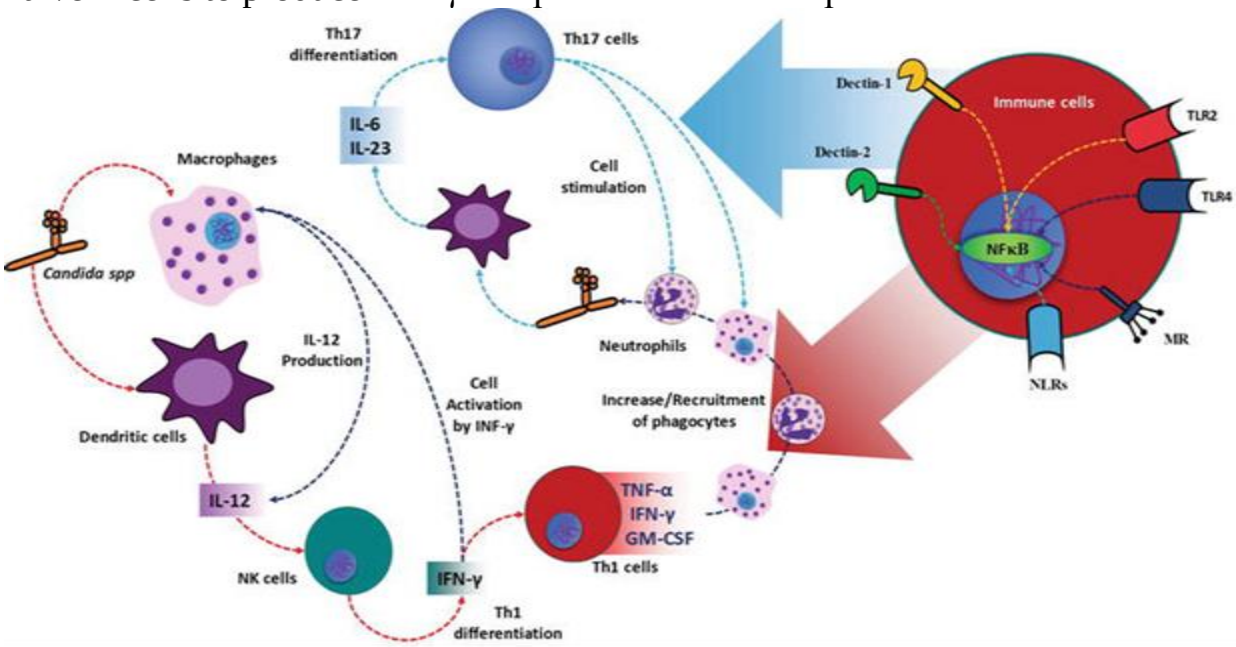
3- IL-17 induces up regulation of granulopoietic cytokines involved in the recruitment of neutrophils.



2- Cytokine profile in fungal infections

The PRRs (C-type lectin receptors CLRs especially Dectin-1 and 2) recognize fungal PAMPs (O-glycosylated oligosaccharide and N-glycosylated polysaccharide moieties, with an inner layer of chitin and β (1, 3) and β (1, 6) glucans, and even internal components such as DNA can be recognized) and initiate downstream signalling, which leads to the activation of the NF-κB and other signalling pathways inducing the production of cytokines such as IL-6, IL-1β, IL-12, TNF-α, GM-CSF, IFN-γ, and IL-23. These cytokines induce the differentiation of Th1 and Th17 immune responses against fungi infection, stimulating the migration, adherence, and phagocytosis of neutrophils and macrophages. IL-12 is produced by

monocytes, macrophages, and dendritic cells, in response to microbial products, and acts on NK and T cells to induce IFN-γ.
The IFN-γ (produced mainly by T and NK cells) stimulates the migration, adherence, and phagocytosis of neutrophils and macrophages, and also production of opsonizing antibodies, and maintains a Th1 response as a protective response against fungi, through Th1release of IFN-γ, TNF-α, and GM-CSF which leads to increasing the permeability in the tissue, as well as the phagocytic cells at the site of infection to efficiently clean the infection.
On the other hand, the late secretion of IL-12 in the lymph nodes induces naive T cells to produce IFN-γ and promoted a Th1 response.

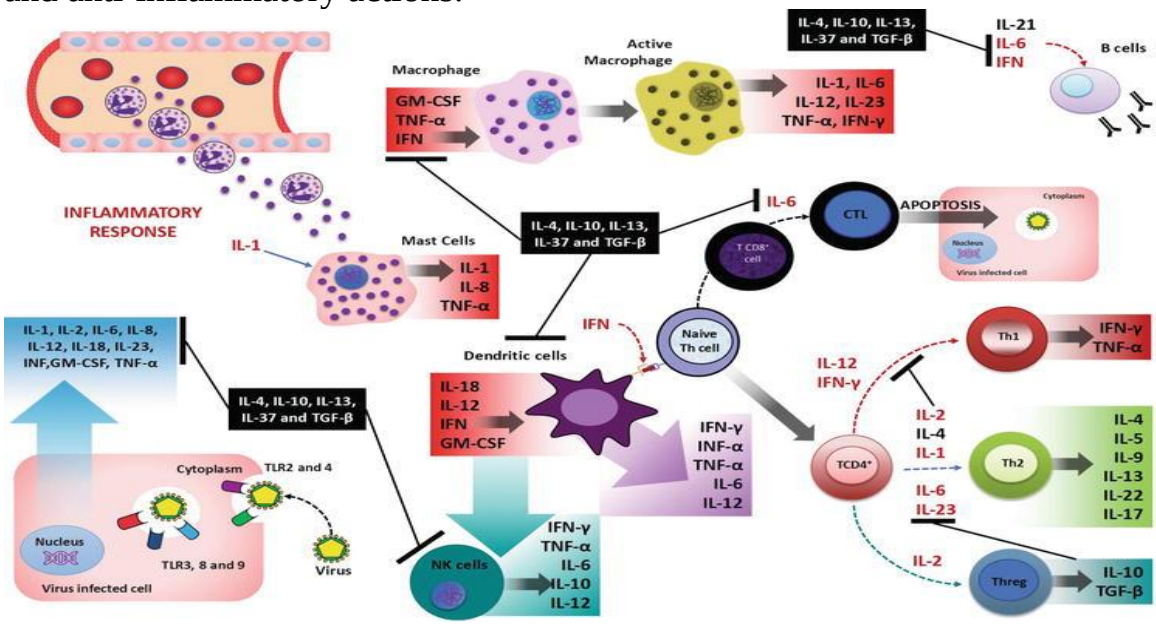


On the other hand, neutrophils kill the extracellular and intracellular fungi through effector mechanism that includes the production of reactive oxygen and nitrogen species, as well as the release of hydrolytic enzymes and their granules containing antimicrobial peptides.
IL-23 is produced primarily by dendritic cells, the binding of β-glucan to Dectin-1 promote IL-23 production, which promotes the Th17 response, through the differentiation of naïve CD4+ T cells into Th17 cells and the release of IL-17A, IL-17F and IL-22 in response to infections caused by mucosal fungi. These cytokines in conjunction with IL-23 have various functions in the body from a proinflammatory, antiinflammatory, or regulatory activity, which depends on the type of microorganism, the site of infection, and the immunological status of the host.

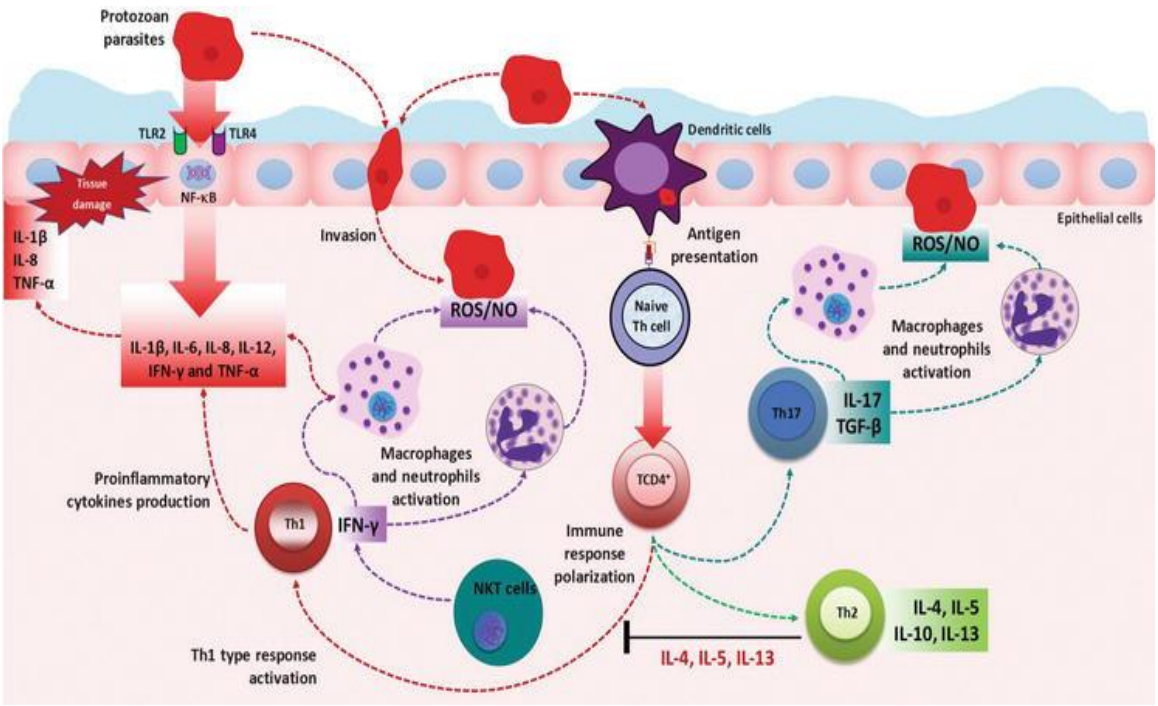
Cytokines profile in viral infections

The immune response against viruses initiates through recognition of viral molecules by PRRs. These PRRs can activate a signal system culminating in the activation of transcription factors involved in the establishment of an antiviral state and an inflammation process.

The infected cell with viruses such as epithelial cell or innate and adaptive cells can produce IFNs, IL-8, IL-6, IL-1, GM-CSF, TNFα, IL-18, IL-12, IL-2 and IL-23, through upregulate multiple cytokine genes involved in different process by inducing a potent inflammatory response, attracting and activating phagocyte cells (e.g. neutrophils, macrophages, dendritic cells), mast cells and NK cells, to the site of infection. Furthermore, these cytokines are involved in the induction of an immune response type Th1/TCL with the purpose of eliminate infected cells and extracellular virus while cytokines such as IL-4, IL-10, IL-13, IL-37, and TGF-β modulate the immune response to a Th2 and Th17 phenotype, which produce immunomodulatory and anti-inflammatory actions.



the initial stage of parasitic protozoan infections, intestinal epithelial cells bind and recognize PAMPs through PRRs such as TLR-2 and TLR-4 which activates NF-κB and leads to the production of proinflammatory cytokines, including IL-1β, IL-6, IL-8, IL-12, IFN-γ, and TNF-α by immune cells such as neutrophils, macrophages, NK cells, and CD4+T cells ,these cytokines induces the activation of a Th1 type response. Likewise, protozoan parasites activate a Th2-type immune response, producing anti-inflammatory cytokines such as IL-4, IL-10, IL-5, and IL-13, , which attenuate the Th1 type response characterized also by the INF-γ production, leading to upregulation of Th2 cytokine responses (IL-4, IL-5, and IL-13) and Th17 (IL-17), suppressing the production of Th1 cytokines.



Cytokines profile in parasitic helminthes infection

PAMPs derived from helminthes parasites induce the activation and maturation of dendritic cells promoting the development of the Th1 immune response, which results in a significant increase of Th1 cytokines such as IL-12, INF-γ, IL-1β, and TNF-α. Then, there is a subsequent predominance of a Th2 type immune response characterized by the release of IL-4, IL-5, IL-10, and IL-13 favoring helminthes parasites expulsion.