All the mechanisms of the immune response, many of them still unknown, are involved in protection against TB.

‘Jail without a jailer and without chains where I eat my bread and drink my water day by day ... Meanwhile, out there, they blossom for me, tremulous, even mine, all the paths of earth.’

Jail of Air
Dulce María Loynaz

The Powerful Hand
Eduardo Roca Salazar (Choco)
Collograph; 109.5 × 82 cm
Immune responses against MTB can stop the infection from becoming established, eliminate it completely, or control it, so, that it becomes latent.

‘... on the black and white of the way, seek and wage their armed battle.’

Chess
Jorge Luis Borges

Guardian Angel
Alfredo Sosabravo
Oil on canvas
OVERVIEW

This chapter provides a significant overview of the immune system and at each step, its relevance to the immunology of TB will be stressed. TB is a disease in which the immune response to a pathogen generates most of the pathological and clinical manifestations. It is estimated that in over ninety percent of individuals who are exposed to MTB, the initial response is one of immunological containment. This initial response, which involves both innate and adaptive immunity, results in an equilibrium state which does not result in disease in the majority of individuals. In a small number of individuals, it is believed that reactivation results in the spread of the bacteria and the initiation of disease. In this chapter, a broad overview of innate immunity and of adaptive immune responses, particularly those mediated by MHC class I, MHC class II and CD1 restricted T cells, will be provided.

INNATE IMMUNITY

The major cell types of innate immunity that are resident in tissues are early sentinels and innate effector cells such as macrophages and mast cells, as well as the sentinel cells that activate the adaptive immune system, the dendritic cells (1). Typically Pathogen Associated Molecular Patterns (PAMPs) such as lipopolysaccharide, flagellin, and peptidoglycan, to name but a few, activate the Pattern Recognition Receptors (PRRs) on these cells (primarily members of the Toll-Like Receptor family, the NOD-like receptor family and the C-type lectin receptor family) and these PAMPs activate mast cells and macrophages to secrete cytokines such as IL-1, TNF and IL-6, as well as chemokines such as IL-8, as well as amines and eicosanoid — prominently histamines and leukotrienes (2-4). These products of activated macrophages and mast cells increase vascular permeability, and orchestrate the recruitment of neutrophils during the acute inflammatory process, and of monocytes (and activated T cells and B cells — as outlined below) as inflammation persists. Some of the prominent PAMPs in mycobacteria include lipoproteins and phosphatidylinositol mannoside and lipoarabinomannan. They can activate PRRs such as mannose receptor, TLR2 and TLR4.
Humoral components of innate immunity include the complement system and soluble pattern recognition receptors, most of which are secreted lectins (5). These soluble PRRs include collectins such as the mannose binding lectin and surfactant proteins, pentraxins such as the C-reactive protein and serum amyloid protein, ficolins and cathelicidins. Some soluble lectins, most notably some of the galectins are directly bactericidal. While many microbes contribute to the activation of complement via the alternative pathway, most soluble pattern recognition receptors also activate the complement pathway. The C3b complement fragment can be covalently attached to microbes and serve as an opsonin. C5a can contribute in a major way as a chemokine and an anaphylatoxin. C5a, IL-8, and N-formyl methionine containing peptides derived from invading bacteria, which serve as the major chemokines that drive acute inflammation.

TLRs in innate immune cells typically drive both the induction of NF-κB inflammation, as well as the induction of IRF7 and the anti-viral state. The anti-viral state will not be considered in depth here — it largely involves type I interferon production and the activation of natural killer cells. The activation of NF-κB results primarily in the induction of inflammatory cytokine activation of NF production and these inflammatory cytokines in turn, activate the neighboring endothelial cells in post-capillary venules to induce the expression of P and E-selectins that bind sialyl Lewis’ on neutrophils to initiate the rolling of the latter cells on the endothelial surface. The cytokines also induce the expression of ICAM-1 on the endothelium. Chemokines activate chemokine receptors on the rolling neutrophils and this activation results in inside-out signaling that induces a major conformation change in integrins on the surface of the neutrophil. The folded integrin dimers flip-out their ectodomains which then bind to the endothelial ICAM-1 and this results in the tight adhesion of the neutrophil to the endothelium, which is followed by the egress of activated neutrophils into the tissue space, and the formation of pus.

In the case of mycobacteria — although the inflammatory process is initiated, the microbe is able to evade killing in the host macrophage in part by inhibiting phago-lysosomal fusion. The ability of mycobacteria to evade innate immunity necessitates the induction of adaptive immunity for containment.
ADAPTIVE IMMUNITY

If the acute inflammatory process fails to eliminate the initiating microbe, the fallback protective mechanism involves more highly specific adaptive immune system, made up of T and B lymphocytes, which have clonally specific and extremely diverse repertoires. These diverse repertoires are generated by gene rearrangement events in developing T and B lymphocytes.

CD4+ T cells that recognize peptide antigens

Conventional dendritic cells in the tissue are activated by PAMPs and this result in the migration of the dendritic cell (DC) through the lymphatics to a draining lymph node and the maturation of the DC, which results in more efficient processing of internalized antigen and increased expression of MHC molecules on the cell surface. The expression of CCR7 on these activated DCs leads to their homing to the T cell zone in the draining lymph node or in other secondary lymphoid organs. The activation of DCs by PRRs also results in the induction of costimulatory ligands such as B7-1 and B7-2 (CD80 and CD86). These costimulatory ligands trigger the CD28 costimulatory receptor on naïve T cells and provide the ‘second’ or ‘danger’ signal that collaborates with T cell receptor signaling to activate T cells. The majority of conventional dendritic cells process internalized antigens in lysosomes and late endosomes, and thus efficiently load the MHC class II molecules with peptides derived from internalized proteins, often of microbial origin. This pathway of antigen presentation results in the activation of naïve CD4+ T cells in lymph nodes.

Activated CD4+ T cells induce the expression of the CXCR5 chemokine receptor, reduce CCR7 levels and migrate towards the follicle, where they can interact with specific B cells that have responded to antigen and are then activated by helper CD4+ T cells via CD40L-CD40 interactions. We will not discuss B cell activation in depth in this review. A major point of relevance to bear in mind from the TB context is that even though dendritic cells initiate T-cell activation, activated B cells are key antigen that presents cells for the generation of CD4+ memory cells.

The polarized effector T helper cell subset that may be the most relevant in TB is the Th1 subset. Mycobacteria activate dendritic cells do not just enhance antigen presentation and express B7 costimulatory proteins, but also induce the secretion by dendritic cells of IL-12. This secreted IL-12 helps drive the polarization of activated CD4+ T cells towards the Th1 polarized phenotype. Th1 cells preferentially synthesize and secrete interferon-γ. This cytokine contributes to macrophage activation and can potentially facilitate the elimination of intracellular pathogens and also of granuloma formation. Some activation of Th17 cells is also likely to
occur even by mycobacteria — Th17 cells are induced by a combination of TGFβ and IL-6 and can contribute to increased barrier function and to the recruitment of neutrophils and monocytes to the site of infection and inflammation (7).

While effector and memory helper T cells that recognize MHC class II-bound extracellular peptides orchestrate some aspects of adaptive host defense against mycobacteria, important protective responses are also likely to be generated by NKT cells and other CD1 restricted T cells that recognize lipid antigens, and also by CD8+ cytotoxic T cells that recognize cytosolic antigens as well as peptides made available by cross-presentation.

T cells that recognize lipid antigens

In humans there are four functional CD1 molecules, CD1a, b, c, and d. CD1 chains molecules structurally resemble MHC class I heavy chains and also associate themselves with β2-microglobulin. They have hydrophobic grooves that can bind to, and present lipid antigens. While invariant natural killer T cells (iNKT) in humans have a TCR α-chain that contains Vα24 and Jα18 segments and recognize lipids bound to CD1d, a range of double negative and CD4 expressing T cells exist, which recognize microbial lipids bound to CD1a, b, and c molecules. Mycobacterial cell wall lipids are known to be presented by CD1c molecules and are recognized by cytokine-producing T cells. CD1 molecules assemble in the endoplasmic reticulum with a self lipid and then traffic to late endosomes where lipid transfer enzymes catalyze the binding of endocytosed microbial lipids, prior to the CD1-lipid complex being presented on the cell surface.

Cytotoxic T lymphocytes

Naïve CD8+ T cells can be activated by dendritic cells in lymph nodes that either have acquired microbial antigens in the cytosol by infection or which have a specialized ability to present internalized antigens on MHC class I molecules (8). The MHC class I pathway typically requires the proteasomal cleavage of a cytosolic protein (either endogenously synthesized by an infected cell or transferred from a membrane bound compartment into the cytosol). Peptides cleaved by the proteasome are transported into the endoplasmic reticulum by the TAP transporter, and the assembly of class I heavy chain, β2-microglobulin and specific peptide that occurs in the endoplasmic reticulum.

A subset of human conventional dendritic cells that express BDCA3/CD141 are capable of cross-priming and cross-presenting internalized antigens. They can thus, deliver proteins internalized into phagosomes into the cytosol, wherein the protein can be proteasomally degraded and peptides translocated into the endoplasmic reticulum for assembly with MHC class I molecules. The activation of CD8+ T cells
into cytolytic cells and/or cytokine secreting cells requires, as for CD4+ T cells, both TCR activation and costimulatory receptor activation. CD4+ T cells enhance CD8+ T cell activation both by producing cytokines, as well as by “licensing” dendritic cells to be better antigen presenting cells.

CD8+ T cell responses to mycobacterial proteins may contribute to inflammation and possibly also to protective immunity. They can, like Th1 cells, make large amounts of interferon-γ.

SUMMARY

A very brief overview of innate and adaptive immunity has been provided emphasizing innate immunity, Th1 cells, lipid recognizing T cells, and activated CD8+ T cells, all of which contribute to inflammation and possibly play their part in the protective responses in TB.

REFERENCES


