dependent on the interferon regulatory factors, IRF3/7, the IKK-related kinase TBK1 and the ER-resident protein STING. However, previously described cytosolic nucleic acid sensors RIG-I, MDA-5, MAVS, RNA Polymerase III, DAI and Nod2 are not required. We also show that hemozoin bound AT-rich DNA gains access to the cytosol during phagocytosis by macrophages.

We demonstrate for the first time that Type I IFN responses are key in regulating the progression of malarial infections. Microarray analysis of patient samples identified type I IFN induced genes (ISGs) as significantly upregulated in human patients infected with-Plasmodium falciparum.Moreover, in a mouse model of cerebral malaria, mice lacking the IFNa/b Receptor (IFNAR-/-), transcription factors IRF3 an IRF7 as well as TANK-binding kinase 1 (TBK1) in the DNA-sensing pathway and the critical adaptor Stimulator of Interferon Genes (STING) are protected from disease. This study therefore highlights the importance of cytosolic DNA sensing pathways in the immune response toPlasmodium falciparumand provides critical insight into the mechanisms by which the early innate immune response determines the end-stage of malarial disease.

http://dx.doi.org/10.1016/j.ijid.2012.05.148

Type: Invited Presentation

Final Abstract Number: 36.003
Session: Innate Immunity and Infectious Diseases
Date: Saturday, June 16, 2012
Time: 15:45-17:45
Room: Ballroom A

Stimulation of macrophage innate immunity to prevent human mycobacterial disease

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Tuberculosis (TB) is a major health problem with 10 million new cases diagnosed each year, causing nearly 2 million deaths. However, from the estimated 2 billion individuals initially being infected withMycobacterium tuberculosis(Mtb), most develop a latent infection, where the microbe will survive and persist for years inside lung macrophages. Following coinfections or immune supression, some may develop active disease. Furthermore, only a small fraction of close house-hold contacts to patients with active TB will develop active disease, despite not being vaccinated against or previously exposed to Mtb. These facts suggest that an effective early innate immune response is important for immune surveillance and early protection against Mtb. We have therefore investigated the innate immune response and how it can be boosted during TB. Our hypothesis were (i) that neutrophils, being recruited early to the site of infection, can modulate the capacity of macrophages to handle Mtb, and (ii) that the production of nitric oxide (NO) may play a vital role, since Mtb is usually very sensitive to reactive nitric intermediates (RNI). In different experimental models we show that Mtb-infected apoptotic neutrophils enhance the proinflammatory cytokine response in human macrophages, and improve their capacity to control infection with virulent Mtb. This activation is triggered through release of heat-chock protein 72 (Hsp72) and formation of neutrophil extracellular traps (NETs), and mediated via Toll- and NOD-like receptors. In clinical studies we furthermore show that that boosting the NO production with arginine or arginine-rich supplement to patients being treated for active TB, will improve treatment and reduce potential spreading of the disease. The important role of NO is furthermore supported by observations that clinical strains exhibiting reduced susceptibility to NO may be more detrimental to the host, and that coinfected (HIV) patients with TB have show reduced production of NO from the lung.

We can conclude that stimulation of the innate immune response may be important for preimmune macrophage activation, and protection against Mtb infection.

http://dx.doi.org/10.1016/j.ijid.2012.05.149

Type: Invited Presentation

Final Abstract Number: 36.004
Session: Innate Immunity and Infectious Diseases
Date: Saturday, June 16, 2012
Time: 15:45-17:45
Room: Ballroom A

MHC Class I antigen presentation and implications for vaccine development

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All cells generate peptides derived from their expressed genes and then display a fraction of them on the cell surface bound to MHC class I molecules through a process called antigen presentation. This process is important because it is the key pathway by which the immune system detects and then eliminates viral infections. Antigen presentation not only controls whether T cell responses will be generated, but also their magnitude, specificity and location. Although this process is essential for host defense, its underlying mechanisms are incompletely understood. The majority of MHC class I presented peptides are generated by the proteasome. Dendritic and many other leukocytes express an alternate form of the proteasome, called the immunoproteasome, that contains a distinct set of proteolytic active sites. In an infection, immunoproteasomes can be induced in most other cell types. We have generated mice that completely lack immunoproteasomes and have characterized their ability to present antigens and respond to viral infections. These mice have major changes in their repertoire of MHC class I-presented peptides and defects in antigen presentation that strongly affect T cell responses to viruses. In other studies we have been examining the source of MHC class I-presented peptides. It had been proposed that the majority of class I presented peptides derive from newly synthesized but defective proteins. We have generated experimental systems to critically test this model and results will be discussed. The implications of these studies for immune responses and vaccine development will also be discussed.

http://dx.doi.org/10.1016/j.ijid.2012.05.150