

Conference Series LLC Joint International Event on 5th European Immunology & Innate Immunity

July 21-23, 2016 Berlin, Germany

How neutrophils influence severity and immune response to tuberculosis infection in mice

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The role of neutrophils in tuberculosis (TB) resistance and pathology is not fully defined. Neutrophil reactions are meant to target the offending pathogen but may lead to destruction of the host lung tissue, making the defending cells an enemy. Mice genetically susceptible to TB demonstrate an unusually high and prolonged neutrophil accumulation in their lungs. Compared to neutrophils from resistant mice, their neutrophils display an increased mobility and tissue influx, prolonged lifespan, low expression of the CD95 (Fas) apoptotic receptor, relative resistance to apoptosis and an increased phagocytic capacity for mycobacteria. These features, along with the poor ability of neutrophils to restrict mycobacterial growth, indicate that the prevalence of neutrophils in TB inflammation contributes to the development of pathology, rather than protection of the host and neutrophils may play the role of a "Trojan horse" for mycobacteria. This conclusion received further support in the BCG vaccination system: An advanced capture of BCG by neutrophils, which occurs in the absence of B-cells, leads to a significant decrease in numbers of IFN- γ producing T-cells and impairs BCG performance. Selective depletion of neutrophils from infected mice results in reduced lung tissue pathology, mycobacterial CFU counts and an increase of the survival time. Furthermore, *in vivo* neutrophil depletion at the onset of TB infection results in a significant increase in numbers of mycobacteria-specific IFN- γ producing T-cells. These results suggest antagonistic activity of neutrophils and immune T-cells in the course of TB infection and provide further evidence of deleterious rather than protective role of the former.

Molecular and *in vivo* studies on new small molecule therapeutics targeting TLR4 by an original mechanism of action

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Toll like Receptors (TLRs) activation by pathogen associated molecular patterns (PAMPs) is a pivotal molecular event in inflammation and innate immunity and TLRs and their agonists are responsible for the efficacy of almost every vaccine. Conversely, TLRs hyper activation by endogenous factors such as oxidized phospholipids or heat shock proteins is the main cause of many inflammatory and autoimmune diseases. Activating or inhibiting specifically TLRs provides access to a new generation of therapeutics. We developed synthetic molecules able to modulate TLR4 activation and signaling and we studied the mechanism of action (MOA) of these non toxic and drug like compounds. Positively or negatively charged synthetic glycolipids are active in blocking TLR4 activation by specifically targeting the CD14 co receptor. These molecules are very efficient in inhibiting TLR4 activation in cells and in contrasting diseases related to TLR4 hyper activation by infectious and endogenous agents in animal models. We investigated at a molecular level the MOA of these molecules by binding experiments with purified CD14, MD-2 and TLR4 receptors and experiments on dendritic cells, macrophages and HEK-TLR4 cells. The unique MOA of these molecules is based on the capacity to dissociate CD14 and TLR4 endocytosis, thus creating an inducible CD14 deficiency at the cell surface. These conditions are expected to antagonize TLR4 signaling more effectively than simply competing with LPS for CD14 and TLR4. Very promising results have been obtained at a preclinical level using these drug hits and recent (2015) data on animal models of atherosclerosis, neuroinflammation and amyotrophic lateral sclerosis will be reported.