Triggering through immunomodulators effectively boost the host immune response against *Mycobacterium tuberculosis*.

Tuberculosis (TB) is not only the leading cause of death, but the patients suffering from the disease are also inflicted with devastating side-effects and toxicity of long-term drug regime. Thus, it accentuates an urgent need to explore newer and safer treatment methods. Recently, an improved understanding of host-pathogen interaction has opened new avenues for TB treatment, which include immunotherapy. This embolden us to devise a novel strategy of bolstering host immunity by delivering signals through NOD-2 and TLR-4 molecules of innate immunity or cross talk between costimulatory molecule CD40 and TLR-4 along with the suboptimal dose of TB drugs; thereby reinforcing the efficacy of drugs to kill *Mycobacterium tuberculosis (Mtb)*. Such approach induced significant enhancement in the secretion of TNF-α, IFN-γ, IL-12 and IL-6; the molecules reported to protect against *Mtb*. Further, there was substantial decline in the mycobacterial burden in the lungs. The mechanism involved in the phenomenon was attributed through nitric oxide and autophagy. Furthermore, the treated animals exhibited increased pool of effector memory CD4 and CD8 T cells. Importantly, this adjunct stratagem employing immunomodulators and chemotherapy will reinvigorate host immunity suppressed due to medication and mycobacterium and boost the potency of the drugs in curing TB.

Summary

Signaling delivered through NOD-2 triggers the generation of innate specialized DCs.

Dendritic cells are the most potent antigen presenting cells endowed with the capability to prime naïve T cells. Although, DCs are considered as the bridging component of innate and adaptive immunity, they have an inferior role in bactericidal activity. However, recently a specialized subset of DCs has been identified with significant production of TNF-α and nitric oxide (TipDCs). However, factors responsible for the generation of such subset of DCs have not been identified yet. In this report we have shown that NOD-2 triggering results in the production of innate specialized DCs. Importantly, these cells produced more nitric oxide, TNF-α, and showed elevated autophagy along with capability to constrain the growth of *Mycobacterium tuberculosis*. These cells were less prone to undergo apoptosis, thereby can retained bacteria for long duration. Further, NOD-2 driven DCs exhibited their classical functions more efficiently than conventional DCs. These cells displayed high expression of costimulatory molecules such as CD40, CD80 and CD86 and were more efficient in antigen uptake and activation of T cells. Further, we have dissected the mechanism responsible for their activated phenotype. We observed that NOD-2 induced DCs exhibited high phosphorylation of Stat-1, Stat-4 and Stat-6; whereas low phosphorylation of Stat-3 molecule which is a negative regulator for DCs activation.

In conclusion, our data indicated that, in addition to a direct affect on APCs functions which is well known, NOD-2 triggering interferes in DCs differentiation and thereby reveals a new mechanism of how MDP can control the outcome of the immune response.

Altered gut microbiome promotes the propagation of *Mycobacterium tuberculosis.*

Commensals bacteria showed significant impact on intestinal immune development. It remains speculative whether the gut microbiota influences extraintestinal biological functions. Antibiotics treatment is one of the major causes of changes in intestinal microbial composition and predisposition of host to enteric infection. Tuberculosis (TB) is the most devastating disease killing around 2 million people annually. In tuberculosis, it is still unanswered, how antibiotic-induced changes in the intestinal microbiota affect the establishment, expansion, and persistence of *Mtb* infection. Furthermore, whether the antibiotic mediated disruption of intestinal microbiota correlates with the dissemination of *Mtb* to different organs. Current study demonstrates that antibiotic treated animals showed significant changes in composition of gut microbiota with decreased in diversity of microflora but simultaneously dominancy of few of the microbes. Further, we demonstrated that antibiotic treated animals pre or post challenged with *Mtb* showed high bacterial load in lungs compared to mice with complete microbiota. Further, significant

lissemination of *Mtb* was observed in spleen. Interestingly, dysbiosis of nicrobiota showed elevation in number of Tregs, whereas IFN-γ releasing CD4 T cells were reduced in number in spleen of *Mtb* challenged mice.