SUMMARY

Effect of N2.T4 signaling on the regime of anti-TB drugs

Tuberculosis (TB) is a major public health concern causing the maximum number of morbidity and mortality. Moreover, TB patients undergo devastating side-effects and toxicities associated with the long-term drug regime. Thus, it highlights an exigent need to explore more effective, newer and safer treatment methods. Recently, immunotherapy has gained enough attention due to its capability of boosting the host immunity. This encouraged us to formulate an innovative strategy of adjunct therapy involving boosting of host immune system through NOD-2 and TLR-4 ligands along with the anti-TB drugs, to reinforce the effectiveness of drugs to eradicate *Mtb*. This approach of adjunct therapy protected animals efficiently at much lesser dose of the drugs, as compared to drugs alone. Interestingly, we could observe more effective killing of *Mtb* at a shorter time interval with our adjunct therapy, as compared to administration of drugs only. Furthermore, the treated animals exhibited increased generation and sustenance of CD4 and CD8 T cell memory response. Importantly, this adjunct strategy engaging immunomodulators and chemotherapeutic agents will strengthen the host immunity and killing potency of drugs at lower doses in a lesser duration of treatment.

Modulation of MSCs by N2.T4 signaling against *Mycobacterium tuberculosis*

Mesenchymal stem cells (MSCs) are known to harbor *Mtb* even after the lengthy treatment of TB, which clearly indicated that MSCs play crucial role in TB reactivation (Beamer et al., 2014). MSCs are known to express various innate receptors for recognition and delivering signals against different pathogens. Moreover, MSC functions are known to be modulated with innate signaling, such as TLRs (Waterman et al., 2010). Hence, we planned an elegant approach of reinvigorating the immunity of MSCs by delivering synergistic signaling through NOD-2 and TLR-4 (N2.T4) and its impact on *Mtb* killing. N2.T4 signaling augmented the secretion of pro-inflammatory cytokines. Additionally, *Mtb* was efficiently co-localized in the lysosomes upon N2.T4 stimulation, which in turn induced autophagy and as a consequence reduced the intracellular bacterial load. Furthermore, N2.T4 signaling of MSCs enhanced NF-κB activity *via* p38 MAPK pathway. Finally, N2.T4 elevated the killing potency of anti-TB drugs, as well. In conclusion, innate stimulation via N2.T4 can be an elegant approach in modulating MSCs and thereby eliminating the hidden *Mtb* inside MSCs.