SUMMARY

NRs modulate macrophage effector functions which are imperative for clearance or survival of *M. tuberculosis*. We present evidence for a crosstalk between LSNRs and *M. tuberculosis* derived components. PPARγ and TR4 positively regulate foamy biogenesis in macrophage by modulating ox-LDL receptor CD36 and a blunted innate response by alternative polarization of the macrophages, which leads to survival of *M. tuberculosis*. The adopted orphan NR Rev-erbα is a constitutive transcriptional repressor as it lacks AF2 domain and is earlier shown to be present in macrophages. We have highlighted the differences in the relative subcellular localization of Rev-erbα in monocytes and macrophages. The nuclear localization of Rev-erbα in macrophages is subsequent to monocyte differentiation. Expression analysis of Rev-erbα elucidated it to be considerably more in M1 phenotype in comparison to M2. Rev-erbα overexpression augments anti-*M. tuberculosis* properties of macrophage by keeping *IL-10* in a basal repressed state. Further, promoter analysis revealed that *IL-10* promoter harbours a Rev-erbα binding site exclusive to humans and higher order primates and not mouse demonstrating a species barrier in its functionality. This direct gene repression is mediated by recruitment of corepressors NCoR and HDAC3. In addition, our data elucidates that its overexpression reduced the survival of intracellular pathogen *M. tuberculosis* by enhancing phagosome lysososme maturation, an event resultant to *IL-10* repression. Thus, these finding suggests that Rev-erbα bestows protection against *M. tuberculosis* infection by direct gene repression of *IL-10* and thus provides a novel target in modulating macrophage microbicidal properties.

Emerging evidence suggests that various members of the NR superfamily perform a decisive role in the modulation of autophagy. The anti-infective property of Rev-erbα suggests the need for an improved understanding of its role in other host-associated anti-*M. tuberculosis* pathways. We demonstrated that in human macrophages either ectopic expression of Rev-erbα or treatment with its agonist, GSK4112, enhanced the number of acidic vacuoles as well as the conversion of MAP1LC3α, a signature molecule for determination of autophagy progression, in a concentration- and time-dependent manner. Conversely, a decrease in the expression level of TFEB in Rev-erbα knockdown condition is suggestive of modulation of lysosome biogenesis. This indicates that Rev-

erbα may have a regulatory role in lysosome biogenesis. Although Rev-erbα is a repressor, its positive regulation on LAMP1 and TFEB is suggestive of an indirect byzantine mechanism of action. Its role in the modulation of autophagy and lysosome biogenesis together with its ability to repress *IL-10* gene expression supports the theory that of Rev-erbα has a pivotal anti-microbial function in *M. tuberculosis* infection in human macrophages.

PTM events are well documented in literature for orchestrating the NR regulatory function in both ligand dependent and independent manner. We identified that Rev-erbα acetylation status is by virtue of its interaction with PCAF and SIRT1, novel partners that are key mediators of this process. Furthermore, acetylation of Rev-erbα was found to negatively regulate its repressive function perhaps by disrupting the repressive complex and enhancing the recruitment of coactivators on gene promoters.

In the last objective we have shown the differential expression of Rev-erbα in autoimmune disease condition in comparison to control. Increase in Rev-erbα expression during the late phase of CIA, could be suggestive of its role in maintaining the T_H17 cell population in the late stage. The precise mechanism underlying this phenomenon needs to be elucidated to decipher Rev-erbα mediated modulation of autoimmunity.