जीव विज्ञान संस्थान
INSTITUTE OF LIFE SCIENCES
(An Autonomous Institute of the Department of Biotechnology, Govt. of India)

Brief Summary

To,

The Selection Committee,

Sun Pharma Science Foundation

8C, 8th Floor, Hansalaya Building, 15-Barakhamba Road,

Connaught Place, New Delhi: 110001(India)

Dated: 21-08-2023

Sub: Brief Summary for the study - *NCoR1 controls Mycobacterium tuberculosis growth in myeloid cells by regulating the AMPK-mTOR-TFEB axis for* Sun Pharma Science Foundation (Science Scholar Awards) - 2023

Dear Selection Committee members,

The study provides the inaugural account of NCoR1's role in meticulously regulating the autophagolysosomal pathway's influence on *Mycobacterium tuberculosis (Mtb)* pathogenesis via the AMPK-mTOR-TFEB signalling axis. Early-stage *Mycobacterium* infection triggers heightened NCoR1 expression in myeloid cells, underscoring its significance in bolstering host defences against infection. NCoR1 deficiency impedes the clearance of H37Rv and *M. smegmatis* infections within myeloid cells, achieved through fine-tuning the AMPK-mTOR signalling axis that, in turn, governs TFEB activity. TFEB autonomously orchestrates autophagic machinery and lysosomal biogenesis, endowing *Mtb* with survival advantages in NCoR1-depleted conditions. Reintroducing TFEB in NCoR1-depleted macrophages restores LC3 and LAMP1 expressions, leading to bacterial load clearance. The active mTOR phosphorylates TFEB, obstructing its nuclear translocation, consequently inhibiting autophagy and lysosome biogenesis. This aligns with previous findings. Inhibition of mTOR and AMPK activation restores autophagy, safeguarding macrophages against *Mtb* infection. Overall, the research underscores NCoR1's capacity to influence *Mtb* survival within myeloid cells through autophagolysosomal machinery modulation. NCoR1's regulation of diverse biological functions is established, including its role in shaping anti-inflammatory macrophage and dendritic cell phenotypes. Yet, its involvement in regulating autophagy, lysosome biosynthesis, and *Mtb* survival remains uncharted, implying NCoR1's pivotal role in early *Mtb* infection stages for host protection. Among myeloid cells, dendritic cells' (cDC1) early TFEB expression during *Mtb* infection accentuates the urgency of TFEB-mediated

autophagy induction. Mechanistically, NCoR1 governs TFEB, with its absence hampering autophagolysosomal formation, heightening susceptibility to *Mtb* pathogenesis. Transcriptomic analysis of *Mtb*-infected NCoR1 KD cells identifies downregulated autophagy-inducing genes like ATG13, ATG3, and ATG5, vital for optimal autophagosome maturation and LC3 lipidation. Additionally, NCoR1's influence on cellular energy processes, including ATP synthesis, is highlighted, impacting *Mycobacterium*-mediated changes in host cell oxidative phosphorylation, which *Mtb* exploits for survival. *Mycobacterium* manipulates cellular energy balance via AMPK-mTOR signalling for its proliferation and survival. NCoR1's energy homeostasis regulation, even in uninfected conditions, supports its role in autophagy modulation. Antimycin-A treatment confirms NCoR1's role in tuning the AMPK-mTOR pathway to control *Mtb* survival by optimizing cellular energy states. NCoR1's dual roles are proposed: interaction with TFEB for functionality or stability, and regulation of AMPK-mTOR signalling. In sum, the study reveals NCoR1's direct involvement in *Mtb* survival control through optimal autophagolysosomal processes, further linking NCoR1's clinical expression during active TB infection and suggesting its potential as a host-directed therapeutic target.

Yours faithfully,

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