National Institute of Technology Rourkela

Synopsis Seminar

Seminar Title	: Mechanistic exploration of autophagy-inducing agents as host-directed therapeutics against intracellular mycobacteria in human macrophages
Speaker	: Salina Patel (Rollno : 520ls2001)
Supervisor	: Rohan Dhiman
Venue	: Seminar Hall, Department of Life Science
Date and Time	: 14 Aug 2025 (4:00 pm)
Abstract	: *Mycobacterium TB* (*M. tb*), the etiological agent of TB (TB), continues to be a major contributor to global mortality rates. To effectively combat this pandemic, TB control has to be enhanced in several areas, including point-of-care diagnostics, shorter and safer drug regimens, and preventative vaccination. Recent findings have highlighted autophagy as a critical host-defense mechanism that eliminates intracellular pathogens, including *M. tb*. Accordingly, this study evaluates novel host-directed strategies using pharmacological and natural compounds to enhance autophagy and immune responses against mycobacterial infection. This study evaluates the anti-mycobacterial potential of Furamidine as an autophagy inducer. The non-cytotoxic concentration of Furamidine (10µM) significantly reduced intracellular mycobacterial growth in differentiated THP-1 (dTHP-1) cells. Multiparametric approaches, including LC3-I to II conversion, protein expression of autophagic markers, and MDC staining, confirmed Furamidine-induced autophagy. Enhanced autophagic flux was validated by LC3-II accumulation under Baf-A1 treatment. Mechanistic studies revealed activation of Ca^{2+}, pAMPK, SIRT1 and FOXO3a upon Furamidine exposure, and inhibition of intracellular Ca^{2+} suppressed FOXO3a activation, confirming the Ca^{2+}/pAMPK/SIRT1/FOXO3a axis in autophagy induction. In a parallel approach, the immunomodulatory effects of Furamidine were explored. Furamidine enhanced IL-23 expression at both mRNA and protein levels, and upregulated IL-12R&beta1 and IL-23R, triggering phosphorylation of TYK2 and STAT3 to regulate intracellular Ca^{2+} and promote autophagy. Inhibiting IL-23, TYK2, or STAT3 disrupted autophagy and increased mycobacterial burden, indicating that IL-23-mediated signaling plays a crucial role in Furamidine-induced bacterial clearance. Furthermore, we study another compound from marine-derived *Streptomyces fradiae* DNS4 revealed 2,4-Di-tert-butylphenol (2,4-(DTBP)) as its key bioactive metabolite through a host-directed approach. At 10µM, 2,4-(DTBP) significantly reduced intracellular mycobacteria through autophagy induction, confirmed via LC3 conversion and autophagic flux assays. Blocking autophagy reversed its effect, affirming its mechanism. Collectively, these findings establish Furamidine and 2,4-(DTBP) as promising autophagy-inducing agents that bolster host immunity and hold potential as adjuncts in TB therapy.