National Institute of Technology Rourkela

Departmental Seminar

Seminar Title	: Mitoxantrone suppresses the intracellular proliferation of mycobacteria in THP-1 cells by activating autophagic machinery via mitochondrial-dependent mechanism
Speaker	: Mousumi Das (Roll No: 520ls2002)
Supervisor	: Santosh Kumar #2787
Venue	: LS Seminar Hall
Date and Time	: 03 Jan 2025 (16:30 hrs)
Abstract	: A widespread havoc of drug-resistant tuberculosis (TB) has arisen as a global public health emergency. As a consequence, there is an urgent need for new and creative therapeutic options, such as host-directed therapies (HDTs) utilizing novel modulators, to address the problems posed by TB. The current investigation examines the anti-mycobacterial properties of Mitoxantrone (MTX). The cell viability assay demonstrated that 1 μM of MTX exhibited non-cytotoxic effect towards Phorbol 12-myristate 13-acetate (PMA) differentiated THP-1 (dTHP-1) cells. We conducted time kinetic experiments using the non-cytotoxic dose of MTX and found optimum autophagy induction potential of the compound after 12 hours of treatment. The inhibition of autophagy by 3-MA and the increased LC3 puncta formation following Baf-A1 administration clarified the targeted impact of the drug on autophagy and autophagic flux. The MTX treatment augmented autophagy in macrophages infected with mycobacteria, which curtailed intracellular mycobacterial proliferation, thereby highlighting the host protective function of MTX-induced autophagy. The autophagic process necessitates stringent regulation, with cellular activities occurring in certain stages and controlled by a diverse molecular apparatus. Reactive oxygen species (ROS) play a significant role in the regulation of autophagy via various signaling pathways, with mitochondria, the primary source of endogenous ROS, serving as crucial signal transducers that facilitate autophagy. Mechanistic studies revealed that MTX downregulated ATP generation and induced mitochondrial membrane protein disruption leading to mitochondrial fission driven by Drp1 phosphorylation. Increased mitochondrial ROS generation was also noted upon MTX administration. Furthermore, MTX-induced autophagy was inhibited by various inhibitors, resulting in reduced clearance of intracellular mycobacteria. Collectively, our findings indicate that MTX-induced mitochondrial dysfunction and mitochondrial superoxide generation exerts impact on the initiation of autophagy in response to mycobacterial infection, facilitating its clearance.