National Institute of Technology Rourkela

Defence Seminar

Seminar Title	: Understanding the role of MTP18 in determining DRP1 signaling for fission and mitophagy to maintain mitochondrial health
Speaker	: Bishnu Prasad Behera (Rollno : 519ls1003)
Supervisor	: Sujit Kumar Bhutia
Venue	: MA Seminar Room
Date and Time	: 27 Mar 2025 (10.00 AM)
Abstract	: MTP18, a nuclear-encoded inner mitochondrial membrane protein, is crucial for mitochondrial integrity. MTP18 is identified as a downstream target of the phosphatidylinositol (PI) 3-kinase and regulated transcriptionally by MTOR. MTP18 is found to promote mitochondrial fission. However, there are limited studies on the mechanistic role of MTP18 in contributing to mitochondrial fission. The current study found that MTP18 regulates the DRP1-MFF-FIS1 signaling axis to regulate mitochondrial fission. In this connection, MTP18 overexpression elevated mitochondrial biogenesis, DNA content, and ATP level and upregulated the symmetric mitochondrial fission by phosphorylating MFF, a DRP1 receptor. MTP18 also increased the recruitment of cytosolic DRP1 to mitochondria by phosphorylating DRP1 at Ser616 to initiate fission. The knockdown of MTP18 resulted in the suppression of DRP1 and MFF activity, resulting in the elongation of mitochondria. In addition, MTP18 was also found to stabilize MFF by inhibiting its priming with ubiquitin and further proteasomal degradation. In addition, MTP18 induced FIS1 mediated asymmetric mitochondrial fission and mitophagy to clear mitochondrial damage during mitochondrial uncoupling by CCCP. MTP18 also reduced mitochondrial stress from proteotoxic and respiratory stress by activating stress response pathways involving Hsp60 and CHOP. Additionally, MTP18-MFF and MTP18-FIS1 signaling maintain survival and proliferation during CDDP assault. In this setting, the modulation of MTP18-mediated mitochondrial fission and mitochondrial stress management could be linked with the early onset of cancer. For this, we have used an MTP18 activating natural molecule butein to check the transition from a precancerous stage to a cancerous one linked with mitochondrial dysfunction. We showed that various early mitochondrial aberration parameters, including an increase in ROS production, a decrease in mitochondrial membrane potential, and mitochondrial hyperfusion, were countered by butein. Butein was found to regulate the SIRT1-PGC1&alpha signaling axis for mitochondrial biogenesis and SIRT1-MTP18 signaling for mitochondrial fission and clearance of damaged mitochondria to maintain a healthy and functional repertoire of mitochondria.