National Institute of Technology Rourkela

Departmental Seminar

Seminar Title	: Clusterin and mitophagy: A potential avenue for targeting oral cancer
Speaker	: Prof. Sujit Kumar Bhutia
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Venue	: LS Seminar Hall
Date and Time	: 13 Nov 2024 (11:00 AM)
Abstract	: Clusterin (CLU) is an evolutionary conserved molecular chaperone present in different human tissues and fluids and established to be a significant cancer regulator. Here, we showed that CLU (clusterin) is localized to mitochondria to induce mitophagy controlling mitochondrial damage in oral cancer cells. CLU acts as an adaptor protein that coordinately interacts with BAX and LC3 recruiting autophagic machinery around damaged mitochondria in response to cisplatin treatment. Interestingly, CLU triggers class III phosphatidylinositol 3-kinase (PtdIns3K) activity around damaged mitochondria, and inhibition of mitophagic flux causes the accumulation of excessive mitophagosomes resulting in reactive oxygen species (ROS)- dependent apoptosis during cisplatin treatment in oral cancer cells. Moreover, CLU exhibits its mitophagy-specific role in clearing damaged mitochondria in cancer stem cells (CSCs) in oral cancer. CLU also regulates mitochondrial fission by activating the Ser/Thr kinase AKT, which triggered phosphorylation of DNM1L/Drp1 at the serine 616 residue initiating mitochondrial fission. More importantly, we also demonstrated that CLU-mediated mitophagy positively regulates oral CSCs through mitophagic degradation of MSX2 (msh homeobox 2), preventing its nuclear translocation from suppressing SOX2 activity and subsequent inhibition of cancer stemness and self-renewal ability. However, CLU knockdown disturbed mitochondrial metabolism generating excessive mitochondrial superoxide, which improves the sensitivity to cisplatin in oral CSCs. Notably, our results showed that CLU-mediated cytoprotection relies on SOX2 expression. SOX2 inhibition through genetic (shSOX2) and pharmacological (KRX0401) strategies reverses CLU-mediated cytoprotection, sensitizing oral CSCs toward cisplatin-mediated cell death.