National Institute of Technology Rourkela

Defence Seminar

Seminar Title	: Investigating the mechanistic role of PPA2 in mitochondrial fission and its modulation for oral cancer therapeutics
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Supervisor	: Prof. Sujit Kumar Bhutia
Venue	: LS Seminar hall (online mode)
Date and Time	: 29 Feb 2024 (3.30PM)
Abstract	: The mitochondrial pyrophosphatase PPA2 is a mitochondrial matrix localized protein known for maintaining mitochondrial function. I found that PPA2 induced mitochondrial fission signaling through the MTP18-DRP1 axis. Interestingly, PPA2 overexpression upregulated mtDNA content and symmetric mitochondrial fission through MFF and DRP1, leading to mitochondrial proliferation. However, during mitochondrial stress following CCCP treatment, PPA2 induced asymmetric mitochondrial fission through FIS1 and DRP1 to segregate damaged mitochondrial parts. Furthermore, PPA2 interacted with MTP18 and induced mitophagy using the C terminal LC3 interacting region (LIR) of MTP18 to clear damaged mitochondria. Furthermore, I found that the expression of PPA2 was significantly increased in OSCC tissue compared to associated normal tissue. PPA2 knockdown inhibited oral cancer cell survival and promoted apoptosis during cisplatin treatment. Moreover, PPA2-mediated cell survival was compromised in mitochondrial fission-deficient conditions, suggesting PPA2 activated mitochondrial fission through the MTP18-DRP1 axis and protected against cisplatin-induced apoptosis. In this connection, therapeutic modulation of mitochondrial fission and mitophagy during cancer progression is an emerging approach to enhance anticancer therapy efficacy. The use of natural compounds as mitophagy modulators is highly encouraging due to their multi-target specificity and low side effects. Here, I explored the anticancer potential of *Bacopa monnieri* (BM) through the induction of mitochondria fission and mitophagy. I identified that the aqueous fraction of the ethanolic extract of BM (BM-AF) had a potent anticancer potential. BM-AF restricted oral cancer cell survival and promoted PARKIN-mediated mitophagy in oral cancer cells. The *in vivo* antitumor effect of BM-AF was further validated by the 4NQO- arecoline-induced oral cancer model in C57BL/6J mice. Further detailed mechanistic investigation revealed that Bacopaside-I (BS-I), a saponin from *Bacopa monnieri,* downregulated the arecoline-induced mitochondrial dysfunction and NLRP3 inflammasome activation in oral cancer cells. Moreover, BS-I induced mitochondrial fission by PPA2-mediated DRP1 activation and triggered PINK1-PARKIN-mediated mitophagy for elimination of the dysfunctional mitochondria to restrict oral cancer initiation and progression.