National Institute of Technology Rourkela

Departmental Seminar

Seminar Title	: Targeting PPA2 dependent mitochondrial fission triggers cisplatin sensitivity in oral squamous cell carcinoma
Speaker	: Prof. Sujit K. Bhutia
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Venue	: LS Seminar Hall
Date and Time	: 21 Feb 2025 (17:30)
Abstract	: The mitochondrial pyrophosphatase PPA2 is a mitochondrial matrix localized protein known for maintaining mitochondrial function. Herein, a critical role of PPA2 in oral squamous cell carcinoma (OSCC) cell survival and therapy resistance is reported. The expression of PPA2 was observed to be significantly increased in human OSCC tissue and cell lines, as well as in a DMBA-induced OSCC hamster model, compared to the respective normal counterparts. Furthermore, cell proliferation, migration, and colony-forming potential were increased in OSCC cells with forced expression of PPA2, whereas in PPA2-depleted conditions, these parameters were reduced. In addition, a significant increase in CDDP-induced apoptotic cell death was observed with PPA2 depletion. The pyrophosphatase activity of PPA2 was required for function, and OSCC cells expressing mutant PPA2-R127A lacking PPA2 pyrophosphatase activity failed to provide a survival advantage during CDDP treatment. Mechanistically, the increased expression of PPA2 countered mitochondrial hyperfusion-induced ROS production and cell death through increased mitochondrial fission. Hence, forced expression of PPA2 failed to protect against CDDP-induced cell death in fission-deficient conditions. Furthermore, PPA2-induced fission was mediated through MTP18; forced expression of PPA2 did not provide cytoprotection without MTP18. A PPA2-mediated increase in mitochondrial DNA content also inhibited apoptosis and enhanced the therapy resistance of OSCC cells. In conclusion, PPA2 expression is increased in OSCC, and PPA2-mediated mitochondrial fission and mitochondrial DNA replication protect OSCC cells against cisplatin-induced apoptosis. Keywords: Apoptosis, Mitochondrial fission, MTP18, Oral cancer, PPA2