National Institute of Technology Rourkela

Synopsis Seminar

Seminar Title	: The role of SETD2-mediated m6A RNA modification in molecular oncogenesis of Glioma
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Venue	: Life Science meeting room
Date and Time	: 07 Aug 2025 (11.15 AM)
Abstract	: Gliomas are fast-growing brain tumors that are highly aggressive and characterized by the presence of genetic and epigenetic heterogeneity. Recent studies highlight the important role of epitranscriptomic modifications, especially N6-methyladenosine (m6A) RNA methylation, in cancer progression and therapy resistance. SET domain-containing protein 2 (SETD2) is the sole histone methyltransferase that catalyzes trimethylation of lysine 36 of Histone H3 (H3K36me3). It is a frequently mutated gene in several cancer types and is associated with poor survival, increased metastasis, and metabolic reprogramming. Studies have shown that SETD2 regulates m6A mRNA methylation (epitranscriptome) via H3K36me3. SETD2 and H3K36me3 have been individually implicated in glioma. SETD2 can directly influence m6A RNA modification, but the SETD2-m6A interplay has not been investigated so far in glioma. The role of SETD2 in shaping m6A landscapes in gliomas remains poorly understood. Therefore, this study aims to thoroughly investigate the coordinated epigenetic-epitranscriptomic axis involving SETD2 and the m6A RNA methylation machinery in driving glioma progression. We analyzed the m6A RNA methylation regulators expression, the molecular pathways leading to tumor progression, and their respective outcomes in SETD2-mediated RNA methylation. A positive correlation observed between SETD2 and RNA modifiers signifies their direct role in epitranscriptomics. In vitro analysis reveals that SETD2 knockdown positively affected the oncogenic properties of the glioma cell line and a global reduction in m6A levels in the transcriptome. The reduced m6A level in the transcriptome is attributed to the decreased Methyltransferase 3 (METTL3) and Methyltransferase 14 (METTL14) levels. Further RNAseq and meRIP-Seq were performed, and we identified 57 differentially expressed genes (log2FC &ge ± 0.5, P < 0.05) and 245 differentially methylated m6A peaks. Enrichment analyses (GO, KEGG, and GSEA) identified cancer-related pathways, like PI3K-Akt, focal adhesion, estrogen response, and oncogenic signals (IL2_STAT5, P53, and MYC). These key signalling pathways might contribute to glioma progression. We then proceeded with quantitative real-time PCR (qRT-PCR) on glioma tissue samples for SETD2 and m6A regulators, and we observed that SETD2 and m6A regulators displayed subtype-specific expression, with increased expression in Astrocytoma, IDH1 mutant, grade 3, and 4. GO analysis highlighted enrichment in RNA stability, methylation, and degradation pathways. Altogether, this study highlights SETD2-mediated m6A methylation in driving glioma progression. Therefore, targeting epitranscriptomic regulation could be a promising therapeutic strategy for treating glioma.