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Emerging role of histone lysine methyltransferase SETDB1 and repressive histone marks H3K9me3, H4K20me3 and H3K4me3 in pediatric brain tumors

Klonou A[1], Gargalionis A[1], Korkolopoulou P[1], Themistocleous M[2], Papavassiliou A G[1], Sgouros S[3] and **Piperi C[1]**
[1]National and Kapodistrian University of Athens, Greece
[2]Agia Sofia Children's Hospital, Greece
[3]Mitera Hospital, Greece

Statement of the Problem: Brain tumors are regarded as the most prevalent solid neoplasms in children and the principal reason of death in this population. Chromatin remodeling alterations such as histone methylation induced by their respective histone methyltransferases are considered to have a prognostic value in gliomagenesis and in pediatric gliomas onset. The aim of the study was to investigate the differential expression of repressive histone marks H3K9me3, H4K20me3, H3K4me3 and linker histone H1x in pediatric gliomas. In addition, expression of lysine N-methyltransferases SETDB1 and the enhancer of zeste homolog 2 (EZH2) was evaluated.

Methodology & Theoretical Orientation: Archival human glioma tissues and normal brain samples were provided by the Neurosurgery Departments of "Mitera" and "Agia Sophia" Pediatric Hospitals and the study was approved by the University of Athens, Medical School Ethics Committee. Protein expression was evaluated immunohistochemically as H-score (intensity multiplied with cell percentage, 0–300) in 36 pediatric tumor samples (30 astrocytomas grade II-III, 6 glioblastomas; age 3–14 years old; 23 males, 13 females) and in five samples of normal brain tissue.

Findings: Increased nuclear staining of H3K9me3 and H4K20me3 repressive marks was observed in astrocytomas (median H-score 298 and 295, respectively). Moderate nuclear staining was obtained for H3K4me3 and SETDB1 (median H-score 190 and 120 respectively), whereas EZH2 and H1x presented no significant nuclear expression. A positive association of H3K9me3 with H3K4me3 histone marks was observed (p=0.043). SETDB1 staining was significantly elevated in males as compared to female children (p=0.007) and tended to be higher in glioblastomas compared to astrocytomas II-III (p=0.05).

Conclusion & Significance: These findings indicate the possible involvement of H3K9me3, H4K20me3 and H3K4me3 histone marks in the pathogenesis of pediatric gliomas. The histone methyltransferase SETDB1 was found to play a significant role in modulating gene expression, possibly by inducing H3K9me3 epigenetic mark. Future studies validating these chromatin remodeling changes in larger cohorts are needed along with elucidation of the underlying molecular mechanisms for potential therapeutic targeting.

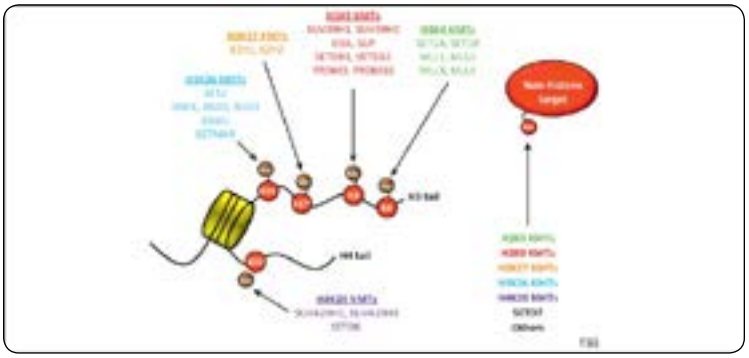

Figure 1: Major histone modifications and their respective enzymes.

Recent Publications:

1. Klonou A, Spiliotakopoulou D, Themistocleous M S, Piperi C and Papavassiliou A G (2018) Chromatin remodeling defects in pediatric brain tumors. Ann Transl Med. 6(12):248.
2. Blionas A, Giakoumettis D, Klonou A, Neromyliotis E, Karydakis P, et al. (2018) Paediatric gliomas: diagnosis, molecular biology and management. Ann Transl Med. 6(12):251.
3. Klonou A, Piperi C, Gargalionis A N and Papavassiliou A G (2017) Molecular basis of pediatric brain tumors. Neuromolecular Med. 19(2–3):256–270.
4. Sepsa A, Levidou G, Gargalionis A, Adamopoulos C, Spyropoulou A, et al. (2015) Emerging role of linker histone variant H1x as a biomarker with prognostic value in astrocytic gliomas. A multivariate analysis including trimethylation of H3K9 and H4K20. PLoS One. 10(1):e0115101.
5. Spyropoulou A, Gargalionis A, Dalagiorgou G, Adamopoulos C, Papavassiliou K A, et al. (2014) Role of histone lysine methyltransferases SUV39H1 and SETDB1 in gliomagenesis: modulation of cell proliferation, migration, and colony formation. Neuromolecular Med. 16(1):70–82.

Biography

Klonou A is a second-year PhD candidate at the Medical School of National and Kapodistrian University of Athens. She is doing her thesis on the "Investigation of genetic and epigenetic factors in pediatric brain tumors" in the Neuro-Oncology lab at the Department of Biological Chemistry. She investigates epigenetic alterations which control chromatin remodeling and alter the genome by modifying the expression of important genes which are involved in brain oncogenesis in children. Another goal of her research is the identification of major enzymes that cause histone modifications as well as the genes that are affected by the expression of these enzymes. Finally, she aims to identify differences in the molecular mechanisms involved in brain oncogenesis between paediatric and adult populations. She has published three review articles and she has been awarded for the best oral presentation at the 32nd Annual Congress of the Hellenic Neurosurgical Society (Greece, May 2018).

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