ABSTRACT

DEMİR I.G. (2026) Investigation of the Effect of G9a Histone Methyl Transferase Inhibition on DNA Methylation. Istanbul University, Institute of Health Sciences, Department of Basic Oncology. Master's Thesis. Istanbul.

Epigenetics refers to reversible changes in gene expression occurring without structural alterations in the DNA sequence. These changes are mediated through chemical modifications of DNA or post-translational modifications of DNA-associated proteins. DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs are the primary epigenetic mechanisms involved in malignant transformation. DNA methylation, catalyzed by the DNMT family, is crucial for DNA repair, recombination, replication, and gene regulation. Histone modifications regulate euchromatin and heterochromatin homeostasis, activating or repressing gene expression. Histone 3 lysine 9 dimethylation (H3K9me2), catalyzed by the G9a histone methyltransferase, is a repressive modification, and its inhibition alters cellular DNA machinery.

This thesis project investigated the effects of chemical G9a inhibition on global DNA methylation and cell-free DNA (cfDNA) fragmentation profiles in breast cancer cell lines representing different molecular subtypes (MCF-7 and MDA-MB-231). Additionally, the role of combining G9a inhibition with cisplatin on chemosensitivity was evaluated.

Analyses revealed that G9a inhibition induced distinct alterations in global DNA methylation levels, particularly in MCF-7 cells. Furthermore, cfDNA fragmentation analysis highlighted dynamics associated with these cellular epigenetic changes. Notably, combining G9a inhibition with cisplatin unexpectedly caused a statistically significant increase in global DNA methylation and did not enhance chemosensitivity. This response is thought to be associated with the activation of an acute/adaptive resistance mechanism against the treatment. These findings suggest that cfDNA fragmentation characteristics could serve as potential biomarkers for treatment monitoring, while demonstrating that G9a and cisplatin combination triggers distinct epigenetic responses in different breast cancer molecular subtypes.

Keywords: Breast cancer, epigenetic, DNA methylation, histone modification, G9a, cisplatin.

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