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Cancer Diagnosis using Inhibitors of Histone Protein Complex

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Editorial

Epigenetics is the study of heritable variations in gene expression unrelated to changes in DNA sequence. The methylation of CpG islands in DNA and the alteration of amino acids in the N-terminal histone tails are the two most prevalent epigenetic regulatory mechanisms. In recent years, it has been clear that alterations in the patterns of epigenetic modifications may also contribute to the genesis and progression of cancer, in addition to genetic mutations. Epigenetic modifications may be reversible in contrast to genetic mutations, which are very difficult to do so. This suggests that they could benefit from pharmaceutical treatments. Therefore, a lot of effort has been put into developing small molecule inhibitors of enzymes like DNA-methyltransferase in recent years. Epigenetics is the study of heritable variations in gene expression unrelated to changes in DNA sequence. The methylation of CpG islands in DNA and the change of amino acids in the N-terminal histone tails, particularly reversible histone acetylation, are the two most prevalent epigenetic regulatory mechanisms. Although these alterations form the molecular basis for epigenetics, epigenetics is not always addressed when they are studied. Thus, the term "epigenetics" is frequently employed in research even though, for example, only brief alterations in histone modifications or gene regulation are seen. This is also true for epigenetic therapy because it must be demonstrated whether the daughter cell generation is treated in the strictest sense [1,2].

The packing of chromatin and the expression of genes are significantly influenced by changes to the N-terminal tails of histone proteins. Reversible acetylation of lysine residues has received the greatest attention of these many changes. By utilising the cofactor acetyl-CoA, histone acetyltransferases transfer acetyl moieties to lysines in the N-terminal histone tails. This causes the negative charge of the nitrogen in the lysine residue's -amino group to be neutralised, which in turn causes chromatin to become more open and related with the activation of gene expression. Histone deacetylases tear off the acetyl groups, which results in a more compact form of chromatin and gene silence. It became clear that are connected to transcriptional as well as gene repression. It has been clear in recent years that HDACs are intriguing therapeutic targets with the capacity to correct cancer-related aberrant epigenetic alterations. The expression of the HDAC enzymes and the levels of acetylation in cancer cell lines and tumour tissue were found to fluctuate in numerous investigations. The abnormal recruitment of HDACs to promoters contributes to carcinogenesis in hematologic malignancies. Oncogenic DNA-binding fusion proteins are produced by chromosomal translocations, which are prevalent in these disorders, or by overexpressing repressive transcription factors. These proteins physically interact with HDACs. The first model disease in which the role of HDACs in the genesis of cancer was shown on a molecular level was acute promyelocytic leukaemia. Here, fusion proteins of the retinoic acid receptor- are present in 100% of the patients [2].

HDAC inhibitors alter the acetylation status of chromatin and other non-histone proteins, altering the expression of genes, inducing apoptosis, arresting the cell cycle, and inhibiting angiogenesis and metastasis. These small molecule inhibitors, in general, are more sensitive to altered cells than to normal cells. A few number of genes are generally controlled by HDACs. The main functions of the genes activated by HDAC inhibitors are cell proliferation, differentiation, and survival. HDACi were initially identified due to their capacity to promote cellular differentiation. This action is related to their capacity to induce G1 and/or G2 cell cycle arrest, which inhibits cell growth. Growing data demonstrates the immunomodulatory properties of HDACi. Because there are more surface antigens present, this may cause the immune system to recognise cancerous cells more frequently. For instance, it has been demonstrated that HDACi can increase the expression of class I and class II MHC proteins. HDACi can also improve immune cell function by modifying cytokine production. However, it has also been shown that the HDAC inhibitor suberoylanilide hydroxamic acid reduces the generation of pro-inflammatory cytokines, which are involved in the development of acute graft-versus-host disease (GVHD). The anti-tumor effectiveness of HDACi may be influenced by these immunomodulatory actions [3,4].

HDAC inhibitors are promising new treatments for cancer that are specifically targeted. The FDA has already given its approval to two drugs for the treatment of refractory cutaneous T-cell lymphoma: vorinostat and romidepsin. Inhibitors for different cancer therapies are currently in the late stages of clinical development. It will be fascinating to observe whether some of the novel compounds can improve efficacy or lessen side effects, and whether such effects can be associated with the selectivity profiles of the HDAC subtypes, specific chemical substructures, or may be substance specific. Data from clinical trials show that HDACi is more active in hematologic malignancies than in solid tumour malignancies, where little to no therapeutic effect has often been shown. Due to the functions played by HDACs in numerous pathways, there were many worries about the hazardous side effects of HDACi in the clinical context; nevertheless, up to now, clinical trials have mainly shown manageable side effects. The clinical development of Mocetinostat was halted in 2008 because to cardiotoxic effects, which are considered a class effect in the HDACi group. However, QT interval prolongation has only sometimes been observed in clinical settings. The incidence of cardiotoxic effects in unselected patient populations needs to be closely studied because this fact may be related to the preselection of individuals in clinical trials [5].

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Conflict of Interest

The author reported no potential conflict of interest.

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