

Epigenetic Drugs - The Future of Cancer Therapy

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Commentary

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Epigenetics refers to any alteration in gene expression that occurs without affecting the underlying DNA sequence. Epigenetic mechanisms regulate the accessibility of chromatin to transcription factors by promoting nucleosomal rearrangement via the addition or removal of acetyl or/and methyl groups to histones. Nucleosomes are basic units of chromosomes comprising of 147 base pairs of DNA wrapped around an octamer of histone proteins [1]. Each octamer comprises of two copies of the histone core proteins—H2A, H2B, H3 and H4. The linker histone H1 binds to the linker DNA and stabilizes the nucleosomal structure. All histone modifications, namely acetylation, methylation and ubiquitination, occur at the N-terminus. These post-translational modifications, coupled with DNA modifications, tightly regulate gene expression. It is now well-established that the maintenance of epigenetic balance is crucial to ensure the normal and healthy functioning of cells. Any aberration in this tightly regulated process can disrupt the epigenetic balance of the cells leading to diseases such as cancer [2].

The field of epigenetics has rapidly evolved over the past decade. Epigenetic aberrations have widely been documented in major diseases, and epigenetic inhibitors are currently of great clinical interest in the field of cancer [3]. The reversible nature of epigenetic aberrations has made the prospect of epigenetic drug therapies an attractive option. Furthermore, epigenetic therapies have proved to be indispensable in cancers with no druggable mutations (blood cancer). Currently, there are seven epigenetic drugs approved by the US Food and Drug Administration (FDA) for the treatment of different types of cancers. This includes two DNA methylation inhibitors -

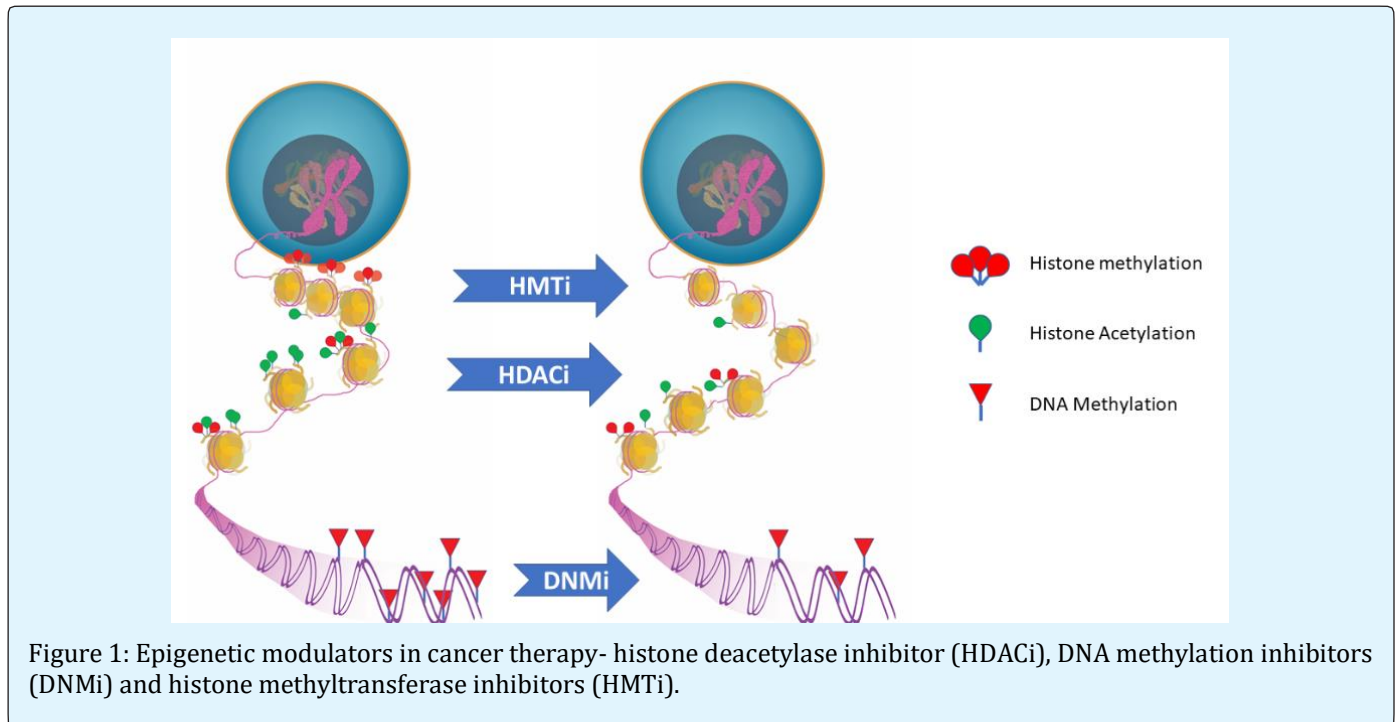
Azacitidine/Vidaza (2004) and Decitabine /Dacogen (2006) for Myelodysplastic syndrome, and four histone deacetylase inhibitors - Vorinostat (2006) and Romidepsin (2009) for cutaneous T-cell lymphoma, Belinostat /Beleodaq for peripheral T cell lymphoma (2014), and Panobinostat /Farydak for multiple myeloma (2015). Other than these, there are several histone methyltransferase inhibitors being investigated in various types of cancer [4].

Inhibitors against H3K27 trimethyltransferase Enhancer of zeste homolog 2 (EZH2), are currently in phase II clinical trials in patients with B-cell lymphoma and showing promising results [5]. Another histone methyltransferase under clinical investigation is DOT1L (an H3K79 methyltransferase) in patients with acute myeloid leukemia [6]. Thus, it seems likely that epigenetic drugs hold the key to the future of hematologic malignancies. The better success of epigenetic therapies in blood cancers, compared to solid tumors, is probably because of the heterogeneous nature of solid tumors, which often renders the drugs ineffective.

Recently, studies have been performed combining epigenetic therapies with immunotherapies and chemotherapies to circumvent the ineffectiveness of single-agent epigenetic modulators in solid tumors [7]. These combination studies have shown a synergistic effect in terms of inhibition of cellular proliferation, DNA damage, and apoptosis in solid tumors such as lung cancers and hepatocellular carcinoma [8-9]. Thus, combining epigenetic modulators with immune checkpoint inhibitors might be the key to the successful treatment for a wide variety of solid tumors.

With the rapidly evolving field of epigenetics, potential drug targets are being discovered every day for novel cancer therapies. It is expected that with further research in this field, soon more epigenetic modulators

will enter clinical trials either as single agents or in conjunction with immunotherapy against both solid tumors as well as hematologic malignancies.



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