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Letter to Editor Open Access

Rethinking Demethylating Agents in Epigenetic Cancer Therapy

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Abstract

DNA methylation inhibitors 5-Azacytidine and 5-Aza-2'-deoxycytidine have been increasingly used in the clinic to treat myeloid disorders and cancer since their FDA approval over a decade ago. Increasing the efficiency and efficacy of these drugs require better understanding on their mechanism of action. Recent studies show that DNA methylation inhibitors have widespread anti-tumor functions and act by modulating oncogenes and tumor suppressor genes expression as well as stimulating the immune system. These findings demonstrate the significant progress that has been made in the field of epigenetic therapy to improve patients' outcome.

Letter to the Editor

Our understanding of how to use DNA methyltransferase (DNMT) inhibitors to target DNA methylation in cancer therapy have come a long way since the nucleotide analogs 5-Azacytidine (5-Aza-CR, Vidaza) and 5-Aza-2'-deoxycytidine (5-Aza-2-CdR, Decitabine) were approved by the FDA over a decade ago for the treatment of myeloid dysplastic syndrome. First developed as chemotherapeutic agents, these compounds (hereon referred collectively as AZA) were found to reduce DNA methylation level in tumor cells, thus acting as demethylating agents [1,2]. DNA methylation is a covalent addition of a methyl group at the fifth carbon of cytosines that are present in the context of CpG dinucleotides. DNA methylation is a component of epigenetic machineries, which in normal cells, is critical for silencing of retrotransposons, and during genomic silencing and X-inactivation. Although the levels may vary, global changes in DNA methylation have been shown to be a key feature of cancer cells. Furthermore, DNA methylation is dynamic and pharmacologically reversible and thus, an attractive target for cancer therapy.

Decades of study have shown that while cancer cells exhibit global decrease in DNA methylation, there are punctate regions throughout the genome that have markedly increased DNA methylation level. This hypermethylation pattern is strongly associated with the silencing of genes, including tumor suppressor genes, leading to gene expression profile that favor uncontrollable cell growth. These observations help shaped the traditional view on DNMT inhibitors therapy that at low-dose, AZA is non-cytotoxic and consequently, can be used to induce DNA demethylation and reactivate tumor suppressor genes to reverse malignant phenotype [3,4]. Yet, while AZA treatment directly results in DNA demethylation, the level of demethylation does not always correlate with the level of tumor suppressor genes reactivation and/or predict clinical outcome. Questions thus remained on the mechanism governing AZA's anti-tumor activities.

The advancement in epigenomic studies in recent years, has revealed that the function of DNA methylation is nuanced and very much dependent on the genomic context in which it occurs [5]. This understanding influences how we approach the use of AZA in epigenetic therapy. While DNA methylation found in promoters is associated with gene silencing, for instance, DNA methylation found in gene bodies is thought to be associated with active transcription. Consequently, in the context of gene bodies, AZA-mediated demethylation has the effect of decreasing overexpressed oncogenes such as c-MYC, as well as other metabolic regulatory genes that are often induced during the initiation of tumorigenesis [6]. This result suggests that downregulation of oncogenes may mediate AZA's antiproliferative effects, and likely complement previously described upregulation of tumor suppressor genes. Kinetically, the effects of AZA also vary, with gene bodies becoming selectively remethylated faster than the promoters following drug withdrawal in DNMT3B-dependent pathway. This mechanism suggests pharmacological specificity in the otherwise non-specific demethylating agents [7].

Recent investigations on the mechanism of actions of AZA in solid tumors further reveal that the anti-tumor activities of AZA are not limited to modulating canonical oncogenes and tumor suppressor genes. Independently, preclinical studies by Chiappinelli et al. [8] and Roulois et al. [9] show that AZA induces demethylation of previously silenced endogenous retrovirus elements (ERVs) in colorectal and ovarian cancer which triggers the robust activation of IRF7 interferon response pathways. ERVs make up about 8% of the human genome, an evolutionary consequence of viral infection and viral sequence insertion. In normal cells, the expression of these ERVs is kept in check by DNA hypermethylation. Upon removal of DNA methylation, bidirectional transcription of ERVs is activated, resulting in the production of dsRNA that stimulates MDA5 and RIG-1 proteins and subsequent IRF7 activation. In turn, the activation of anti-viral defense mechanism sensitizes tumor cells to anti-CTLA4 immune checkpoint therapy [8]. These results build upon previous studies that show that AZA treatment activates the expression of tumor antigens and the immunosuppressive PDL1, demonstrating an immune layer by which AZA works to promote anti-tumor activities [10]. Altogether, these findings represent an exciting potential for the future use of AZA both

as a stand-alone drug and as a bridge between epigenetic and immune cancer therapy.

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