Commentary

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Epigenetics Therapy and its Role in Cancer Diagnosis

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Description

Epigenetic modifications have fundamental functions in cancer progression considered by reversibility and vulnerability to external factors. They are emerging as promising targets for cancer therapies. The drugs that target the epigenome, called epi-drugs, have been developed more than 40 years. DNMT inhibitors are powerful anticancer therapeutics to reverse the DNA hyper methylation status of TSGs. Conferring to the regulatory mechanisms to the nucleotides, DNMTIs can be divided into two classes: cytosine analogue inhibitors and non-nucleotide analogue inhibitors. In general regards, cytosine analogues can integrate into the DNA or RNA backbone to replace C-5 of cytosine with N-5 and disturb the methylation, as well as persuade DNMTs degradation. They include azacytidine, decitabine, zebularine, SGI-110, pseudois cytidine, fazarabine, etc. Currently, they are extensively concerned in different solid tumors. Azacytidine has a great portion combined into RNA, while decitabine is only combined into DNA. The action of decitabine starts with DNA addition. After that, the formed azacytosine-guanine dinucleotides trap DNMTs with irreversible covalent bindings, thereby exhausting DNMTs and removing the DNA methylation marks on the promoters of TSGs. Also, DNA damage response is activated along with this process and leads to cell cycle arrest, growth suppression, and apoptosis. As for azacytidine, assumed to its capacity in the incorporation of RNA, current studies demonstrated that it can block gene translation via disrupting tRNA-rRNA interactions and inhibit the adaptation of deoxyribonucleotides. Apart from azacytidine and decitabine, there are many other cytosine analogues that function in dissimilar mechanisms, such as 6-thioguanine, and 4′-thio-2′-deoxycytidine, zebularine (ZEB). ZEB contains a 2-(1H)-pyrimidinone ring that leads to degradation of DNMTs via forming a covalent complex with DNMTs at location 6 of the pyrimidinone ring after DNA incorporation. Though ZEB alone is not as efficient as azacytidine or decitabine due to the competitive effect of cytidine deaminase, it facilitates preventing re-methylation of the gene after treatment of other DNMTIs and may lower doses of DNMTIs. For example, p16 expression may happen re-silence by DNA methylation after decitabine treatment in bladder cancer cells. Consequently, it also combines with azacytidine and decitabine and displays much safer in various cancer treatments, such as AML and EBV-positive Burkitt's lymphoma. HDAC inhibitors are capable of correcting the aberrant acetylation status of histones and non-histone proteins in cancers via reactivation of TSGs. Similarly, cancer cells exhibit a higher sensitivity in answer to HDACIs-induced apoptosis. Those features make them develop a promising target in cancer therapy. Founded on their structure, HDACIs can be alienated into four groups: hydroxamic acids, aliphatic fatty acids, cyclic peptides, and benzamides. The hydroxamic acid HDACIs contain a hydroxamic acid moiety that can bind to the zinc atom, a constituent in the catalytic sites of HDACs, thus inactivating HDACs. Multiple studies have demonstrated their success in treating both hematologic malignancies and other solid tumours. Currently, three general hydroxamic acid HDACIs have been approved by FDA: (i) Vorinostat (SAHA) which is responsible for cutaneous T-cell lymphoma. SAHA is a non-selective broad-spectrum HDACIs that inducing acetylation of histones. It has been stated to enhance the expression of p21 by inducing acetylated histone H3 and H4 in bladder carcinoma and endometrial stromal sarcomas. Similarly, there are other hydroxamic acid HDACIs similarly showing inhibitory effects on HDACs either selectively or generally, including resminostat, givinostat, abexinostat, pracinostat, and quisinostat, etc. They have been concerned in phase I or II clinical trials for multiple cancers. Romidepsin (FK2280) is a member of cyclic peptide HDACIs and has received approval of the FDA in 2009 and 2011 for the treatment of CTCL and PTCL respectively. Val Proic Acid (VPA) is an example of aliphatic fatty acid HDACIs and selectively targets class I/II HDACs. It was originally industrialized for the treatment of epilepsy, and its application was then extended to anti-tumour treatment due to its ability in suppressing the propagation and stimulating the differentiation of cancer cells. Moreover, VPA has a property of low toxicity, well tolerance, and stability, which makes it a promising epi-drug. Phenylbutyrate, AR-42, and pivanex (AN-9) are other members of short-chain fatty acid HDACIs.

Conclusion

Cancer topographies properties of heterogeneity and plasticity, the request for a precise and effective personalized therapy using epi-drugs is being brought into anxiety. The standard anti-cancer therapy for general cancer patients has received very incomplete prognosis due to separate differences. With the advent of high throughput epi-genome mapping

technologies, the genome and epi-genome map of a specific cell population from the patient are obtainable for drug sensitivity testing and drug screening. In this way, the treatments can be enhanced for each patient while having much competence and less off-target effects.