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Medicinal Plants and DNA Methylation of Cancer

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Editorial

It is common sense since more than three decades that genetic alterations are a hallmark of carcinogenesis and that compounds targeting mutated and reregulated gene products in cancer cells are attractive anticancer drugs. There are numerous examples not only for synthetic drugs but also for natural products targeting mutated gene products in cancer cells [1,2].

More recently, epigenetics emerged as new field of research and the question arises, whether medicinal plants may serve as resource to identify phytochemicals that modify epigenetic patterns to kill cancer cells. The concept behind this question is to develop novel epigenetic drugs for cancer treatment based on chemical scaffolds isolated from medicinal plants.

Epigenetics concern with regulation of transcription and control of gene expression. It is a phenomenon of alteration in gene expression due to DNA modification, yet without any changes at the DNA sequence level [3]. It consists of two main mechanisms, histone modification and DNA methylation. Different types of histone modifications are known, such as acetylation, phosphorylation, and methylation of lysine and arginine residues [4].

DNA methylation is the process of adding a methyl groups in the 5′-position of cytosine residues in the CpG dinucleotides, called CpG island, which is commonly present in the promoter region of the genes leading to gene silencing [5,6]. DNA methylation is carried out by a variety of nuclear enzymes known as DNA methyltransferases (DNMTs) [7]. DNMT1 is responsible for maintenance of methylation. This enzyme adds methyl groups to the hemimethylated DNA during replication. DNMT3a and DNMT3b are de novo methyltransferases. They are crucial for normal development of organisms, for the regulation of gene expression and for cellular differentiation [5]. DNA methylation plays a great role in organismic differentiation. Despite the presence of identical cells with the same DNA sequences, organisms can still have a wide variety of tissues and cell types. This can be explained by the epigenetic control of gene expression [8]. DNA methylation is critical for several biological phenomena such as imprinting, chromosome X inactivation, tissue-specific genes, and for the maintenance of chromosomal stability in differentiated cells. Therefore, failure in maintaining DNA methylation and establishment of abnormal patterns are linked with under-expression or over-expression of certain proteins, eventually leading to pathological disorders, such as cancer [4]. From an evolutionary point of view, DNA methylation suppresses the expression of harmful DNA sequences such as endogenous retroviral genes that have been integrated into the host genome during evolution [9].

DNA is naturally wrapped with histone proteins to form nucleosomes so that DNA methylation results in the compaction of nucleosomes and formation of heterochromatin, which is transcriptionally inaccessible [8].

DNA methyl transferases require S- adenosylmethionine (SAM) as methyl group donor and cytosine nucleotide as acceptor to form S-adenosylhomocysteine. If CpG islands are methylated, the respective genes are repressed, as a result of one of the two following mechanisms: Due to the presence of the methyl group, transcription factors cannot recognize the promoter region of the corresponding gene or repressor molecules such as methyl-binding proteins MDB are recruited, that causes silencing to the gene [10].

Cancer therapies face a serious problem due to the development of drug resistance and severe side effects to currently used therapeutics [11]. Therefore, identification of new candidate compounds and investigation of their mechanism of action within the cell are required to improve cancer therapy.

Cancer is closely linked to alterations in DNA methylation in several researches, since both, hypo- and hypermethylation affect the repeated DNA sequences and tumor suppress genes, which are critical players in the development of cancer. Hypomethylation is the decrease of the methylation state, which leads to overexpression of affected DNA sequences. Hypomethylation of repeated sequence such as Alu sequences or long interspersed elements (LINE) and gene-encoding proteins such as PLAU/uPA (protease urokinase) has been associated with tumor progression in breast cancers and prostate cancers [12].

Hypermethylation has been observed in several tumor types, however the increase of the methylation state of tumor suppressor genes, cell adhesion molecules, and growth-regulatory proteins leads to genes silencing. For instance Rb, APC, BRCA1, ER-α and VHL are hypermethylated in retinoblastoma, colorectal cancers, breast cancer, prostate cancer and renal cell cancers, respectively [13]. Surprisingly both, hypo- and hypermethylation events can be found in the same cancer type, but at different DNA sequences [12,14]. In contrast to gene mutations, DNA methylation is a reversible process by the removal of methyl groups. This property makes DNA methylation a promising drug target to treat cancer [15].

The strategy of DNMTs inhibition has been widely used in drug research. Currently two DNMT inhibitors (DNMTIs) have been approved by the American Food and Drug Administration (FDA); 5-azacytidine (5-azaCdR) and 2'-deoxy-5-azacytidine (decitabine) for the treatment of hematological malignancies [16]. There are mainly two families of DNMTIs: nucleoside analogues and non-nucleoside analogues [4]. Overexpression of DNMT has been detected in different types of cancer, including prostate, lung, and colorectal tumors [17].

Decitabine and 5-azacytidine are incorporated into DNA and RNA, respectively. DNMTs covalently bind to these agents and will be unavailable for methylation resulting in induction of DNA damage and

cell death. Demethylation by decitabine allows re-expression of silenced genes and cellular differentiation. Furthermore, incorporation of these drugs into RNA causes inhibition in protein production as a result of ribosomal disassembly and defective tRNA function. A different mechanism for DNMT inhibition is achieved by the use of antisense oligodeoxynucleotides (ODNs). The hybridization of short synthetic nucleic acids to a specific mRNA can block mRNA translation and lead to mRNA degradation and then decrease in DNMT mRNA and protein levels [18]. DNMTIs show poor specificity for tumor suppressor genes and globally affect the methylation state. Another pitfall is that DNA hypomethylation activates transposition of endogenous retroviral elements. More recently, the consequences of demethylation of a highly methylated LINE-1 antisense promoter result in stimulation of an illegitimate c-MET transcription, which leads to reduced c-MET receptor signaling [19].

Natural products hold a great promise to overcome not only cancer therapy problems, but also antibiotic resistance, the emergence of new diseases, and toxicity as well. The emergency of new technologies such as high-performance liquid chromatography profiling, genomics, combinatorial synthesis, proteomics, genetic manipulation, and bioinformatics enables to evaluate the activities of extracts and to separate the active compounds from natural products [20]. DNMT inhibitors that are currently used in clinical trials are non-selective cytosine analogues with considerable cytotoxic side effects. Based on the above ideas, the development of new DNMTs inhibitors is of urgent importance. Several natural products, from diverse chemical classes, have shown DNMT inhibitory activity, but this property needs more in-depth investigations. In 2011, López et al. provided experimental data of two prominent natural products, epigallo cathechin-3-gallate (EGCG) and curcumin [21].

Different methods have been used to detect DNMT inhibitors. There are basically two approaches, enzymatic assays and cellular-based assays. Enzymatic assays are usually linked to luciferin/luciferase, while cellular approaches rely on treated cell clones with epigenetic drugs that have the ability to express a reporter gene [22].

Significant interest has emerged to use non-nucleoside inhibitors. They do not incorporate into DNA, in order to inhibit the DNMTs. Natural products inhibitors falls into this category. Thus, epigallocatechin-3-O-gallate (EGCG), flavonoids extracted from green tea, and genistein isolated from *Genista tinctoria* are profound DNMTIs. Other non-nucleoside molecules have been reported, such as hydralazine, procainamide, and procaine, as well as oxazolines and isoxazolines, psammaplin A, nanaomycin A, RG108 (phthalimido-L-tryptophan), SGI-1027, and MG98. Most of these molecules are compounds that have already demonstrated biological activities against other targets such as protein kinases or highly reactive hydrogen peroxides [4].

In conclusion, DNA methylation is currently a promising drug target for cancer therapies. Several clinical phase 2 trials are presently going on for both, DNMTI monotherapy or in combination with other chemotherapeutic drugs. At present, many efforts aim to find new nucleoside or non-nucleoside inhibitors of DNA methyltransferases to modulate gene expression of tumors. Natural products are rich sources, containing a plethora of molecules and the opportunity to find a DNMTI with a good pharmacokinetic profile and lower side effects. Moreover currently approved DNA methylation modification drugs have limitations so that the development of new DNMTI is a challenging, but rewarding goal. The progress in epigenetic research opens new avenues for medicinal plants as resources for natural product-based drug development.

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