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Reversal of Hypermethylation and Activation of Tumor Suppressor Genes Due to Plant Extracts in Prostate Cancer

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Abstract

Across the world Prostate Cancer is found to be the common malignity among men. It is one of leading cause of death among men as compared to other types of cancer. Studies show that abnormal epigenetic events such as DNA hypermethylation are one of the causes of prostate cancer which is needed to be identified. The reversibility of epigenetic abnormalities has made them most attractive targets for cancer treatment. Some studies shows that the plant extracts plays a major role in the reversibility of hypermethylation in many cancers occurring in different organs like lung, breast, colon and prostate etc. In prostate cancer, the plant extracts like genestein from soy, mahanine from curry leaves and GTP (Green Tea Polyphenols) have a major impact on reversibility of hypermethylation. Hypermethylation of promoters at CpG sequences affects the transcription factors and represses gene transcription. These genes include P53 and RB1, Cyclin-Dependent Kinase inhibitors (CDK) and more recently the BTG1, BTG2 and BTG3 known as antiproliferative genes. Before the cancer epigenome can be safely manipulated with therapeutics as a treatment more studies about the mechanism of demethylation are required. This review focuses on the recent literature on epigenetic changes in prostate cancer and the possible potential of Plant extracts for the reversal of hypermethylation that can act as therapeutics.

Keywords: BTGs; CDK; Demethylation; Epigenetics; Epigenome; GSTP1; Hypermethylation; P53; RB1

Abbreviations: GTP: Green Tea Polyphenols; CDK: Cyclin-Dependent Kinase; APC: Adenomatous Polyposis Coli; AR: Androgen Receptor; PIN: Prostatic Intraepithelial Neoplasia

Introduction

Cancer is a disease becoming a major cause of death worldwide. In India approximately four lakhs of people are affected by cancer every year and about 2 lakhs of people die every year. This is mainly due to the late detection and lack of awareness among people about cancer. Cancer has the ability to spread throughout our body; they are different from the normal cells. Normal cells remain adhered to one another. They have definite life span. As some old cells die, they are replaced by new cells which arise due to cell division and differentiation. Both functioning of cells as well as division and differentiation of new cells are highly regulated. Whenever there is a breakdown of any regulatory mechanism, a cell develops the ability to undergo uncontrolled repeated divisions forming a cluster of cells called Neoplasm or Tumor. Tumor results in suppressing of normal cells and tissues.

Tumors are of two types, benign and malignant

a. Benign tumor is a non-cancerous tumor which remained constricted to the original area of its formation. Its size ceases after attaining certain growth and it gets encapsulated in connective tissue so that it unable to affect adjacent tissues.

b. Malignant tumor is defined as a cancerous tumor which grows rapidly because the dividing cells continue to proliferate.

Malignant tumor is not encapsulated, so these cells can reach to other parts of the body through blood and lymph. They form new malignant tumor in invaded parts. The phenomenon is called metastasis. Genetic and epigenetic modifications of DNA are associated with gene expression alterations in the cell and any aberrant alteration in this mechanism can lead to cancer. It was

suggested that in cancer epigenetic changes are about alterations in DNA and histone modifications that lead to the deactivation of tumor suppressor genes and the activation of oncogenic genes. There are many types of cancers affecting large number of population worldwide every year like skin, lungs, cervix, breast, prostate etc. It is the most commonly found in men, the chance of having it to occur is rare in men below the age of 40 but it rises rapidly after the age of 50 and is was found that every 6 in 10 prostate cancers known to occur in men older than 65. The countries like Australia, North America, northwestern Europe, and Caribbean islands are mostly affected by prostate cancer. There are many factors affecting the potential to develop prostate cancer, one of the most affecting factor is epigenetic alterations. Unlike genetic alterations such as mutations, epigenetic changes such as DNA methylation are found to be potentially reversible. This property of reversibility makes epigenetic changes an attractive target for cancer therapy [1].

Epigenetic alterations in prostate cancer progression

Epigenetic mechanisms are important for normal development of cells and maintenance of tissue-specific gene expression patterns in mammals. Disruption of epigenetic mechanisms leads to alteration in gene functioning and results in malignant cellular transformation. Epigenetics includes DNA methylation and histone modifications which are important mechanisms of gene regulation and play essential roles both independently in tumor initiation and progression. Large number of genes shows abnormality in prostate cancer due to aberrant epigenetic events such as DNA hypomethlyation and hypermethylation and altered histone acetylation. Aberrant DNA hypermethylation occurs when there is a gain of DNA methylation at regions that are normally unmethylated and when this occurs at gene promoters can lead to gene inactivation. Hypermethylation of gene promoters has been reported in almost all types of cancers, including prostate cancer. On the other hand, DNA hypomethylation can be considered as demethylation of normally methylated DNA that lead to the instability of chromosomes and activation of proto-oncogenes [2, 3, 4].

DNA hypermethylation

DNA Hypermethylation is the most common epigenetic abnormality in human malignancies, including prostate cancer. In prostate cancer it has been identified that many genes have been abnormally hypermethylated and these genes includes tumor suppressor, repair genes, for damaged DNA and genes involved in cell cycle control. The process of hypermethylation of DNA causes aberrant gene silencing, disrupting gene function and, thus, results in tumour initiation, progression and metastasis [5]. Silencing of tumour suppressor genes by DNA methylation is also often observed in prostate cancer. Study shows DNA hypermethylation of the Adenomatous Polyposis Coli (APC) gene in prostate cancer individuals [6], which examined promoter methylation of a number of genes. Hypermethylation of APC alone, and hypermethylation of APC and the cell cycle regulation gene cyclin D2 in combination were found to be significant predictors of prostate cancer progression. DNA methylation is also involved in regulation of the Androgen Receptor (AR). AR is activated by androgen, which plays a critical role in the development, growth and maintenance of the prostate [7]. In the initial stages, prostate cancer is androgen dependent, but eventually becomes androgen independent, due to the loss of AR expression [8-11].

DNA hypomethylation

DNA methylation in mammalian genomes is a defense mechanism by which repetitive DNA (which accounts for at least 50% of genome's content) is transcriptionally silenced to prevent it from propagating [12].Hypomethylation is a process of demethylating a DNA which is already normally methylated that can disrupt a defense mechanism, leading to structural and functional alterations of the genome. There are two types of hypomethylation global or genomic hypomethylation, which refers to an overall decrease of 5-methylcytosine content in the genome; and localized or gene specific hypomethylation, which refers to a decrease in cytosine methylation relative to the normal methylation level. The latter process affects specific regions of the genome, such as the promoter regions of proto-oncogenes or sequences which is highly methylated such as repetitive sequences and oncogenes [2]. Both global hypomethylation and gene-specific hypomethylation have been implicated in human cancer.

Epigenetic reversal in prostate cancer due to plant extracts

Herbs, plant extracts, botanicals, spices, and supplements are now a day's popular with patients struggling with serious illnesses like cancer. There are many plant extracts known to impact epigenetic mechanism. Silencing of many important gene expressions due to hypermethylation of CpG islands in the promoter regions is an important mechanism involved in cancer. Increases in the methylation of CpG dinucleotides congregate into CpG islands which is near the transcriptional regulatory regions of critical genes is one of the characterization of DNA in cancer cell. As a result, suppression of genes occurs, and its expression is inhibited due to DNA hypermethylation. Reversal of CpG island hypermethylation presents one of the captivating therapeutic target for the restoration of silenced gene expression. Nucleoside analogue inhibitors of DNA methyltransferases like 5-Aza-cytidine (5-aza-C) and 5-aza-deoxycytidine (5-aza-dC), have been widely used to reverse the abnormal hypermethylated DNA in cancer cells and helps in the restoration of genes that has been silenced.

Genistein: impact on prostate cancer

Genistein is a type of isoflavone which has been known to promote the health of human beings by reducing the incidence of specific chronic diseases like atherosclerosis and cancer. The recent investigation provides a novel method of extraction of genistein from soy. Genistein (4,5,7-trihydroxyisoflavone) is

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a phytoestrogen and belongs to the category of isoflavones. Isoflavones are defined as a secondary metabolite found in nature as minor constituents of soybeans and other leguminous plants. Initially, most cancers were thought to arise through activation of oncogene, however, increasing evidence indicates that loss of function of tumor suppressor genes represents a major cause to tumor development. Many researches led to the identification of a number of antiproliferative genes including P53 and RB1, Cyclin-Dependent Kinase inhibitors (CDK) and more recently the BTG1, BTG2 and BTG3 genes [13-15]. Expression of BTG3 Genistein proved to induce expression of BTG3 genes through promoter de-methylation and induction of active chromatin modifications in prostate cancer. Studies shows that BTG3 is silenced in prostate cancer and can be reactivated by genistein induced promoter demethylation and active histone modification. Genistein showed similar effects to that of 5Aza-C, which is recently undergoing phase II clinical trials as a treatment for prostate cancer. Results show that transcriptional silencing of the BTG3 gene is due to promoter hypermethylation which can be reversed by genistein and 5Aza-C treatments. Since genistein is a natural, non-toxic, dietary isoflavone, these results indicate that genistein is one of the advantageous therapeutic agent for treating prostate cancer.

Mahanine: impact on prostate cancer

Several recent studies indicate that suppression of RASSF1A is cognate with the advanced grade stage of prostate cancer and many other cancers. In investigation, it is demonstrated that, mahanine is a plant derived carbazole alkaloid, induced RASSF1A expression in both androgen-responsive (LNCaP) and androgen-negative (PC3) prostate cancer cells by repressing DNA Methyltransferase (DNMT) activity. The DNA methyltransferase (DNMT) family of enzymes known to be associated with the epigenetic silencing of gene expression, including RASSF1A, and are often over expressed in the case of prostate cancer. The present study showed how mahanine, a plant-derived carbazole alkaloid, reimpose RASSF1A expression by down-regulating specific members of the DNMT family of proteins in prostate cancer cells. Ras-association domain family 1A gene has been found to be the most frequently methylated gene described in human cancers [16]. Hypermethylation of the promoter of RASSF1A gene at its CpG-island has been found in 70% of prostate cancer [17, 18]. In tumor cell lines the restoration of RASSF1A expression diminishes the tumorigenicity [19], factors that restore RASSF1A expression have extensive importance in preventing tumor growth. By using methylation-specific PCR it has been establish that mahanine restores the expression of RASSF1A by inducing the demethylation of its promoter in prostate cancer cells. Furthermore, it shows that mahanine treatment induces the degradation of DNMT1 and DNMT3B, but not DNMT3A, by the ubiquitin-proteasome pathway. The inactivation of Akt by wortmannin, a PI3K inhibitor, shows a similar down-regulation in the levels DNMT1 and DNMT3B. Mahanine treatment results in decreasing phospho-Akt levels and create disturbance in the interaction of Akt with DNMT1 and DNMT3B. Conversely, the exogenous expression of active Akt inhibits the ability of mahanine to down-regulate these DNMTs, suggesting that the degradation of DNMT1 and DNMT3B by mahanine occurs via Akt inactivation. Mahanine treatment induces the proteasomal degradation of DNMT1 and DNMT3B via the inactivation of Akt, which promote the demethylation of the RASSF1A promoter and restores its expression in prostate cancer cells. Therefore, Mahanine considered to be the potential therapeutic agent for advanced prostate cancer when RASSF1A expression is silenced.

Green tea polyphenols (Gtps): impact on prostate cancer

A molecular hallmark of human prostate cancer is epigenetic silencing of gluthathione-S-transferase pi (GSTP1). GSTP1 is a member of the glutathione S-transferase superfamily that play an important role in detoxification by catalyzing the conjugation of the glutathione peptide with electrophilic and hydrophobic compounds, including carcinogens, resulting in less toxic and more readily excretable metabolites. [20, 21]. Methylation of the GSTP1 promoter is the most often detected abnormality, verifiable in over 90% of invasive cancers and in about 70% of Prostatic Intraepithelial Neoplasia (PIN) lesions. Therefore, promoter methylation and loss of GSTP1 expression has been proved as markers of prostate cancer in recent studies [22, 23, 24]. Furthermore, inhibition of abnormal methylation of GSTP1 may be effective in the prevention of pathogenic process. The effects of Green Tea Polyphenols (GTPs) on GSTP1 re-expression and its mechanism of action is compared with nucleoside-analog inhibitor of DNA methyltransferase (DNMT), 5- aza-2-deoxycitidine shows some similarity. It has beem observed that restoration of GSTP1 expression in LNCaP cells treated with GTP is accompanied by reversal of epigenetic silencing at 2 levels, which include both promoter demethylation and histone modification, was the first report where the dual role played by GTP in the reactivation of an epigenetically silenced gene has been reported [25-28].

Conclusion

The latest advances in cancer treatment have created a whole new outlook on how to treat cancer. These advances have developed from a deeper understanding of the molecular basis of cancer. Some of the earlier treatments are still valuable however they have some drawbacks. For example, surgery and radiation are effective but they only treat one local area of the cancer. Chemotherapy can treat cancer cells that are spread all over the body, but they have extremely toxic side effects. Natural compounds isolated from sources like plants, fungi and marine life forms revolutionized the field of anticancer therapeutics and preclinical studies. Early and accurate diagnosis of prostate cancer is essential, and available studies suggest that gene-specific DNA methylation analysis may prove to be useful as a prostate cancer biomarker. Hypermethylation of the GSTP1 promoter, particularly in combination with other genes implicated in tumorigenesis, is

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proving to be a highly specific and sensitive measure of prostate cancer. Further studies are, therefore, required to identify panels of genes that are aberrantly methylated in prostate cancer and may be useful in early detection of the disease.

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