Minireview Article

The role of G9a gene in various cancers

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ABSTRACT

G9a is an epigenetic regulator that methylate the lysine 9 of histone 3 and has a role in gene silencing. G9a generally causes repression of gene expression and participates in diverse cellular functions such as DNA repairing, proliferation and differentiation. This gene is overexpressed in some types of cancers include lung, colorectal, endometrial, head and neck cancers. The role of this gene in the basic processes can be used as a therapeutic goal. The purpose of this study was to evaluate the expression of G9a gene in various cancers and cancer related activities in this gene.

Keywords: Green Synthesis; G9a gene, cancer, differentiation, proliferation

INTRODUCTION

G9a or euchromatic histone-lysine methyltransferase 2 (EHMT2) early was found in MHC class 3 region by chromosome walking and pulsed field gel electrophoresis [1]. Primary transcript product of G9a is a longer product which is broken into two small pieces containing G9a and NG36 by splicing. G9a has 3 domain includes SET domain that involved in methyltransferase activity, ankyrin repeat

domain with a role of protein protein interaction and nuclear localization signals which are located in N-terminal region [2, 3] (Fig. 1). G9a is expressed in many tissues such as, thymus, bone marrow, peripheral blood leukocytes, lymph node, spleen fetal liver, and skeletal muscles [2, 4]. This protein transfers methyl groups from S-adenosyl-l-methionine (SAM) to amino group of lysine residue and form H3K9me1 and H3K9me2 [5]. So that G9a is an epigenetic regulator that methylate the lysine 9 of histone 3 and has a role in gene silencing [6, 7]. G9a generally causes repression of gene expression, and participates in diverse cellular functions such as DNA repairing, proliferation and differentiation [8, 9]. The purpose of this study was to evaluate the expression of g9a gene in various cancers and cancer related activities in this gene.

Fig. 1: Schematic of G9a structure (on chromosome 6) in human. The site for methylation (Me), nuclear localization signal (NLS), glutamic acid (E) rich region, cysteine (Cys) rich region, ankyrin repeats (ANK) and the catalytic SET domain are shown.

The role of G9a in proliferation and differentiation and DNA repairing

The three main cellular functions that play an important role in the normal function of the cells including proliferation, differentiation and DNA repairing that disorder in all three pathways can lead to cancer [10, 11].

The results have shown that G9a is expressed in many tissue including thymus, bone marrow, fetal liver, peripheral blood leukocytes, lymph node, spleen and skeletal muscles [2]. Early evidences show that G9a gene can play an important role in cell growth and differentiation which were obtained by experiments on mice. In this study, we have observed that embryos with G9a knock out will die in the early stage of growth because apoptosis increases [12]. Embryonic stem (ES) cells with G9a may do not show growth defect in cell culture at early stage but they show several defects in differentiation, suggesting a role in differentiation [13]. Also many studies have shown an important role of G9a in alteration of pluripotency in ES cells with repression by repression of Oct-3/4, Nanog and DNMT3L which are required gene in maintenance of pluripotency [14]. G9a has been implicated in genomic imprinting by H3k9 methylation, which results in suppressing

transcription in many tissues [15]. G9a can suppress the expression of several genes in different tissue. Suppression JAK2 gene by methylation that occurs during retinoic acid induced differentiation of the leukemic cell line HL-60 is an example that G9a is recruited to the JAK2 promoter and repress its transcription [16]. G9a also has a role in t-cell differentiation [17]. In adipocytes and skeletal myogenesis, the overexpression of G9a decline their differentiation [18, 19]. In brain G9a/GLP complex is a main regulator for specific gene expression. Defects in this complex are associated with mental disorders such as learning difficulties and mental retardation [2, 20]. The mechanism of G9a affects cell proliferation is still unknown. Some studies have shown that G9a promotes cell proliferation by activating E2F gene and mediated molecules such as cyclin $D^1$and DHFR in a methylation-independent manner [21]. Many studies have shown that repression of G9a with drug can arrest cell cycle in G1 and can reduce proliferation such as fetal pulmonary arterial smooth muscle cells that proliferation reduces in them by BIX-01294 drug. In this cells level of p21 gene increases and the cell cycle arrests in G1 phase [22].

Based on several studies, G9a has an important role for DNA damage repair and in response to DNA damage. G9a has a direct and positive effects on homologous recombination (HR). When DNA damages, G9a is recruited to chromatin with phosphorylation at ser211 and interacting with RPA and RAD51 and finally homologous recombination occurs in break site. Disturbance in this pathway causes instability in genomes which is a major characteristic of cancer cells [23, 24].

G9a has important role in cell proliferation, differentiation and DNA repairing. Therefore, this gene will change in a variety of some cancers such as colon, head and neck, lung and invasive transitional cell carcinomas and in B cell chronic lymphocytic leukemia. Increased G9a level causes silence tumor suppressor genes that are involved in cancer pathogenesis [25]. In hypoxia situation the G9a is increased without changing the expression level and transcription G9a RNA. The stability of G9a is increased in cancers with a hypoxia situation and therefore leads to hyper methylation H3K9 at its target promoters [26, 27].

G9a and lung cancer

In cell cycle, the epidermal growth factor receptor (EGFR) has an important role in cell growth and proliferation. Elevated G9a level causes auto phosphorylation EGFR and are associated with pathogenesis some cancers specially lung cancer. Many studies have shown that EGFR increases in more than 90% cases with lung cancer. In non-small cell lung cancer

(NSCLC), up regulation G9a promotes cancer cell growth, colony formation, invasion and migration through silencing expression of CASP1 (caspase1). Caspase1 is a component of a complex in which suppresses tumor cell invasion and migration in NSCLC cells [28, 29].

G9a and breast cancer

H3K9 methylation by G9a represses many genes which are associated with poor prognosis and progression of breast cancer.so that G9a can be used as a therapeutic target in breast cancer. A series of epigenetic changes occur in tumors, such as the conversion of mesenchymal to epithelial tissue (MET or EMT). Loss of E-cadherin expression is a main hallmark of EMT and some transcriptional factors that have a role in this process include Snail, Twist, and ZEB1. Many studies have been shown that H3K9 methylation and G9a are required for EMT-induced E-cadherin promoter DNA methylation in breast cancer. Therefore knock down of G9a restores E-cadherin expression by suppressing H3K9me2 and DNA methylation [2, 29].

G9a and head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is an aggressive cancer and has a poor prognosis. In mentioned cancer, epithelial to mesenchymal transition (EMT) has a key role in metastasis and causes lymph node metastasis that are associated with E-cadherin repression. G9a interacts with snail and mediates snail-induced transcriptional repression of E-cadherin and EMT through methylation. Thus the G9a-snail axis can be a good choice for target therapy because inhibition of G9a expression could suppress HNSCC cells growth [2, 25].

G9a and colorectal cancer

Many studies have shown the increasing of G9a expression in colorectal cancer whereas knock down of G9a inhibited CRC cells proliferation. The knockout of G9a gene is associated with chromosome aberration and double strand breaks in DNA. Topoisomerase 1 inhibitors suppress G9a and increase the expression of γH2AX, which ultimately results in the death of colorectal cancer cells. In a study on colorectal cancer, scientists have observed that G9a was highly expressed in both clinical samples and CRC cell lines .Thus G9a has a potential role in preserving tumor cell phenotypes. An important point to be made here is that inhibiting G9a expression may be a good option for therapeutic purposes in colorectal cancer [30, 31].

G9a and endometrial cancer

A study was conducted to investigate the role of G9a in endometrial cancer, which was associated with knock down of this gene in endometrial cancer cells using a tetracycline-controllable system and followed by functional assays. The results of this study suggest increasing in the expression of this gene in endometrial cancer cells. This study, examine the effect of G9a on endometrial cancer and mechanistic investigations suggest that E-cadherin repression is related to the effects of G9a [32].

CONCLUSION

G9a is an epigenetic regulator and plays key role in basic process such as proliferation, differentiation and DNA repairing. The G9a is overexpressed in many different types of cancers and based on studies this gene has an important role in tumorigenesis and carcinogenesis. Therefore, working on regulating switches of this gene and related pathway can be a good option for therapeutic purposes in cancer cells.

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