Review Article

Mechanism of methylation and acetylation of high *GDNF* transcription in glioma cells: A review

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ABSTRACT

Gliomas are the most common primary malignant tumors in the central nervous system. High expression of glial cell line-derived neurotrophic factor (GDNF) is an important prerequisite for the initiation and development of gliomas. However, the underlying transcription mechanism is poorly understood. Epigenetic alterations are common and important hallmarks of various types of tumors, and lead to abnormal expression of genes. Several recent studies have suggested that epigenetic modifications contribute to increased *GDNF* transcription. Specifically, aberrant DNA methylation and histone acetylation in the promoter regions of *GDNF* are related to high *GDNF* transcription in glioma cells, where transcription factors have extremely important roles. Therefore, elucidating the importance and features of this underlying molecular mechanism will enhance our understanding and provide clues for the accurate diagnosis and efficacious treatment of gliomas. This review summarizes the latest thinking on the potential epigenetic mechanisms of high expression of *GDNF* in glioma cells focusing primarily on DNA methylation and histone acetylation.

1. Introduction

Glioma is the most common type of brain tumors. Gliomas have been divided into four grades by the World Health Organization (WHO), grade I to IV, according to histologic features [1, 2]. Grade I and II gliomas are known as "low-grade", whereas grade III and IV are termed "high-grade" [3]. The 2016 WHO classification of central nervous system tumors used, for the first time, molecular parameters in addition to histology to define many tumors (including gliomas). This strategy has allowed for improved "tailoring" of therapy to patients, and better classification for clinical trials and experimental studies [4]. Glioma resection can greatly reduce tumor bulk, and adjuvant radiotherapy and chemotherapy improves survival. Nevertheless, complete excision is virtually impossible due to the infiltrative nature of gliomas, and death occurs inevitably from recurrent or progressive disease (for review, see [2]). Therefore, clarifying the underlying mechanisms is key to developing new strategies for glioma treatment.

Glial cell line-derived neurotrophic factor (GDNF) is closely associated with the development and progression of gliomas [5, 6]. GDNF

expression increases significantly in glioma cells, and there is no change in the base sequences of the promoter region of *GDNF* [7]. Given that altered expression of genes usually results from mutations or epigenetic alterations (see below), several studies have highlighted the influence of epigenetics on tumorigenesis, and epigenetic alterations appear to be common hallmark of various cancer types [8]. Gliomas are not exceptions to this hypothesis, and epigenomic studies have allowed more comprehensive understanding of the pathogenesis of gliomas [9].

"Epigenetics" is the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself. Epigenetics studies can be extremely extensive, but are centered mainly on DNA methylation, histone modification, noncoding RNA and chromatin remodeling. Because they are reversible, epigenetic alterations are being targeted for therapeutics in cancer clinical trials [10]. With regard to glioma cells, although epigenetic alterations have been studied thoroughly (for review, see [11]), little effort has been made to elucidate the epigenetic mechanism of high *GDNF* transcription. This review explores recent advances regarding the epigenetic mechanism of high *GDNF* expression in glioma cells, and its potential clinical

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implications, to improve treatment for this lethal disease.

2. Main text

2.1. GDNF expression in glioma cells

2.1.1. Basic features of GDNF

GDNF is a growth factor related most closely to gliomas [12, 13, 14]. GDNF is a member of the transforming growth factor-β (TGF-β) superfamily, and was cloned initially from the rat B49 glial cell line [15]. GDNF exerts its effects primarily through binding to GDNF-family receptor-α1 (GFRα1) and activation of tyrosine kinase signaling. In humans, *GDNF* is a single-copy gene mapped to chromosome 5 at p12-p13.1, and contains six exons and two promoters (Fig. 1A): upstream of exon IV is the promoter I region, and upstream of exon I is the promoter II region. The latter contains two enhancers, two silencers, and multiple binding sites of transcription factors (Fig. 1B) [16, 17]. The structure of *GDNF* can be the basis for studies of the epigenetic mechanism of *GDNF* expression.

Initially, GDNF was discovered to be a potent survival factor for midbrain dopaminergic neurons [15]. Subsequent research showed that GDNF exhibited nutritional and protective effects in the periphery, for sympathetic, parasympathetic, sensory, and motor neurons (for review, see [18]). Due to its neuroprotective properties, most studies have focused on the protective effects of GDNF in Parkinson's disease. GDNF have be envisaged to be a crucial factor for the survival and maintenance

of dopaminergic and serotonergic neurons [19, 20, 21]. However, various studies have demonstrated that GDNF is a powerful proliferation- and migration-promoting factor, and closely related to glioma development [5, 22, 23]. Therefore, given that GDNF strongly promotes glioma development, clarifying the roles of GDNF in gliomas and its mechanism of action may provide new insights for molecular-based therapy of gliomas.
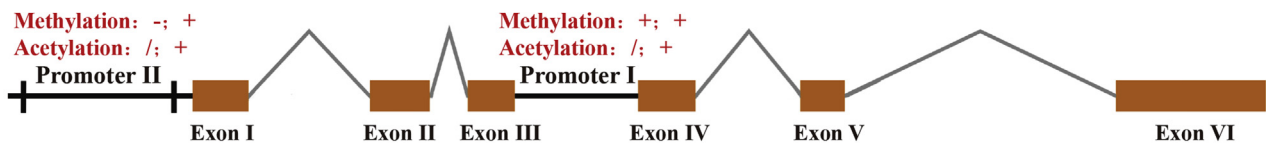
2.1.2. Aberrantly high GDNF expression in glioma cells

Expression of growth factors in glioma cells has garnered considerable interest due to their importance in the regulation of growth and differentiation. Indeed, this strategy has led to new therapeutic interventions. Wiesenhofer and colleagues found that GDNF showed high expression not only in rat glioma cells *in vitro* but also in human glioma cells *in vivo*, and that high GDNF expression may be important for the proliferation of glioma cells [24]. Similarly, it was elucidated that, compared with normal brain tissues, GDNF expression was significantly higher in glioma tissues at protein and mRNA levels [6], and increased along with the increasing pathologic grade of glioma tissues [7]. The proliferation- and metastasis-promoting mechanisms of GDNF have been studied thoroughly, but few scholars have investigated the mechanism of aberrantly high *GDNF* transcription in glioma cells.
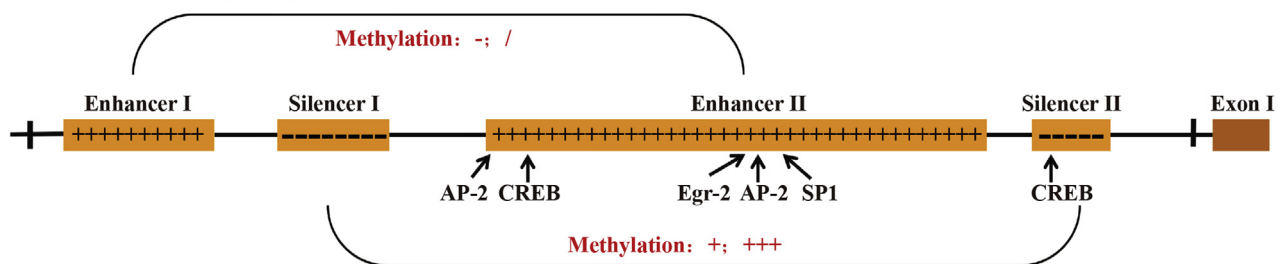
2.1.3. GDNF mutation is absent in glioma cells

Markedly increased expression of any gene is usually the result of gene mutations or epigenetic alterations [25]. Recent large-scale
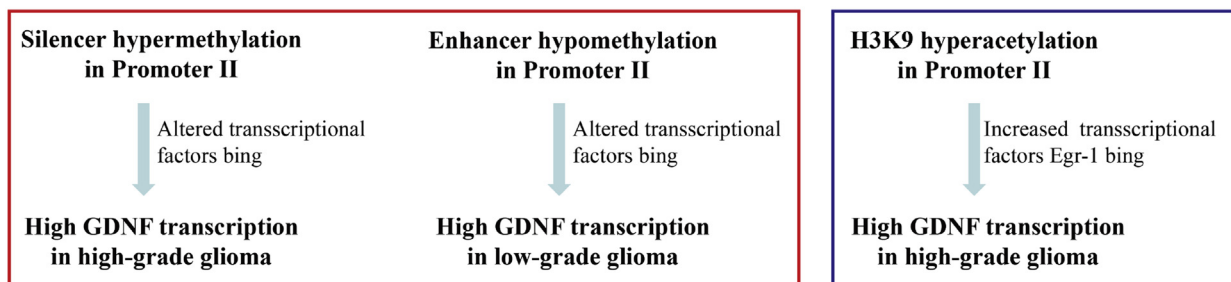

Fig. 1. Epigenetic mechanisms of high GDNF expression in glioma cells (adapted from Zhang et.al [54]). (A) Structure of human *GDNF* gene. Relative positions of the promoters, exons, and introns of human *GDNF* gene, and the status of methylation and histone H3K9 acetylation of *GDNF* promoters. -: down; +: up;/: unchanged. For example, "Methylation: -; +" denotes that, compared with normal tissue, the methylation level in low-grade glioma and high-grade glioma was decreased and increased, respectively. (B) Structure of *GDNF* promoter II. The promoter region II of *GDNF* contains two enhancers, two silencers, and multiple binding sites for transcription factors (AP-2, CREB, Egr-2, SP1). (C) Methylation- and acetylation-based mechanisms of high *GDNF* expression in glioma cells. The methylation or acetylation status in promoter II are more closely associated with high *GDNF* transcription. Abbreviation: GDNF, glial cell line-derived neurotrophic factor; AP-2, activator protein-2; CREB, cAMP-response element binding protein; Egr-2, early growth response protein 2; SP1, specificity protein 1.

genomic and epigenomic profiling studies, such as The Cancer Genome Atlas (TCGA), have engendered massive novel data and provided deeper insights into tumorigenesis [9, 26]. Alongside known genetic changes, aberrant epigenetic alterations have emerged as common hallmarks of many cancers types [27]. Also, the genetic and epigenetic "landscapes" of gliomas have been studied extensively [28, 29, 30]. Yu and colleagues [7] revealed no changes in DNA copy numbers, GDNF promoters and coding-region sequences in glioma cells, indicating that abnormally high GDNF transcription is not related to gene mutations. Hence, one could speculate that epigenetic modifications contribute to increased expression of GDNF, and some scholars have attempted to explore the underlying epigenetic mechanism of high GDNF expression in glioma cells [7, 31, 32].

2.2. DNA methylation-mediated high GDNF transcription in glioma cells

2.2.1. DNA methylation

DNA methylation regulating non-genetic alterations is the most stable epigenetic characteristic, where a methyl group is attached to the $5'$ position of cytosine-guanine dinucleotide (CpG) with tendency to form clusters or CpG islands (CGIs) [33]. Typically, CGIs are free of DNA methylation, which is extremely important for gene expression. However, in many cancer types, a proportion of CGIs is hypermethylated, which is associated with silencing of tumor-suppressor genes [34, 35]. Different patterns of DNA methylation occur in different cancers, and hypermethylation and hypomethylation have emerged as significant fators in tumorigenesis [5, 36]. The loci of DNA hypermethylation are in the promoter regions of tumor-suppressor genes, which results in the associated silencing of these genes [37, 38]. However, DNA hypomethylation tends to be found at repetitive DNA sequences, which results in reduced stability of the cancer genome sequences [39, 40, 41, 42].

2.2.2. Methylation-based regulation of gene expression

The patterns of DNA methylation are also likely to have important roles in developmental processes in the brain and in brain tumors, such as gliomas. Bai and colleagues found that a small proportion of CpG sites maintained hypermethylation, whereas the global level of methylation was decreased, during glioma progression [43]. The authors proposed that these changes may enable glioma cells to self-renew perpetually, a hypothesis that is consistent with the increased cell proliferation observed in glioblastoma [43]. With regard to gliomas, isocitrate dehydrogenase (IDH) mutations are strongly associated with a distinct phenotype of DNA methylation [9, 44], and methylation of O6-methylguanine DNA methyltransferase (MGMT) helps to predict therapeutic responses [45, 46]: these are the two most well-characterized types of DNA methylation. Based on IDH and 1p/19q status, Wiestler et al. [47] demonstrated a molecular (rather than histological) classifcation, which allows for better prediction of outcome. Glioma patients carrying the IDH mutation have signifcantly improved survivals [47, 48]. Therefore, clarification of the underlying patterns of DNA methylation in glioma cells is clinically important.

2.2.3. Methylation mechanism of high GDNF expression in glioma

Gene expression is affected profoundly by the methylation status of CGIs. Differentially methylated regions within gene bodies or at regulatory elements (e.g. enhancers and promoters) have been documented [49, 50, 51, 52]. Intrestingly, ~60% of human gene promoters are related to CGIs [53], which has led to a greater focus on DNA methylation of promoters. Yu et al. [7] elucidated that the methylation level of promoter regions I and II of GDNF was changed in glioma tissues. That is methylation in promoter region I was increased significantly in high- and low-grade gliomas; methylation in promoter region II was decreased markedly in low-grade gliomas (hypomethylated sites located mainly in the enhancer region), but increased notably in high-grade gliomas (hypermethylated sites located mainly in the silencer region) (Fig. 1A). Consistent with that result, Chen et al. showed that methylation level in

promoter region I of GDNF was increased in glioma cells compared with that in normal glial cells, and that there was no marked difference between low- and high-grade gliomas [31]. The authors also showed that changes in the binding capacity of transcriptional factors mediated by methylation of promoter regions contributed to aberrantly high GDNF expression in glioma cells [7]. Subsequently, based on the different levels of methylation at different cis-acting elements in promoter region II of GDNF, in-depth investigation was undertaken by Zhang et al. [54]. Based on "specific sequence methylation", they found that hypermethylation of silencer II of GDNF promoted high GDNF transcription in high-grade gliomas, in accordance with their previous results (Fig. 1B) [7].

2.3. Histone acetylation-medicated high GDNF transcription in glioma cells

2.3.1. Histone acetylation

During the development and progression of cancers, altered DNA methylation is not the only epigenetic process. Histone modifications (histone acetylation and methylation), as another vital branch of non-genetic alterations, exert considerable influences on various DNA-templated processes [10]. Histone acetylation was described first by Allfrey et al. [55] in 1964. Originally, they proposed that histone modifications might be "dynamic and reversible mechanisms for activation as well as repression of RNA synthesis", and that hypothesis has been validated. The level of histone acetylation has been collaborated in two main ways. First, histone acetyltransferases (HATs) [56] disrupt the interactions between the histone and DNA [57]. This action causes relaxation of chromatin, which allows access of transcriptional factor to DNA. Second, histone deacetylases (HDACs) [58] cause condensation of chromatin, thereby repressing transcription (for reviews, see [59]). Discoveries of HATs and HDACs enable linkage of transcription regulation with histone acetylation. Thus, histone modifications dictate whether the chromatin state is transcriptionally permissive. Tightly controlled homeostasis between HATs and HDACs enables the dynamic control of transcription in health, and scholars have implicated the possibility of HATs/HDACs misbalance in diseases [60, 61].

2.3.2. Acetylation-based regulation of gene expression

Heterochromatin and euchromatin are regarded as repositories of silenced genes and active genes, respectively. Repressed and non-transcribing genes are considered to be in a state of "stable hypoacetylation", whereas histone hyperacetylation are regarded as a hallmark of nucleosomes at active genes (for reviews, see [62]). A recent study supports this hypothesis of the role of histone hyperacetylation in active genes [63]. Xie et al. [64] also showed that hyperacetylation of histone H3 within the NR4A1 promoter induced NR4A1 expression in hypercholesterolaemia. However, there are several exceptions related to hyperacetylation and hypoacetylation, as well as the effects of HDAC inhibitors [65, 66, 67] and their role in gene activation/repression, which suggests a dynamic perspective (for reviews, see [68]). Histone acetylation has been investigated in a variety of tumors. In glioma cells, expression of some tumor-suppressor genes (e.g., NAG-1, NECL1, RRP22) is decreased through histone deacetylation in the promoter regions of these genes [69, 70, 71].

2.3.3. Acetylation mechanism of high GDNF expression in glioma

Castro and colleagues demonstrated that valproic acid (VPA), which is a HDAC inhibitor, increased the expression of GDNF in C6 glioma cells [72]. However they did not assess if VPA altered histone acetylation in promoter regions. Subsequently, in astrocytes, histone hyperacetylation at the GDNF promoter was shown to mediate activation of GDNF transcription by HDAC inhibitors [73, 74]. These studies suggested that, in glioma cells, GDNF expression could be affected by changes in histone acetylation, but how histone acetylation modulates GDNF transcription is not known Some recent studies have attempted to understand the relationship between histone acetylation and increased GDNF expression in glioma cells. Based on histone acetylation in the promoter regions of

GDNF, Yu et al. [75] verified the presence of hyperacetylated histone H3K9 in promoter regions I and II of *GDNF* in high-grade glioma tissues and the C6 cells (Fig. 1A). Further experiments by Yu et al. [75] revealed that acetylation of histone H3 in promoter region II was significantly and positively correlated with *GDNF* transcription based on curcumin-induced H3K9 hypoacetylation and Trichostatin A-induced H3K9 hyperacetylation. They showed that hyperacetylation of histone H3K9 in the promoter region II of *GDNF* caused its aberrantly high transcription [75] in glioma cells, in accordance with the traditional mechanism of acetylation regulation.

However, how histone hyperacetylation mediates abnormally high *GDNF* transcription remains unclear. Kim and co-workers investigated if histone hyperacetylation at Egr-1 (a transcription factor involved in *GDNF* activation) binding sites in *GDNF* promoter region II in glioma cells could upregulate the binding capability of Egr-1 [76], and then induced aberrantly high *GDNF* transcription (Fig. 1C) [32]. Subsequently, Zhang et al. [77] illustrated the detailed mechanism by which Egr-1 is involved in enhanced expression of *GDNF* by histone hyperacetylation. They found that high Egr-1 expression may participate in the recruitment of RNA POL II in promoter region II of *GDNF* in a non-binding manner; this action was dependent upon histone hyperacetylation in promoter region II of *GDNF*, and enhanced *GDNF* transcription.

3. Conclusions

In recent years, the proliferation- and metastasis-promoting effects of GDNF have been studied in depth, but few research teams have investigated the underlying mechanism of abnormally high expression of GDNF in glioma cells. Usually, markedly altered expression of any gene is the result of mutations or epigenetic modifications. Yu et al. [7] revealed no gene mutation in *GDNF* promoters in glioma cells, indicating that abnormally high *GDNF* transcription may be related to epigenetic modifications. We explored recent advances regarding the epigenetic mechanism of high *GDNF* expression in glioma cells based mainly on DNA methylation and histone acetylation (Table 1).

In general, hypermethylation of promoter regions is correlated negatively with the corresponding gene expression, whereas hyperacetylation of promoter regions is usually correlated positively with gene expression. With regard to *GDNF* in glioma cells, hypermethylation of promoter I does not lead to *GDNF* silencing; instead *GDNF* is overexpressed in glioma cells. This is because activation of promoter II can compensate for "inhibition" of promoter I. In detail, hypermethylation of promoter II in high-grade gliomas lead to silencer deactivation, whereas hypomethylation of promoter II in low-grade glioma results in enhancer

activation. Therefore, increased *GDNF* transcription is more closely associated with methylation changes in different *cis*-acting elements in *GDNF* promoter II. Different from the complex methylation mechanism that regulates *GDNF* expression, the regulatory mechanism of acetylation is simpler. Histone hyperacetylation in *GDNF* promoter II in glioma cells enhances *GDNF* transcription, in which Egr-1 has an important role.

In conclusion, compared with promoter I, the status of methylation or acetylation in *GDNF* promoter II is more closely related to *GDNF* expression. Changes in the binding of transcription factors to the promoter regions of *GDNF* by methylation or acetylation contributes to high *GDNF* expression in glioma cells [7, 32]. However, the co-regulation mechanism of methylation and acetylation during high expression of *GDNF* is not known, and merits investigation. Also, more studies are needed to explore the other epigenetic characteristics associated with increased *GDNF* transcription. Collectively, this review provides a comprehensive understanding of the epigenetic mechanisms of high expression of *GDNF* in glioma cells.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Table 1
Studies on the epigenetic characteristics of high GDNF transcription in glioma cells.

Epigenetic characteristic	Mechanism	Reference
Methylation	Promoter I hypermethylation; enhancer hypomethylation and silencer hypermethylation in promoter II; changes in transcriptional factor binding capacity by promoter region methylation	Yu et al., 2013
	Promoter I hypermethylation	Chen et al., 2014
	Silencer II hypermethylation in promoter II	Zhang et al., 2016
Acetylation	Histone hyperacetylation upregulating GDNF expression	Wu et al., 2008
	Hyperacetylation of histone H3K9 in promoter II	Yu et al., 2014
	Histone hyperacetylation at Egr-1 binding sites in promoter II	Zhang et al., 2014
	Egr-1 interacting with RNA POL II under histone hyperacetylation in a non-binding manner in promoter II	Zhang et al., 2017

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