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A concise review on the role of BDNF-AS in human disorders

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ABSTRACT

Brain-derived neurotrophic factor-antisense (BDNF-AS) is a long non-coding RNA with tens of alternatively spliced variants being transcribed from 11p14 cytogenetic band. As a naturally occurring anti-sense, it regulates expression of BDNF, a factor which as essential roles in the pathoetiology of neurodevelopmental diseases. Notably, BDNF-AS has been reported to be down-regulated in colorectal cancer, osteosarcoma, esophageal cancer, glioblastoma, prostate cancer, cervical cancer and breast cancer. This lncRNA has direct/indirect functional interactions with GSK-3β, EZH2, miR-214, PABPC1, RAX2, DLG5, p53 and ADAR as well as RNH1/TRIM21/mTOR signaling. In prostate and breast cancers, down-regulation of BDNF-AS has been associated with poor clinical outcome. In the present review, we assessed the existing literature on the role of BDNF-AS in this process and summarized the available data in three distinct sections based of the methodology of experiments and source of expression assays. We also summarized the role of BDNF-AS in non-neoplastic conditions.

1. Introduction

The gene encoding Brain-derived neurotrophic factor-antisense (BDNF-AS) is located on 11p14.1. This long non-coding RNA (lncRNA) has been identified in 2005 through a search in EST databases and subsequent RT-PCR experiments [1]. This experiment has led to recognition of 7 splice variants from the antisense strand of *BDNF* gene, all of them predicted to be noncoding [1]. Most of these transcripts have been shown to be expressed in diverse areas of the human brain and to a lesser extent in peripheral tissues [1]. A subsequent experiment by Pruunsild et al. has reported that *BDNF-AS* has more than 300 transcripts produced by alternative splicing events with all of them having exon 1 of *BDNF-AS* as the most 5′ exon. While some transcripts have been shown to be expressed in almost all tissues examined, others exhibited tissue-specific expression [2].

BDNF-AS has been found to repress expression of BDNF sense transcript by changing chromatin configuration at the BDNF region, which consecutively decreases levels of endogenous BDNF protein and function [3]. BDNF-AS has been shown to regulate synaptic plasticity through epigenetic reprogramming, thus contributing in the pathoetiology of early onset alcohol use disorders [4]. Dysregulation of BDNF-AS has been reported in a variety of disorders including autism spectrum disorder [5] and acute spinal cord injury [6]. Moreover, it has been shown to protect neurons from local anesthetic-associated toxicity [7]. Consistent with the importance of BDNF in the function of nervous systems, the role of BDNF-AS has been firstly assessed in disorders of this system. However, an emerging bulk of evidence has highlighted the impact of BDNF-AS in the carcinogenic process. We assessed the existing literature on the role of BDNF-AS in this process and summarized the available data in three distinct sections based of the methodology of experiments and source of expression assays. We also summarized the role of BDNF-AS in non-neoplastic conditions.

2. BDNF-AS in cancers

2.1. Experiments in cancer cell lines

Experiments in colorectal cancer cell lines have revealed down-regulation of BDNF-AS parallel with up-regulation of glycogen synthase kinase-3β (GSK-3β). Functionally, BDNF-AS could inhibit proliferation, migratory ability, and invasive properties of colorectal cancer cells through suppressing expression of GSK-3β. This effect is mediated via recruitment of EZH2 to the promoter region of GSK-3β [8].

In osteosarcoma cells, BDNF-AS up-regulation could inhibit

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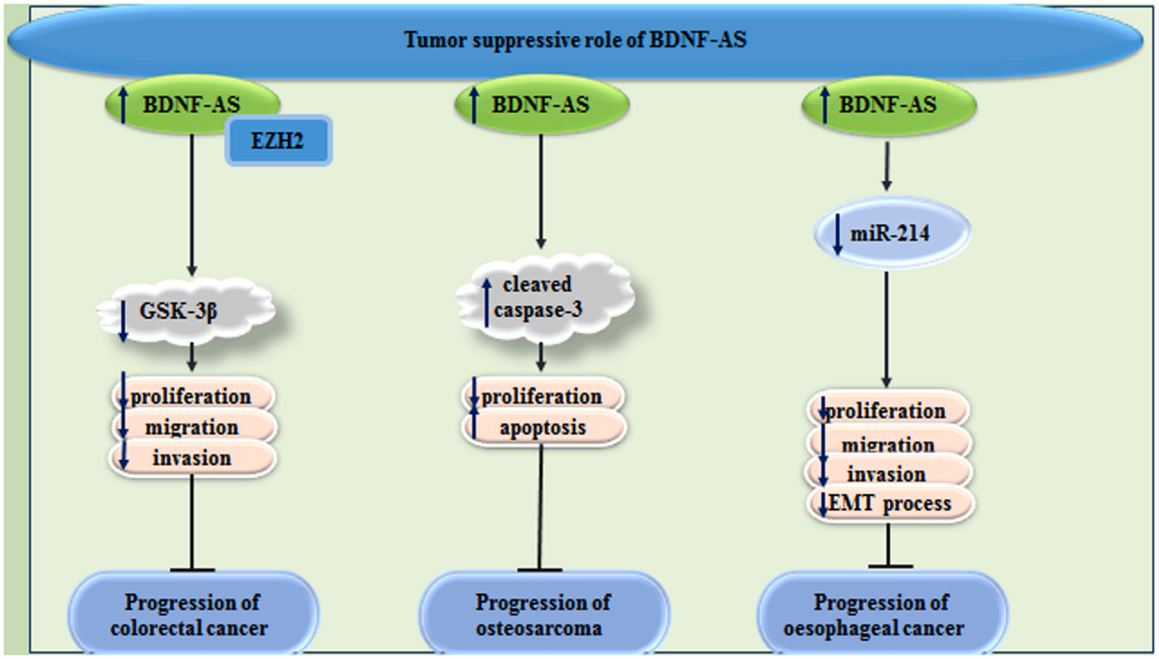

Fig. 1. Tumor suppressive role of BDNF-AS in colorectal cancer, osteosarcoma and esophageal cancer.

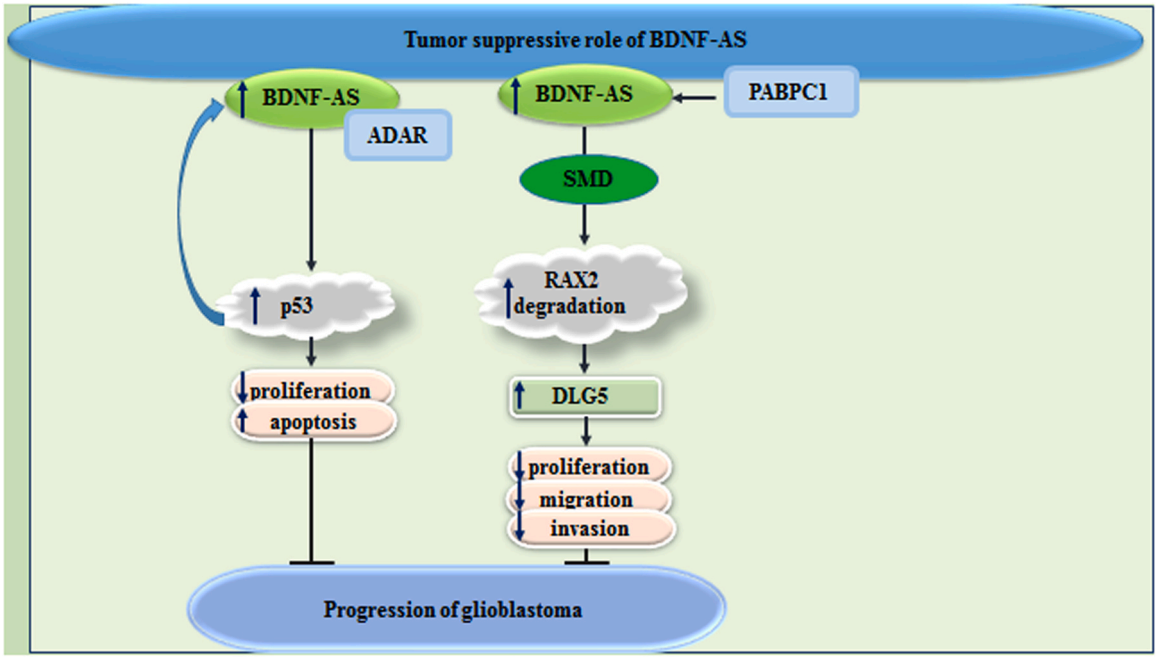

Fig. 2. Tumor suppressor role of BDNF-AS in glioblastoma.

proliferation and induce cell apoptosis via modulating levels of cleaved caspase-3 [9]. In esophageal cancer cells, down-regulation of BDNF-AS has been accompanied by up-regulation of miR-214, a miRNA which has been further verified as the target of BDNF-AS. Up-regulation of BDNF-AS has suppressed proliferation and migration of esophageal cancer cells and reduced their invasiveness. Most notably, this lncRNA could suppress epithelial-mesenchymal transition (EMT) of these cells as well [10]. Fig. 1 shows tumor suppressive role of BDNF-AS in colorectal cancer, osteosarcoma and esophageal cancer.

In glioblastoma cells, polyadenylate-binding protein cytoplasmic 1 (PABPC1) has been shown to interact with and stabilize BDNF-AS (Fig. 2). Up-regulation of BDNF-AS has resulted in suppression of proliferation, migration, and invasiveness of malignant cells, and induced their apoptosis. Furthermore, BDNF-AS has been shown to induce RAX2 transcript decay via STAU1-mediated decay (SMD). RAX2 silencing has conferred tumor-suppressive effects in these cells and enhanced expression of the Hippo pathway-activating factor DLG5. Cumulatively, PABPC1/BDNF-AS/RAX2/DLG5 has been identified as a molecular axis with potential therapeutic utility in glioma [11]. Another study in glioblastoma cells has shown that BDNF-AS interacts with ADAR protein to stabilize of p53 transcript, therefore increasing p53 levels. Moreover, p53 could act as a transcription factor to increase expression of BDNF-AS. Thus, BDNF-AS/ADAR/p53 axis is a functional axis for modulation of proliferation of glioblastoma cells [12].

Table 1
Summary of experiments in cancer cell lines.

Tumor type	Targets/ Regulators and signaling pathways	Cell line	Function	Ref.
Colorectal cancer	GSK-3β, EZH2	HCT116, LoVo, NCM460	↑ BDNF-AS: ↓ proliferation, ↓ migration, ↓ invasion	[8]
Osteosarcoma	cleaved caspase-3	Saos-2, MG-63, HOS	↑ BDNF-AS: ↓ proliferation, ↑ apoptosis	[9]
Esophageal cancer	miR-214	SHEE, OE19, KYSE-70, KYSE-170, KYSE-180, OE33, Eca-109, TE-1, TE-13	↑ BDNF-AS: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process	[10]
Glioblastoma	PABPC1, RAX2, DLG5	HA, U87, U251, 293T	↑ BDNF-AS: ↓ proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[11]
	p53, ADAR	U251, SNB19, U87, A172, NHAs	↑ BDNF-AS: ↓ proliferation, ↑ apoptosis	[12]
Prostate cancer	–	LNCaP, VCaP, MDA/Pca/2b, PC-3, DU145, NCI-H660	↑ BDNF-AS: ↓ growth, ↓ invasion	[13]
Cervical cancer	–	Ect1/E6E7, SiHa, DoTc2-4510, Ca-Ski, HeLa, 3 HeLa/S3, C-4I, C-4II, C-33-A,	↑ BDNF-AS: ↓ proliferation, ↓ migration	[14]
Breast cancer	RNH1/ TRIM21/ mTOR signaling	MCF-7, MCF-7R, MDA-MB-231, T47D, T47DR	–	[15]

Table 2
Summary of experiments in animal models.

Tumor type	Animal models	Results	Ref.
Glioblastoma	female BALB/C nude mice	↑ BDNF-AS +↑ PABPC1: ↓ tumor growth, ↑ survival time	[11]
Prostate cancer	athymic nu/nu mice	↑ BDNF-AS: ↓ tumor volume	[13]
Cervical cancer	male athymic nu/ nu mice	↑ BDNF-AS: ↓ tumor growth	[14]
Breast cancer	nude mice	↑ BDNF-AS: ↑ tumor growth, ↑ resistant to tamoxifen	[15]

In prostate cancer cells, lentivirus-induced BDNF-AS up-regulation has suppressed cell proliferation and invasiveness [13]. Lentivirus-mediated over-expression of this lncRNA has been shown to exert similar anti-proliferative effects in SiHa and DoTc2-4510 cervical cancer cells. Moreover, BDNF over-expression could reverse the anti-cancer effect of BDNF-AS in these cells, suggesting a possible mechanism for anti-proliferative effects of BDNF-AS in cervical cancer [14].

In breast cancer cells, expression of BDNF-AS has been found to be induced by a MEF2A-regulated enhancer. BDNF-AS serves as a scaffold to increase degradation of RNH1 through a TRIM21-mediated ubiquitination mechanism. Moreover, BDNF-AS stops RNH1-regulated and RISC-associated mTOR transcript decay, thus supporting induction of mTOR pathway. Notably, BDNF-AS-associated induction of tamoxifen resistance could be reversed by mTOR inhibitor, but not PI3K inhibitor [15]. Table 1 shows summary of experiments in cancer cell lines regarding the role of BDNF-AS.

2.2. Experiments in animal models

Experiments in animal models of glioblastoma have shown that up-regulation of BDNF-AS-stabilizing factor PABPC1 along with BDNF-AS up-regulation lead to decreased tumor size and the longer survival times [11]. While in cervical [13] and prostate cancers [14], up-regulation of BDNF-AS has decreased tumor growth, this lncRNA could enhance tumor growth and tamoxifen resistance in breast cancer [15]. Table 2 shows summary of experiments in animal models.

2.3. Experiments in clinical samples

Except for a single study in breast cancer which could not detect significant difference in expression of BDNF-AS between cancerous and non-cancerous samples [5], almost all other studies have reported down-regulation of BDNF in neoplastic tissues compared with non-neoplastic samples from the same origin (Table 3). In osteosarcoma patients, down-regulation of BDNF-AS has been associated with advanced Enneking stage, larger tumor dimension and poor outcome. Moreover, BDNF-AS has been recognized an independent prognostic factor for prediction of overall survival [9]. In prostate cancer, down-regulation of BDNF-AS has been associated with poor prognosis and short overall survival, indicating a role for this lncRNA as a potential prognostic marker in this malignancy [13]. BDNF-AS up-regulation in breast cancer tissues has been correlated with hormone receptor-positive status but poor outcomes in both hormone receptor-positive and triple negative breast cancer patients [15]. Table 3 shows summary of experiments in clinical samples regarding the role of BDNF-AS.

2.4. BDNF-AS in non-neoplastic conditions

In order to assess the impact of BDNF-AS in the pathoetiology of acute spinal cord injury, Zhang et al. have established a rat model of this disorder as well as a hypoxic cellular model for conduction of functional studies. They have reported up-regulation of BDNF-AS, PRDM5 and c-caspase 3, while down-regulation of miR-130b-5p in injured animals and neurons cultured in hypoxic conditions. BDNF-AS silencing has suppressed apoptosis of neuronal cells. This lncRNA could function as a molecular sponge for miR-130b-5p in neurons to enhance expression of PRDM5 in these cells. Thus, BDNF-AS/miR-130b-5p/PRDM5 axis has been suggested as a target for therapeutic interventions in acute spinal cord injury [6]. Another experiment in dorsal root ganglion neurons treated with the local anesthetic bupivacaine has shown up-regulation of BDNF-AS during the course in induced neurotoxicity. BDNF-AS silencing has enhanced neurite outgrowth, decreased neuron apoptosis, and reduced activity of phosphorylated TrkB signaling in this cellular model of neurotoxicity. Thus, BDNF-AS has a possible role in neurotoxic effects of local anesthetics via modulation of neurotrophin TrkB signaling [7].

Fan et al. have established an MPTP-induced mouse model of Parkinson's disease as well as the MPP+-induced SH-SY5Y cell model of this condition. They have reported up-regulation of BDNF-AS in both animal and cell models of this disorder, parallel with down-regulation of miR-125b-5p. Up-regulation of BDNF-AS has been correlated with the MPP+ levels. BDNF-AS silencing has enhanced cell proliferation, while inhibiting both apoptosis and autophagy of SH-SY5Y cells exposed to MPP+. In animal models, BDNF-AS silencing has increased the number of TH positive neurons and suppressed autophagy. Functional studies have revealed that these effects are mediated through sponging miR-125b-5p [18].

Guo et al. have exposed PC12 cells to $A\beta_{25–35}$ in order to establish cell models of Alzheimer's disease. $A\beta_{25–35}$ could increase BDNF-AS levels, while decreasing BDNF in these cells. These effects have been accompanied by reduction of cell viability and induction of apoptosis of PC12 cells. BDNF-AS silencing has enhanced levels of BDNF in $A\beta_{25–35}$-treated PC12 cells, increased their viability and suppressed their apoptosis as

Table 3
Summary of experiments in clinical samples (ANCTs: adjacent non-cancerous tissues, OS: Overall survival, RFS: Relapse-free survival).

Tumor type	Samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis (impact of BDNF-AS down-regulation)	Univariate/Multivariate cox regression	Association of low expression BDNF-AS with Clinicopathologic characteristics	Ref.
Colorectal cancer (CRC)	20 pairs of CRC tissues and ANCTs	low	–	–	–	[8]
Osteosarcoma	35 pairs of cancer tissues and ANCTs	low	–	–	–	[9]
	114 cancer samples and 35 paired ANCTs	low	–	Enneking stage, large tumor size, and BDNF-AS low expression were indicated to be unfavorable prognostic factors for OS.	advanced Enneking stage, and large tumor size	
Oesophageal cancer (EC)	54 pairs of EC tissues and ANCTs	low	–	–	–	[10]
Glioblastoma	–	low	–	–	–	[11]
	50 GBM tissues and normal brain tissues	low	–	–	–	[12]
Prostate cancer	114 cancer samples and ANCTs	low	Worse OS	–	high Gleason score, advanced clinical stage, and positive lymph-node metastasis	[13]
Cervical cancer (CC)	125 epithelial cervical tissues and non-cancer tissues	low	–	–	–	[14]
Gastric cancer	30 tumor tissues and ANCTs	low	–	–	There was a trend toward upregulation of BDNF-AS in tumors with lymphatic/vascular invasion.	[16]
Breast cancer (BC)	GEO analysis: (GSE98931)	low	Worse RFS and OS	–	–	[17]
	162 cases of BC tissue	lower in the endocrine-sensitive breast tissues compared with the TNBC and endocrine-resistant cancer tissues	–	–	positive correlation in endocrine-resistant BC	[15]
	54 pairs of BC tissues and ANCTs	–	–	–	Its expression was associated with tumor grade and mitotic rate.	[5]

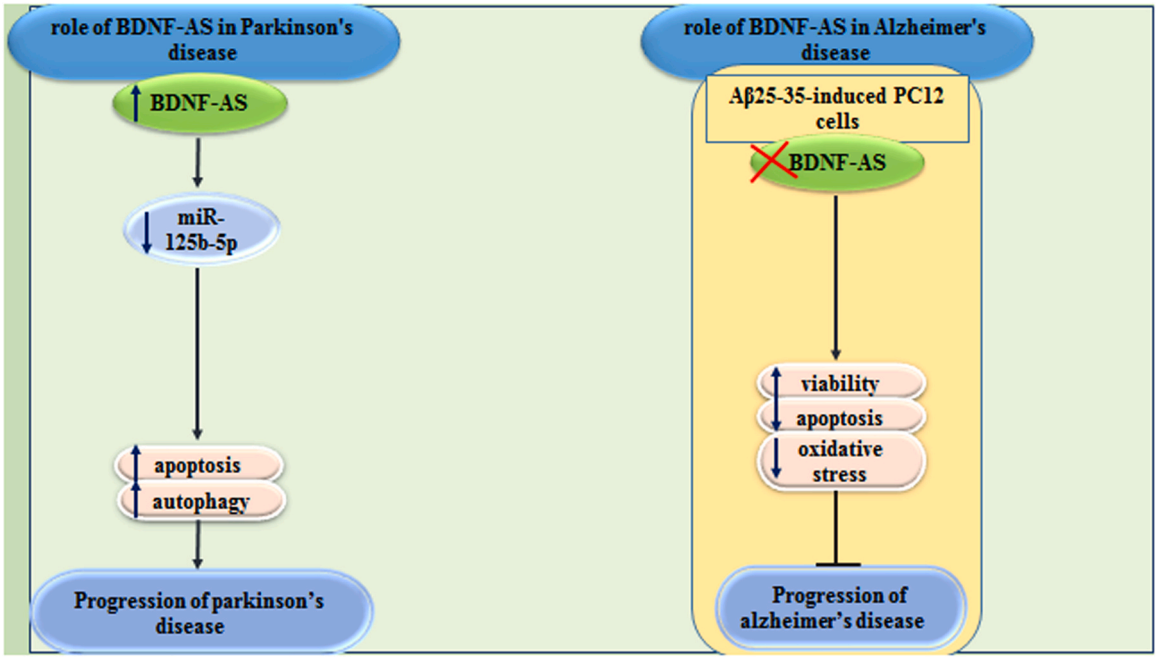

Fig. 3. Role of BDNF-AS in the pathogenesis of Parkinson's and Alzheimer's diseases.

being evident by suppression of the release of Cytochrome C, reduction of levels cleaved caspase-3 and Bax, while elevation of Bcl-2 levels. Moreover, BDNF-AS silencing has decreased reactive oxygen species intensity and MDA level, but increased SOD and CAT activities [19]. Fig. 3 shows the role of BDNF-AS in the pathogenesis of Parkinson's and Alzheimer's diseases.

Table 4
BDNF-AS in non-neoplastic conditions.

Disorder type	Targets/Regulators and signaling pathways	Cell line/animal models	Function	Ref.
Acute spinal cord injury (ASCI)	miR-130b-5p, PRDM5	AGE1.HN, PC12/male Sprague-Dawley (SD) rats	Δ BDNF-AS: ↓ apoptosis, ↓ c-caspase 3 expression, ↑ neural functional recovery	[6]
Parkinson's disease (PD)	miR-125b-5p	SH-SY5Y/PD mice	↑ BDNF-AS: ↑ MPP+-induced autophagy, ↑ MPP+-induced apoptosisΔ BDNF-AS: ↓ autophagy	[18]
Alzheimer's disease (AD)	–	PC12	Δ BDNF-AS: ↑ viability, ↓ apoptosis, ↓ release of Cyt C, ↓ cleaved caspase-3 and Bax, ↓ ROS intensity and MDA content, ↑ activities of SOD and CAT	[19]
Ischemic injury	BDNF, TNF-α, IL-2, IL-6	RGCs	Δ BDNF-AS: ↑ survive of RGCs against ischemia	[20]
Diabetic retinopathy	BDNF	ARPE-19	50 mM D-glucose: ↑ BDNF-AS and ↑apoptosis	[21]
Osteoporosis	–	BMMSCs	↑ BDNF-AS: ↑ proliferation, ↓ osteogenic differentiation	[25]
Neurotoxicity in dorsal root ganglion neurons	TrkB signaling pathway	DRG	Δ BDNF-AS: ↑ neurite regrowth in local anesthetic injured DRG neurons, ↓ apoptosis	[7]
Neurotoxicity in neural stem cell derived neurons	TrkB signaling pathway	differentiated mouse embryonic neural stem cells	Δ BDNF-AS: ↓ apoptosis after ketamine-induced neurotoxicity, ↑ neurite regrowth in ketamine-injured mouse embryonic neural stem cells-derived neurons, ↑ TrkB signaling pathway in ketamine-injured mouse embryonic neural stem cells-derived neurons	[22]
Heart attack	BDNF, VEGF, Akt	Murine neonatal cardiomyocytes	Δ BDNF-AS: ↑ cardiomyocyte survival under H/R condition, ↑ BDNF/VEGF/Akt in H/R-treated cardiomyocyte	[23]
Hypoxia/reoxygenation-induced nerve cell apoptosis	BDNF/TrkB/PI3K/Akt signaling pathway	human cortical neurons, human astrocytes	Δ BDNF-AS: ↓ H/R-induced neuron apoptosis	[24]

In addition, BDNF-AS has a role in retinal ganglion cells ischemia through suppression of BDNF. Functionally, BDNF-AS could directly target BDNF transcript in these cells to regulate expression of BDNF and its related genes. BDNF-AS silencing has enhanced viability and reduced the number of apoptotic retinal ganglion cells cultured in oxygen and glucose deficiency condition [20].

Another experiment in high glucose-treated retinal pigment epithelial cells has shown down-regulation of BDNF while up-regulation of BDNF-AS. BDNF-AS silencing has ameliorated D-glucose-induced apoptosis and enhanced expression of BDNF in retinal pigment epithelial cells. Thus, BDNF-AS can partake in the process of D-glucose-induced apoptosis in diabetic retinopathy via down-regulating BDNF [21].

Up-regulation of BDNF-AS has also been demonstrated in ketamine-injured mice embryonic neural stem cell-originated neurons. This up-regulation has been accompanied by down-regulation of BDNF. BDNF-AS silencing has reduced neuron apoptosis, increased neurite outgrowth, and enhanced activity of phosphorylated TrkB signaling following ketamine-induced neurotoxicity [22].

BDNF-AS silencing has also rescued cell death and apoptosis in hypoxia/reoxygenation injured cardiomyocytes of mice [23]. Similarly, in hypoxia/reoxygenation-injured neurons, BDNF-AS silencing has decreased apoptosis via modulation of BDNF/TrkB/PI3K/Akt signaling [24]. Table 4 shows role of BDNF-AS in non-neoplastic conditions.

3. Discussion

As a naturally occurring antisense, BDNF-AS can regulate expression of BDNF [3]. Although this mode of action is the most probable mechanism of involvement of BDNF-AS in neurological disorders, it is not the main mechanism of its participation in the carcinogenic processes. Experiments in different cancer cells have shown direct/indirect functional interactions between BDNF-AS and a variety of molecules such as GSK-3β, EZH2, miR-214, PABPC1, RAX2, DLG5, p53 and ADAR as well as RNH1/TRIM21/mTOR signaling. Except for breast cancer in which different studies have reported conflicting results regarding the role of BDNF-AS, experiments in other types of cancers point to a tumor suppressive role for this lncRNA.

Although BDNF-AS has been shown to repress expression of BDNF sense transcript by changing chromatin configuration at the BDNF region [3], recent studies have suggested positive correlations between BDNF expression and BDNF-AS expression. This pattern of correlation has been detected in gastric cancer tissues [16] and breast cancer tissues [5]. More recently, Ishima et al. have demonstrated down-regulation of expression of BDNF transcripts in induced pluripotent stem cells (iPSC) of patients with bipolar disorder, in spite of higher levels of this transcript in neural stem cells (NSCs) of these patients compared with control subjects. On the other hand, authors have reported similar levels of BDNF-AS transcripts in both iPSC and NSC between patients and controls. While expression of BDNF transcript has been decreased in the BA46 of patients with bipolar disorder, its expression in the corpus callosum and BA8 regions has not been different between cases and controls. Moreover, expression levels of BDNF-AS transcripts in these brain regions have been similar between cases and controls. Most notably, authors have reported significant positive correlations between levels of BDNF and BDNF-AS transcripts in the autopsy brain specimens [26]. These investigations cast doubt on the reported suppressive role of BDNF-AS on expression of BDNF.

Three independent studies have simultaneously assessed expressions of BDNF and BDNF-AS in cancer cells. In gastric cancer, expressions of both genes tended to be lower in gastric cancer tissues in comparison with non-cancerous samples [16]. In breast cancer tissues, expressions of these genes have been positively correlated [5]. This pattern of correlation in cancer tissues is not in accordance with the inhibitory role of BDNF-AS on expression of BDNF, further supporting the speculation that BDNF-AS affect carcinogenesis through BDNF-independent routes. However, in cervical cancer, expression of BDNF-AS has been negatively correlated with its sense transcript. In this type of cancer, in vitro studies has supported the impact of BDNF-AS in suppression of BDNF expression [14].

In non-neoplastic conditions, the role of BDNF-AS has mostly assessed in neurons. In these cells, BDNF-AS silencing has led to suppression of apoptosis and enhancement of neuron survival through up-regulation of BDNF. Similar effects have been demonstrated in cardiomyocytes.

Taken together, BDNF-AS has prominent roles in the pathoetiology of both neoplastic and non-neoplastic conditions. In the former types of disorders, it exerts its role mainly through BDNF-independent routes; while in the latter group of disorders, BDNF mediates its effects.

Authors statement

SGF wrote the draft and revised it. MT designed and supervised the study. TK and MG collected the data and designed the figures and tables. All the authors read and approved the submitted version.

Conflict of interest statement

The authors declare they have no conflict of interest.

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