Review

DOI: 10.5582/bst.2024.01305

Growth and differentiation factor 15: An emerging therapeutic target for brain diseases

Yingying Zhou[1,§], Lei Dou[1,§], Luyao Wang[1], Jiajie Chen[1], Ruxue Mao[1], Lingqiang Zhu[2], Dan Liu[3], Kai Zheng[1,*]

[1] Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China;
[2] Department of Pathophysiology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China;
[3] Department of Medical Genetics, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.

SUMMARY: Growth and differentiation factor 15 (GDF15), a member of the transforming growth factor-β superfamily, is considered a stress response factor and has garnered increasing attention in recent years due to its roles in neurological diseases. Although many studies have suggested that GDF15 expression is elevated in patients with neurodegenerative diseases (NDDs), glioma, and ischemic stroke, the effects of increased GDF15 expression and the potential underlying mechanisms remain unclear. Notably, many experimental studies have shown the multidimensional beneficial effects of GDF15 on NDDs, and GDF15 overexpression is able to rescue NDD-associated pathological changes and phenotypes. In glioma, GDF15 exerts opposite effects, it is both protumorigenic and antitumorigenic. The causes of these conflicting findings are not comprehensively clear, but inhibiting GDF15 is helpful for suppressing tumor progression. GDF15 is also regarded as a biomarker of poor clinical outcomes in ischemic stroke patients, and targeting GDF15 may help prevent this disease. Thus, we systematically reviewed the synthesis, transcriptional regulation, and biological functions of GDF15 and its related signaling pathways within the brain. Furthermore, we explored the potential of GDF15 as a therapeutic target and assessed its clinical applicability in interventions for brain diseases. By integrating the latest research findings, this study provides new insights into the future treatment of neurological diseases.

Keywords: GDF15, Alzheimer's disease, Parkinson's disease, glioma, ischemic stroke

1. Introduction

The number of patients with brain disease in European populations almost doubled from 2010 (179 million) to 2017 (324 million) (*1,2*). The diseases with the top five medical costs per patient are multiple sclerosis (MS), brain tumors, stroke, dementia, and Parkinson's disease (PD) (*1*). In 2017, brain diseases caused 1.2 million deaths in European populations, the primary causes of which were dementia and stroke (*2*). Brain diseases are undoubtedly urgent and major challenges for neuroscientists. Therefore, a detailed understanding of the mechanism of brain diseases is crucial for the development of effective therapeutic strategies.

Growth and differentiation factor 15 (GDF15), a key cellular stress responsive factor, is a member of the transforming growth factor-β (TGF-β) superfamily of proteins and is widely distributed throughout peripheral tissues and the brain. The basal expression of GDF15 is low; however, its expression can be strongly induced in response to cellular stress following tissue injury (*3*). GDF15 expression is significantly increased in individuals with various neurological diseases (*4,5*), including Alzheimer's disease (AD), PD, amyotrophic lateral sclerosis (ALS), MS, glioma and acute ischemic stroke (*6,7*). Notably, identifying whether the overall physiological functions of upregulated GDF15 play protective or harmful roles in brain diseases is important. A body of evidence has indicated that GDF15 helps suppress the inflammatory response, regulates energy homeostasis and body weight, protects endothelial cell function, and inhibits the growth of early cancers but facilitates the proliferation and invasion of advanced cancers (*8-10*). However, the functions of GDF15 and the associated signaling pathways in nerve cells and brain diseases are poorly understood.

Additionally, several epidemiological studies have revealed the relationships between high levels of GDF15

and the risks of dementia and AD (*11*), PD (*12*), and the severity of MS (*13*). In contrast, based on current experimental studies, upregulated GDF15 has beneficial effects on the pathogenesis of neurodegenerative diseases (NDDs), such as AD (*14,15*), PD (*16,17*), and Huntington's disease (HD), through many pathways (*18*). Similarly, contradictory findings concerning the effects of GDF15 on glioma have been reported. On the one hand, GDF15 promotes the proliferation and invasion of cancer cells and is involved in immune escape (*19-21*). On the other hand, GDF15 can be transcriptionally activated by the tumor suppressor gene p53 (*22*). Given these contrasting discoveries, the physiological roles of GDF15 in brain diseases appear to be much more complicated than expected.

Importantly, previous studies have reported that exogenous GDF15 promotes the clearance of amyloid-β (Aβ), inhibits neuroinflammation and apoptosis, and increases synaptic activity in an AD model (*14,15,23,24*). GDF15 is also essential for maintaining the survival of midbrain dopaminergic neurons and contributes to alleviating PD-like motor symptoms (*16,17*). In addition, decreasing the level of GDF15 derived from glioma inhibits tumor growth (*19,20*). GDF15 expression in tumors is associated with the regulation of the immune microenvironment (*25*). Neutralizing antibodies against GDF15 and the GDF15 receptor, glial cell-derived neurotrophic factor family receptor α-like (GFRAL), are useful for relieving cachexia in patients with advanced cancer through increased food intake(*26*). GDF15 deficiency also has beneficial effects on atherosclerotic plaque stabilization and the inhibition of plaque progression (*27,28*), which provides a theoretical foundation for the clinical application of GDF15 in preventing cerebrovascular diseases. A series of robust studies have suggested that GDF15 is a promising potential therapeutic target for the treatment of brain diseases. Therefore, in this review, we systematically summarize the effects of GDF15 and the potential mechanisms involved in brain diseases. Moreover, we comprehensively evaluated the clinical applicability of GDF15 as a new therapeutic target for treatment of brain diseases.

2. GDF15-related mechanisms

2.1. Synthesis and secretion of GDF15

GDF15 is also known as macrophage inhibitory cytokine 1 (MIC-1) and nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1). The human GDF15 locus is located on chromosome 19p12-13.1, as shown by fluorescence *in situ* hybridization, and comprises only two exons of 309 bp and 891 bp separated by a 2.9-kb intron (*29*). The GDF15 mRNA contains a long open reading frame encoding a protein of 308 amino acids, including a signal peptide of 29 amino acids, a propeptide of 165 amino acids and a mature peptide of 114 amino acids (*30*). GDF15, a member of the TGF-β superfamily, presents high sequence homology and a conserved nine-cysteine region (*31*). The crystal structure of GDF15 reveals an unexpected disulfide bonding configuration that contains a novel (1→2, 3→7) disulfide arrangement not previously identified for the other nine cysteine family members (1→3, 2→7) (*32*). The 6th cysteine forms a disulfide bond with a free 6th cysteine from another pro-GDF15 monomer to form a pro-GDF15 homodimer (*33*). Through proteolytic cleavage of the dimeric pro-GDF15 precursor at a furin-like site, mature GDF15 is secreted as a 25 kDa disulfide-linked homodimer in the endoplasmic reticulum (*33,34*). Mature GDF15 is subsequently secreted into the extracellular matrix and can be detected in the blood and cerebrospinal fluid (CSF). In addition, matrix metalloproteinase-26 (MMP-26) and paired basic amino acid-cleaving enzyme 4 (PACE4) mediate the maturation of pro-GDF15 (*35*). Unlike other TGF-β superfamily proteins, the propeptide is not required for proper GDF15 folding and secretion (*33*). We knew very little about the function of pro-GDF15 before Min KW *et al.* reported that pro-GDF15 is also expressed in the nucleus and plays a role in transcriptional regulation by interrupting the DNA-binding activity of the small mother against decapentaplegic (Smad) complex, as shown in Figure 1 (*36*). They reported that nuclear pro-GDF15 attenuates TGF-β signaling through the interruption of DNA binding to the Smad complex upon TGF-β stimulation

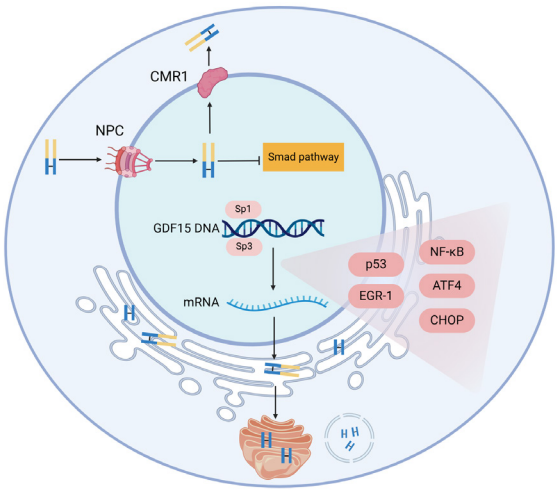

Figure 1. Synthesis and transcriptional regulation of GDF15. The basal physiological transcriptional regulation of GDF15 is mediated by Sp1 and Sp3. Pro-GDF15 monomer consists of a propeptide (yellow short-lines) and a mature peptide (blue lines). Two pro-GDF15 monomers form a homodimer linker by disulfide bond (black lines). The maturation of pro-GDF15 occurs in endoplasmic reticulum, through proteolytic cleavage of the pro-GDF15 dimeric at a conserved furin-like site. Pro-GDF15 can translocate from cytoplasm to nucleus by nuclear pore complex (NPC), followed by its exportation by chromosome region maintenance 1 (CMR1). In addition, nuclear pro-GDF15 interrupts the DNA-binding activity of Smad complex.

(*36*). Moreover, the antitumorigenic activity of GDF15 is increased by blocking the translocation of GDF15 from the cytoplasm to the nucleus (*37*). Whether this regulation of GDF15 translocation is beneficial for alleviating neurological pathological changes is worthy of further in-depth study.

2.2. Transcriptional regulation of GDF15 expression

A promoter analysis revealed a TATA-like motif (TATAAA) upstream of the ATG start codon in the *GDF15* gene, which is conserved among the human, rat and mouse genes (*31,38*). Numerous transcription factors, including p53, early growth response-1 (EGR-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Sp1 (specificity protein 1), Sp3 (specificity protein 3), and activator proteins 1 and 2, have been identified as transcriptional regulators of GDF15 expression (*22,38-40*).

Under healthy conditions, the basal physiological transcriptional regulation of GDF15 is mediated by Sp1 and Sp3, and the level of *GDF15* gene expression depends on the availability of specific proteins and cofactors (*40*). Researchers cloned the GDF15 promoter region and revealed that the region between -133 and +41 base pairs contains three Sp1 binding sites, which confer basal transcription-specific activity of GDF15 expression (*40*).

p53, a tumor suppressor gene, can transactivate the GDF15 promoter in a p53 dose-dependent and p53 binding site-dependent manner (*22*). At least two p53 binding sites are present in the GDF15 promoter, both of which can transactivate the GDF15 promoter (*22*). In glioma cell lines, GDF15 mRNA and protein expression is decreased in cell lines with p53 mutations or deletions (*41*). GDF15 is an important intercellular mediator of p53-mediated suppression of tumor function. Overexpression or pharmacological induction of p53 strongly upregulates GDF15 expression in lung, osteosarcoma, and prostate cancer cells and in breast cancer cell lines (*42-44*). However, p53-induced expression of GDF15 also confers resistance to cisplatin in ovarian tumors (*45*). The biological functions of GDF15 induced by p53 in different tumors may be complex and inconsistent. The phenotypes likely depend on the specific type of cancer cell and stage.

EGR-1, which regulates differentiation, growth, and apoptosis and is significantly upregulated in patients with AD and glioma (*46,47*), is another transcriptional regulator of GDF15 expression that contains three zinc finger domains. EGR-1 increases GDF15 promoter activity and expression in a dose-dependent manner and thereby contributes to silibinin-induced apoptosis in HT29 colon carcinoma cells (*48*). Another study reported that troglitazone induces GDF15 expression and correlates with EGR-1 levels; cotransfection and gel shift assays suggested that EGR-1-binding sites are located within the -73 to -51 region of the GDF15 promoter (*39*). Furthermore, methylation of the GDF15 promoter at the -53 site blocks EGR-1 binding and thereby suppresses GDF15 induction (*49*).

Furthermore, NF-κB has been validated as a direct transcriptional regulator of GDF15 that suppresses macrophage-mediated immune surveillance during the early stages of tumorigenesis (*50*). GDF15 is also regulated by circular RNAs, long noncoding RNAs, microRNAs, hormones and drugs (*24,51*). In primary mouse hepatocytes, metformin stimulates the secretion of GDF15 by increasing the expression of activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) (*52*). ATF4 binds to the GDF15 promoter and positively regulates GDF15 expression, which suppresses lipopolysaccharide-induced inflammation in human nasal epithelial cells (*53*). Importantly, ATF4 levels are increased in both the AD-affected brain and an AD mouse model (*54*). Under glucose deprivation, ATF4-dependent fructolysis is required to maintain glioblastoma multiforme cell growth (*55*). These results indicate that the ATF4/GDF15 pathway possibly contributes to the pathogenesis of AD and glioblastoma.

2.3. The receptor of GDF15

GFRAL has been identified as the high-affinity receptor of GDF15, which requires the coreceptor rearranged during transfection (RET) to elicit intracellular signaling in response to GDF15 stimulation (*56*). GFRAL is encoded by the *GFRAL* gene, which is located on the short arm of chromosome 6 in humans; it consists of 9 exons and encodes a 394 amino acid protein (*31*). GFRAL is a distant member of the TGF-β family of receptors, and GDF15 binds to this receptor with high affinity but has no interaction with other members of the TGF-β family of receptors (*57*). *In vivo*, GDF15 induces the activation of neurons in the area postrema (AP) and nucleus tractus solitarius (NTS), which coexpress GFRAL and RET; then, the activated GFRAL–RET heterodimer induces stimulatory phosphorylation of extracellular signal-regulated kinase (ERK) (*32*). *In vitro*, in a cell line with stable overexpression of human GFRAL and RET, the phosphorylation level of protein kinase B (AKT) was also increased (*56*).

Current findings concerning tissues expressing GFRAL are inconsistent. Several previous groups reported that the GFRAL transcript is only detected in the brain and is not detected in peripheral tissues. In terms of the temporal and spatial characteristics of mRNA, the GFRAL mRNA level in the cerebral cortex and hippocampus peaks at birth and then decreases, whereas in adult mice, GFRAL transcripts are relatively abundant in the substantia nigra, hippocampus and spinal cord (*58*). However, a series of subsequent studies provided convincing evidence that GFRAL protein expression occurs only in neurons in the AP and NTS

(*32,56,57,59*). This expression distribution is conserved in rodents, monkeys and humans(*59*). These studies also showed that GDF15-mediated reductions in food intake and body weight in obese mice are abolished in GFRAL knockout mice (*56,57,59*). Emmerson *et al.* reported that increased membrane-type I matrix metalloproteinase (MT1-MMP) activation induced by obesity is an endogenous negative regulator of GFRAL in the context of obesity (*60*). In addition, treatment with a neutralizing monoclonal antibody against GFRAL prevented the cisplatin-induced decrease in wheel running and accelerated recovery, indicating that the GDF15/GFRAL axis mediates cisplatin-induced fatigue in mice (*61*). Importantly, recent study not only confirmed the results for GFRAL expression in the brainstem but also revealed that the GFRAL protein is detectable in the prefrontal cortex, hippocampal CA1 region, arcuate nucleus and peripheral tissues (including the liver, small intestine, fat, kidney and muscle tissues) (*62*). In addition, GFRAL is an endothelial cell receptor for GDF15 because GDF15 signaling events in endothelial cells are blocked by small interfering RNA-mediated knockdown of GFRAL (*63*).

GDF15, with various biological functions, is widely expressed in the periphery and brain; thus, the widespread expression of its receptor is plausible. The current understanding of the physiological function of the GDF15/GFRAL axis focuses solely on its metabolic effects. We urgently need to determine the distribution of GFRAL expression and the mechanism of action of the GDF15/GFRAL axis under physiological and pathological conditions. In addition, whether other signaling pathways, rather than associations with the GFRAL-RET heterodimer, are involved is another interesting issue.

2.4. Biological functions of GDF15 in brain diseases

GDF15 is expressed at relatively low levels in healthy individuals. However, GDF15 expression can be strongly induced in response to cellular stress during tissue injury (*3*). As shown in Figure 2, GDF15 is upregulated in patients with various brain diseases, which is likely associated with the activation of the transcription factors EGR-1, p53, NF-κB, ATF4, and CHOP, resulting in increased survival of neurons and neurogenesis, a reduced inflammatory reaction, increased repair ability after injury, the regulation of energy metabolism, and the promotion or inhibition of tumor growth. In Table 1, we provide a detailed summary of the effects of GDF15 and the associated potential mechanisms in brain diseases.

In humans, the physiological concentration of GDF15 in the serum ranges from 200 to 1200 pg/mL (*64*), with a positive correlation with age (*65*). The CSF GDF15 level is positively correlated with the serum GDF15 level in the same subject (*66*). The author also reported that mature GDF15 protein expression (predominantly localized in neurons) in the hippocampus of older individuals is greater than that in adults, but no differences were observed in the cortex or cerebellum (*66*). GDF15 may be involved in the regulation of hippocampus-related learning and memory deficits during aging and dementia.

Healthy neonatal and adult rat brain synthesizes GDF15 at the site of choroid plexus epithelial cells, where the GDF15 mRNA can be detected *via in situ* hybridization, after which the protein is secreted into the CSF to nourish the brain and spinal cord neurons (*3,17,67*). In addition, the GDF15 protein can be visualized in ependymal cells and the subventricular zone (SVZ) (*3*). The SVZ is one of the major regions involved in adult neurogenesis (*68*). GDF15 is involved in neurogenesis in the developing brain (*69*); notably, exogenous GDF15 has also been shown to promote hippocampal adult neural stem cell (NSC) proliferation and neuronal differentiation in an AD model (*23*).

Following a cryogenic lesion of the cortex, the GDF15 mRNA and protein are highly upregulated in regions adjacent to the lesion site and the dorsal thalamus (*3*). Colocalization analysis suggested that the upregulated GDF15 protein is predominantly

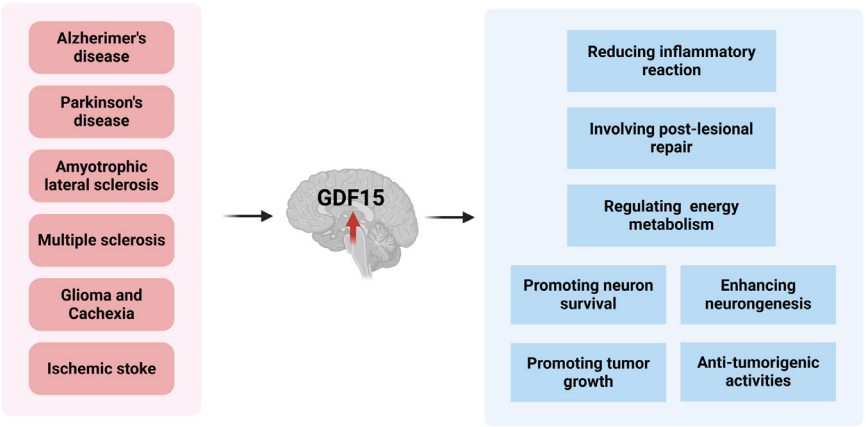

Figure 2. The biological functions of GDF15 in brain diseases.

Table 1. The effects of GDF15 and associated potential mechanisms on brain diseases

Diseases	Effects	Mechanisms	References
AD	Aβ clearance↑	Increasing the expression of IDE in microglia through TGFβRII; Upregulating IDE and NEP through activation of AKT/GSK-3β/β-catenin pathway	(*14*,*15*)
	Synaptic activity↑	Unknown	(*23*)
	Hippocampal NSC proliferation and differentiation↑	Promoting EGFR signaling	(*23*,*69*)
	Neuronal apoptosis and neuroinflammation↓	Activating the AKT/GSK-3β/β-catenin pathway; Upregulating SIRT1 expression to inhibit the Nrf2/HO-1 axis	(*15*,*24*)
	Oxidative stress↓	Upregulating SIRT1 expression to inhibit the Nrf2/HO-1 axis	(*24*)
	Mitochondria function↑	Unknown	(*66*)
PD	Dopaminergic neurons survival↑	Probably acts directly on neurons but not glial cells	(*16*,*17*)
	Microglial response↑	Unknown	(*16*)
	Neuronal apoptosis↓	Upregulating PGC1α *via* p53, dependent on Akt/mTOR phosphorylation	(*84*)
	Mitochondria function↑	Upregulating PGC1α *via* p53; regulating the PI3K/Akt signaling pathway	(*83*,*84*)
MS	Neuroinflammation↓	Unknown	(*13*)
HD	ER stress-induced apoptosis↓	Glucocorticoids inhibit the transcription of GDF15	(*18*)
Protumorigenic activity of GDF15 in glioma	Migration and invasion↑	Decreasing GDF15 expression inhibits the NF-κB pathway; The invasive capacity is coordinately regulated by RSU-1 and GDF15	(*20*,*21*); (*50*,*92*); (*94*)
	Proliferation↑	Unknown	(*20*,*21*)
	Immune escape↑	Inhibiting maturation and function of DCs; Suppressing infiltration and cytotoxicity of T cells, B cells, and NK cells; Interfering with LFA-1/β2-integrin-mediated T cells adhesion to activated endothelial cells	(*19*),*20*); (*25*,*100*)
	Radioresistance↑	Regulated by the transcription factor WWTR1/TAZ; activating the ERK1/2 pathway	(*93*,*98*)
Cancer cachexia	Food intake↓	Activating hypothalamic neurons through the formation of the GDF15-GFRAL-RET complex	(*26*,*103*)
Ischemic stroke	Atherosclerotic plaque stability↓	GDF15 deficiency inhibits CCR2-mediated macrophage chemotaxis	(*28*)
	Atherosclerotic plaque progression↑	GDF15 deficiency suppresses the IL-6-dependent inflammatory response and decreases cell apoptosis	(*27*)
	Platelet aggregation↓	In DVT, GDF15 reduces platelet aggregation induced by ADP in concentration-dependent manner	(*114*)
	Angiogenesis↑	In acute MI, the activation of GDF15-TRPV4 axis can promote angiogenesis	(*115*)

Abbreviations: ↑ (enhancement); ↓ (inhibition); Alzheimer's disease (AD); Amyloid-β (Aβ); Neural stem cell (NSC); Insulin-degrading enzyme (IDE); Transforming growth factor-β receptor II (TGFβRII); Neprilysin (NEP); Epidermal growth factor receptor (EGFR); Silent information regulator sirtuin 1 (SIRT1); Nuclear respiratory factor (Nrf2); Heme oxygenase 1 (HO-1); Peroxisome proliferator-activated receptor γ co-activator-1 alpha (PGC1α); Parkinson's disease (PD); Phosphoinositide 3-kinase (PI3K); Protein kinase B (AKT); Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); Ras suppressor 1 (RSU-1); Glycogen synthase kinase 3β (GSK-3β); Multiple sclerosis (MS); Huntington's disease (HD); Endoplasmic reticulum (ER); Dendritic cells (DCs); Natural killer cells (NK); Lymphocyte function-associated antigen 1 (LFA-1); WW Domain containing transcription regulator 1 (WWTR1); extracellular signal-regulated kinase (ERK); glial cell-derived neurotrophic factor family receptor α-like (GFRAL); rearranged during transfection (RET); C-C chemokine receptor type 2 (CCR2); Interleukin-6 (IL-6); Deep venous thrombosis (DVT); Adenosine diphosphate (ADP); Myocardial infarction (MI); Transient receptor potential vanilloid 4 (TRPV4)

expressed in lesioned neurons but is expressed in only a few microglia (approximately 15%), not astroglia (*3*). However, Mailk *et al.* found that GDF15 is an astrocyte-derived trigger of astrocyte remodeling associated with tight junction strengthening at the blood-brain barrier (*70*). Additionally, treatment with kainic acid increased GDF15 expression in activated astrocytes throughout the hippocampal region, and lipopolysaccharide (100 ng/mL) dramatically increased GDF15 expression in primary astrocytes in a time-dependent manner (*71*). GDF15 mRNA expression is strongly upregulated in the hippocampus and parietal cortex after an ischemic lesion caused by occlusion of the middle cerebral artery (*72*). A similar pattern of GDF15 induction was observed in a cell model of AD, in which GDF15 mRNA and protein levels were specifically increased in cells cocultured with Aβ-treated microglia (*14*). Thus, extensive evidence suggests that GDF15, a pivotal stress response cytokine, probably exerts positive effects on the repair of brain lesions.

Importantly, GDF15-deficient mice exhibit progressive postnatal losses of spinal cord motor and dorsal root ganglionic neurons, reaching an approximately 20% maximum at 6 months (*73*). Sensory

neurons in the dorsal root ganglia are also involved, whereas sympathetic neurons are not affected (*73*). This evidence suggests that GDF15 is an important trophic factor for motor and sensory neurons. Using GDF15 knockout mice, Day *et al.* observed that GDF15 is required for the reductions in food intake, body mass, fasting insulin and glucose intolerance caused by metformin in high-fat diet-fed mice (*52*). In addition, GDF15 deficiency exacerbates dopaminergic neuron death and reduces the microglial response in a 6-hydroxydopamine (6-OHDA) mouse model of PD (*16*). The effects of GDF15 on cancers are different and complex, partially depending on the specific type of cancer cell. However, in glioma, high GDF15 expression is an independent risk factor for the overall survival of patients with lower-grade gliomas (*21*), indicating that GDF15 predicts tumor progression (*19*). Moreover, many experimental studies support the protumorigenic functions of GDF15 in glioma.

3. The roles of GDF15 in neurological diseases

3.1. AD

AD is the most common NDD and is characterized by decreased learning and memory, the deposition and aggregation of Aβ, tau neurofibrillary tangles and neuronal loss. The potential pathogenic mechanisms of AD are not entirely clear. Accumulating evidence indicates that GDF15 is related to cognitive decline, all-cause dementia and the AD risk (*11,74-78*). GDF15 is also regarded as a biomarker of aging, and the circulating level of GDF15 is positively correlated with age (*65*). A relationship between serum GDF15 levels and cognitive performance and decline has been reported by Fuchs. T *et al.*, who investigated a large community-dwelling elder cohort and first reported the association of higher serum GDF15 levels with poorer global cognitive function; their results indicated that the serum GDF15 level is a biomarker of cognitive decline, and an analysis of receiver operating characteristic (ROC) curve revealed that a GDF15 level exceeding 2764 pg/ml was associated with a 20% chance of decline from normal cognition to mild cognitive impairment (MCI) or dementia (*11*). In addition, two recent studies involving plasma proteomics analysis of healthy adults revealed that GDF15 is one of the genes most strongly associated with the risk of AD and dementia (*74,78*). In general, GDF15 can be considered a biomarker of age-related cognitive dysfunction. However, the specific potential molecular mechanisms of this regulation are less well known. Conclusive evidence on whether elevated levels of GDF15 are helpful or harmful for cognitive performance is still unavailable.

The expression of mature GDF15 protein is upregulated in the frontal cortex and hippocampus of AD patients (*66*). Although this study did not discuss the effects and mechanisms of increased levels of endogenous GDF15 in the brains of AD patients, this protein is definitely not detrimental. Exogenous recombinant GDF15 leads to a decrease in Aβ plaque deposition in *in vitro* and *in vivo* models of AD, and this effect is abolished by treatment with a GDF15-specific siRNA(*14*). Increased GDF15 levels in individuals AD, which potentially indicate neural injury, do not likely represent a cause of the disease but rather a compensatory response to stresses. Increased GDF15 levels are likely a beneficial adaptive reaction to AD-related pathology.

Previous studies have elucidated the potential signaling pathways mediated by GDF15 in the

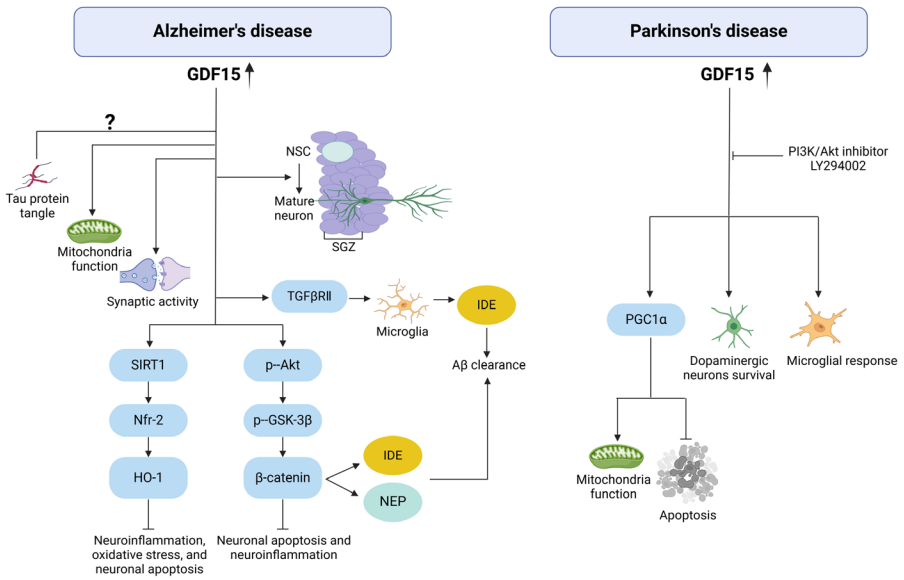

Figure 3. The effects and potential associated pathways of increased GDF15 in Alzheimer's disease and Parkinson's diseases. Neural stem cell (NSC); Subgranular zone (SGZ); Insulin-degrading enzyme (IDE); Transforming growth factor-β receptor II (TGFβRII); Neprilysin (NEP).

pathogenesis of AD (as shown in Figure 3). In APP/PS1 mice, human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) promoted endogenous adult hippocampal neurogenesis and synaptic activity through the secretion of the paracrine factor GDF15 (*23*). Notably, in the developing hippocampus, GDF15 promotes epidermal growth factor receptor (EGFR) expression in hippocampal precursors through the activation of active CXC chemokine receptor (CXCR) 4 and the regulation of the proliferation and migration of precursors (*69*). The inhibition of GDF15 expression in hUCB-MSCs *via* a GDF15 siRNA reduced the proliferation of NSCs, and this effect was restored by the addition of recombinant GDF15 (*23*). Another study revealed that hUCB-MSCs promote the ability of microglia to clear Aβ through the regulation of GDF15 secretion (*14*). Moreover, exogenous recombinant GDF15 injection in the hippocampus of 5XFAD mice led to an increase in Aβ degradation through increased insulin-degrading enzyme (IDE) expression in microglia (*14*). These researchers also reported that this process was mediated by TGF-β receptor type II, whereas Mullican *et al.* reported no interaction between the TGF-β family receptor and GDF15, except for GFRAL (*57*). More convincing studies are needed to support these findings. In Aβ42-treated SH-SY5Y cells, GDF15 derived from mesenchymal stem cells (MSCs) promoted the degradation of the Aβ42 protein, thereby increasing cell viability and suppressing apoptosis and inflammation through the activation of the AKT/ glycogen synthase kinase 3β(GSK-3β)/β-catenin pathway to upregulate neprilysin (NEP) and IDE (*15*). In addition, mitochondrial dysfunction has been implicated in the pathophysiology of AD(*26*), and GDF15 is likely involved in counteracting mitochondrial dysfunction and neuroinflammation in the AD-affected brain (*66*).

However, the abovementioned studies did not include behavioral experiments to validate improvements in learning and memory abilities. Although exogenous recombinant GDF15 promotes Aβ clearance in both cell and mouse models of AD, the function of endogenously unregulated GDF15 in the AD environment is still unclear. Pathological tau accumulation is another prominent characteristic of AD and is driven by Aβ plaque deposition (*79*). However, to date, no related studies on how GDF15 affects tau pathology in individuals with AD have been reported.

In contrast, Conte *et al.* reported that plasm GDF15 levels in AD patients are similar to those in controls without dementia (*80*). One study reported that GDF15 levels are decreased in both APP/PS1 mouse brains and Aβ-treated SH-SY5Y cells (*24*). We believe that these results should be interpreted with caution because the specific brain areas of APP/PS1 mice analyzed by Western blotting were not noted. The experimental materials and methods used for Aβ-treated cells were inconsistent with those used in previous studies (*14*). However, these studies also demonstrated the protective effects of GDF15 on AD, and overexpression of the GDF15 plasmid protected SHSY5Y cells from Aβ-induced inflammation, oxidative stress, and neuronal apoptosis through the silent information regulator sirtuin 1 (SIRT1)/ nuclear respiratory factor (Nrf2)/ heme oxygenase 1(HO-1) axis (*24*).

We believe that GDF15 expression in the brain likely increases in a compensatory manner under AD conditions to protect neurons from injury caused by AD-related pathology. The stresses that can lead to chronically elevated GDF15 expression may be the same as those that cause the pathogenesis of AD. However, under pathophysiological conditions, the compensatory effect is not sufficient to counteract such severe injury. In centenarians who do not present with cognitive impairment or neuropathological features of AD, functionally mature GDF15 is even more highly secreted than it is in AD patients (*66*). In these centenarian individuals, the higher expression of GDF15 than in AD patients may delay the onset of age-related diseases such as AD by decades (*66*). Thus, given the strong association between higher levels of GDF15 and poorer cognitive performance, the upregulation of GDF15 in patients with AD seems to be an unsuccessful attempt to address this issue. Therefore, GDF15 and its involved signaling pathways are potential new therapeutic targets for AD. Recently, GFRAL expression has been detected in the hippocampal CA1 region, but the function of the GDF15/GFRAL axis in the hippocampus of individuals with AD has not been fully elucidated. Whether targeting GFRAL can alleviate AD-related pathology is worthy of further investigation.

3.2. PD

PD is an age-related neurodegenerative disorder of unknown origin that ranks second only to AD in prevalence (*81*). PD neuropathology is characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta. The serum GDF15 level is significantly higher in PD patients than in healthy controls (*12,82*) and is an independent risk factor for the severity of motor symptoms (*12*). GDF15 is considered a trophic factor for midbrain dopaminergic neurons (as shown in Figure 3). *In vivo*, exogenous application of GDF15 significantly prevents 6-OHDA-mediated pathological rotational behavior and reduces the loss of dopaminergic neurons in the substantia nigra (*17*). GDF15 may also increase the mitochondrial function and proliferation of neuronal HT22 cells by regulating the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway (*83*). Importantly, endogenous GDF15 can ameliorate the deleterious consequences of 6-OHDA-mediated lesions (*16*). Compared with that in $GDF15^{+/+}$ mice, the reduction in the number of dopaminergic neurons caused by 6-OHDA is aggravated in GDF15-deficient mice, as are the numbers of total

and activated microglia (*16*). A recent study revealed that overexpression of GDF15 by plasmid transfection protects mitochondrial function and inhibits apoptosis in SH-SY5Y cells treated with rotenone, a broadly used inducer of PD (*84*). Mechanistically, the neuroprotective effect of GDF15 is mediated by the upregulation of peroxisome proliferator-activated receptor γ coactivator-1 alpha (PGC1α) through the regulation of p53, and this effect is eliminated by treatment with the PI3K/Akt-specific inhibitor LY294002 (*84*).

However, in another 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mouse model of PD, the absence of GDF15 did not affect the susceptibility and recovery capacity of dopaminergic neurons in the substantia nigra (*85*). The authors suggested that this result was caused by the intrinsic difference between the two mouse models (*85*). In both AD and PD, GDF15 presents a similar pattern of phenotypes and advantages; GDF15 is upregulated and exerts neuroprotective effects. In summary, GDF15 is indispensable for the intrinsic physiological function of dopaminergic neurons. When dopaminergic neurons are lesioned by 6-OHDA and rotenone, GDF15 expression increases, which is mediated by the upregulation of PGC1α through the regulation of p53. Blocking the PI3K/Akt signaling pathway can eliminate the neuroprotective effects of GDF15.

3.3. Other NDDs

ALS is one of the most devastating NDDs and involves the selective loss of upper and lower motor neurons, leading to progressive paralysis. Research on the association between GDF15 and ALS is still in the initial stage. Mutations in the *CHCHD10* gene, which encodes a mitochondrial intermembrane space protein that is upregulated under stress conditions, are rare genetic causes with autosomal dominant inheritance (*86*). Subsequent research revealed that GDF15 transcripts and proteins are upregulated in the fibroblasts of ALS patients with *CHCHD10* mutations(*87*). Moreover, Younes *et al.* reported that the transcripts of the GDF15 low-affinity receptors TGF-βR1 and TGF-βR2, but not the cognate high-affinity receptor GFRAL, are detected in the spinal cord of a mouse model of ALS (*88*). However, no evidence of interactions between GDF15 and other TGF-β family receptors, except for GFRAL, has been reported. In a cell-based PathHunter dimerization assay, GDF15 failed to induce a response in any of the cell lines tested, including those expressing more than twenty TGF-β family receptors (*57*). The role of the GDF15/TGF-βR axis in ALS should be carefully examined.

MS is a chronic, immune-mediated NDD. MS patients, especially patients with primary progressive MS, have higher CSF and serum levels of GDF15 than healthy controls do (*89,90*). Moreover, GDF15 is a potential biomarker for stable MS, and a longitudinal study (mean observation time of 4.6–5.9 years) revealed that the serum level of GDF15 is significantly higher in patients with stable MS than in those with active MS (*13*). Increased GDF15 level may reflect an endogenous anti-inflammatory mechanism in patients with stable MS, but this mechanism is disrupted by unknown causes in patients with active MS (*13*).

In addition, GDF15 can antagonize endoplasmic reticulum stress-induced apoptosis and prevent HD-mediated neurodegeneration in flies through the antiapoptotic functions of glucocorticoids (*18*).

3.4. Glioma

GDF15 is one of the most important molecules in cancers. The effects of GDF15 on cancer development and progression are complicated and different, likely depending on the specific cancer type and stage (*91*).

In primary brain glioma, the most common type of brain cancer, extensive evidence suggests that GDF15 possesses protumorigenic activity, contributing to proliferation, invasion, metastasis, immune escape and radioresistance (*19-21,92-94*). Consistent with these findings, the mRNA and protein levels of GDF15 are elevated in glioma patients and are associated with poor clinical outcomes (*19,20,95-97*). Specifically, in patients with lower-grade gliomas, higher GDF15 expression is significantly associated with a higher histological grade and poorer histology and is an independent risk factor for shorter survival (*19,21*).

The protumorigenic activities of GDF15 have been documented in many studies. Silencing of GDF15 reduces the proliferation of malignant glioma cells, and the depletion of tumor-secreted GDF15 increases immune surveillance and delays the growth of glioma (*20*). Exogenous GDF15 stimulates the migration and invasion of glioma cells (*94*). Moreover, the invasive capacity is coordinately regulated by the relative expression of Ras suppressor 1 (RSU-1) and GDF15 in specific glioma cell lines (H4, SW1088 and A172)(*92*). Glioma stem cells (GSCs) are characterized by high radioresistance and are highly challenging to treat. High levels of GDF15, regulated by irradiation and WW domain-containing transcription factor 1 (WWTR1/TAZ), promote the intrinsic radioresistance of GSCs, while targeting GDF15 expression and blocking WWTR1/TAZ *via* the specific siRNAs in GSCs sensitizes the cells to irradiation (*93*). In addition, Zhu *et al.* reported that GDF15 promotes a GSC-like phenotype *via* activation of the ERK1/2 signaling pathway (*98*).

However, the molecular mechanisms underlying this GDF15 upregulation are less well known. NF-κB directly participates in the production of GDF15, as the colocalization of activated NF-κB and GDF15 was observed in the epithelial ducts of human patients with pancreatic adenocarcinoma (*50*). Decreasing

GDF15 expression inhibits the invasion and migration of glioma cell lines by regulating the NF-κB pathway (*50*). Therefore, targeting the expression of tumor-derived GDF15 is a promising therapeutic approach for brain glioma. Notably, GDF15 is also involved in modulating the tumor microenvironment and plays a detrimental immunoinhibitory role; tumor-secreted GDF15 suppresses the activity of macrophages, natural killer (NK) cells and dendritic cells (DCs) and reduces the infiltration of lymphocytes and T cells (*25*). DCs are antigen-presenting cells that play indispensable roles in antigen-specific immune responses. Tumor-derived GDF15 can suppress the maturation and function of DCs and contribute to tumor immune escape (*99*). GDF15 inhibits the infiltration and cytotoxicity of immune cells, including T cells, B cells, and NK cells (*19,20*). GDF15 also interferes with lymphocyte function-associated antigen 1 (LFA-1)/β2-integrin-mediated T-cell adhesion to activated endothelial cells, while neutralizing antibodies against tumor-induced GDF15 improve both T-cell trafficking and therapeutic efficacy in murine tumor models (*100*). Thus, neutralizing antibodies against GDF15 may be potential immunotherapeutic strategies for glioma

Conversely, some studies have suggested that GDF15 is a tumor suppressor gene in glioblastoma (*49,101*). As discussed above, the tumor suppressor gene p53 can transactivate the GDF15 promoter and inhibit tumor cell growth (*22*). In addition, Kadowaki *et al.* reported that the basal expression of GDF15 in glioblastoma cell lines is low and that GDF15 overexpression significantly increases cell apoptosis. These researchers reported that hypermethylation of specific promoter sequences (-53 and +55 CpG sites) causes the transcriptional silencing of GDF15 (*49*). The proteasome inhibitor MG132 exerts antiglioblastoma effects by increasing the phosphorylation of protein in the p38 mitogen-activated protein kinase (MAPK) pathway followed by the induction of GDF15 expression (*101*).

Definite explanations for these conflicting conclusions are still lacking. In fact, in addition to its roles in glioma, GDF15 has dual roles in prostate cancer, breast cancer, gastric cancer and colorectal cancer (*25*). The effects of GDF15 (tumor-promoting or tumor-inhibiting) may depend on the cancer type and stage. In the early stages of cancer or in lower-grade malignancies, GDF15 seems to inhibit cancer cell growth, while it promotes cancer cell invasion and migration in the late stages or in higher-grade malignancies. Glioblastoma is the most malignant form of glioma, and the degree of malignancy likely results in this discrepancy. Additionally, the source of GDF15 may be another potential reason; compared with tumor-derived GDF15, drug/stress-induced GDF15 likely has opposite effects. Similar to pregnancy, fetal and placenta-derived GDF15, the major sources of GDF15 in maternal blood confirmed by mass spectrometry, are associated with an increased

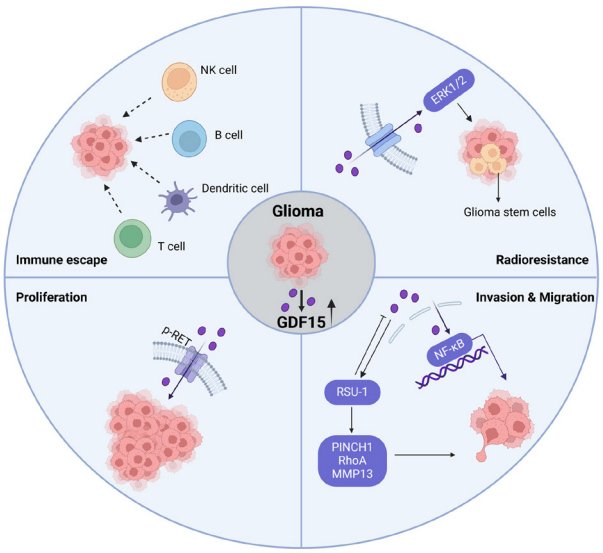

Figure 4. The protumorigenic activities of tumor-derived GDF15 in glioma. Including promoting invasion and migration, proliferation, immune escape and radioresistance of tumor cell.

risk of nausea and vomiting during human pregnancy (*102*). Blocking GDF15 activity in pregnant mothers may be an effective therapy for women suffering from hyperemesis gravidarum. Both tumor and feto-placental unit-derived GDF15 are foreign objects, that differ from individual stress-induced GDF15. Different sources may result in different variants and activities. Further studies can consider the use of mass spectrometry for detection. Notably, validating this supposition using primary neurons cocultured with GDF15 derived from cancer cell lines would be interesting. Most studies have suggested that GDF15 promotes the development of cancers; therefore, we focused on the protumorigenic activity of GDF15 in glioma (as shown in Figure 4), and decreasing tumor-derived GDF15 expression may contribute to suppressing tumor growth and improving patient prognosis. However, high-grade malignant glioma is likely to be an exception.

In the terminal stage of cancer, severe loss of appetite and weight loss are common symptoms that deteriorate the patient's condition and are associated with poor outcomes. Tumor-derived GDF15 was reported to be responsible for cancer cachexia through the activation of hypothalamic neurons, resulting in decreased food intake, which was reversed by antibodies against GDF15 (*103*). Importantly, Suriben R *et al.* reported a therapeutic antagonistic monoclonal antibody, 3P10, that targets GFRAL and blocks RET signaling by preventing RET recruitment to the GDF15-GFRAL complex (*26*). In tumor-bearing mice, treatment with 3P10 reversed excessive lipid oxidation and prevented cancer cachexia independently of food intake (*26*). Nevertheless, detailed studies on the pharmacokinetics of neutralizing antibodies against GDF15 and GFRAL are needed to better understand this therapeutic target.

3.5. Ischemic stroke

Ischemic stroke is one of the most prevalent neurological disorders and is characterized by recurrence and high disability and mortality rates. Atrial fibrillation (AF) is a risk factor for ischemic stroke. Importantly, in a cohort of 14,798 AF patients, those with high GDF15 levels were more vulnerable to stroke or systemic embolism events (0.9% *vs*. 2.03%) (*104*). In addition to the serum GDF15 level, the genotype and allele frequencies of the GDF15 rs1804826G/T polymorphism are related to ischemic stroke in the Chinese population (*105*). In addition, several studies have consistently shown that GDF15 is a prognostic biomarker for mortality and unfavorable outcomes after ischemic stroke (*106-108*). A high baseline serum GDF15 concentration (> 1,800 ng/L) can predict poor clinical outcomes in acute ischemic stroke patients (*107*). The baseline serum GDF15 concentration is independently associated with 3-month mortality in ischemic stroke patients after acute revascularization therapy (*109*). The relationships between increased GDF15 levels and depression and cognitive impairment after ischemic stroke have been identified recently (*110,111*). In contrast, in a prospective study with more than 20 years of follow-up, after controlling for competing events, Bao *et al.* reported that GDF15 is a strong biomarker for all-cause mortality but is less reliable for ischemic stroke (*112*). Thus, the baseline serum GDF15 concentration can provide additional information for screening ischemic stroke patients at high risk of an unfavorable prognosis.

In an ischemic stroke mouse model generated the occlusion of the middle cerebral artery, the expression of the GDF15 mRNA in the hippocampus and parietal cortex was dramatically upregulated at 3 h and 24 h after lesion induction (*72*). However, the size of the infarct area in the brain did not differ between GDF15 wild-type and knockout mice, suggesting that upregulated GDF15 may be involved in integrating postlesional responses (*72*). Although increased GDF15 expression may be associated with the development and progression of ischemic stroke, this increase does not indicate that GDF15 promotes ischemic stroke. A more plausible explanation is that GDF15 acts as a stress response factor involved in the repair of ischemic lesions.

In contrast, patients with carotid artery and cerebral atherosclerosis are more susceptible to ischemic stroke. The vital question is not how to stop the formation of atherosclerosis but rather how to inhibit the progression of unstable plaques complicated with luminal thrombosis. GDF15 deficiency has a beneficial effect on plaque stabilization by inhibiting C-C chemokine receptor type 2 (CCR2)-mediated macrophage chemotaxis and regulating cell death (*28*). In addition, GDF15 deletion inhibits atherosclerotic progression by regulating cell apoptosis and interleukin-6 (IL-6)-dependent inflammatory responses to vascular injury (*27*). GDF15 inhibition may be a therapeutic strategy for preventing atherosclerotic plaque progression and ischemic stroke. However, in the late stage of atherosclerosis, GDF15 may exert beneficial effects on atherosclerosis by inhibiting monocyte recruitment and macrophage activation (*113*).

In patients with deep venous thrombosis (DVT), increased GDF15 levels are associated with an increased thrombus severity and can inhibit platelet aggregation induced by adenosine diphosphate (ADP) *in vitro* in a concentration-dependent manner (*114*). Moreover, the activation of GDF15/transient receptor potential vanilloid 4 (TRPV4) signaling promotes angiogenesis in individuals with acute myocardial infarction (MI) (*115*). The antiplatelet aggregation and proangiogenic effects of GDF15 need to be identified in individual with ischemic stroke.

4. Concluding remarks and future prospects

In clinical trials, therapies targeting GDF15 show potential in patients with cancer and cachexia. Ponsegromab is a humanized monoclonal antibody that is a highly selective and potent inhibitor of GDF-15 (*116*). In an open-label clinical trial (n = 10), participants with cancer and cachexia received 200 mg of ponsegromab, which was administered subcutaneously every 3 weeks for 12 weeks (five doses total). Ponsegromab is generally safe and well tolerated (*117*). Ponsegromab prominently reduce serum GDF-15 concentrations (*117*). Recently, researchers published findings from a randomized, doble-blind, 12-week phase 2 clinical trial, and reported that ponsegromab results in increased weight gain and appetite, along with ameliorated cachexia symptoms and improved physical activity (*118*). Visugromab (CTL-002) is a GDF-15 neutralizing IgG4 monoclonal antibody, that can suppress the growth of tumors and displays promising clinical activities when used as neoadjuvant immunotherapy for advanced/metastatic relapsed/refractory tumors (*119*). In addition, a therapeutic antagonistic monoclonal antibody against GFRAL, 3P10, inhibits GDF15-driven GFRAL-RET signaling by preventing RET recruitment to the GDF15–GFRAL complex on the cell surface (*26*). In HT1080 mice, 3P10 reversed metabolic changes and weight loss induced by tumors, independent of food intake (*26*). However, several limitations of GDF15/GFRAL neutralizing antibodies in practical clinical applications should be acknowledged. First, the safety and efficacy of these treatments must be validated in a larger cohort of patients with cancer. Second, all three of these monoclonal antibodies produce a marked effect by blocking the interaction of GDF15 with GFRAL, which is likely applicable only to patients with elevated serum GDF15 levels. In glioblastoma cell lines and primary oligodendroglioma tumors, the basal expression of GDF15 is low, through DNA methylation-mediated transcriptional silencing (*49*). In these patients,

the abovementioned monoclonal antibodies may be ineffective. Third, whether these drugs can pass through the blood-brain barrier is another worthwhile problem to slove. Finally, we believe that upregulated GDF15 may be a double-edged sword; on the one hand, it exerts neuroprotective effects on NDDs and ischemic stroke; on the other hand, it is detrimental to tumor inhibition. We suppose that these effects likely depend in part on the source of GDF15; the former, which is induced by intrinsic stress responses, plays protective roles, whereas the latter, which is derived from deleterious tumors, plays harmful roles. Thus, the actual clinical value of GDF15 is likely to depend on the specific type of disease. In NDDs, additional exogenous recombinant GDF15 seems to be protective. Notably, close monitoring of the onset of tumors is essential when exogenous GDF15 is administered to treat neurological diseases.

In summary, although most of the available preclinical evidence initially showed that targeting GDF15 and related pathways has promising clinical application prospects in the treatment of brain diseases, especially AD, PD, glioma and cancer cachexia, several key problems remain to be solved. To date, we understand only the metabolic effects of the GDF15/GFRAL axis; thus, identifying further physiological functions is the top priority. In addition to the GDF15/GFRAL axis, the other potential signaling pathways affected by GDF15 need to be clarified. In addition, the efficacy and safety of these targets in humans need to be thoroughly studied in the future. Further studies should review and correct the controversial findings concerning GDF15 in glioma.

Funding: This work was supported by the Fundamental Research Funds for the Central Universities (item number: 2019kfyXKJC055), the National Key Research and Development Program of China (Project No. 2020YFC2004803), the Tongji Hospital Scientific Research Fund (2022A19) and the National Natural Science Foundation of China (Project No. 82371442).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. DiLuca M, Olesen J. The cost of brain diseases: a burden or a challenge? Neuron. 2014; 82:1205-1208.
2. Raggi A, Leonardi M. Burden of brain disorders in Europe in 2017 and comparison with other non-communicable disease groups. J Neurol Neurosurg Psychiatry. 2020; 91:104-105.
3. Schober A, Böttner M, Strelau J, Kinscherf R, Bonaterra GA, Barth M, Schilling L, Fairlie WD, Breit SN, Unsicker K. Expression of growth differentiation factor-15/macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in the perinatal, adult, and injured rat brain. J Comp Neurol. 2001; 439:32-45.
4. Conte M, Giuliani C, Chiariello A, Iannuzzi V, Franceschi C, Salvioli S. GDF15, an emerging key player in human aging. Ageing Res Rev. 2022; 75:101569.
5. Burtscher J, Soltany A, Visavadiya NP, Burtscher M, Millet GP, Khoramipour K, Khamoui AV. Mitochondrial stress and mitokines in aging. Aging cell. 2023; 22:e13770.
6. Xue XH, Tao LL, Su DQ, Guo CJ, Liu H. Diagnostic utility of GDF15 in neurodegenerative diseases: A systematic review and meta-analysis. Brain behav. 2022; 12:e2502.
7. Giudici KV, de Souto Barreto P, Guyonnet S, Morley JE, Nguyen AD, Aggarwal G, Parini A, Li Y, Bateman RJ, Vellas B. TNFR-1 and GDF-15 Are Associated With Plasma Neurofilament Light Chain and Progranulin Among Community-Dwelling Older Adults: A Secondary Analysis of the MAPT Study. J Gerontol A Biol Sci Med Sci. 2023; 78:569-578.
8. Tsai VWW, Husaini Y, Sainsbury A, Brown DA, Breit SN. The MIC-1/GDF15-GFRAL Pathway in Energy Homeostasis: Implications for Obesity, Cachexia, and Other Associated Diseases. Cell Metab. 2018; 28:353-368.
9. Baek SJ, Eling T. Growth differentiation factor 15 (GDF15): A survival protein with therapeutic potential in metabolic diseases. Pharmacol Thers. 2019; 198:46-58.
10. Eddy AC, Trask AJ. Growth differentiation factor-15 and its role in diabetes and cardiovascular disease. Cytokine Growth Factor Rev. 2021; 57:11-18.
11. Fuchs T, Trollor JN, Crawford J, Brown DA, Baune BT, Samaras K, Campbell L, Breit SN, Brodaty H, Sachdev P, Smith E. Macrophage inhibitory cytokine-1 is associated with cognitive impairment and predicts cognitive decline - the Sydney Memory and Aging Study. Aging cell. 2013; 12:882-889.
12. Yao X, Wang D, Zhang L, Wang L, Zhao Z, Chen S, Wang X, Yue T, Liu Y. Serum Growth Differentiation Factor 15 in Parkinson Disease. Neurodegener Dis. 2017; 17:251-260.
13. Amstad A, Coray M, Frick C, Barro C, Oechtering J, Amann M, Wischhusen J, Kappos L, Naegelin Y, Kuhle J, Mehling M. Growth differentiation factor 15 is increased in stable MS. Neurol Neuroimmunol Neuroinflamm. 2020; 7:e675.
14. Kim DH, Lee D, Lim H, Choi SJ, Oh W, Yang YS, Chang JH, Jeon HB. Effect of growth differentiation factor-15 secreted by human umbilical cord blood-derived mesenchymal stem cells on amyloid beta levels in *in vitro* and *in vivo* models of Alzheimer's disease. Biochem Biophys Res Commun. 2018; 504:933-940.
15. Xiong WP, Yao WQ, Wang B, Liu K. BMSCs-exosomes containing GDF-15 alleviated SH-SY5Y cell injury model of Alzheimer's disease *via* AKT/GSK-3β/β-catenin. Brain Res Bull. 2021; 177:92-102.
16. Machado V, Haas SJ, von Bohlen Und Halbach O, Wree A, Krieglstein K, Unsicker K, Spittau B. Growth/differentiation factor-15 deficiency compromises dopaminergic neuron survival and microglial response in the 6-hydroxydopamine mouse model of Parkinson's disease. Neurobiol Dis. 2016; 88:1-15.
17. Strelau J, Sullivan A, Böttner M, Lingor P, Falkenstein E, Suter-Crazzolara C, Galter D, Jaszai J, Krieglstein K, Unsicker K. Growth/differentiation factor-15/macrophage inhibitory cytokine-1 is a novel trophic factor for midbrain dopaminergic neurons *in vivo*. J Neurosci. 2000; 20:8597-8603.
18. Varadarajan S, Breda C, Smalley JL, Butterworth M,

Farrow SN, Giorgini F, Cohen GM. The transrepression arm of glucocorticoid receptor signaling is protective in mutant huntingtin-mediated neurodegeneration. Cell Death Differ. 2015; 22:1388-1396.
19. Guo L, Chen Y, Hu S, Gao L, Tang N, Liu R, Qin Y, Ren C, Du S. GDF15 expression in glioma is associated with malignant progression, immune microenvironment, and serves as a prognostic factor. CNS Neurosci Ther. 2022; 28:158-171.
20. Roth P, Junker M, Tritschler I, Mittelbronn M, Dombrowski Y, Breit SN, Tabatabai G, Wick W, Weller M, Wischhusen J. GDF-15 contributes to proliferation and immune escape of malignant gliomas. Clin Cancer Res. 2010; 16:3851-3859.
21. Wang Y, Chen J, Chen C, Peng H, Lin X, Zhao Q, Chen S, Wang X. Growth differentiation factor-15 overexpression promotes cell proliferation and predicts poor prognosis in cerebral lower-grade gliomas correlated with hypoxia and glycolysis signature. Life Sci. 2022; 302:120645.
22. Tan M, Wang Y, Guan K, Sun Y. PTGF-beta, a type beta transforming growth factor (TGF-beta) superfamily member, is a p53 target gene that inhibits tumor cell growth *via* TGF-beta signaling pathway. Proc Natl Acad Sci U S A. 2000; 97:109-114.
23. Kim DH, Lee D, Chang EH, Kim JH, Hwang JW, Kim JY, Kyung JW, Kim SH, Oh JS, Shim SM, Na DL, Oh W, Chang JW. GDF-15 secreted from human umbilical cord blood mesenchymal stem cells delivered through the cerebrospinal fluid promotes hippocampal neurogenesis and synaptic activity in an Alzheimer's disease model. Stem Cells Dev. 2015; 24:2378-2390.
24. Xiong W, Li D, Feng Y, Jia C, Zhang X, Liu Z. CircLPAR1 Promotes Neuroinflammation and Oxidative Stress in APP/PS1 Mice by Inhibiting SIRT1/Nrf-2/HO-1 Axis Through Destabilizing GDF-15 mRNA. Mol Neurobiol. 2023; 60:2236-2251.
25. Siddiqui JA, Pothuraju R, Khan P, Sharma G, Muniyan S, Seshacharyulu P, Jain M, Nasser MW, Batra SK. Pathophysiological role of growth differentiation factor 15 (GDF15) in obesity, cancer, and cachexia. Cytokine & growth factor reviews. 2022; 64:71-83.
26. Suriben R, Chen M, Higbee J, *et al.* Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. Nat Med. 2020; 26:1264-1270.
27. Bonaterra GA, Zügel S, Thogersen J, Walter SA, Haberkorn U, Strelau J, Kinscherf R. Growth differentiation factor-15 deficiency inhibits atherosclerosis progression by regulating interleukin-6-dependent inflammatory response to vascular injury. J Am Heart Assoc. 2012; 1:e002550.
28. de Jager SC, Bermúdez B, Bot I, *et al.* Growth differentiation factor 15 deficiency protects against atherosclerosis by attenuating CCR2-mediated macrophage chemotaxis. J Exp Med. 2011; 208:217-225.
29. Lawton LN, Bonaldo MF, Jelenc PC, Qiu L, Baumes SA, Marcelino RA, de Jesus GM, Wellington S, Knowles JA, Warburton D, Brown S, Soares MB. Identification of a novel member of the TGF-beta superfamily highly expressed in human placenta. Gene. 1997; 203:17-26.
30. Bootcov MR, Bauskin AR, Valenzuela SM, *et al.* MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A. 1997; 94:11514-11519.
31. Lockhart SM, Saudek V, O'Rahilly S. GDF15: A Hormone Conveying Somatic Distress to the Brain. Endocr Rev. 2020; 41.
32. Hsu JY, Crawley S, Chen M, *et al.* Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. Nature. 2017; 550:255-259.
33. Bauskin AR, Zhang HP, Fairlie WD, He XY, Russell PK, Moore AG, Brown DA, Stanley KK, Breit SN. The propeptide of macrophage inhibitory cytokine (MIC-1), a TGF-beta superfamily member, acts as a quality control determinant for correctly folded MIC-1. EMBOJ. 2000; 19:2212-2220.
34. Fairlie WD, Moore AG, Bauskin AR, Russell PK, Zhang HP, Breit SN. MIC-1 is a novel TGF-beta superfamily cytokine associated with macrophage activation. J Leukoc Biol. 1999; 65:2-5.
35. Couture F, Sabbagh R, Kwiatkowska A, Desjardins R, Guay SP, Bouchard L, Day R. PACE4 Undergoes an Oncogenic Alternative Splicing Switch in Cancer. Cancer Res. 2017; 77:6863-6879.
36. Min KW, Liggett JL, Silva G, Wu WW, Wang R, Shen RF, Eling TE, Baek SJ. NAG-1/GDF15 accumulates in the nucleus and modulates transcriptional regulation of the Smad pathway. Oncogene. 2016; 35:377-388.
37. Lee J, Kim I, Yoo E, Baek SJ. Competitive inhibition by NAG-1/GDF-15 NLS peptide enhances its anti-cancer activity. Biochem Biophys Res Commun. 2019; 519:29-34.
38. Böttner M, Laaff M, Schechinger B, Rappold G, Unsicker K, Suter-Crazzolara C. Characterization of the rat, mouse, and human genes of growth/differentiation factor-15/macrophage inhibiting cytokine-1 (GDF-15/MIC-1). Gene. 1999; 237:105-111.
39. Baek SJ, Kim JS, Nixon JB, DiAugustine RP, Eling TE. Expression of NAG-1, a transforming growth factor-beta superfamily member, by troglitazone requires the early growth response gene EGR-1. J Biol Chem. 2004; 279:6883-6892.
40. Baek SJ, Horowitz JM, Eling TE. Molecular cloning and characterization of human nonsteroidal anti-inflammatory drug-activated gene promoter. Basal transcription is mediated by Sp1 and Sp3. J Biol Chem. 2001; 276:33384-33392.
41. Strelau J, Schmeer C, Peterziel H, Sackmann T, Herold-Mende C, Steiner H, Weller M, Unsicker K. Expression and putative functions of GDF-15, a member of the TGF-beta superfamily, in human glioma and glioblastoma cell lines. Cancer lett. 2008; 270:30-39.
42. Li PX, Wong J, Ayed A, Ngo D, Brade AM, Arrowsmith C, Austin RC, Klamut HJ. Placental transforming growth factor-beta is a downstream mediator of the growth arrest and apoptotic response of tumor cells to DNA damage and p53 overexpression. J Biol Chem. 2000; 275:20127-20135.
43. Kannan K, Amariglio N, Rechavi G, Givol D. Profile of gene expression regulated by induced p53: connection to the TGF-beta family. FEBS lett. 2000; 470:77-82.
44. Cheng JC, Chang HM, Leung PC. Wild-type p53 attenuates cancer cell motility by inducing growth differentiation factor-15 expression. Endocrinology. 2011; 152:2987-2995.
45. Izaguirre DI, Ng CW, Kwan SY, Kun EH, Tsang YTM, Gershenson DM, Wong KK. The Role of GDF15 in Regulating the Canonical Pathways of the Tumor Microenvironment in Wild-Type p53 Ovarian Tumor and Its Response to Chemotherapy. Cancers. 2020; 12:3043.
46. Gómez Ravetti M, Rosso OA, Berretta R, Moscato P.

Uncovering molecular biomarkers that correlate cognitive decline with the changes of hippocampus' gene expression profiles in Alzheimer's disease. PloS One. 2010; 5:e10153.
47. Choi BH, Kim CG, Bae YS, Lim Y, Lee YH, Shin SY. p21 Waf1/Cip1 expression by curcumin in U-87MG human glioma cells: role of early growth response-1 expression. Cancer Res. 2008; 68:1369-1377.
48. Woo SM, Min KJ, Kim S, Park JW, Kim DE, Chun KS, Kim YH, Lee TJ, Kim SH, Choi YH, Chang JS, Kwon TK. Silibinin induces apoptosis of HT29 colon carcinoma cells through early growth response-1 (EGR-1)-mediated non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) up-regulation. Chem Biol Interact. 2014; 211:36-43.
49. Kadowaki M, Yoshioka H, Kamitani H, Watanabe T, Wade PA, Eling TE. DNA methylation-mediated silencing of nonsteroidal anti-inflammatory drug-activated gene (NAG-1/GDF15) in glioma cell lines. Int J Cancer. 2012; 130:267-277.
50. Ratnam NM, Peterson JM, Talbert EE, Ladner KJ, Rajasekera PV, Schmidt CR, Dillhoff ME, Swanson BJ, Haverick E, Kladney RD, Williams TM, Leone GW, Wang DJ, Guttridge DC. NF-κB regulates GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest. 2017; 127:3796-3809.
51. Jiang WW, Zhang ZZ, He PP, Jiang LP, Chen JZ, Zhang XT, Hu M, Zhang YK, Ouyang XP. Emerging roles of growth differentiation factor-15 in brain disorders (Review). Exp Ther Med. 2021; 22:1270.
52. Day EA, Ford RJ, Smith BK, *et al.* Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. Nat Metab. 2019; 1:1202-1208.
53. Li A, Zhao F, Zhao Y, Liu H, Wang Z. ATF4-mediated GDF15 suppresses LPS-induced inflammation and MUC5AC in human nasal epithelial cells through the PI3K/Akt pathway. Life Sci. 2021; 275:119356.
54. Wei N, Zhu LQ, Liu D. ATF4: A Novel Potential Therapeutic Target for Alzheimer's Disease. Mol Neurobiol. 2015; 52:1765-1770.
55. Chen C, Zhang Z, Liu C, Wang B, Liu P, Fang S, Yang F, You Y, Li X. ATF4-dependent fructolysis fuels growth of glioblastoma multiforme. Nat Commun. 2022; 13:6108.
56. Yang L, Chang CC, Sun Z, *et al.* GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. Nat Med. 2017; 23:1158-1166.
57. Mullican SE, Lin-Schmidt X, Chin CN, *et al.* GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. Nat Med. 2017; 23:1150-1157.
58. Li Z, Wang B, Wu X, Cheng SY, Paraoan L, Zhou J. Identification, expression and functional characterization of the GRAL gene. J Neurochem. 2005; 95:361-376.
59. Emmerson PJ, Wang F, Du Y, *et al.* The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. Nat Med. 2017; 23:1215-1219.
60. Chow CFW, Guo X, Asthana P, *et al.* Body weight regulation *via* MT1-MMP-mediated cleavage of GFRAL. Nat Metab. 2022; 4:203-212.
61. Chelette B, Chidomere CL, Dantzer R. The GDF15-GFRAL axis mediates chemotherapy-induced fatigue in mice. Brain Behav Immun. 2023; 108:45-54.
62. Fichtner K, Kalwa H, Lin MM, Gong Y, Müglitz A, Kluge M, Krügel U. GFRAL Is Widely Distributed in the Brain and Peripheral Tissues of Mice. Nutrients. 2024; 16.
63. Lee J, Jin YJ, Lee MS, Kim YM, Lee H. Macrophage inhibitory cytokine-1 promotes angiogenesis by eliciting the GFRAL-mediated endothelial cell signaling. J Cell Physiol. 2021; 236:4008-4023.
64. Wiklund FE, Bennet AM, Magnusson PK, Eriksson UK, Lindmark F, Wu L, Yaghoutyfam N, Marquis CP, Stattin P, Pedersen NL, Adami HO, Grönberg H, Breit SN, Brown DA. Macrophage inhibitory cytokine-1 (MIC-1/GDF15): a new marker of all-cause mortality. Aging cell. 2010; 9:1057-1064.
65. Cimino I, Kim H, Tung YCL, *et al.* Activation of the hypothalamic-pituitary-adrenal axis by exogenous and endogenous GDF15. Proc Natl Acad Sci U S A. 2021; 118:e2106868118
66. Chiariello A, Valente S, Pasquinelli G, *et al.* The expression pattern of GDF15 in human brain changes during aging and in Alzheimer's disease. Front Aging Neurosci. 2022; 14:1058665.
67. Böttner M, Suter-Crazzolara C, Schober A, Unsicker K. Expression of a novel member of the TGF-beta superfamily, growth/differentiation factor-15/macrophage-inhibiting cytokine-1 (GDF-15/MIC-1) in adult rat tissues. Cell Tissue Res. 1999; 297:103-110.
68. Tong CK, Alvarez-Buylla A. SnapShot: adult neurogenesis in the V-SVZ. Neuron. 2014; 81:220-220.e221.
69. Carrillo-García C, Prochnow S, Simeonova IK, Strelau J, Hölzl-Wenig G, Mandl C, Unsicker K, von Bohlen Und Halbach O, Ciccolini F. Growth/differentiation factor 15 promotes EGFR signalling, and regulates proliferation and migration in the hippocampus of neonatal and young adult mice. Development. 2014; 141:773-783.
70. Malik VA, Zajicek F, Mittmann LA, Klaus J, Unterseer S, Rajkumar S, Pütz B, Deussing JM, Neumann ID, Rupprecht R, Di Benedetto B. GDF15 promotes simultaneous astrocyte remodeling and tight junction strengthening at the blood-brain barrier. J Neurosci Res. 2020; 98:1433-1456.
71. Yi MH, Zhang E, Baek H, Kim S, Shin N, Kang JW, Lee S, Oh SH, Kim DW. Growth Differentiation Factor 15 Expression in Astrocytes After Excitotoxic Lesion in the Mouse Hippocampus. Exp Neurobiol. 2015; 24:133-138.
72. Schindowski K, von Bohlen und Halbach O, Strelau J, Ridder DA, Herrmann O, Schober A, Schwaninger M, Unsicker K. Regulation of GDF-15, a distant TGF-β superfamily member, in a mouse model of cerebral ischemia. Cell Tissue Res. 2011; 343:399-409.
73. Strelau J, Strzelczyk A, Rusu P, Bendner G, Wiese S, Diella F, Altick AL, von Bartheld CS, Klein R, Sendtner M, Unsicker K. Progressive postnatal motoneuron loss in mice lacking GDF-15. J Neurosci. 2009; 29:13640-13648.
74. Guo Y, You J, Zhang Y, Liu WS, Huang YY, Zhang YR, Zhang W, Dong Q, Feng JF, Cheng W, Yu JT. Plasma proteomic profiles predict future dementia in healthy adults. Nat Aging. 2024; 4:247-260.
75. Wu PF, Zhang XH, Zhou P, Yin R, Zhou XT, Zhang W. Growth Differentiation Factor 15 Is Associated With Alzheimer's Disease Risk. Front Genet. 2021; 12:700371.
76. McGrath ER, Himali JJ, Levy D, Conner SC, DeCarli C, Pase MP, Ninomiya T, Ohara T, Courchesne P, Satizabal CL, Vasan RS, Beiser AS, Seshadri S. Growth Differentiation Factor 15 and NT-proBNP as Blood-Based Markers of Vascular Brain Injury and Dementia. J Am Heart Assoc. 2020; 9:e014659.
77. Lu WH, Gonzalez-Bautista E, Guyonnet S, Lucas A, Parini A, Walston JD, Vellas B, de Souto Barreto P. Plasma inflammation-related biomarkers are associated

with intrinsic capacity in community-dwelling older adults. J Cachexia Sarcopenia Muscle. 2023; 14:930-939.
78. Walker KA, Chen J, Shi L, *et al.* Proteomics analysis of plasma from middle-aged adults identifies protein markers of dementia risk in later life. Sci Transl Med. 2023; 15:eadf5681.
79. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci. 1991; 12:383-388.
80. Conte M, Sabbatinelli J, Chiariello A, Martucci M, Santoro A, Monti D, Arcaro M, Galimberti D, Scarpini E, Bonfigli AR, Giuliani A, Olivieri F, Franceschi C, Salvioli S. Disease-specific plasma levels of mitokines FGF21, GDF15, and Humanin in type II diabetes and Alzheimer's disease in comparison with healthy aging. Geroscience. 2021; 43:985-1001.
81. Miller DB, O'Callaghan JP. Biomarkers of Parkinson's disease: Present and future. Metabolism. 2015; 64:S40-46.
82. Miyaue N, Yabe H, Nagai M. Serum growth differentiation factor 15, but not lactate, is elevated in patients with Parkinson's disease. J Neurol Sci. 2020; 409:116616.
83. Liu H, Liu J, Si L, Guo C, Liu W, Liu Y. GDF-15 promotes mitochondrial function and proliferation in neuronal HT22 cells. J Cell Biochem. 2019; 120:10530-10547.
84. Li P, Lv H, Zhang B, Duan R, Zhang X, Lin P, Song C, Liu Y. Growth Differentiation Factor 15 Protects SH-SY5Y Cells From Rotenone-Induced Toxicity by Suppressing Mitochondrial Apoptosis. Front Aging Neurosci. 2022; 14:869558.
85. Machado V, Gilsbach R, Das R, Schober A, Bogatyreva L, Hauschke D, Krieglstein K, Unsicker K, Spittau B. Gdf-15 deficiency does not alter vulnerability of nigrostriatal dopaminergic system in MPTP-intoxicated mice. Cell Tissue Res. 2016; 365:209-223.
86. Müller K, Andersen PM, Hübers A, Marroquin N, Volk AE, Danzer KM, Meitinger T, Ludolph AC, Strom TM, Weishaupt JH. Two novel mutations in conserved codons indicate that CHCHD10 is a gene associated with motor neuron disease. Brain. 2014; 137:e309.
87. Straub IR, Weraarpachai W, Shoubridge EA. Multi-OMICS study of a CHCHD10 variant causing ALS demonstrates metabolic rewiring and activation of endoplasmic reticulum and mitochondrial unfolded protein responses. Hum Mol Genet. 2021; 30:687-705.
88. Younes R, Issa Y, Jdaa N, Chouaib B, Brugioti V, Challuau D, Raoul C, Scamps F, Cuisinier F, Hilaire C. The Secretome of Human Dental Pulp Stem Cells and Its Components GDF15 and HB-EGF Protect Amyotrophic Lateral Sclerosis Motoneurons against Death. Biomedicines. 2023; 11:2152.
89. Kosa P, Wu T, Phillips J, Leinonen M, Masvekar R, Komori M, Wichman A, Sandford M, Bielekova B. Idebenone does not inhibit disability progression in primary progressive MS. Mult Scler Relat Disord. 2020; 45:102434.
90. Baeva ME, Tottenham I, Koch M, Camara-Lemarroy C. Biomarkers of disability worsening in inactive primary progressive multiple sclerosis. J Neuroimmunol. 2024; 387:578268.
91. Hasanpour Segherlou Z, Nouri-Vaskeh M, Noroozi Guilandehi S, Baghbanzadeh A, Zand R, Baradaran B, Zarei M. GDF-15: Diagnostic, prognostic, and therapeutic significance in glioblastoma multiforme. J Cell Physiol. 2021; 236:5564-5581.
92. Louca M, Gkretsi V, Stylianopoulos T. Coordinated Expression of Ras Suppressor 1 (RSU-1) and Growth Differentiation Factor 15 (GDF15) Affects Glioma Cell Invasion. Cancers. 2019; 11:1159
93. Bentaberry-Rosa A, Nicaise Y, Delmas C, Gouazé-Andersson V, Cohen-Jonathan-Moyal E, Seva C. Overexpression of Growth Differentiation Factor 15 in Glioblastoma Stem Cells Promotes Their Radioresistance. Cancers. 2023; 16:27.
94. Codó P, Weller M, Kaulich K, Schraivogel D, Silginer M, Reifenberger G, Meister G, Roth P. Control of glioma cell migration and invasiveness by GDF-15. Oncotarget. 2016; 7:7732-7746.
95. Scrideli CA, Carlotti CG, Jr., Okamoto OK, Andrade VS, Cortez MA, Motta FJ, Lucio-Eterovic AK, Neder L, Rosemberg S, Oba-Shinjo SM, Marie SK, Tone LG. Gene expression profile analysis of primary glioblastomas and non-neoplastic brain tissue: identification of potential target genes by oligonucleotide microarray and real-time quantitative PCR. J Neurooncol. 2008; 88:281-291.
96. Shnaper S, Desbaillets I, Brown DA, Murat A, Migliavacca E, Schluep M, Ostermann S, Hamou MF, Stupp R, Breit SN, de Tribolet N, Hegi ME. Elevated levels of MIC-1/GDF15 in the cerebrospinal fluid of patients are associated with glioblastoma and worse outcome. Int J Cancer. 2009; 125:2624-2630.
97. Tsai SF, Tao M, Ho LI, Chiou TW, Lin SZ, Su HL, Harn HJ. Isochaihulactone-induced DDIT3 causes ER stress-PERK independent apoptosis in glioblastoma multiforme cells. Oncotarget. 2017; 8:4051-4061.
98. Zhu S, Yang N, Guan Y, Wang X, Zang G, Lv X, Deng S, Wang W, Li T, Chen J. GDF15 promotes glioma stem cell-like phenotype *via* regulation of ERK1/2-c-Fos-LIF signaling. Cell Death Discov. 2021; 7:3.
99. Zhou Z, Li W, Song Y, Wang L, Zhang K, Yang J, Zhang W, Su H, Zhang Y. Growth differentiation factor-15 suppresses maturation and function of dendritic cells and inhibits tumor-specific immune response. PloS One. 2013; 8:e78618.
100. Haake M, Haack B, Schäfer T, *et al.* Tumor-derived GDF-15 blocks LFA-1 dependent T cell recruitment and suppresses responses to anti-PD-1 treatment. Nat Commun. 2023; 14:4253.
101. Shimizu S, Kadowaki M, Yoshioka H, Kambe A, Watanabe T, Kinyamu HK, Eling TE. Proteasome inhibitor MG132 induces NAG-1/GDF15 expression through the p38 MAPK pathway in glioblastoma cells. Biochem Biophys Res Commun. 2013; 430:1277-1282.
102. Fejzo M, Rocha N, Cimino I, *et al.* GDF15 linked to maternal risk of nausea and vomiting during pregnancy. Nature. 2024; 625:760-767.
103. Johnen H, Lin S, Kuffner T, *et al.* Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. Nat Med. 2007; 13:1333-1340.
104. Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, Horowitz JD, Hylek EM, Lopes RD, Asberg S, Granger CB, Siegbahn A. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation. 2014; 130:1847-1858.
105. Xiang Y, Zhang T, Guo J, Peng YF, Wei YS. The

Association of Growth Differentiation Factor-15 Gene Polymorphisms with Growth Differentiation Factor-15 Serum Levels and Risk of Ischemic Stroke. J Stroke Cerebrovasc Dis. 2017; 26:2111-2119.
106. Guo D, Zhu Z, Zhong C, *et al.* Prognostic Metrics Associated with Inflammation and Atherosclerosis Signaling Evaluate the Burden of Adverse Clinical Outcomes in Ischemic Stroke Patients. Clin Chem. 2020; 66:1434-1443.
107. Yin J, Zhu Z, Guo D, Wang A, Zeng N, Zheng X, Peng Y, Zhong C, Wang G, Zhou Y, Chen CS, Chen J, Zhang Y, He J. Increased Growth Differentiation Factor 15 Is Associated with Unfavorable Clinical Outcomes of Acute Ischemic Stroke. Clin Chem. 2019; 65:569-578.
108. Gröschel K, Schnaudigel S, Edelmann F, Niehaus CF, Weber-Krüger M, Haase B, Lahno R, Seegers J, Wasser K, Wohlfahrt J, Vollmann D, Stahrenberg R, Wachter R. Growth-differentiation factor-15 and functional outcome after acute ischemic stroke. J Neurol. 2012; 259:1574-1579.
109. Brenière C, Méloux A, Pédard M, Marie C, Thouant P, Vergely C, Béjot Y. Growth Differentiation Factor-15 (GDF-15) Is Associated With Mortality in Ischemic Stroke Patients Treated With Acute Revascularization Therapy. Front Neurol. 2019; 10:611.
110. Yang P, Wang S, Zhong C, Yin J, Yang J, Wang A, Xu T, Zhang Y. Association of Cardiac Biomarkers in Combination With Cognitive Impairment After Acute Ischemic Stroke. J Am Heart Assoc. 2024; 13:e031010.
111. Zang Y, Zhu Z, Xie Y, Liu Z, Yin J, Yang P, Zhang K, Bu X, Wang A, Chen J, Zhang Y, He J. Serum Growth Differentiation Factor 15 Levels Are Associated With Depression After Ischemic Stroke. J Am Heart Assoc. 2022; 11:e022607.
112. Bao X, Borné Y, Xu B, Orho-Melander M, Nilsson J, Melander O, Engström G. Growth differentiation factor-15 is a biomarker for all-cause mortality but less evident for cardiovascular outcomes: A prospective study. Am HeartJ. 2021; 234:81-89.
113. Wang D, Day EA, Townsend LK, Djordjevic D, Jørgensen SB, Steinberg GR. GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. Nat Rev Endocrinol. 2021; 17:592-607.
114. Liang W, Wei F, Yang C, Xie F, Shuai XX, Wang M, Yu M. GDF-15 is associated with thrombus burden in patients with deep venous thrombosis. Thromb Res. 2020; 187:148-153.
115. Wei BY, Hou JN, Yan CP, Wen SY, Shang XS, Guo YC, Feng T, Liu TF, Chen ZY, Chen XP. Shexiang Baoxin Pill treats acute myocardial infarction by promoting angiogenesis *via* GDF15-TRPV4 signaling. Biomed Pharmacother. 2023; 165:115186.
116. Breen DM, Kim H, Bennett D, *et al.* GDF-15 Neutralization Alleviates Platinum-Based Chemotherapy-Induced Emesis, Anorexia, and Weight Loss in Mice and Nonhuman Primates. Cell Metab. 2020; 32:938-950. e936.
117. Crawford J, Calle RA, Collins SM, Weng Y, Lubaczewski SL, Buckeridge C, Wang EQ, Harrington MA, Tarachandani A, Rossulek MI, Revkin JH. A Phase Ib First-In-Patient Study Assessing the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Ponsegromab in Participants with Cancer and Cachexia. Clin Cancer Res. 2024; 30:489-497.
118. Groarke JD, Crawford J, Collins SM, *et al.* Ponsegromab for the Treatment of Cancer Cachexia. N Engl J Med. 2024; 391:2291-2303.
119. Bermejo IM, Miguel MJd, Alonso G, *et al.* Initial results from the phase 2A trial of visugromab (CTL-002) + nivolumab in advanced/metastatic anti-PD1/-L1 relapsed/refractory solid tumors (The GDFATHER-TRIAL). J Clin Oncol. 2023; 41:2501-2501. https://doi.org/10.1200/JCO.2023.41.16_suppl.2501

Received September 30, 2024; Revised November 23, 2024; Accepted January 22, 2025.

[§]These authors contributed equally to this work.

**Address correspondence to:*
Kai Zheng, Department of Geriatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Rd. Wuhan 430030, Hubei, China.
E-mail: diazna2002@sina.com

Released online in J-STAGE as advance publication January 25, 2025.