Role of growth differentiation factor 15 in cancer cachexia (Review)

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Abstract. Growth differentiation factor 15 (GDF15), a member of the transforming growth factor-β family, is a stress-induced cytokine. Under normal circumstances, the expression of GDF15 is low in most tissues. It is highly expressed during tissue injury, inflammation, oxidative stress and cancer. GDF15 has been established as a biomarker in patients with cancer, and is associated with cancer cachexia (CC) and poor survival. CC is a multifactorial metabolic disorder characterized by severe muscle and adipose tissue atrophy, loss of appetite, anemia and bone loss. Cachexia leads to reductions in quality of life and tolerance to anticancer therapy, and results in a poor prognosis in cancer patients. Dysregulated GDF15 levels have been discovered in patients with CC and animal models, where they have been found to be involved in anorexia and weight loss. Although studies have suggested that GDF15 mediates anorexia and weight loss in CC through its neuroreceptor, glial cell-lineage neurotrophic factor family receptor α-like, the effects of GDF15 on CC and the potential regulatory mechanisms require further elucidation. In the present review, the characteristics of GDF15 and its roles and molecular mechanisms in CC are elaborated. The targeting of GDF15 as a potential therapeutic strategy for CC is also discussed.

Contents

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1. Introduction

Cachexia is a fatal disease that is associated with several conditions, including acquired immunodeficiency syndrome, multiple sclerosis, chronic obstructive pulmonary disease (COPD), tuberculosis, congestive heart failure, chronic kidney disease and cancer (1,2). Cancer-associated cachexia is a serious wasting syndrome characterized by a continuous reduction in skeletal muscle mass, with or without the loss of fat mass. Distinct from hunger and nutritional deficiencies, cancer cachexia (CC) cannot be reversed by food supplements, and leads to progressive functional impairment (3,4). It is prevalent in 50-80% of patients with advanced cancer (5). Unfortunately, cancer treatments such as chemotherapy and radiotherapy aggravate cachexia (6). CC can have a negative impact on physical function, tolerance to anticancer treatment, overall survival and well-being in patients with cancer (7). Moreover, it can also increase psychological stress and the financial burden on patients and their families (2,8).

In 2011, an international panel of experts identified a weight loss of >5% over 6 months, any degree of weight loss >2% in an individual with a body mass index <20 kg/m^2, or sarcopenia, defined as a skeletal muscle index <7.26 kg/m^2 in men and <5.45 kg/m^2 in women, as diagnostic criteria for CC (3). CC can be divided into three clinical stages according to the degree of weight loss and metabolic changes, namely pre-cachexia, cachexia and refractory cachexia (3). The main clinical symptoms of CC include anorexia, asthenia, fever, anemia, edema and wasting (7,9). The occurrence of CC has been attributed to systemic inflammation generated by tumor-host interactions and tumor-derived catabolic factors such as proteolysis-inducing factor, zinc-α2-glycoprotein (ZAG), parathyroid hormone-related protein and microRNAs (miRNAs) (6,7). Systemic inflammation is characterized by increased circulating levels of cytokines, including tumor necrosis factor (TNF)-α, TNF-like weak inducer of apoptosis,

interleukin (IL)-1, IL-6, IL-8, IL-20, interferon-γ, leukemia inhibitory factor, myostatin, activin and growth differentiation factor 15 (GDF15) (10-13). These factors drive metabolic disorders in multiple tissues and organs during CC, including the muscles (10,11,13,14), adipose tissue (10-12,15,16), heart (17), brain (10,11), liver (10,18-21), gallbladder (19), bone (22), pancreas (21), spleen (18), intestines (23), gonads (24) and blood (18,22,25). Table I summarizes the cytokines involved in the damage of various organs or tissues associated with CC. In addition, other factors such as cancer type, stage, tumor size, inter-individual genetics and sex can also influence the development and progression of CC (3,26,27). The current treatment protocol advocated for CC is a comprehensive treatment system based on drug therapy, including anti-inflammatory drugs, and measures to increase metabolism, inhibit catabolism and stimulate appetite, supplemented by nutrition, exercise and psychological support (28). However, the effectiveness of these treatment options for CC is unclear. Thus, an in-depth understanding of the key factors associated with CC is crucial for the early identification and development of novel therapeutic options.

GDF15 is a stress-induced cytokine that regulates food intake, energy metabolism and body weight (29). Its levels have been shown to be upregulated in patients with CC, as well as in animal models of pancreatic, colon, head and neck, breast and prostate cancers (30-33). Elevated circulating levels of GDF15 may lead to anorexia, weight loss and decreased survival in cases of CC (32). Notably, GDF15 plasma levels have been reported to be significantly higher in patients with pre-cachexia than in those with cachexia and refractory cachexia (30). These studies imply that GDF15 is closely associated with CC. The present review aims to clarify the role and molecular mechanisms of GDF15 in CC.

2. Characteristics of GDF15

GDF15 is a novel transforming growth factor (TGF)-β superfamily member that was first identified in activated macrophages (34). It is also known as macrophage inhibitory cytokine-1, nonsteroidal anti-inflammatory drug activated gene-1, prostate-derived factor, placental TGF-β and placental bone morphogenetic protein (29,35). The human *GDF15* gene is located on chromosome 19p13.1-13.2 and consists of two exons separated by an intron (36). GDF15 is synthesized as an inactive precursor protein consisting of a chain of 308 amino acids, including a signal peptide comprising 29 amino acids, a pro-peptide comprising 167 amino acids and a mature peptide comprising 112 amino acids (29,35). Following removal of the signal peptide, the remaining GDF15 pre-peptide dimerizes in the endoplasmic reticulum through specific disulfide bonding to form a pro-GDF15 dimer precursor. This precursor is subsequently cleaved by furin-like proteases at the RXXR site (amino acid 196), thereby releasing the C-terminal dimeric mature homodimer GDF15. Mature GDF15 eventually diffuses into the circulation as a 25-kD dimer (Fig. 1) (29,35).

GDF15 is widely expressed in body tissues at different levels under normal conditions, with high expression in the placenta, medium expression in the prostate and bladder, and low expression in the kidney, liver, colon, pancreas, stomach, gallbladder, breast, lung and endometrium (37-39). It has multiple biological functions (Fig. 2). The circulating concentrations of GDF15 range between 0.2 and 1.2 ng/ml in healthy individuals (38). These levels increase with age, pregnancy, exercise, smoking and obesity, and are also influenced by genetic and environmental factors (29,40). GDF15 is highly expressed in vascular smooth muscle cells, cardiomyocytes, endothelial cells, macrophages and adipocytes during oxidative stress, inflammation, tissue damage and cancer (41,42). GDF15 is elevated in a variety of cancers, including those of the prostate, colon, pancreas and breast (31,39). In one study, the mean value of serum GDF15 was almost two-fold higher in cancer patients compared with that in healthy controls (32). GDF15 plays a number of roles in tumorigenesis. In the initial stages of cancer, it induces tumor cell apoptosis and inhibits cancer progression (43). In later stages of cancer, it promotes tumor cell proliferation and metastasis (44,45). GDF15 has been recognized as a tumor biomarker that is closely implicated in tumor progression, cachexia and reduced survival (31,46).

As a member of the TGF-β superfamily, GDF15 signals through both Smad and non-Smad pathways. In the former pathway, GDF15 binds to the type II TGF-β receptor (TGFβRII) and activates the type I TGF-β receptor (TGFβRI), also known as activin receptor-like kinase (47,48). Subsequently, TGFβRII and TGFβRI form a heteromeric complex that induces the phosphorylation of Smad2/3 and Smad1/5/8. The phosphorylated Smad2/3 and Smad1/5/8 are then able to bind to co-Smad (Smad4) and enter the nucleus to regulate gene expression (47,48). In addition, GDF15 exerts its biological functions through non-Smad-dependent pathways such as phosphoinositide 3-kinase/Akt/mammalian target of rapamycin and TGF-β-activated kinase-1 (TAK-1)/nuclear factor-κB (NF-κB), or through other receptors such as glial cell-derived neurotrophic factor receptor α-like (GFRAL) and epidermal growth factor receptor 2 (Fig. 3) (16,45,49,50).

3. GDF15 and anorexia in CC

A clinical study evaluated the association between serum levels of GDF15 and anorexia in patients with cancer and reported that GDF15 levels were significantly higher in anorexic patients than in non-anorexic ones (51). This implies that high levels of GDF15 in patients with cancer are associated with anorexia. There is a body of evidence suggesting that GDF15 induces anorexia in patients with CC (16,33,51). Johnen *et al* (33) originally described the role of GDF15 in CC and anorexia. They observed that food intake was reduced in tumor-bearing mice that were transgenically modified to overexpress GDF15. Lower food intake indirectly resulted in fat loss, tibial and gastrocnemius muscle atrophy and 28% weight loss in tumor-bearing mice (33). These effects were blocked by the administration of a GDF15 monoclonal antibody and reproduced by the injection of recombinant GDF15 (33). Johnen *et al* (33) further demonstrated that GDF15 promoted anorexia by interacting with TGFβRII to induce the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and transducer and activator of transcription 3 (STAT3) in the hypothalamus. This process ultimately inhibited orexigenic neuropeptide Y (NPY) neurons and stimulated anorexigenic pro-opiomelanocortin (POMC) neurons (Fig. 4). GFRAL is a specific receptor for GDF15 that is uniquely expressed in

Table I. Cytokines involved in organ or tissue damage during CC.

Organ or tissue	Alterations in CC	Relevant cytokines	(Refs.)
Muscle	Increased muscle proteolysis, increased myocyte apoptosis, reduced muscle synthesis, decreased regeneration, impaired mitochondrial metabolism	TNF-α, TWEAK, IL-6, LIF, IL-1-β, IFN-γ, GDF15, IL-8, myostatin, activin	(10,11,13,14)
Adipose	Increased lipolysis, reduced synthesis, white adipose tissue browning	IL-6, LIF, TNF-α, IFN-γ, IL-1-β, IL-8, GDF15, IL-20	(10-12,15,16)
Heart	Atrophy, mitochondrial dysfunction, heart failure	IL-6, TNF-α, TWEAK	(17)
Brain	Anorexia	TNF-α, IL-1β, IL-6, IFN-γ, LIF, GDF15	(10,11)
Liver	Increased acute phase response, increased gluconeogenesis, increased bile acid metabolism, mitochondrial dysfunction	IL-6, myostatin, activin, TNF-α	(10,18-21)
Gallbladder	Cholestasis	IL-6	(19)
Bone	Osteoclast activation, bone loss, hypercalcemia	IL-6	(6,22)
Pancreas	Insulin resistance	TNF-α	(13,21)
Spleen	Splenomegaly	Myostatin, activin	(18)
Intestine	Intestinal barrier dysfunction, increase in Enterobacteriaceae	IL-6	(23)
Gonad	Decreased testis size, hypogonadism	IL-6	(24)
Blood system	Decreased hemoglobin, increased platelets	IL-6, TNF-α, myostatin, activin	(18,22,25)

CC, cancer cachexia; TNF-α, tumor necrosis factor-α; TWEAK, TNF-like weak inducer of apoptosis; IL, interleukin; IFN-γ, interferon-γ; LIF, leukemia inhibitory factor; GDF15, growth differentiation factor 15.

the hindbrain area postrema and nucleus tractus solitarius (52). The binding of GDF15 to GFRAL induces the activation of its co-receptor Ret proto-oncogene (RET), which further promotes the phosphorylation of ERK, Akt and phospholipase C γ, resulting in decreased appetite in cachectic mice (Fig. 4) (16). The GDF15/GFRAL/RET pathway therefore is considered a novel therapeutic target for anorexia and weight loss in CC (16).

GDF15 may also influence CC anorexia through other mechanisms. It has been shown that GDF15 activates the hypothalamic-pituitary-adrenal (HPA) axis in a GFRAL-dependent manner, leading to the secretion of corticotropin-releasing hormone (CRH) and glucocorticoids (53). CRH has been found to promote anorexia in CC, due to the inhibition of NPY neurons (Fig. 4) (54).

4. GDF15 and muscle atrophy in CC

As GDF15 is a myokine, its circulating levels are negatively correlated with muscle mass in numerous diseases, including COPD, intensive care unit-acquired weakness (ICUAW), Crohn's disease, pulmonary hypertension (PH) and CC (30,55-58). Muscle atrophy, including that of skeletal, chest, diaphragm and cardiac muscle, is a hallmark of CC and a major cause of mortality in patients with cancer (4,59).

One study indicated that GDF15 indirectly induced muscle atrophy in CC via the inhibition of feeding centers in the hypothalamus (33). However, in other *in vitro* studies, GDF15 increased the expression of muscle ring finger 1 (MuRF1) and muscle atrophy F-box (MAFbx)/atrogin-1 and decreased myotube diameter (55,57). Researchers also found that the expression of GDF15 and MAFbx/atrogin-1 was elevated in the atrophied rectus abdominis muscle of patients with ICUAW (55). The muscle-specific E3 ubiquitin ligases MuRF1and MAFbx/atrogin-1 are primary factors that drive muscle protein degradation in CC (2). These studies indicate that GDF15 may contribute to muscle atrophy in CC, independently of food intake. It has been reported that GDF15/GFRAL/RET directly induces muscle atrophy in CC (16). In addition, GDF15 has been shown to directly regulate muscle mass in CC through other mechanisms. Lerner *et al* (30) demonstrated that the activation of mitogen-activated protein kinase 11 (MAP3K11) by GDF15 promoted gastrocnemius and flounder muscle reduction in

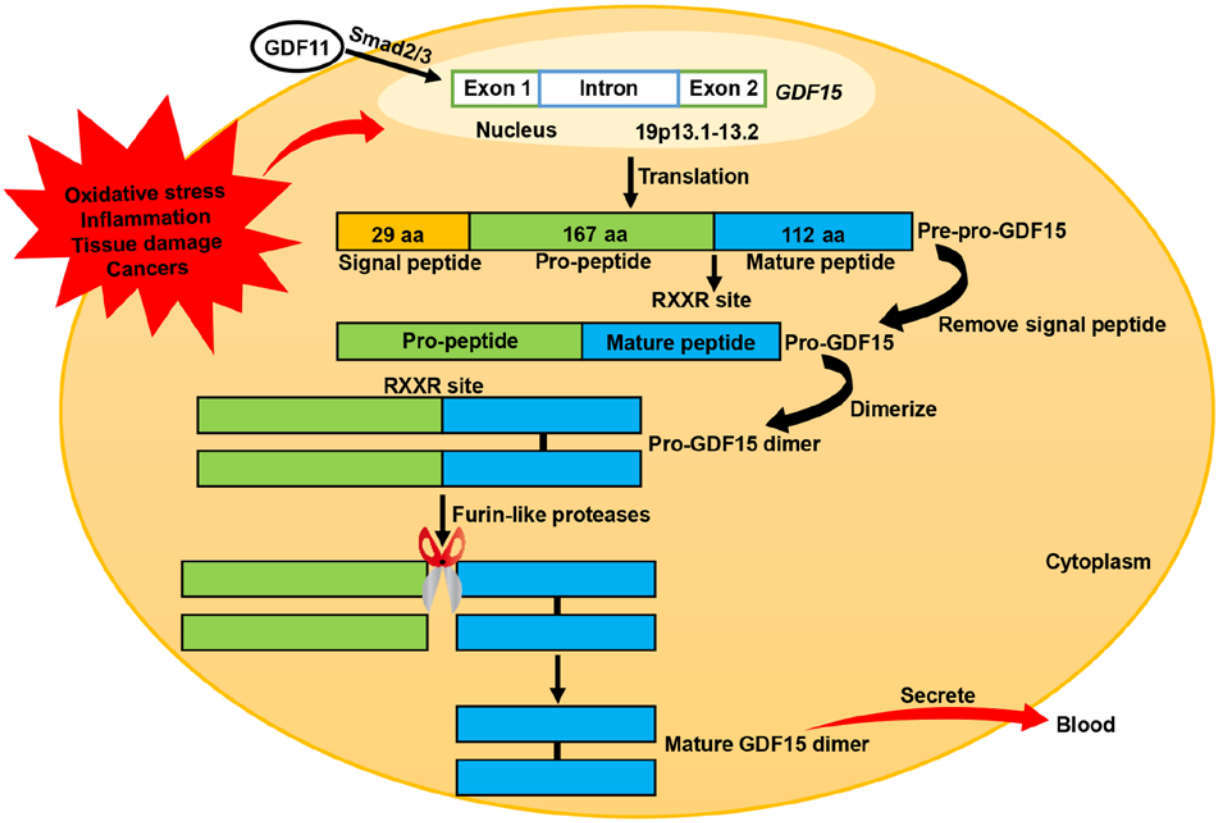

Figure 1. Synthesis process of GDF15. The *GDF15* gene is located on chromosome 19p 13.1-13.2 and consists of two exons and an intron. In response to oxidative stress, inflammation, tissue damage and cancer, GDF15 is synthesized into pre-pro-GDF15, an inactive precursor protein, by intracellular translation. Pre-pro-GDF15 is a 308-aa peptide that comprises a 29-aa signal peptide, 167-aa pro-peptide and 112-aa mature peptide. After removal of the signal peptide, the residual pro-GDF15 is dimerized, cleaved by furin-like proteases at an RXXR site and secreted into the circulation as a mature GDF15 dimer. Another member of the transforming growth factor superfamily, GDF11, promotes GDF15 synthesis by inducing Smad2/3 to bind to the GDF15 promoter. GDF15, growth differentiation factor 15; GDF11, growth differentiation factor 11; aa, amino acid.

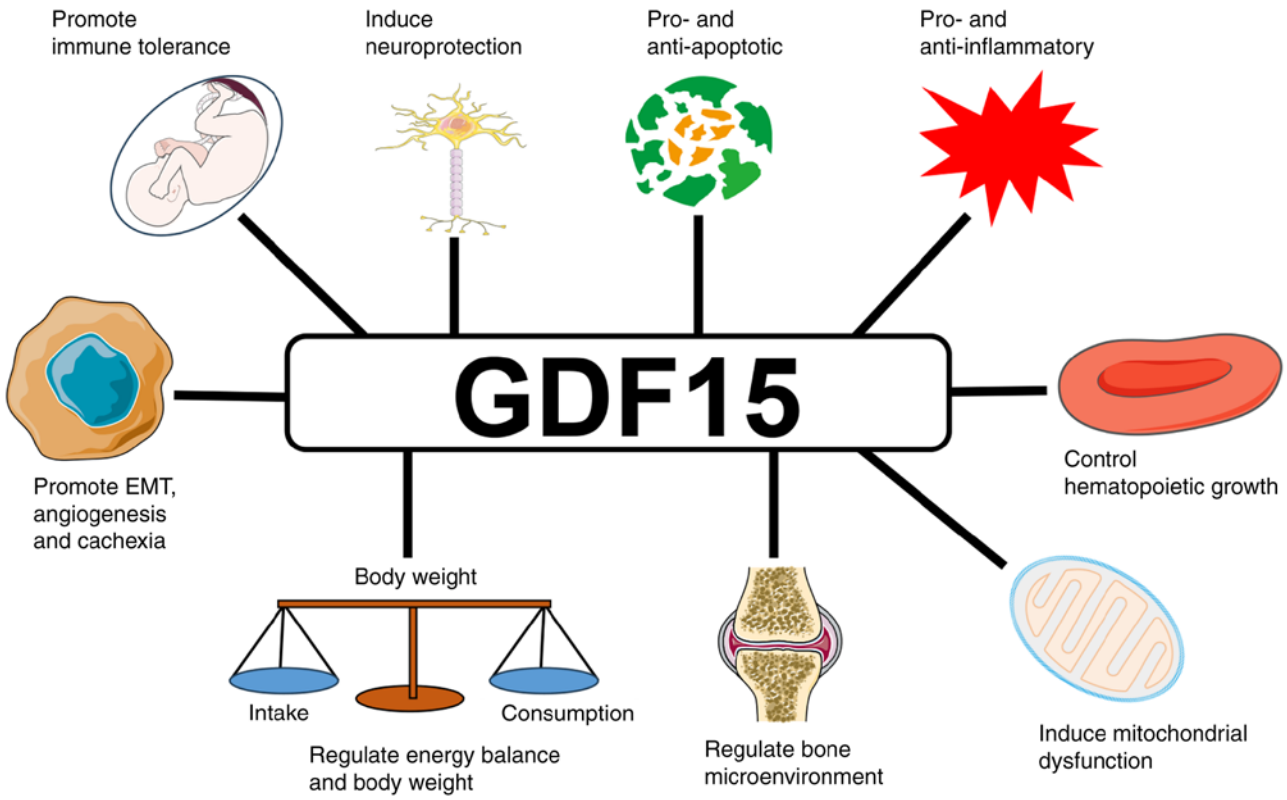

Figure 2. Biological functions of GDF15. GDF15, growth differentiation factor 15; EMT, epithelial-mesenchymal transition.

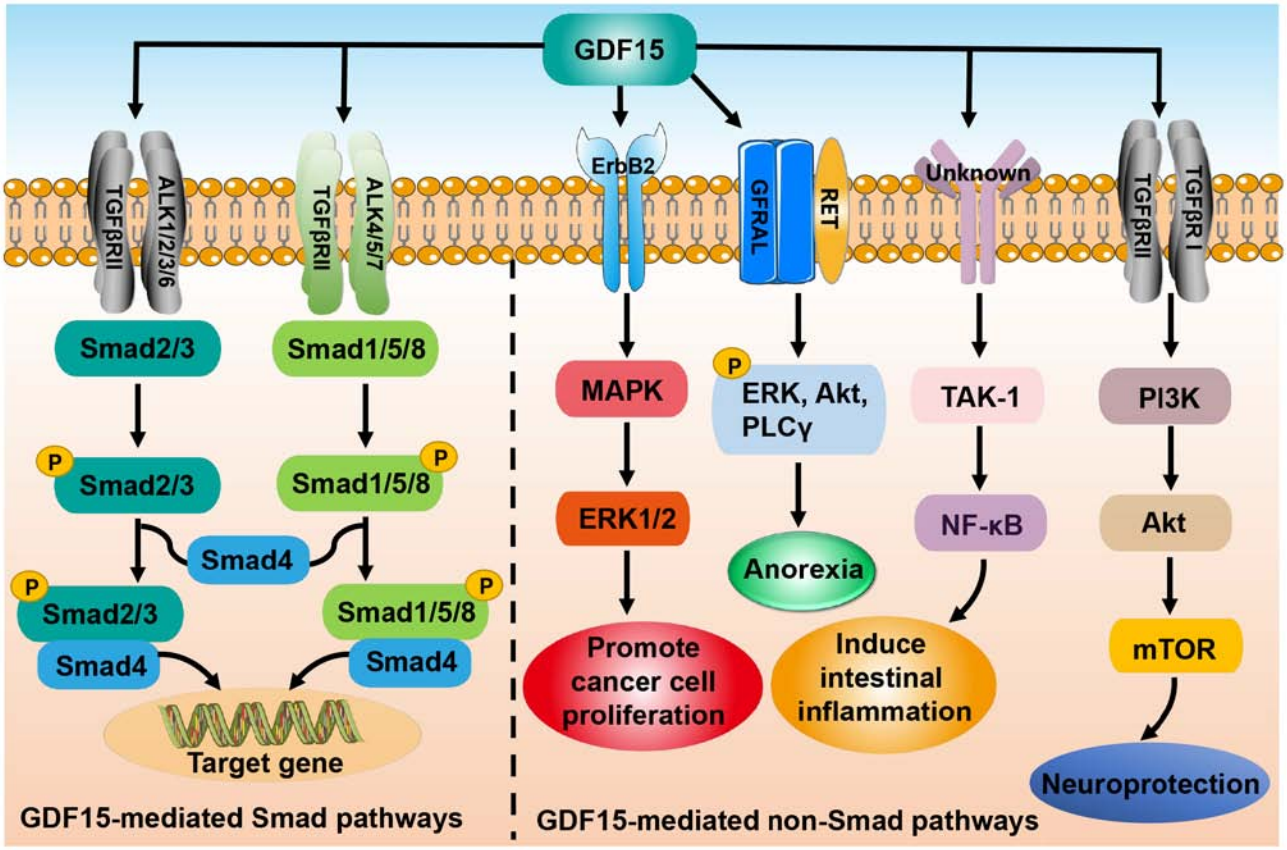

Figure 3. GDF15-mediates Smad and non-Smad signaling pathways. In the Smad pathways (left), GDF15 binding to TGFβRII activates ALK1/2/3/6 and ALK4/5/7, leading to the phosphorylation of Smad2/3 and Smad1/5/8. The phosphorylated Smads form complexes with Smad4 and thereby regulate gene transcription. In the non-Smad pathways (right), GDF15 exerts neuroprotective effects via PI3K/Akt/mTOR pathway and promotes intestinal inflammation through the TAK-1/NF-κB pathway. In addition, GFRAL interacts with RET receptors after binding to GDF15 to initiate ERK, Akt and PLCγ phosphorylation which induces anorexia. GDF15 also interacts with the receptor ErbB2 to activate the MAPK/ERK1/2 pathway and promote cancer cell proliferation. GDF15, growth differentiation factor 15; TGFβRII, type II transforming growth factor-β receptor; ALK, activin receptor-like kinase; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; TAK-1, transforming growth factor-β-activating kinase-1; NF-κB, nuclear factor-κB; GFRAL, glial cell-derived neurotrophic factor receptor α-like; RET, ret proto-oncogene; ERK, extracellular signal-regulated kinase; PLCγ, phospholipase C γ; ErbB2, epidermal growth factor receptor 2; MAPK, mitogen-activated protein kinase; p, phosphorylation.

a genetically engineered mouse model of cachexia. These cachectic mice exhibited weight gain and the retention of skeletal muscle when treated with anti-GDF15 antibody (30). Subsequently, Zhang *et al* (60) showed that elevated GDF15 levels in the serum exosomes of mice with colon cancer caused the loss of gastrocnemius muscle mass via the B cell lymphoma-2/caspase-3 pathway (Fig. 4).

Despite these studies, the mechanism by which GDF15 facilitates the loss of skeletal muscle mass in CC remains unclear. It has been reported that GDF15 reduces muscle mass in patients with PH and ICUAW through TAK-1/NF-κB/atrogin-1 signaling, and downregulates the expression of various miRNAs, including miR-1, miR-133a and miR-499, in muscle (55,57). In one study, the upregulated phosphorylation of Smad2/3 was observed in the muscles of patients with ICUAW, suggesting that GDF15 may mediate muscle atrophy via the classical Smad pathway; however, this was not observed in C2C12 murine cell-based myotubes exposed to GDF15 *in vitro* (55). In addition, high levels of GDF15 are known to inhibit the expression of hepcidin and lead to iron overload (61). A recent study revealed that iron overload induced muscle atrophy in patients with gastric cancer and cachexia (62). Moreover, GDF15/GFRAL signaling has been shown to activate the HPA axis and trigger the release of glucocorticoids (53). Animal models of colon, Lewis lung carcinoma (LLC) and pancreatic CC have shown that dysregulated glucocorticoid levels increase the expression of MuRF1 and MAFbx/atrogin-1 in skeletal muscle, driving the breakdown of muscle protein (63). Additional studies are warranted to identify whether GDF15 regulates muscle atrophy in CC through these mechanisms (Fig. 4).

5. GDF15 and adipose tissue depletion in CC

GDF15 is expressed in adipose tissue and secreted by adipocytes (64). Physiological concentrations of GDF15 trigger lipolysis in human adipose tissue (64). Although skeletal muscle is the main tissue that is affected by CC, a study found that fat loss occurs rapidly and earlier than muscle tissue depletion in CC (65).

The molecular mechanisms of GDF15-induced fat loss in CC have not been well studied, and pre-clinical models have mainly been used. In one study, for example, mice with prostate CC and high GDF15 expression lost all retroperitoneal fat and exhibited a reduction of fat in the groin and epididymis of 54 and 89%, respectively, due to decreased food intake (33).

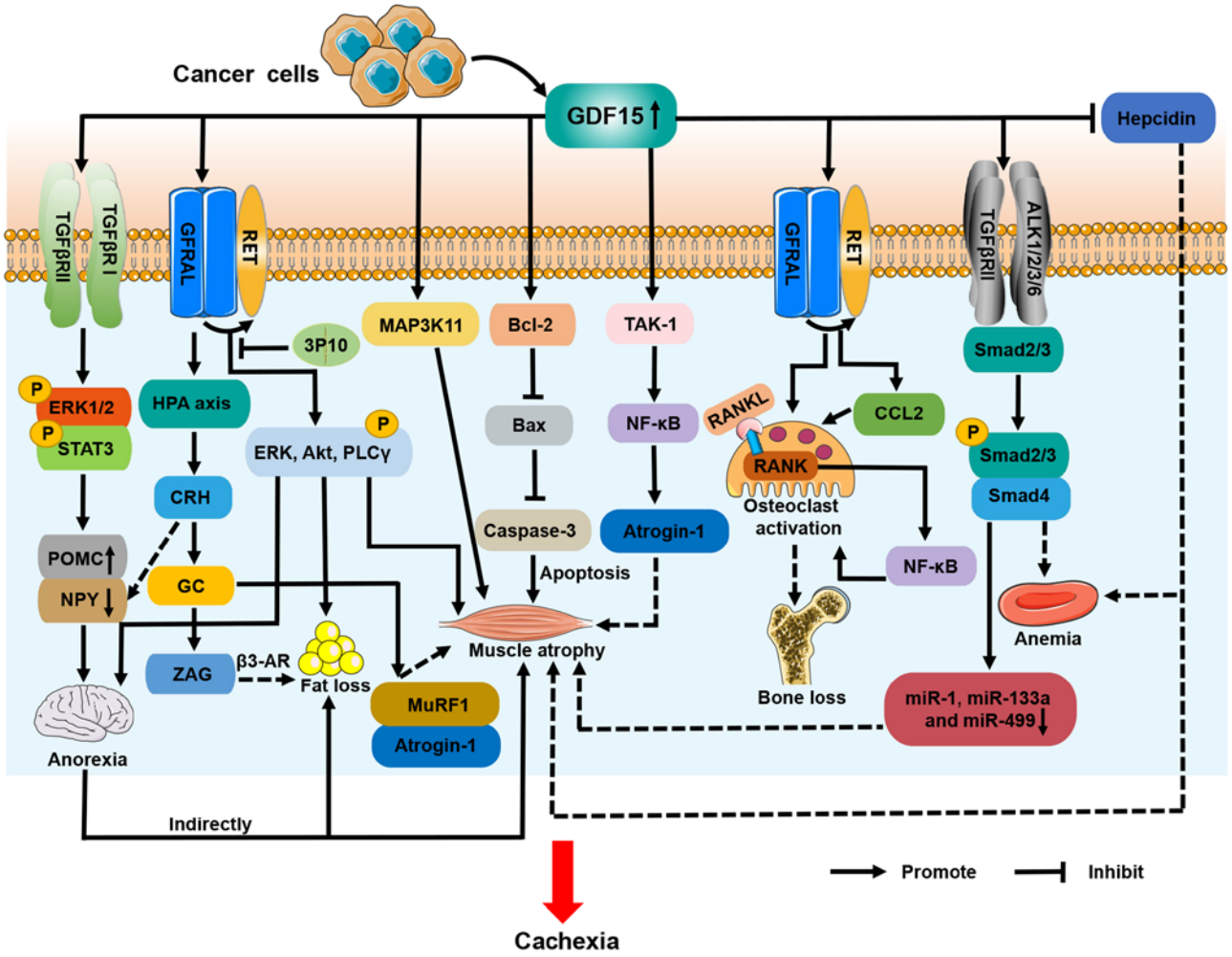

Figure 4. Roles and mechanisms of GDF15 in CC. Solid lines indicate demonstrated mechanisms and dashed lines indicate possible mechanisms. GDF15 initiates the phosphorylation of ERK, Akt and PLCγ via GFRAL/RET signaling to mediate anorexia, muscle atrophy and fat loss in CC; the antibody 3P10 can inhibit these processes. Binding of GDF15 to TGFβRII and TGFβRI leads to the phosphorylation of ERK1/2 and STAT3. This pathway downregulates NPY and upregulates POMC to induce anorexia. Reduced food intake indirectly contributes to muscle wasting and fat depletion in cancer cachexia. Activation of MAP3K11/GDF15 and Bcl-2/caspase-3 apoptotic pathways is responsible for CC muscle atrophy, but their specific receptors are unknown. GDF15 may also reduce muscle mass through the TAK-1/NF-κB signaling pathway, and downregulates the expression of miR-1, miR-133a and miR-499 in muscle. In addition, GDF15 may promote muscle atrophy and fat loss by stimulating the HPA axis. Moreover, the GDF15/Smad2/3 pathway may be involved in CC-induced anemia. High levels of GDF15 directly inhibit the expression of hepcidin, which could further trigger anemia and muscle wasting in CC. GDF15, growth differentiation factor 15; CC, cancer cachexia; ERK, extracellular signal-regulated kinase; PLCγ, phospholipase C γ; GFRAL, glial cell-derived neurotrophic factor receptor α-like; RET, ret proto-oncogene; TGFβRII, type II transforming growth factor-β receptor; TGFβRI, type I transforming growth factor-β receptor; ERK1/2, extracellular signal-regulated kinase1/2; STAT3, signal transducer and activator of transcription 3; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; MAP3K11, mitogen-activated protein kinase 11; Bcl-2, B cell lymphoma-2; TAK-1, transforming growth factor-β-activating kinase-1; NF-κB, nuclear factor-κB; miR, microRNA; HPA, hypothalamus-pituitary-adrenal; CRH, corticotropin-releasing hormone; GC, glucocorticoids; ZAG, zinc-α2-glycoprotein; β3-AR, β3-adrenergic receptor; MuRF1, muscle ring finger 1; Bax, Bcl-2 associated X protein; RANK, receptor activation of NF-κB; RANKL, RANK ligand; CCL2, CC motif chemokine ligand 2; p, phosphorylation.

In addition, in another study GDF15 increased the expression of differentiation and thermogenic genes in brown adipocytes; the upregulated expression of iodothyronine deiodinase 2, β3-adrenergic receptor (β3-AR), and very long chain fatty acid-3 through GFRAL/RET signaling in cachectic mouse adipose tissue led to a loss of fat and body weight (Fig. 4) (16). The therapeutic monoclonal antibody 3P10, which is a GFRAL antagonist and RET signaling inhibitor, has been reported to reverse lipid hyperoxidation and prevent CC in mice (16). Furthermore, ZAG is known to be a lipid-mobilizing factor and has been demonstrated to stimulate lipolysis via β3-AR during CC (66). Glucocorticoids have been shown to increase ZAG expression and thereby promote lipolysis (67), suggesting that GDF15 may increase adipose tissue depletion in CC via the HPA axis (Fig. 4).

6. GDF15 and bone loss in CC

Bone loss is caused by an imbalance between bone-resorbing osteoclasts and bone-forming osteoblasts, which can result in decreased bone mineral density (BMD), bone mass and bone strength (68). Abnormal activation of osteoclasts is the cause of various bone diseases, including osteoporosis, rheumatoid arthritis, multiple myeloma and metastatic cancers (69). A link between CC and bone loss has been established in patients with CC and in animal models (5,70-72). Elevated levels of

Table II. Clinical trials targeting GDF15 in patients with cancer and CC.

Clinical trial identifier	Start year	Compound/drug	Participants, n	Disease	Phase	Status	Results	Locations	(Refs.)
NCT05865535	2023	AV-380	30 (estimated)	Colorectal and pancreatic CC	I	Recruiting	NA	USA	NA
NCT05546476	2022	Ponsegromab	168 (estimated)	Non-small cell, pancreatic and colorectal CC	II	Recruiting	NA	Spain, Taiwan, USA, Australia, Bulgaria, Canada, China, Czechia, Hungary, Japan, Poland, Slovakia	NA
NCT04803305	2021	Ponsegromab	18 (actual)	Non-small cell lung, pancreatic, colorectal, prostate, breast and ovarian CC	I	Completed	NA	Canada, USA	NA
NCT04299048	2020	Ponsegromab	11 (actual)	Non-small cell lung, pancreatic and colorectal CC	Ib	Completed	Compared with controls, patients treated with ponsegromab had lower circulating GDF-15 levels and increased body weight, physical activity and appetite	USA	(92)
NCT04725474	2020	CTL-002	155 (estimated)	Adult solid tumor	I/II	Recruiting	NA	Germany, Spain, Switzerland	NA
NCT05397171	2022	AZD8853	16 (actual)	Bladder, colorectal and non-small cell lung cancers	II	Terminated	NA	Canada, USA	NA

Data in the table are from ClinicalTrials.gov. CC, cancer cachexia; GDF15, growth differentiation factor 15; NCT, National Clinical Trial; NA, not available.

C-telopeptide of type I collagen (CTX-1) in serum have been demonstrated to be indicative of increased bone resorption and accelerated bone loss (73). Also, studies in humans have shown that serum CTX-1 is significantly elevated in patients with ovarian, lung and gastrointestinal CC compared with non-cachectic controls (70-72). In a retrospective study, patients with pancreatic CC were found to have significantly lower BMD than control patients who underwent benign gall-bladder surgery, and those patients with pancreatic CC with osteopenia exhibited lower median and 2-year postoperative survival times than those without osteopenia (74). In an animal model of LLC-induced CC, Yu *et al* (5) observed a reduction

in bone trabecular volume and BMD, and an increase in osteoclast activation. This result was consistent with the findings of a previous study regarding cachectic mice with colon cancer (71). The researchers further established that the bone loss was induced via the Janus kinase/STAT3 pathway, with the involvement of glucocorticoids (5). Surprisingly, bone loss preceded the onset of muscle and fat loss in the LLC-induced model of cachexia (5). These studies all demonstrate that bone loss is closely associated with CC.

It has been demonstrated that GDF15 increases osteoclast differentiation and inhibits osteoblast differentiation *in vivo* and *in vitro*, leading to disturbances in bone metabolism and bone loss (75,76). Wakchoure *et al* (77) injected a Du-145 human prostate cancer cell line overexpressing GDF15 into the tibias of C57/B6 mice, and found that increased GDF15 was associated with osteoclast activation and cachexia. This result implies that GDF15 is involved in bone loss in CC, but the biological mechanism underlying this has not yet been identified. In a hypoxic mouse model induced by right femoral artery ligation, the upregulation of GDF15 expression in osteoblasts was observed, which stimulated the receptor activator of NF-κB ligand (RANKL)-induced NF-κB signaling pathway and promoted osteoclast activation in the mice, resulting in decreased bone mass (76). An anti-GDF15 antibody inhibited this process and the associated bone loss (76). Moreover, Siddiqui *et al* (78) demonstrated that elevated GDF15 in prostate cancer upregulated the expression of C-C motif chemokine ligand 2 and RANKL through the GFRAL/RET pathway, thereby activating osteoclasts and leading to decreased bone mass. Other studies have reported that the GDF15/GFRAL/RET receptor signaling complex in the brain mediates anorexia in CC (16,79). GFRAL and RET receptors have also been shown to be expressed in the tibiae (Fig. 4) (78). These findings indicate that GDF15 may activate GFRAL and RET receptors expressed on osteocytes, thereby inducing bone loss in CC.

7. GDF15 and anemia in CC

A recent retrospective cohort study conducted across multiple centers indicated that patients with CC had lower hemoglobin levels than those without cachexia (80). The study demonstrated that patients with CC developed anemia. However, the molecular mechanisms underlying the CC-induced anemia remain unclear. A study in mice with lung CC found that TGF-β activated the Smad2/3 signaling pathway and inhibited hematopoietic stem cell and erythropoietic cell production. The mice exhibited a significant reduction in hemoglobin and erythrocyte levels in the peripheral blood (81). Additionally, GDF15 is produced by erythroid precursor cells, and high levels of GDF15 are known to inhibit effective erythropoiesis and the expression of hepcidin, leading to anemia and iron overload (61). Hepcidin is a hepatic peptide hormone that coordinates the systemic homeostasis of iron. Jiang *et al* (82) showed that increased serum levels of GDF15 in patients with cancer are associated with downregulated hepcidin levels and cancer-related anemia. According to these findings, we hypothesize that GDF15 may play a role in CC-associated anemia (Fig. 4).

8. GDF15 and other TGF-β superfamily factors in CC

The TGF-β superfamily is a class of secreted peptide cytokines with multiple members that are involved in the development of CC (83). They are categorized into four main subfamilies based on sequence similarity, namely bone morphogenetic proteins/GDFs, activins/inhibins/nodal, TGF-βs and others (84). GDF8, which is also known as myostatin, and activin A have been reported to bind to activin receptor type 2B on skeletal muscle to promote the phosphorylation of Smad2/3 and inhibit Akt phosphorylation, leading to activation of the ubiquitin-proteasome system that eventually leads to muscle atrophy (54). Greco *et al* (85) demonstrated that blocking TGF-β reduces skeletal muscle catabolism and weight loss in mouse models of pancreatic CC, and decreases phosphorylated Smad2/3 signaling in muscle tissues. This suggests that TGF-β is also involved in skeletal muscle atrophy in CC, via activation of the Smad2/3 signaling pathway. Another member of the TGF-β superfamily, GDF11, is highly homologous to GDF8 (86). GDF11 directly increases the expression of MuRF1 and MAFbx/atrogin-1 in skeletal muscle, leading to muscle atrophy and cachexia (87). In addition, Zimmers *et al* (88) demonstrated that elevated circulating levels of GDF11 are associated with cardiac atrophy.

CC is accompanied by a complex pro-inflammatory environment in the body (Table I). Therefore, it is possible that proteins of the TGF-β superfamily may coordinate with one another to promote the development and progression of CC. One preclinical study found that GDF11 induced the upregulation of GDF15 expression by activating the binding of Smad2/3 to the GDF15 promoter (Fig. 1) (87). The upregulated GDF15 further suppressed appetite and indirectly induced weight loss (87). However, no further studies have identified the relationships between GDF15 and other TGF-β family members that may be involved in cachexia, such as GDF8, activin A and TGF-β. It would be of great significance to investigate the associations and roles of these proteins in CC in future clinical studies.

9. Targeting GDF15 in CC

CC is a complex syndrome of multiple organ and tissue depletion (6). Despite advances in cancer treatment, there are no effective therapies for CC. To improve the quality of life of patients, it is currently advocated to take a multimodal approach to treatment, based on medication supplemented by nutrition, exercise and psychological counseling (28). As the basis for the treatment of CC, pharmacotherapeutic strategies can stimulate appetite, reduce inflammation, increase anabolism and decrease catabolism (54). During conferences on cachexia, researchers have also reported some novel therapeutic targets for the treatment of CC, such as ZRT/IRT-like protein14, fibroblast growth factor-inducible receptor 14, serum amyloid A1, MuRF1 and GDF15 (89,90).

Several clinical trials have been conducted to investigate the role of GDF15 antibodies in CC. Ponsegromab is a human monoclonal antibody that targets GDF15 (91). It binds to GDF15 and prevents it from binding to GFRAL, thereby blocking GDF15/GFRAL-mediated signaling. A recent phase-1b clinical trial (NCT04299048) conducted by Pfizer

evaluated the safety and efficacy of ponsegromab in patients with non-small cell lung, colorectal and pancreatic cancers accompanied by cachexia. In addition to standard anticancer treatments, patients with cachexia received ponsegromab subcutaneously every 3 weeks for a total of 12 weeks (92). The results showed that the median circulating GDF15 levels in patients treated with ponsegromab were lower than the those in healthy controls (92). Moreover, ponsegromab treatment significantly increased weight, physical activity and appetite in patients with CC (92). Clinical studies of ponsegromab in CC remain ongoing and are currently in phase II (91). Table II summarizes clinical trials regarding GDF15 that have been conducted in patients with cancer and CC (https://clinicaltrials.gov/). The information obtained from these studies may ultimately enable patients with CC to benefit from these treatments, and also guide future studies.

Animal experiments further illustrate that the inhibition of GDF15 is an effective strategy for the treatment of CC (30,33,93). In several animal models, including prostate, ovarian, colon and breast cancer, leukemia and fibrosarcoma models, cachectic mice treated with GDF15 antibodies exhibited increased food intake, muscle mass and adipose tissue, ultimately leading to weight gain (30,33,93). These studies illustrate that targeting GDF15 alleviates CC via the prevention of anorexia, and the loss of muscle and fat. In addition, Hinoi *et al* (76) demonstrated that an anti-GDF15 antibody inhibited bone loss and osteoclast activation in the tibias of hypoxic mice. The inhibition of GDF15 has also been observed to inhibit ineffective erythropoiesis and improve anemia in patients with cancer (94). Thus, GDF15 may be a potential target for the treatment of bone loss and anemia in CC. Moreover, one study revealed that the combination of an anti-GDF15 antibody with the angiogenesis inhibitor tivozanib significantly increased body weight and survival in mice with CC, when compared with tivozanib alone (30). This implies that the inhibition of tumor growth and amelioration of CC may prolong the lifespans of patients with this condition. The strategy represents a new therapeutic prospect, but requires translation into clinical studies.

10. Discussion and future prospects

In the present review, the roles and mechanisms of GDF15 in CC are summarized. Studies have indicated that the effects of GDF15 on CC are associated with inhibition of the feeding center. However, since GFRAL was identified as an exclusive receptor for GDF15, further studies have demonstrated that GDF15 also induces metabolic effects that are independent of food-intake behavior. It has been established that GDF15 interacts with GFRAL in the brainstem to suppress appetite, promote fat loss and reduce muscle mass in CC. GDF15 also directly promotes muscle atrophy in CC via the apoptotic pathway and MAP3K11, but the receptors involved in these processes are currently unknown. It also appears that GDF15 may have a role in bone loss and anemia in CC. However, it remains uncertain whether other GDF15 receptors or pathways, such as the GDF15/GFRAL/HPA axis, promote the development of CC. Therefore, the roles and potential molecular mechanisms of GDF15 in CC, particularly its receptors and downstream signaling pathways, require further investigation. In addition, GDF15 is a potential therapeutic target for CC, and clinical trials are being conducted to study the safety and therapeutic value of GDF15 antibodies in patients with CC. Notably, since CC is attributed to complex interactions between tumor cells and the host, it may be necessary to combine GDF15-targeting antibodies with anticancer therapies such as immunotherapy or targeted therapy to improve the outcomes of patients with CC.

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Competing interests

The authors declare that they have no competing interests.

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