Received: 26 April 2024 | Accepted: 3 July 2024

DOI: 10.1111/eci.14290

SYSTEMATIC REVIEW

WILEY

# The implicated role of GDF15 in gastrointestinal cancer

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**Funding information**
National Research Foundation of Korea, Grant/Award Number: NRF-2022K2A9A1A06091879

## Abstract

**Background:** Growth differentiation factor 15 (GDF15), a stress-responsive cytokine from transforming growth factor superfamily, is highly expressed in mammalian tissues, including pancreas, stomach and intestine under pathological conditions. In particular, elevated levels of GDF15 might play an important role in the development and progression of various gastrointestinal cancers (GCs), suggesting its potential as a promising target for disease prediction and treatment.

**Methods:** In this review, systematic reviews addressing the role of GDF15 in GCs were updated, along with the latest clinical trials focussing on the GDF15-associated digestive malignancies.

**Results:** The multiple cellular pathways through which GDF15 is involved in the regulation of physiological and pathological conditions were first summarized. Then, GDF15 was also established as a valuable clinical index, functioning as a predictive marker in diverse GCs. Notably, latest clinical treatments targeting GDF15 were also highlighted, demonstrating its promising potential in mitigating and curing digestive malignancies.

**Conclusions:** This review unveils the pivotal roles of GDF15 and its potential as a promising target in the pathogenesis of GCs, which may provide insightful directions for future investigations.

**KEYWORDS**
gastrointestinal cancer, growth differentiation factor 15, immunotherapy, predictive marker

## 1 | INTRODUCTION

Approximately 332 million people are estimated to die from gastrointestinal cancers (GCs) annually worldwide (*gco.iarc.fr/*). A considerable segment of these occurrences involves malignancies, contributing to elevated morbidity and mortality rates.[1] Despite advancements in medical technology, the rapid progression of GCs, often characterized by benign clinical symptoms during the early stages, presents challenges in timely diagnosis and effective treatment, thereby impacting overall survival rates.[2] Certain environmental risk factors associated with an increased susceptibility to GCs were identified, including obesity, smoking, alcohol and infection with helicobacter pylori.[3] Meanwhile, emerging evidence has illuminated the role of genetic risk factors in predisposing individuals to GCs, fostering the prospect of prognosticating GCs through the identification of specific genetic biomarkers. Diverse a variety of serum biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9), are currently utilized for the detection and evaluation of GCs treatments, the accuracy remains suboptimal, potentially leading to misdiagnosis and deferred instruction.[4] In this case, there exists an urgent imperative to investigate novel targets endowed with enhanced predictive capabilities, while offering promising directions for GCs treatment.

Growth differentiation factor 15 (GDF15) is a member of the transforming growth factor-beta (TGFβ) superfamily, which plays a crucial role in metabolic and cancerous diseases.[5,6] Under physical conditions, GDF15 is typically expressed at low levels across most somatic tissues; however, it exhibits abundant expression in specific organs such as prostate and placenta.[7] Notably, GDF15 expression often increase in the context of various cancers, including those affecting digestive system.[8] Correlations have been observed between GDF15 expression and critical tumour characteristics, including size, stage and invasiveness, implicating GDF15 in cancer progression.[9] Functionally, GDF15 is implicated in cancer cell proliferation, immune escape and disruption of metabolic balance, which may initiate and exacerbate cancer development.[10] In this regard, accumulating research tends to explore the value of GDF15 in cancer biology and its potential implications for diagnostic and therapeutic strategies. This review offers an updated overview of the cellular mechanisms driven by GDF15 in both physiological and pathological contexts, with a specific focus on its emerging significance as a biomarker in GCs, which may provide insightful direction for further immunotherapy.

## 2 | GDF15-RELATED SIGNALLING PATHWAYS

### 2.1 | SMAD and non-SMAD pathways

TGFβ is a superfamily conveying signals to the intracellular messengers, SMADs, through cell-surface serine/threonine kinase receptors. Phosphorylated SMADs transfer from the cytoplasm into the nucleus to modulate gene expression and fundamental cellular processes. As a divergent member of TGFβ, GDF15 can also activate and regulate SMADs, contributing to its involvement in cancer, inflammation and other diseases (Figure 1A). GDF15 in both serum and the nucleus can operate through the SMAD pathway,[11–14] but the precise biological roles, such as anti−/pro-tumour advancement, remain to be clarified through further research. In addition to SMADs, GDF15 also engages in non-SMAD pathways to reinforce or attenuate multicellular functions.[15] GDF15 exhibits precise binding to its receptor, GDNF family receptor α–like (GFRAL) and forms GDF15-GFRAL complex.[16] This complex necessitates interaction with the coreceptor, rearranged during transfection (RET), to initiate intracellular signalling cascades activated by GDF15 stimulation. Due to the restricted expression of GFRAL to specific neurons in the hindbrain, the central mechanism serves as the pathway through which the GDF15-GFRAL complex modulates feeding behaviour and maintains energy homeostasis.[17] This modulation is implicated in numerous pathological conditions, including obesity, cachexia and cancer. Except for GFRAL, evidence suggesting that GDF15 may also exhibit peripheral activities to exert physical or pathological conditions.[18] Latest studies reported that GDF15 promotes the growth, survival and infiltration of diverse tumours, such as oesophageal cancers,[19] glioblastoma,[20] liver cancers[21] and multiple myeloma,[22] mainly through the activation of PI3K/Akt and MEK/Erk cascades (Figure 1B).

### 2.2 | Wnt pathway

The classic Wnt signalling was characterized for its pivotal role in oncogenesis,[23] while recent findings have revealed its broader indications in modulating immune response,[24] and orchestrating a myriad of physiological processes in diverse tissues.[25] Latest research has revealed that Wnt signalling may intervene in the expression of GDF15 across various contexts. Wnt signalling activation has been demonstrated to induce GDF15 expression in regulatory T cells, establishing a feed-forward mechanism that exacerbates inflammation.[26] Besides, modulation of Wnt pathway

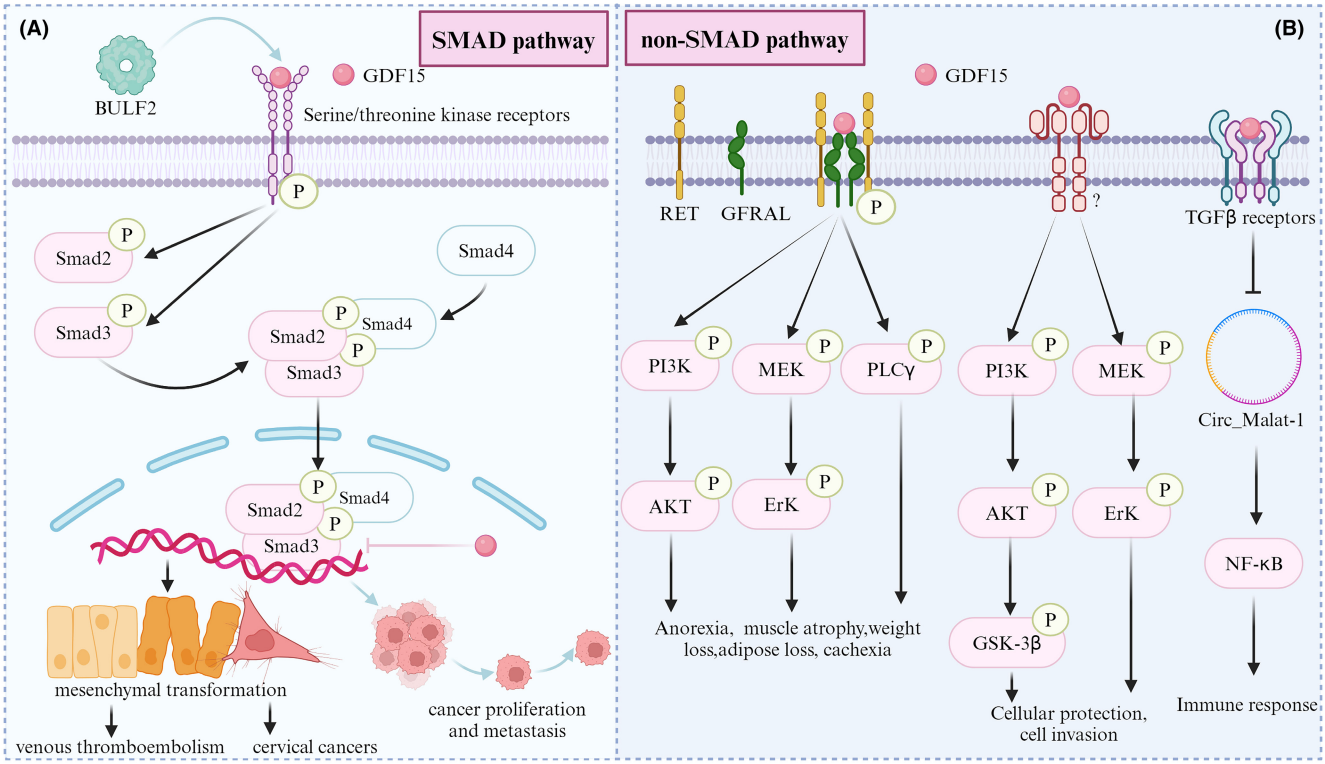


**FIGURE 1** Diagram of SMAD and non-SMAD pathways activated by GDF15. (A) GDF15 phosphorylates serine/threonine kinase receptors, leading to the activation of Smad2/3, which subsequently form SMAD protein complexes through interaction with Smad4. Then, SMADs translocate into the cellular nucleus where they regulate gene expression. This process ultimately promotes cancer growth, proliferation and metastasis. Nuclear GDF15 can inhibit the binding of SMAD complexes to DNA, thereby suppressing cellular migration. (B) GDF15 can also activate non-SMAD pathways by binding to GFRAL, TGFβ receptors and other unknown receptors. This activation leads to the phosphorylation of downstream signalling pathways, resulting in various cellular functions, such as cachexia-related symptoms, cellular protection, cell invasion and immune response. AKT, protein kinase B; Circ_Malat-1, malat-1 circular RNA; ErK, extracellular signal-regulated kinase; GFRAL, GDNF family receptor α–like; GSK-3β, glycogen synthase kinase-3β; MEK, methyl ethyl ketone; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinases; PLCγ, phosphoinositide phospholipase C; TGFβ, Transforming growth factor beta.

evidently upregulated GDF15 expression at both transcriptomic and translational levels, aiding in the recovery of myocardial contractile function.[27] It is noteworthy that, although current evidence directly linking Wnt and GDF15 within the tumour context remains limited, we might derive certain insights from several potential indications. The interplay between Wnt signalling and its regulators, exemplified by FOXM1 and HER2, has been confirmed to accelerate the progression of various cancers.[28,29] However, accumulating evidence has demonstrated the promotive effects of GDF15 in breast cancer development, notably via the p-AKT/FOXM1 and IGF-1R-FOXM1 pathways[30,31] and HER2 phosphorylation.[32] Thus, it is plausible that GDF15 might influence the regulation of the Wnt pathway through these components. This hypothesis is supported by recent studies showing that GDF15, through the Wnt/β-catenin axis, contributes to enhancing stemness and drug resistance in the advancement of breast cancer.[33] Furthermore, Wnt activation may also provide pro-carcinogenic networks, serving as a prerequisite for the tumour-promoting effects of GDF15.[34] However, mechanistic studies elucidating the direct interaction between Wnt signalling and GDF15 remain imperative, particularly within the oncological context, as they would facilitate the development of targeted therapeutic strategies and enhance our understanding of tumorigenesis and cancer progression.

## 3 | GDF15 IN PHYSIOLOGICAL CONTEXTS

Under physiological conditions, human serum typically contains secreted GDF15 at levels below 1200 ng/L, with an average concentration of 450 ng/L.[35] However, recent studies have shed light on the modulation of GDF15 expression by various factors (Figure 2A).[36,37] Increased fatty acids culminate GDF15 expression in the peripheral circulation of mice, which reduced dietary consumption via GDF15-GFRAL axis.[38] Besides, metformin could enhance GDF15 generation, serving as an anti-inflammation agent and improving insulin secretion. Skeletal muscle exercise also contributed to GDF15 secretion, subsequently

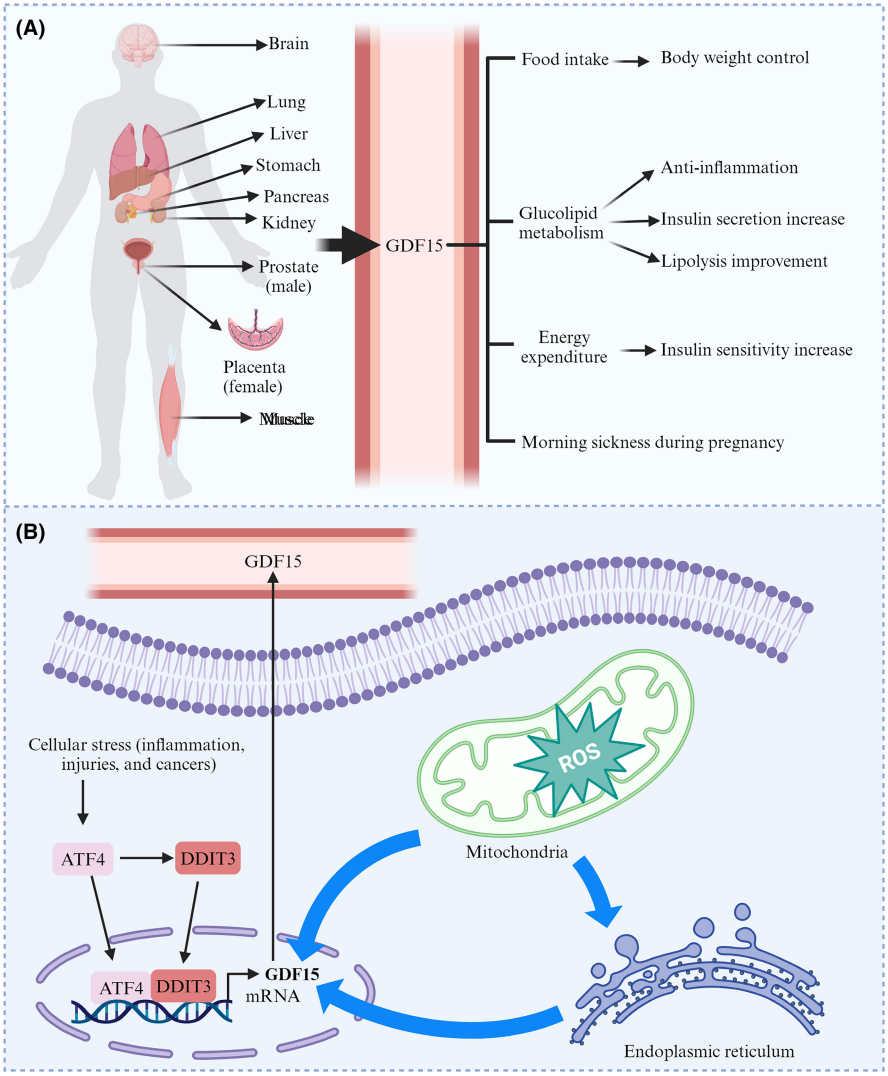


**FIGURE 2** Inter-organ and inter-organelle connection regulates GDF15 expression and function. (A) Inter-organ connection. GDF15 is secreted from placenta, prostate, liver, stomach and many other organs, regulating food intake, glucolipid metabolism, energy expenditure and morning sickness contributing to the human physiological environment. (B) Inter-organelle connection. ATF4/DDIT3-mediated cellular stress responses can regulate the GDF15 expression. Meanwhile, mitochondria and endoplasmic reticulum also adjust the expression of GDF15 in nuclear. ATF4, activating transcription factor 4; DDIT3, DNA damage-inducible transcript 3; ROS, Reactive oxygen species.

improving the insulin sensitivity of β cells in individuals with type 2 diabetes.[39–42] Interestingly, fetal-derived circulating GDF15 has been implicated as the key factor in morning sickness during pregnancy.[43] These findings collectively underscore the essential implications of GDF15 in physiological contexts, highlighting its significant roles in metabolic regulation, inflammation and biological responses.

## 4 | GDF15 IN CANCER CONTEXTS

GDF15 is upregulated regarding various pathological stress signals, such as inflammation, stress and a spectrum of cancer types. Translation factors such as activating transcription factor 4 and DNA damage-inducible transcript 3 involve in this procession.[44] Endoplasmic reticulum stress may contribute to the stabilization of GDF15 transcription, consequently upregulating its expression.[45] Additionally, excessive reactive oxygen species can instigate GDF15 overproduction in muscle cells during myopathic conditions. This implies that oxidative stress also contributes to the heightened levels of GDF15 observed in mitochondrial myopathies (Figure 2B). Of note, GDF15 is gaining increasing disputation for its molecular activities in multiple and intricate roles in carcinogenesis.[46] Under physiological conditions, GDF15 functions an anti-tumorigenic role, suppressing both tumour formation and growth by inducing apoptosis.[47] However, in cancers at advanced stage, the plasma levels of GDF15 sharply raised, ranging from 10,000 to 100,000 ng/L,[48] which expediates tumour invasion and metastasis.[49] The GDF15-GFRAL-RET axis has been proved to undergo autophosphorylation, thus affecting various downstream signalling targets including Ras-MAPK, PI3K-Akt and PLCγ pathways. This intricate involvement serves as a pivotal regulator in orchestrating cellular response related to growth, proliferation and metastasis, resulting in the progression of malignancies.[50] GDF15 has also been acknowledged for its role in promoting the development of SULF2 gene-mediated cancer proliferation and metastasis through GDF-SMAD signalling.[51] Conversely, GDF15

depletion retarded the development of cervical cancer by restraining TGFβ-Smad2/3 axis.[12] Likewise, the suppression of GDF15 decelerated gastric cancer progression via the modulation of STAT3 pathway and subsequent EMT inhibition.[52] Interestingly, beyond its pro-carcinogenesis effects, GDF15 is currently recognized as a significant contributor to cancer-related cachexia and malnutrition,[53] which largely due to the anorexia-related metabolic balance disturbance.[54,55] Elevated GDF15 level is also linked to impaired physical activity and muscle atrophy,[56] while neutralizing GDF15 contributed to the reversal of muscle dysfunction and improved physical performance in mouse cancer cachexia models.[57,58] Likewise, GDF15-GFRAL pathway has been found to augment lipid metabolism, causing weight loss in cancer-bearing mice models. These findings emphasize the importance of GDF15 not only in cancer development but also in its complications, with neutralization displaying promising curative values.

## 5 | GDF15 AS A PREDICTIVE INDEX IN DIGESTIVE SYSTEM TUMOURS

The diagnosis and monitoring of GCs pose significant challenges globally. Clinical utilization of existing biomarkers, such as CEA and alpha-fetoprotein (AFP), exhibits limitations in sensitivity and specificity, potentially contributing to misdiagnosis and deferred treatment.[59,60] Moreover, the progression of GCs is typically rapid, and managing advanced-stage GCs presents formidable challenges in treatment strategies and prognosis. Therefore, there exists an imperative to delineate novel and effective biomarkers for early indications of disease development. Previous studies have indicated that serum GDF15 levels exhibit elevation among GC patients and are intricately implicated in various biological processes pertinent to cancer tumorigenesis and progression. These discernments strongly posit that GDF15 holds promise as a discerning biomarker for the surveillance and management of GCs (Table 1).[8]

### 5.1 | Liver cancer

The expression of GDF15 mRNA, which peaks in the liver compared to other organs, undergoes a substantial and rapid increase in response to liver injury.[61] Previous studies have reported that partial hepatectomy may induce an enhanced expression of GDF15.[62] Overproduced GDF15 has been observed in hepatocytes following exposure to alcohol or carbon tetrachloride, which could mitigate the inflammatory response and reduce the liver fibrosis.[63] In the context of hepatocellular carcinoma (HCC), GDF15 has been shown to be closely linked to tumorigenesis. Hepatic stellate cells secreted abundant GDF15 mediated by autophagy, which promoted the proliferation of hepatoma cells contributing to HCC development.[64] GDF15 produced by normal hepatocytes under certain pathologic conditions may trigger the self-reproduction of liver cancer cells leading to the liver carcinogenesis. Similar results have also been observed in numerous clinical studies. For instance, the combination of GDF15 with AFP and vitamin K absence-induced protein demonstrated relatively high sensitivity and specificity for detecting primary liver cancer in patients with HCC compared with healthy controls.[65] Additionally, a notable difference was observed in plasma GDF15 levels between HCC patients with hepatitis C virus and healthy individuals.[66] Collectively, GDF15 displays high possibility as a diagnostic biomarker and

**TABLE 1** Sensitivity and specificity at diagnosis of GCs using GDF15.

| Objects | Cut-off (ng/L) | Sensitivity | Specificity | AUC | Ref |
|---|---|---|---|---|---|
| HCC, benign liver disease and controls | 1573.23 | 81.23% | 83.99% | 83.62% | 68 |
| | 817.46 | 67.30% | 66.70% | 0.693 | 65 |
| | 1945 | 63.10% | 86.60% | 0.84 | 114 |
| | 122.3 | 53.30% | 86.70% | 0.692 | 66 |
| APC, benign pancreatic disease and controls | 3356.6 | / | / | / | 78 |
| | 1070 | 0.71 | 0.78 | 0.81 | 74 |
| | 1259 | 81% | 73% | 0.88 | 75 |
| PDAC and controls | 1000 | 65.8% | 96.4% | 0.935 | 115 |
| CRC and controls | 3500 | 72.16% | 97.47% | 0.921 | 88 |
| | 1881 | 82.9% | 82.4% | 0.867 | 87 |
| OC and controls | 705 | 74% | 61% | 0.70 | 95 |

Abbreviations: APC, advanced pancreatic cancer; CRC, colorectal cancer; OC, oesophageal cancer; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PDAC, pancreatic ductal adenocarcinoma.

may be closely involved in liver cancer tumorigenesis. While elevated GDF15 levels contribute to the clinical differentiation of liver cancers from healthy cases, achieving diagnostic application solely based on GDF15 levels may be challenging. Combining GDF15 with other biomarkers may enhance accuracy and diagnostic value in liver cancers.

Apart from tumorigenesis, elevated level of GDF15 was also found to facilitate liver cancer progression. GDF15 overexpression significantly facilitated hepatoma cell viability, invasion and migration in vitro, while this enhancement was reversed by GDF15 depletion.[67] In clinics, GDF15 levels in plasma gradually increased as patients advance to the late stages of liver cancer, highlighting the clinical significance and cancer stage assessment of GDF15 in HCC progression.[68] Mechanically, GDF15 activated Akt/GSK-3β/β-catenin cascades, triggering excessive proliferation and metastasis of stem-like liver cancer cells, contributing to the development of hepatic cancers.[69] However, conflicting evidence has emerged from certain murine studies. In GDF15 knockout mice, there was no observed decrease in the growth rate or invasiveness of hepatocellular carcinoma.[70] These contradictory findings underscore our limited understanding of the underlying mechanisms, highlighting the necessity for more extensive research to elucidate GDF15's role in HCC progression.

## 5.2 | Pancreatic cancer

Diagnosing advanced pancreatic cancer (APC) remains challenging, particularly due to the deep location of pancreas within the abdomen and the lack of specific early-stage symptoms, which contributes significantly to the high death rate among pancreatic cancer patients.[71] So far, CA 19–9 is widely used in the investigation of pancreatic carcinoma, while limitations still exist as elevated CA 19–9 levels are also detected in many pancreatic or hepatobiliary disorders characterized by inflammation or obstruction.[72] GDF15 has also demonstrated the capability to distinguish from benign pancreatic disease based on elevated circulating concentrations in serum (3356.6 ng/L as the cut-off). Similarly, latest investigation has discovered the superior diagnostic accuracy of GDF15 for early-stage pancreatic ductal adenocarcinoma (PDAC), compared with CA19-9, CA242 and CEA.[73] Consistently, certain studies also supported the diagnostic value of GDF15 in pancreatic carcinomas, as its levels increased notably in patients with malignant pancreatic diseases compared to those with benign diseases or healthy controls.[74,75] These findings collectively emphasize the essential involvements of GDF15 in pancreatic cancer tumorigenesis.

Evidence indicating the roles of GDF15 in pancreatic cancer progression has advanced in recent investigations. GDF15 protein has been found to attach GFRAL, triggering the advancement and migration of PDAC cells.[76] Additionally, GDF15 expression is upregulated through Akt/CREB1 pathway activated by the solid stress in pancreatic adenocarcinoma microenvironment, which promotes pancreatic cancer cell metastasis.[77] In depth, the levels of phosphorylated-Jun N-terminal kinase and Akt increased in the high-GDF15 group of patients with APC, highlighting the involvement of GDF15 and its regulatory targets regarding APC development.[78] Collectively, GDF15 is implicated in the tumorigenesis and progression of pancreatic cancers, with elevated levels potentially serving as a biomarker to aid in the diagnosis and therapy of advanced-stage pancreatic cancers. Further investigations are imperative to decipher detailed underlying mechanisms of GDF15 in diverse pancreatic cancers.

## 5.3 | Gastric cancer

Gastric cancer commonly metastases to liver, lungs, bones and peritoneum, contributing significantly to cancer-related fatalities.[79] Early-stage patients often present with nonspecific symptoms such as abdominal pain or indigestion, making early detection challenging. Although biomarkers like CEA and CA19-9 have been utilized as predictors for gastric tumours, their diagnostic accuracy for gastric cancer remains limited (73.7% and 68.5%, respectively).[80] Therefore, there is a pressing need for novel biomarkers in detecting gastric cancer to enhance diagnostic accuracy and to identify more effective targeted therapies. Based on recent meta-analysis research, GDF15 has been proposed as a potential diagnostic biomarker for gastric cancer, as both GDF15 mRNA and protein were found to be overexpressed in gastric cancer patients.[81] GDF15 exhibits significantly elevated expression in gastric tumour tissues, with particularly heightened levels observed in metastatic gastric cancer.[82] Besides, GDF15 overexpression in gastric cancer cells can activate STAT3 signalling, thus triggering their proliferation and migration,[52] facilitating tumour progression. Tissue immunohistochemistry studies have similarly demonstrated the positive correlation between GDF15 levels and the advancement of gastric cancer. While cisplatin serves as an optimized therapy for advanced gastric cancer, the occurrence of cisplatin resistance can diminish its effectiveness. Specifically, the activation of the GDF15-GFRAL-GCN2 pathway has been identified as a mechanism that boosts the production of glutathione, thereby inducing cisplatin resistance.[82,83] Additionally, cellular senescence occurs in

cisplatin-resistant cancer cells, which often accompanied by mitochondria dysfunction. GDF15 is secreted in response of the mitochondrial stress, potential bridging the gap between mitochondrial dysfunction, cellular ageing and gastric cancer progression.[84] In this regard, targeting GDF15 may represent a promising therapeutic strategy for gastric cancer, warranting further preclinical investigations to develop targeted therapy.

### 5.4 | Colorectal cancer

Colorectal cancer (CRC) is the major reason leading to mortality among GCs.[85] Elevated serum CEA levels in CRC patients make it an extensive used protein marker in clinical studies for diagnosing and predicting CRC outcomes.[86] However, false-positive results with CEA occur, given that upregulated CEA expression can also be observed in other diseases including gastrointestinal inflammation. Serum GDF15 level in CRC patients showed an aberrant increase than that in healthy individuals.[87,88] Consistently, tumour tissues from CRC patients also exhibited higher levels of GDF15 compared with tumour-free tissues from the same CRC patients, which highlighted the potential utility of GDF15 as a diagnostic marker indicating CRC tumorigenesis.[89] Notably, heightened GDF15 expression in both serum and tissues was linked to poor prognosis, suggesting its involvement in CRC progression.[8,90] Overexpression of GDF15 could induce CRC cells transition towards a mesenchymal phenotype, accelerating cell growth, relocation and invasion, which ultimately contributes to the development of CRC. Along with these, hypoxia could initiate CRC dissemination by activating PERK-GDF15 cascades, further underscoring the crucial involvement of GDF15 in CRC metastasis.[91] Taken together, GDF15 levels may contribute to discriminating CRC patients as well as impacting tumour development, while further extensive research involving larger sample sizes is warranted to elucidate the criteria and underlying mechanisms involved.

### 5.5 | Oesophageal cancer

Oesophageal cancer (OC) poses a significant threat to lives, particularly in China and other Asian countries, where it is a leading cause of death.[92] Young people with OCs often exhibit few clinical manifestations in the early stage, making the diagnosis challenging and fastening the disease progression, thereby worsening the survival rate.[93] GDF15 has been recognized for its overexpression in OC occurrence and regulatory role in promoting OC progression.[94] A retrospective human cohort exhibited a relatively higher plasma GDF15 level in OC patients than normal population.[95] In-depth study discovered that GDF15 could activate TGFβ-RII and Akt-Erk1/2 pathways, thereby modulating the proliferation and migration of oesophageal squamous cells.[96] In this case, GDF15 could potentially serve as a diagnostic and prognostic marker in OC development, while functioning as a promising target for personalized therapy in OC management.

## 6 | TARGETING GDF15 FOR CANCER THERAPY

### 6.1 | GDF15 neutralization functions in cancer immunotherapy

The blockade of GDF15 has emerged with novel significance in counteracting immunosuppression after immune checkpoint inhibition. T cells are commonly recognized for their ability to activate, proliferate and secrete specific cytokines upon recognizing antigens, thereby actively engaging in the adaptive immune response. Mounting evidence has suggested that GDF15 is probably a tumour-derived factor that negatively regulates the immune response in the tumour microenvironment (TME).[97,98] Tumour-derived GDF15 may restrain T-cell function via different mechanisms, including interacting with its receptor CD48,[99] antagonizing CD4 and CD8,[63] and suppressing the activation of lymphocyte function-associated antigen 1/intercellular adhesion molecule 1 axis,[100] to interfere with T-cell emigration (Figure 3). To this end, GDF15 has been acknowledged as a crucial suppressor of T-cell stimulation and recruitment against tumours, giving rise to the immunotherapy approach of neutralizing GDF15 to reverse T-cell immunosuppression. Based on this context, a class of humanized antibodies inhibiting GDF15 has been developed and has demonstrated success in the early phases of prospective clinical trials. CTL-002 (Visugromab) is a monoclonal antibody that targets GDF15, interfering with GDF15-mediated signalling.[101] In a Phase 1 clinical trial, the injection of CTL-002 to patients with solid tumours facilitated the infiltration of CD4/CD8 positive and cytotoxic T cells, hence inducing antitumoral activity that effectively counteracted the immunosuppression by GDF15. Additionally, another monoclonal antibody named AZD8853 could bind to and neutralize GDF15, thereby suppressing tumour progression in patients with advanced cancers.[102] So far, this Phase 1/2a trail is ongoing to assess the adverse effects and evaluate the efficacy, with the enrolment of 165 participants suffering from different cancers. These clinical trials highlight the possibility of using GDF15 inhibition in checkpoint blockade therapy, which activates T cells for eliminating cancer cells.

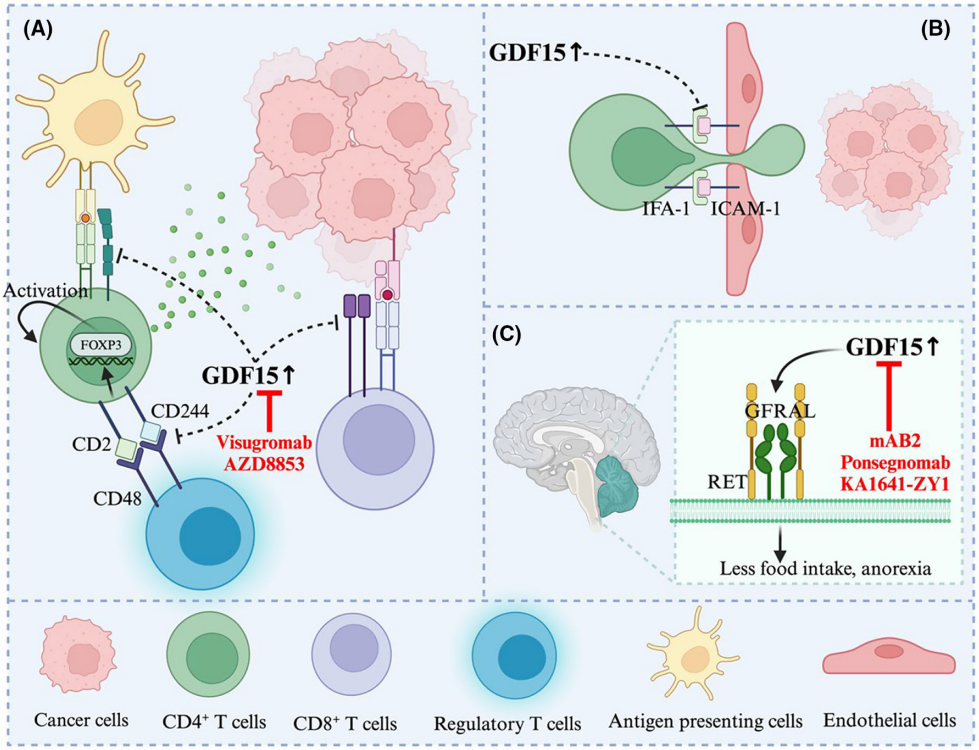


**FIGURE 3** Mechanisms of humanized immunoglobulin antibodies that neutralize GDF15 for cancer therapy. (A) Activation of $CD4^+$ and $CD8^+$ T cells by GDF15 neutralization. On one hand, serum GDF15 can suppress $CD4^+$ and $CD8^+$ T cells, thereby attenuating the T cell-mediated tumour response. On the other hand, GDF15 can also competitively bind to the receptor CD48, inhibiting the degradation of FOXP3 which results in the immunosuppression. Thus, visugromab and AZD8853 are able to neutralize circulating GDF15 in order to reactivate the T cell function. (B) GDF15 suppresses T-cell recruitment via blocking the LFA-1/ICAM-1 axis. (C) Serum GDF15 phosphorylated GFRAL leading to cachexia. In the hindbrain, the activation of GDF15-GFRAL pathway leads to the central anorexia and malnutrition. Therefore, utilizing the humanized antibodies such as mAB2, Ponsegnomab and KA1641-ZY1, contributes to the restoration of muscle function and energy intake. FOXP3, forkhead box P3; LFA-1, lymphocyte function-associated antigen 1; ICAM-1, intercellular adhesion molecule 1.

Apart from its functions in counteracting immunosuppression, tumour-derived GDF15 has been reported to block the secretion of tumour necrosis factor (TNF) and nitric oxide (NO) from macrophages regulated by the activated NF-κB pathway, which impaired the innate immune surveillance of macrophages and promoted the tumour invasion.[103] GDF15 binds to TGFβ receptors on dendritic cells (DCs), leading to the inactivation of Circ_Malat-1 and subsequent the inhibition of NF-κB pathway. This ultimately suppresses the maturation of DCs resulting in the induction of immune tolerance. In consist, tumour-derived GDF15 aided cancer cells in immune escape by transforming myeloid cells into phenotypes that support tumour growth.[104] Moreover, recent investigations have indicated that GDF15 triggers immune escape and suppresses the growth of DCs, contributing to the development of liver and ovarian cancers.[105,106] Furthermore, GDF15 expression could also be upregulated by the tumour suppresser, CXXC finger protein 4, consequently inducing apoptosis in gastric cancer cells and contributing to anti-tumour effects. This complexity may be strongly associated with the intricate nature of TME, prompting further investigations within specific cancer contexts. Taken together, these findings collectively emphasize the significance of GDF15 neutralization in cancer immunotherapy, presenting advanced promises in ameliorating the prognosis of cancer individuals.

## 6.2 | GDF15 inhibition suppresses cancer drug resistance

Drug resistance in cancer arises through various mechanisms, enabling cancer cells to remain viable and become drug-tolerant overtime.[107] Chemotherapy stimulation induced elevated GDF15 secreted from human pancreatic stellate cells, contributing to chemoresistance of PDAC. GDF15 could also induce the drug resistance in breast cancers through the Forkhead box protein M1 pathway.[30] Moreover, GDF15 secretion is detected exclusively during the state of drug tolerance persistence, while it is not expressed in cells sensitive to eribulin, a medication

**TABLE 2** Preclinical and clinical trials targeting GDF15.

| ID | Drugs | Inhibit | Phase | Country | Start date | Condition |
|---|---|---|---|---|---|---|
| NCT04725474 | CTL-002 (Visugromab) | GDF15 neutralizing antibody | 1 | Germany | 2022.01 | Solid tumours |
| NCT05397171 | AZD8853 | GDF15 neutralizing antibody | 1/2a | United States | 2022.06 | Solid tumours |
| NCT05546476 | Ponsegnomab | GDF15 neutralizing antibody | 2 | United States | 2022.11 | Cancer, cachexia |
| / | 3P10 | antagonistic monoclonal antibody | Preclinical | United States | / | Cancer cachexia |
| / | KA1641-ZY1 | GDF15 neutralizing antibody | Preclinical | China | / | Cancer cachexia |

targeting advanced breast cancer. In-depth investigations have confirmed enhanced efficacy of breast cancer treatment through the synergistic use of eribulin with GDF15 inhibitors.[108] Additionally, GDF15 overexpression is positively linked to chemotherapy resistance in oesophageal cancers, while this resistance is significantly reversed by GDF15 neutronization, resulting in improved chemotherapy efficacy.[109] These findings suggest that GDF15 may be a crucial factor in maintaining drug-tolerant persistence during cancer treatment, while inhibiting GDF15 secretion holds promise in preventing the development of drug resistance, potentially enhancing the effectiveness of cancer therapies.

### 6.3 | GDF15 blockade alleviates cancer cachexia

With regards to cancer cachexia, applying GDF15 neutralization might also have beneficial effects in alleviating the cachexia syndrome. GDF15 was proved to ameliorate cisplatin-induced side effects in vivo.[100] Cachectic mice with mAB2 treatment, a type of GDF15 antibody, displayed restoration in muscle function and enhancement in physical activity.[57] Similarly, GDF15 antibody, 3P10, can inhibit the GDF15-GFRAL-RET pathway, which facilitates in reversing GDF15-mediated lipid oxidation and alleviating cancer cachexia in tumour-bearing mice.[110] As a highly specific GDF15 inhibitor, Ponsegnomab exhibited its capacity to safely and well-tolerated increase the body weight of cancer patients in the Phase 1b clinical trial.[111] Likewise, KA1641-ZY1, a novel GDF15 blockage agent superior to Ponsegnomab, was newly developed regarding its anti-cachexia effects.[112] Whereas multiple studies elucidated the antitumor activity of GDF15 neutralization, there is still tremendous knowledge gap concerning the pharmacokinetic and pharmacodynamic of GDF15 in cancers. Therefore, further explorations are still warranted to figure out the mechanisms and effectiveness of the GDF15 antibodies as potential therapeutic strategies.

## 7 | PERSPECTIVES

GDF15 is appraised as a potential biomarker, given that it is observed at a high concentration among patients with GCs. Discouragingly, other conditions, including obesity, diabetes and neurogenerative diseases, have also witnessed elevations in serum GDF15 levels, potentially compromising the diagnostic accuracy for GCs.[10,113] With the complementary of GDF15 and other biomarkers, the results could demonstrate higher specificity and sensitivity in predicting and diagnosing GCs, hence improving the evaluating efficiency. Therefore, further studies can aim to improve the diagnostic precision of early-stage GCs by combining several validated biomarkers. The past few years have witnessed a revolutionary shift in cancer immunotherapy, targeting molecules which directly regulate the immune response against tumours instead of relying on non-specific chemotherapy or radiotherapy which may cause severe side effects. Currently, some humanized antibodies, working as GDF15 neutralization, have been developed and have demonstrated efficacy in T-cell activation and alleviating the symptoms of cancer cachexia in both Phase 1 and 2 clinical trials (Table 2). As GDF15 intervention is considered to be beneficial in disparate types of tumours, the precise therapeutic role of GDF15 in GCs has not yet been fully elucidated. Accordingly, there exists a compelling necessity to further elucidate the intricate landscape of the tumour immune microenvironment, deciphering the downstream signalling governed by GDF15 that intricately contribute to the initiation and advancement of GCs. These insights will catalyse the development of exceedingly targeted immunotherapeutic modalities for GCs, ultimately culminating in enhanced therapeutic efficacy and augmented survival rates.

## AUTHOR CONTRIBUTIONS

Conceptualization: Y.X., D.R. and S.W. writing—original draft preparation: Y.X., Y.Z., Y.S., J.Z. and D.Y. writing—review and editing: Y.J., J.J. and H.J.L. supervision: D.R. and S.W. project administration: D.R. and S.W. All

authors have read and agreed to the published version of the manuscript.

## ACKNOWLEDGEMENTS

This work was supported under the framework of international cooperation programme managed by the National Research Foundation of Korea (NRF-2022K2A9A1A06091879).

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

No new data were created or analysed in this study. Data sharing is not applicable to this article.

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## REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.
2. Huang J, Lucero-Prisno DE 3rd, Zhang L, et al. Updated epidemiology of gastrointestinal cancers in East Asia. *Nat Rev Gastroenterol Hepatol*. 2023;20(5):271-287.
3. Ben-Aharon I, van Laarhoven HWM, Fontana E, Obermannova R, Nilsson M, Lordick F. Early-onset cancer in the gastrointestinal tract is on the rise-evidence and implications. *Cancer Discov*. 2023;13(3):538-551.
4. Chen Y, Chen T, Fang JY. Burden of gastrointestinal cancers in China from 1990 to 2019 and projection through 2029. *Cancer Lett*. 2023;560:216127.
5. Shin MY, Kim JM, Kang YE, et al. Association between growth differentiation factor 15 (GDF15) and cardiovascular risk in patients with newly diagnosed type 2 diabetes mellitus. *J Korean Med Sci*. 2016;31(9):1413-1418.
6. Kang SG, Choi MJ, Jung SB, et al. Differential roles of GDF15 and FGF21 in systemic metabolic adaptation to the mitochondrial integrated stress response. *iScience*. 2021;24(3):102181.
7. Wischhusen J, Melero I, Fridman WH. Growth/differentiation Factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. *Front Immunol*. 2020;11:951.
8. Wang Y, Jiang T, Jiang M, Gu S. Appraising growth differentiation factor 15 as a promising biomarker in digestive system tumors: a meta-analysis. *BMC Cancer*. 2019;19(1):177.
9. Yang L, Wang J, Li J, et al. Identification of serum biomarkers for gastric cancer diagnosis using a human proteome microarray. *Mol Cell Proteomics*. 2016;15(2):614-623.
10. Asrih M, Wei S, Nguyen TT, Yi HS, Ryu D, Gariani K. Overview of growth differentiation factor 15 in metabolic syndrome. *J Cell Mol Med*. 2023;27(9):1157-1167.
11. Li Y, Zhu H, Xin W, Wang J, Yan C, Ying K. GDF15 affects venous thrombosis by promoting EndMT through smad2/p-smad2 pathway. *Thromb J*. 2023;21(1):98.
12. Li L, Zhang R, Yang H, et al. GDF15 knockdown suppresses cervical cancer cell migration in vitro through the TGF-beta/Smad2/3/Snail1 pathway. *FEBS Open Bio*. 2020;10(12):2750-2760.
13. Lu Y, Ma J, Li Y, et al. CDP138 silencing inhibits TGF-beta/Smad signaling to impair radioresistance and metastasis via GDF15 in lung cancer. *Cell Death Dis*. 2017;8(9):e3036.
14. Min KW, Liggett JL, Silva G, et al. NAG-1/GDF15 accumulates in the nucleus and modulates transcriptional regulation of the Smad pathway. *Oncogene*. 2016;35(3):377-388.
15. Wang D, Townsend LK, DesOrmeaux GJ, et al. GDF15 promotes weight loss by enhancing energy expenditure in muscle. *Nature*. 2023;619(7968):143-150.
16. Lee BY, Jeong J, Jung I, et al. GDNF family receptor alpha-like antagonist antibody alleviates chemotherapy-induced cachexia in melanoma-bearing mice. *J Cachexia Sarcopenia Muscle*. 2023;14(3):1441-1453.
17. Chung HK, Ryu D, Kim KS, et al. Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. *J Cell Biol*. 2017;216(1):149-165.
18. Chang JY, Hong HJ, Kang SG, Kim JT, Zhang BY, Shong M. The role of growth differentiation factor 15 in energy metabolism. *Diabetes Metab J*. 2020;44(3):363-371.
19. Urakawa N, Utsunomiya S, Nishio M, et al. GDF15 derived from both tumor-associated macrophages and esophageal squamous cell carcinomas contributes to tumor progression via Akt and Erk pathways. *Lab Invest*. 2015;95(5):491-503.
20. Roth P, Junker M, Tritschler I, et al. GDF-15 contributes to proliferation and immune escape of malignant gliomas. *Clin Cancer Res*. 2010;16(15):3851-3859.
21. Si Y, Liu X, Cheng M, et al. Growth differentiation factor 15 is induced by hepatitis C virus infection and regulates hepatocellular carcinoma-related genes. *PLoS One*. 2011;6(5):e19967.
22. Corre J, Labat E, Espagnolle N, et al. Bioactivity and prognostic significance of growth differentiation factor GDF15 secreted by bone marrow mesenchymal stem cells in multiple myeloma. *Cancer Res*. 2012;72(6):1395-1406.
23. Fotopoulos G, Gousia A, Bareta E, et al. Prognostic significance of WNT and hedgehog pathway activation markers in cancer of unknown primary. *Eur J Clin Invest*. 2015;45(11):1145-1152.
24. Ma B, Hottiger MO. Crosstalk between Wnt/beta-catenin and NF-kappaB signaling pathway during inflammation. *Front Immunol*. 2016;7:378.
25. Kaur S, Singh J, Kaur M. Multifaceted role of galectin-4 in cancer: a systematic review. *Eur J Clin Invest*. 2023;53(7):e13987.
26. Harb H, Stephen-Victor E, Crestani E, et al. A regulatory T cell Notch4-GDF15 axis licenses tissue inflammation in asthma. *Nat Immunol*. 2020;21(11):1359-1370.
27. Sasaki T, Hwang H, Nguyen C, Kloner RA, Kahn M. The small molecule Wnt signaling modulator ICG-001 improves contractile function in chronically infarcted rat myocardium. *PLoS One*. 2013;8(9):e75010.
28. Jung Da H, Bae Yoo J, Kim J-H, Shin You K, Jeung H-C. HER2 regulates cancer stem cell activities via the Wnt signaling pathway in gastric cancer cells. *Oncology*. 2019;97(5):311-318.
29. Moparthi L, Koch S. FOX transcription factors are common regulators of Wnt/beta-catenin-dependent gene transcription. *J Biol Chem*. 2023;299(5):104667.
30. Modi A, Purohit P, Roy D, et al. FOXM1 mediates GDF-15 dependent stemness and intrinsic drug resistance in breast cancer. *Mol Biol Rep*. 2022;49(4):2877-2888.

31. Peake BF, Eze SM, Yang L, Castellino RC, Nahta R. Growth differentiation factor 15 mediates epithelial mesenchymal transition and invasion of breast cancers through IGF-1R-FoxM1 signaling. *Oncotarget*. 2017;8(55):94393-94406.
32. Joshi JP, Brown NE, Griner SE, Nahta R. Growth differentiation factor 15 (GDF15)-mediated HER2 phosphorylation reduces trastuzumab sensitivity of HER2-overexpressing breast cancer cells. *Biochem Pharmacol*. 2011;82(9):1090-1099.
33. Gadwal A, Purohit P, Khokhar M, et al. GALNT14 in association with GDF-15 promotes stemness and drug resistance through beta-catenin signalling pathway in breast cancer. *Mol Biol Rep*. 2024;51(1):691.
34. Maass T, Marquardt J, Lee JS, et al. Increased liver carcinogenesis and enrichment of stem cell properties in livers of Dickkopf 2 (Dkk2) deleted mice. *Oncotarget*. 2016;7(20):28903-28913.
35. Xiao QA, He Q, Zeng J, Xia X. GDF-15, a future therapeutic target of glucolipid metabolic disorders and cardiovascular disease. *Biomed Pharmacother*. 2022;146:112582.
36. Hubens WHG, Kievit MT, Berendschot T, et al. Plasma GDF-15 concentration is not elevated in open-angle glaucoma. *PLoS One*. 2021;16(5):e0252630.
37. Andersson-Hall U, Svedin P, Mallard C, Blennow K, Zetterberg H, Holmang A. Growth differentiation factor 15 increases in both cerebrospinal fluid and serum during pregnancy. *PLoS One*. 2021;16(5):e0248980.
38. Wang D, Jabile MJT, Lu J, et al. Fatty acids increase GDF15 and reduce food intake through a GFRAL signaling Axis. *Diabetes*. 2024;73(1):51-56.
39. Zhang H, Mulya A, Nieuwoudt S, et al. GDF15 mediates the effect of skeletal muscle contraction on glucose-stimulated insulin secretion. *Diabetes*. 2023;72(8):1070-1082.
40. Zhao J, Li M, Chen Y, et al. Elevated serum growth differentiation factor 15 levels in hyperthyroid patients. *Front Endocrinol (Lausanne)*. 2018;9:793.
41. Niu Y, Zhang W, Shi J, et al. The relationship between circulating growth differentiation factor 15 levels and diabetic retinopathy in patients with type 2 diabetes. *Front Endocrinol (Lausanne)*. 2021;12:627395.
42. Kosi-Trebotic L, Thomas A, Harreiter J, Chmelik M, Trattnig S, Kautzky-Willer A. Gliptin therapy reduces hepatic and myocardial fat in type 2 diabetic patients. *Eur J Clin Invest*. 2017;47(11):829-838.
43. Fejzo M, Rocha N, Cimino I, et al. GDF15 linked to maternal risk of nausea and vomiting during pregnancy. *Nature*. 2024;625(7996):760-767.
44. Miyake M, Zhang J, Yasue A, et al. Integrated stress response regulates GDF15 secretion from adipocytes, preferentially suppresses appetite for a high-fat diet and improves obesity. *iScience*. 2021;24(12):103448.
45. Park SH, Choi HJ, Yang H, et al. Two in-and-out modulation strategies for endoplasmic reticulum stress-linked gene expression of pro-apoptotic macrophage-inhibitory cytokine 1. *J Biol Chem*. 2012;287(24):19841-19855.
46. Arfsten H, Cho A, Freitag C, et al. GDF-15 in solid vs non-solid treatment-naive malignancies. *Eur J Clin Invest*. 2019;49(11):e13168.
47. Xu G, Chen J, Jo S, et al. Deletion of Gdf15 reduces ER stress-induced Beta-cell apoptosis and diabetes. *Endocrinology*. 2022;163(5):bqac030.
48. Deng J, Zhang M, Zhang H, et al. Value of growth/differentiation factor 15 in diagnosis and the evaluation of chemotherapeutic response in lung cancer. *Clin Ther*. 2021;43(4):747-759.
49. Fang L, Li F, Gu C. GDF-15: a multifunctional modulator and potential therapeutic target in cancer. *Curr Pharm Des*. 2019;25(6):654-662.
50. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. *Nat Rev Cancer*. 2020;20(2):74-88.
51. He R, Shi J, Xu D, et al. SULF2 enhances GDF15-SMAD axis to facilitate the initiation and progression of pancreatic cancer. *Cancer Lett*. 2022;538:215693.
52. Joo M, Kim D, Lee MW, Lee HJ, Kim JM. GDF15 promotes cell growth, migration, and invasion in gastric cancer by inducing STAT3 activation. *Int J Mol Sci*. 2023;24(3):2925.
53. Worth AA, Shoop R, Tye K, et al. The cytokine GDF15 signals through a population of brainstem cholecystokinin neurons to mediate anorectic signalling. *Elife*. 2020;9:e55164.
54. Ahmed DS, Isnard S, Lin J, Routy B, Routy JP. GDF15/GFRAL pathway as a metabolic signature for cachexia in patients with cancer. *J Cancer*. 2021;12(4):1125-1132.
55. Borner T, Shaulson ED, Ghidewon MY, et al. GDF15 induces anorexia through nausea and emesis. *Cell Metab*. 2020;31(2):351-362. e355.
56. Conte M, Martucci M, Mosconi G, et al. GDF15 plasma level is inversely associated with level of physical activity and correlates with markers of inflammation and muscle weakness. *Front Immunol*. 2020;11:915.
57. Kim-Muller JY, Song L, LaCarubba PB, et al. GDF15 neutralization restores muscle function and physical performance in a mouse model of cancer cachexia. *Cell Rep*. 2023;42(1):111947.
58. Zhang W, Sun W, Gu X, et al. GDF-15 in tumor-derived exosomes promotes muscle atrophy via Bcl-2/caspase-3 pathway. *Cell Death Dis*. 2022;8(1):162.
59. Gan L, Ren S, Lang M, et al. Predictive value of preoperative serum AFP, CEA, and CA19-9 levels in patients with single small hepatocellular carcinoma: retrospective study. *J Hepatocell Carcinoma*. 2022;9:799-810.
60. Johnson P, Zhou Q, Dao DY, Lo YMD. Circulating biomarkers in the diagnosis and management of hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):670-681.
61. Jiang P, Liu Z, Fang T, et al. Growth differentiation factor 15 is dispensable for acetaminophen-induced liver injury in mice. *Basic Clin Pharmacol Toxicol*. 2023;132(4):343-353.
62. Emmerson PJ, Duffin KL, Chintharlapalli S, Wu X. GDF15 and growth control. *Front Physiol*. 2018;9:1712.
63. Chung HK, Kim JT, Kim HW, et al. GDF15 deficiency exacerbates chronic alcohol- and carbon tetrachloride-induced liver injury. *Sci Rep*. 2017;7(1):17238.
64. Myojin Y, Hikita H, Sugiyama M, et al. Hepatic stellate cells in hepatocellular carcinoma promote tumor growth via growth differentiation factor 15 production. *Gastroenterology*. 2021;160(5):1741-1754. e1716.
65. Chen J, Tang D, Xu C, et al. Evaluation of serum GDF15, AFP, and PIVKA-II as diagnostic markers for HBV-associated hepatocellular carcinoma. *Lab Med*. 2021;52(4):381-389.
66. Wifi M-N, Zayed RA, Fouad N, Hassan AY, Hussien MA, Sokar MG. Association of serum growth differentiation factor 15 and hepatocellular carcinoma in Egyptian patients. *Egyptian J Intern Med*. 2019;31(1):57-63.

67. Wang L, Liu Y, Li W, Song Z. Growth differentiation factor 15 promotes cell viability, invasion, migration, and angiogenesis in human liver carcinoma cell line HepG2. *Clin Res Hepatol Gastroenterol*. 2017;41(4):408-414.
68. Shen Y, Zhang Z-B, Wu S-D, Wu X-B, Li J. Research on values of GDF-15 level in the diagnosis of primary liver cancer and evaluation of chemotherapeutic effect. 2018 (2284–0729 (Electronic)).
69. Xu Q, Xu H-X, Li J-P, et al. Growth differentiation factor 15 induces growth and metastasis of human liver cancer stem-like cells via AKT/GSK-3β/β-catenin signaling. *Oncotarget*. 2017;8(10):16972-16987.
70. Zimmers TA, Jin X, Gutierrez JC, et al. Effect of in vivo loss of GDF-15 on hepatocellular carcinogenesis. *J Cancer Res Clin Oncol*. 2008;134(7):753-759.
71. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. *World J Gastroenterol*. 2018;24(19):2047-2060.
72. Ahmadipour M, Bhattacharya A, Sarafbidabad M, et al. CA19-9 and CEA biosensors in pancreatic cancer. *Clin Chim Acta*. 2024;554:117788.
73. Qin H, Chen J, Bouchekioua-Bouzaghou K, et al. Immunization with a multi-antigen targeted DNA vaccine eliminates chemo-resistant pancreatic cancer by disrupting tumor-stromal cell crosstalk. *J Transl Med*. 2023;21(1):702.
74. Koopmann J, Buckhaults P, Brown DA, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other Periampullary cancers. *Clin Cancer Res*. 2004;10(7):2386-2392.
75. Ozkan H, Demirbas S, Ibis M, Akbal E, Koklu S. Diagnostic validity of serum macrophage inhibitor cytokine and tissue polypeptide-specific antigen in pancreatobiliary diseases. *Pancreatology*. 2011;11(3):295-300.
76. Zhao Z, Zhang J, Yin L, et al. Upregulated GDF-15 expression facilitates pancreatic ductal adenocarcinoma progression through orphan receptor GFRAL. 2020 (1945–4589 (Electronic)).
77. Kalli M, Minia A, Pliaka V, Fotis C, Alexopoulos LG, Stylianopoulos T. Solid stress-induced migration is mediated by GDF15 through Akt pathway activation in pancreatic cancer cells. *Sci Rep*. 2019;9(1):978.
78. Suzuki H, Mitsunaga S, Ikeda M, et al. Clinical and tumor characteristics of patients with high serum levels of growth differentiation factor 15 in advanced pancreatic cancer. *Cancers (Basel)*. 2021;13(19):4842.
79. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. *J Hematol Oncol*. 2023;16(1):57.
80. Matsuoka T, Yashiro M. Biomarkers of gastric cancer: current topics and future perspective. *World J Gastroenterol*. 2018;24(26):2818-2832.
81. Liu JY, Dong XX, Lu JN, et al. Utility of GDF-15 as a diagnostic biomarker in gastric cancer: an investigation combining GEO, TCGA and meta-analysis. *FEBS Open Bio*. 2019;9(1):35-42.
82. Wang SF, Chang YL, Fang WL, et al. Growth differentiation factor 15 induces cisplatin resistance through upregulation of xCT expression and glutathione synthesis in gastric cancer. *Cancer Sci*. 2023;114(8):3301-3317.
83. Wang X, Xu Z, Sun J, et al. Cisplatin resistance in gastric cancer cells is involved with GPR30-mediated epithelial-mesenchymal transition. *J Cell Mol Med*. 2020;24(6):3625-3633.
84. Cavinato M. Mitochondrial dysfunction and cisplatin sensitivity in gastric cancer: GDF15 as a master player. *FEBS J*. 2024;291(6):1111-1114.
85. Granados-Romero JJ, Valderrama-Treviño AI, Contreras-Flores EH, et al. Colorectal cancer: a review. *Int J Res Med Sci*. 2017;5(11):4667.
86. Alves Martins BA, de Bulhoes GF, Cavalcanti IN, Martins MM, de Oliveira PG, Martins AMA. Biomarkers in colorectal cancer: the role of translational proteomics research. *Front Oncol*. 2019;9:1284.
87. Xue H, Lü B, Zhang J, et al. Identification of serum biomarkers for colorectal cancer metastasis using a differential Secretome approach. *J Proteome Res*. 2010;9(1):545-555.
88. Zhang Y, Wang X, Zhang M, Zhang Z, Jiang L, Li L. GDF15 promotes epithelial-to-mesenchymal transition in colorectal [corrected]. *Artif Cells Nanomed Biotechnol*. 2018;46(2169–141X (Electronic)):652-658.
89. Robotycka J, Mielcarska S, Dawidowicz M, et al. Evaluation of the associations between GDF-15, OPG, and IL-15 levels in CRC: preliminary results. *Med Res J*. 2022;7(3):208-214.
90. Wallin U, Glimelius B, Jirstrom K, et al. Growth differentiation factor 15: a prognostic marker for recurrence in colorectal cancer. *Br J Cancer*. 2011;104(10):1619-1627.
91. Zheng H, Wu Y, Guo T, Liu F, Xu Y, Cai S. Hypoxia induces growth differentiation factor 15 to promote the metastasis of colorectal cancer via PERK-eIF2alpha signaling. *Biomed Res Int*. 2020;2020:5958272.
92. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and Esophagogastric junction cancers, version 2.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2023;21(4):393-422.
93. Zhu H, Ma X, Ye T, et al. Esophageal cancer in China: practice and research in the new era. *Int J Cancer*. 2023;152(9):1741-1751.
94. Dong G, Huang X, Jiang S, et al. SCAP mediated GDF15-induced invasion and EMT of esophageal cancer. *Front Oncol*. 2020;10:564785.
95. Fisher OM, Levert-Mignon AJ, Lord SJ, et al. MIC-1/GDF15 in Barrett's oesophagus and oesophageal adenocarcinoma. *Br J Cancer*. 2015;112(8):1384-1391.
96. Okamoto M, Koma YI, Kodama T, Nishio M, Shigeoka M, Yokozaki H. Growth differentiation factor 15 promotes progression of esophageal squamous cell carcinoma via TGF-beta type II receptor activation. *Pathobiology*. 2020;87(2):100-113.
97. Moon JS, Goeminne LJE, Kim JT, et al. Growth differentiation factor 15 protects against the aging-mediated systemic inflammatory response in humans and mice. *Aging Cell*. 2020;19(8):e13195.
98. Jung SB, Choi MJ, Ryu D, et al. Reduced oxidative capacity in macrophages results in systemic insulin resistance. *Nat Commun*. 2018;9(1):1551.
99. Wang Z, He L, Li W, et al. GDF15 induces immunosuppression via CD48 on regulatory T cells in hepatocellular carcinoma. *J Immunother Cancer*. 2021;9(9):e002787.
100. Haake M, Haack B, Schafer 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(1):4253.
101. Melero I, De Miguel MJ, Alonso Casal G, et al. 729MO final results of the first-in-human clinical trial of the GDF-15 neutralizing antibody CTL-002 in combination with nivolumab in subjects with solid tumors relapsed/refractory to prior anti-PD1/PD-L1 treatment. *Ann Oncol*. 2022;33:S876.
102. Carneiro BA, Diab M, Van Tine BA, et al. Abstract CT116: first-in-human study of AZD8853, an anti-growth and

differentiation factor 15 (GDF15) antibody, in patients (pts) with advanced/metastatic solid tumors. *Cancer Res*. 2023;83(8_Supplement):CT116.
103. Ratnam NM, Peterson JM, Talbert EE, et al. NF-kappaB regulates GDF-15 to suppress macrophage surveillance during early tumor development. *J Clin Invest*. 2017;127(10):3796-3809.
104. Haake M, Haack B, Genßler S, et al. Abstract 6118: tumor-derived GDF-15 promotes immune escape of tumors by functional alteration of the myeloid compartment. *Cancer Res*. 2022;82(12_Supplement):6118.
105. Gao Y, Xu Y, Zhao S, et al. Growth differentiation factor-15 promotes immune escape of ovarian cancer via targeting CD44 in dendritic cells. *Exp Cell Res*. 2021;402(1):112522.
106. Zhou Z, Li W, Song Y, et al. Growth differentiation factor-15 suppresses maturation and function of dendritic cells and inhibits tumor-specific immune response. *PLoS One*. 2013;8(11):e78618.
107. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: a brief review. *Adv Pharm Bull*. 2017;7(3):339-348.
108. Bellio C, Emperador M, Castellano P, et al. GDF15 is an Eribulin response biomarker also required for survival of DTP breast cancer cells. *Cancers (Basel)*. 2022;14(10):2562.
109. Du Y, Ma Y, Zhu Q, et al. GDF15 negatively regulates chemosensitivity via TGFBR2-AKT pathway-dependent metabolism in esophageal squamous cell carcinoma. *Front Med*. 2023;17(1):119-131.
110. Suriben R, Chen M, Higbee J, et al. Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. *Nat Med*. 2020;26(8):1264-1270.
111. Crawford J, Calle RA, Collins SM, et al. A phase 1b first-in-patient study assessing the safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Ponsegromab in Participants with Cancer and Cachexia. *Clin Cancer Res*. 2024;30(3):489-497.
112. He F, Peng H, Li J, et al. Abstract 368: neutralizing antibody against GDF-15 restores cachexia. *Cancer Res*. 2023;83(7_Supplement):368.
113. 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(2):e2502.
114. Liu X, Chi X, Gong Q, et al. Association of serum level of growth differentiation factor 15 with liver cirrhosis and hepatocellular carcinoma. *PLoS One*. 2015;10(5):e0127518.
115. Wang X, Li Y, Tian H, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. *BMC Cancer*. 2014;14(1):578.

**How to cite this article:** Xue Y, Zhang Y, Su Y, et al. The implicated role of GDF15 in gastrointestinal cancer. *Eur J Clin Invest*. 2024;00:e14290. doi:10.1111/eci.14290