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REVIEW PAPER

Growth differentiation factor 15 – a review of current literature on biological roles and clinical significance

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ABSTRACT

Introduction and aim. Growth differentiation factor 15 (GDF15), a member of the TGF-β superfamily, plays crucial roles in various physiological and pathological processes including inflammation, apoptosis, angiogenesis, cell repair, growth, metabolic regulation, and immune response. This review aims to discuss the biological roles and clinical significance of GDF15 and to analyze its impact across different medical fields such as cardiology, oncology, neurology, gynecology, and areas related to aging and metabolic disorders.

Material and methods. A review was constructed through a literature search on PubMed and Google Scholar databases, focusing on studies from 2014 to 2024, using relevant keywords.

Analysis of the literature. Recent research highlights GDF15's potential as a biomarker in cardiovascular diseases, its role in cancer progression and resistance to therapies, and its significance in metabolic regulation affecting conditions like obesity, diabetes, and cachexia. Emerging research also points to its role in aging, mitochondrial diseases, and systemic conditions such as sepsis, liver, and lung disorders.

Conclusion. GDF15's involvement in multiple pathological states and its broad impact across various medical disciplines underline its potential for future clinical applications. Understanding GDF15's complex roles could lead to novel therapeutic strategies and enhance prognostic assessments in diverse medical fields.

Keywords. biomarker, GDF15, GFRAL

Introduction

Growth differentiation factor 15 (GDF15), an approximately 25 kDa protein encoded by the GDF15 gene in humans, is a member of the transforming growth factor beta (TGF-β) superfamily.[1,2] Initially identified as macrophage inhibitory cytokine-1 (MIC-1), GDF15 is also known by several other names, including nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1), prostate differentiation factor (PDF), placental bone morphogenetic protein (PLAB), placental transforming growth factor-beta (PTGF-beta/PTGFB).

GDF15 is expressed at low concentrations in various organs under normal conditions and is upregulated in response to cellular damage and organ injuries, including those affecting the liver, kidney, heart, and lungs.[1,3,4,5] Its levels in the blood increase with age, inflammation and in response to cellular stress.[6,7]

The effects of GDF15, including cell proliferation and differentiation, are mediated through binding to transmembrane receptor with kinase activity, GFRAL (glial-cell-derived neurotrophic factor family receptor α-like).[1,3] GFRAL is an orphan receptor suggested to

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play a role in neuroprotection and brain development, and it is a distant homolog of the glial-cell-line-derived neurotrophic factor (GDNF) family of receptors. GDF15 was found not to interact with other, GFRAL related, neurotrophic factor receptors GDNF family receptor α (GFRA) 1–4.[8] Experimental data indicate that the interaction between GDF15 and GFRAL leads to the internalization of the ligand-receptor complex within the cell. Further studies have shown that GFRAL signaling via GDF15 depends on the co-receptor RET, forming a GFRAL-RET-dependent complex.[8]

While the precise functions of GDF15 are still being elucidated, current understanding suggests its involvement in regulating inflammatory pathways and influencing processes such as apoptosis, angiogenesis, cell repair, and growth. Elevated levels of GDF15 have been associated with cardiovascular and neoplastic disorders as well as neurodegeneration, highlighting its broad impact on health and disease.[1,4,6,9,10,11] The discovery of the GFRAL receptor offers new therapeutic avenues, particularly in improving prognosis in cancer patients.[12] Additionally, GDF15 plays a crucial role in processes such as cancer drug persistence and metastasis.[13,14] It was also linked to poor prognosis in cancer patients post-radiation therapy, with radiation-resistant cancer cells exhibiting higher GDF15 expression levels.[15]

In terms of metabolic regulation, GDF15 influences body mass by reducing food intake, improving insulin resistance, and promoting fat breakdown. This positions GDF15 as a promising target in addressing the global obesity epidemic.[16,17] On the other hand, elevated GDF15 levels are associated with anorexia/cachexia syndromes in various diseases, such as cancer, renal failure, heart failure, and chronic obstructive pulmonary disease. Thus, targeting GDF15-GFRAL interaction could be a therapeutic goal for anorexia/cachexia syndrome.[18]

GDF15 is emerging as a pivotal biomarker and therapeutic target in various pathological states. This review aims to comprehensively examine the biological functions of GDF15 and its potential clinical applications across various medical disciplines. The rationale behind this review is to consolidate the emerging evidence of GDF15's multifaceted roles in disease pathology and therapy, providing a cohesive understanding that can facilitate future research and clinical strategies.

The novelty of this review lies in its interdisciplinary approach, synthesizing data from cardiology, oncology, neurology, gynecology, metabolic disorders, and aging (Table 1). By highlighting GDF15's widespread impact, the review underscores its potential as a universal biomarker and therapeutic target, thereby opening new avenues for treatment and management across diverse medical fields.

Table 1. Roles and clinical implications of GDF15 across various medical disciplines[1,6,7,13,15-17,19-86]

Medical field	Key findings	Potential therapeutic applications
Cardiology	- Elevated levels indicate cardiovascular risk and correlate with disease severity and mortality. - Protective effects include antioxidative, anti-inflammatory, and anti-apoptotic actions.	- Biomarker for stratification and management of heart disease risk. - Therapeutic target for modulating metabolic activity and aiding cardiac regenerative processes.
Oncology	- Elevated levels in various cancers correlate with poor prognosis and survival. - Involvement in drug resistance and metastasis. - Interaction with immune responses.	- Prognostic biomarker. - Target for therapeutic intervention to counteract drug resistance and metastasis.
Metabolic disorders	- Reduces food intake and promotes fat breakdown. - Improves insulin resistance. - Elevated levels linked to anorexia/cachexia syndromes.	- Potential therapy for the management of obesity and diabetes. - Therapeutic target for anorexia/cachexia syndrome.
Aging and mitochondrial diseases	- Unclear correlation with age. - Marker for mitochondrial disease severity. - Involvement in cellular stress responses.	- Diagnostic marker for aging and mitochondrial diseases. - Therapeutic target to modulate aging processes and mitochondrial function.
Gynecology	- Increased levels during pregnancy. - Associated with nausea and vomiting in pregnancy, hyperemesis gravidarum, and gestational diabetes mellitus. - Lower plasma levels linked to miscarriages.	- Target for managing nausea and vomiting in pregnancy and hyperemesis gravidarum. - Early detection marker for gestational diabetes mellitus. - Potential therapy for reducing miscarriage risk.
Neurology	- Elevated levels in neurodegenerative diseases and stroke outcomes.	- Diagnostic biomarker for neurodegenerative diseases. - Prognostic marker for stroke outcomes.
Liver diseases	- Reduced expression in liver fibrosis. - Protective role in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.	- Therapeutic target for treating liver fibrosis and non-alcoholic fatty liver disease.
Sepsis	- Elevated levels in sepsis correlate with inflammatory markers and organ damage. - Modulates macrophage inflammation and polarization.	- Diagnostic marker for sepsis. - Therapeutic target to modulate immune response and improve sepsis outcomes.
Pulmonology	- Protective role in acute lung injury. - Potentially protecting cells from fatty acid overload.	- Biomarker for bronchopulmonary dysplasia, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary hypertension, and coronavirus disease 2019.
Thrombosis	- Elevated levels in deep vein thrombosis patients and mouse models. - Potential role in endothelial cell function and thrombosis.	- Therapeutic target to improve anticoagulant and fibrinolytic functions in thrombosis.
Systemic autoimmune diseases	- Linked to acute and chronic inflammation. - Potential role in systemic autoimmune diseases like type I diabetes and rheumatoid arthritis. - Increased plasma levels in lupus erythematosus, rheumatoid arthritis, and idiopathic inflammatory myopathies.	- Target for modulating immune responses in autoimmune diseases. - Diagnostic and prognostic biomarker in lupus erythematosus, rheumatoid arthritis, and idiopathic inflammatory myopathies.
Dermatology	- Reduced levels in psoriasis. - Role in age-related pigmentation and melanogenesis. - Influences skin inflammation and keratinocyte proliferation.	- Therapeutic target for treating psoriasis and age-related pigmentation alterations.

Aim

This comprehensive overview seeks to bridge existing knowledge gaps and propose new directions for research and clinical practice, emphasizing the significance of GDF15 in improving patient outcomes.

Material and methods

A review was conducted based on a literature search of the PubMed and Google Scholar databases, concentrating on studies published between 2014 and 2024. The search utilized relevant keywords, including "GDF15", "GDF-15", "growth differentiation factor 15", "MIC-1", "MIC1", "NAG-1", "PDF", "PLAB", and "PTGFB".

Analysis of the literature

Role of GDF15 in cardiovascular disorders

In the cardiovascular context, GDF15 exhibits protective actions, including antioxidative, anti-inflammatory, and anti-apoptotic effects.[6] GDF15 expression is markedly increased in cardiomyocytes after ischemia/reperfusion. It inhibits leukocyte activation and recruitment by directly interfering with chemokine signaling and integrin activation. Additionally, GDF15 activates the nitric oxide pathway (NOS/NO/nuclear factor κB or NFκB) and the forkhead box (FOX) transcription factor Foxo3. This leads to antioxidant effects and promotes neovascularization.[6] Its potential as a therapeutic target in modulating metabolic activity and aiding cardiac regenerative processes in cardiovascular diseases presents an exciting avenue for research. However, *in vitro* studies indicate that the expression of GDF15 mRNA (messenger ribonucleic acid) and its protein levels tend to be increased in the vessel walls affected by atherosclerosis.[7] Furthermore, the absence of GDF15 may result in a significant reduction of aortic arch lumen stenosis, decrease in fluorodeoxyglucose uptake, reduced presence of inflammatory CD11b(+) (cluster of differentiation 11b) and IL-6(+) (interleukin 6) leukocytes, as well as apoptotic cells.[7] The varying research findings on GDF15 highlight the complexity of its function and emphasize the need for further investigation to fully understand its implications in cardiovascular diseases. Future studies should aim to elucidate the precise mechanisms by which GDF15 influences cardiovascular pathology and identify potential therapeutic applications.

GDF15's role as a predictive biomarker for adverse cardiac events further underscores its clinical relevance.[6,19,20] GDF15 appears in the blood in many pathological conditions, making it a nonspecific marker. The conditions where increased levels of GDF15 are detected include: vascular diseases (e.g., atherosclerosis, acute coronary syndrome, stroke), heart failure, arterial hypertension, acute inflammatory states, atrial fibrillation, chronic kidney disease, anemia, bleeding, metabolic syndromes, diabetes, tobacco smoking, cancers, and advanced age.[1,20]

In the general population, cardiovascular diseases are the main cause of increased GDF15 levels in the blood.[1] Due to its relatively simple method of precise measurement, GDF15 represents a promising element in the prevention of both primary and secondary cardiovascular events. Studies indicate three cardiovascular risk ranges based on GDF15 concentrations: concentrations <1200 ng/l correspond to low cardiovascular risk (the upper limit of reference values for healthy individuals), 1200–1800 ng/l indicate moderate (average) risk, and >1800 ng/l suggest high risk.[21,22] The strong association between GDF15 concentration and cardiovascular disease risk factors, susceptibility to these diseases, their severity, and overall mortality (including due to cancer) designates GDF15 as a 'predictor of death'.[1,21] The large randomized controlled trial conducted by Hagström et al. demonstrated that higher concentrations of GDF15 are associated with an increased risk of various cardiovascular and non-cardiovascular events in patients with stable coronary heart disease.[20] GDF15 was independently linked to mortality from cardiovascular causes and hospitalization for myocardial infarction, heart failure and stroke. These findings underscore the significance of GDF15 as a biomarker in assessing the risk of adverse outcomes in patients with stable coronary heart disease.[20]

In the realm of chronic heart failure, GDF15 distinguishes itself as an independent prognostic marker, adding incremental value to NT-proBNP in the prediction of long-term mortality.[22,23] Notably, there is emerging evidence suggesting that GDF15 might even surpass NT-proBNP as a predictive marker, thereby highlighting its potential as a significant tool in the risk assessment and management of heart failure.[23] GDF15 has been observed to increase over time in heart failure patients.[24]

While GDF15 shows promise as a biomarker and therapeutic target, several limitations exist, including its nonspecificity due to elevated levels in various pathological conditions, unclear mechanisms of its influence on cardiovascular pathology, and the need for robust, large-scale studies to transition from research to clinical practice. Future research should focus on clarifying the detailed mechanisms of GDF15 in cardiovascular diseases, conducting large-scale, longitudinal studies to validate its predictive and prognostic utility, and exploring therapeutic interventions to modulate its effects. Addressing these limitations will enhance the potential of GDF15 in improving cardiovascular health and patient outcomes.

GDF15 in oncology

GDF15 appears to be a multifaceted player in cancer biology, with its role ranging from participating in various cellular processes that influence cancer development

and progression to serving as a potential biomarker for diagnosis and prognosis.[25] Further research is needed to unravel the intricacies of GDF15's involvement in different cancer types and to explore its therapeutic implications.

Increased expression of GDF15 is observed in tumors of various organs, particularly in the gastrointestinal system, prostate gland, breast, skin, and brain.[25,26] Elevated levels of secreted GDF15 are associated with poorer prognosis and survival in certain types of cancer. GDF15 is regulated by tumor suppressor pathways such as p53 (tumor protein 53), GSK-3β (glycogen synthase kinase-3 beta), and EGR-1 (early growth response protein 1), and can be induced by drugs and dietary substances exhibiting anti-cancer properties.[25]

GDF15 is implicated in colorectal cancer (CRC), exhibiting higher expression in CRC tissues compared to adjacent normal tissues. Excessive GDF15 expression significantly promotes cell viability, invasion, and migration, along with inducing changes favoring epithelial-to-mesenchymal transition (EMT), including increased N-cadherin, vimentin, and Twist1 (Twist-related protein 1) expression, and reduced E-cadherin expression. Utilizing GDF15-shRNA (short hairpin RNA) strategies demonstrated that reducing GDF15 inhibited cell viability, invasion, and migration in colorectal cancer cells.[27]

Elevated levels of GDF15 were observed in various malignant phenotypes of glioma. It is associated with the progression of malignancy through the NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) pathway. GDF15 is closely linked to inflammatory responses, immune cell infiltration, and immune system regulatory components, particularly in low-grade glioma (LGG). High expression levels of GDF15 predict poor survival in LGG. Thus, GDF15 emerges as a promising prognostic biomarker for LGG.[28]

It has been discovered that GDF15 is increased during the carcinogenesis of cervical cancer. The introduction of additional GDF15 stimulated the growth of cervical cancer cells, accelerating the cell cycle transition from G0/G1 (gap 0/gap 1) to S (synthesis) phase. GDF15, by transactivating receptor tyrosine-protein kinase ErbB2, promotes the proliferation of cervical cancer cells by increasing the expression of cyclin D1 and cyclin E1, and reducing the expression of p21 (protein 21), through the activation of PI3K/AKT (phosphoinositide 3-kinase/protein kinase B) and MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) signaling pathways.[26]

In a study on hepatocellular carcinoma (HCC), it was discovered that GDF15 is associated with an increase in regulatory T cells (Tregs), which suppress the immune response.[29] Deletion of the GDF15 gene in HCC transforms the tumor microenvironment from immunosuppressive to inflammatory. GDF15 supports the generation of peripherally induced regulatory T cells (iTregs) and enhances the inhibitory function of naturally occurring regulatory T cells (nTregs). GDF15 achieves this through interaction with the CD48 (cluster of differentiation 48) receptor on T cells, regulating the activity of STUB1 (stabilin 1), an E3 (ubiquitin) ligase responsible for the degradation of forkhead box P3 (FOXP3) protein. Neutralizing antibodies against GDF15 effectively eliminate HCC in mice, suggesting the potential use of GDF15 blockade in the treatment of this cancer.[29]

Fatigue associated with cancer is a debilitating sense of exhaustion related to the disease or its treatment. Blocking the GFRAL receptor, involved in the action of GDF15, counteracted cisplatin-induced fatigue. These findings suggest that the GDF15/GFRAL axis may be a promising therapeutic target for treating cancer-related fatigue.[30] Furthermore, GDF15 contributes to weight loss due to anorexia and cachexia. Blocking GDF15 and GFRAL can reverse weight loss in tumor-bearing mice, suggesting a potential therapeutic strategy. Neutralizing antibodies against GDF15 and GFRAL, such as NGM120, are currently being clinically tested for the treatment of cancer and cancer-related anorexia-cachexia syndrome.[31]

GDF15 plays a significant role in cancer cell resistance to therapy, particularly evident in breast cancer studies. GDF15, along with the GFRAL receptor, was found to be involved in inducing the formation of DTP (drug-tolerant persister) cells following eribulin therapy. GDF15 is excessively secreted after eribulin treatment. The direct involvement of GDF15 and its GFRAL receptor in inducing DTP by eribulin was confirmed by increased killing of DTP cells by eribulin in loss-of-function studies of GDF15 and GFRAL. Combined therapy of eribulin and anti-GDF15 antibody kills breast cancer DTP cells. These findings suggest that targeting GDF15 may help eliminate DTP cells and prevent the development of acquired resistance.[13] Moreover, GDF15 was identified as a gene associated with an unfavorable prognosis in breast cancer patients after radiotherapy. Breast cancer cells resistant to radiotherapy exhibited elevated GDF15 expression compared to radiation-sensitive cells. These resistant cells not only showed increased EMT features, including enhanced migration and invasion, but also displayed stem cell-like characteristics such as mammosphere-forming ability, a high percentage of stem cells, and expression of stem cell markers. Silencing GDF15 increased the sensitivity of radioresistant cells to radiation while inhibiting EMT and stem cell-like features. These findings indicate that GDF15 contributes to the resistance of breast cancer cells to radiotherapy by promoting EMT and stem cell properties. The potential use of GDF15 as a novel prognostic bio-

marker for breast cancer patients after radiotherapy and its consideration as a therapeutic target to enhance radiotherapy effectiveness in breast cancer treatment are noteworthy.[15]

In conclusion, GDF15 plays a crucial role in cancer biology, offering significant potential as a biomarker and therapeutic target. However, its complex functions and the variability of its effects across different cancer types necessitate a comprehensive and critical approach to fully harness its clinical potential.

Role of GDF15 in food intake regulation, anorexia/cachexia, diabetes and obesity

GDF15 has been recognized for its intriguing connection with food intake, regulation of appetite and energy balance.[16] GDF15 exerts its effects on food intake through its interaction with GFRAL receptor. GFRAL is expressed in the hindbrain, particularly in the area postrema and nucleus of the solitary tract, which are regions involved in the regulation of appetite and energy homeostasis. It has been discovered that GFRAL signals through the co-receptor of the tyrosine kinase receptor (RET).[16]

The data from preclinical animal studies suggest that endogenous GDF15 plays a protective role in the development of obesity, and its absence exacerbates the progression of obesity.[32] Using various methods, including GFRAL null mice, viral-mediated knockdown of GFRAL in the hindbrain, and anti-GFRAL blocking antibodies, researchers demonstrated that GDF15 causes a significant and dose-dependent reduction in food intake in rodents through the GFRAL receptor, which is specifically expressed in the hindbrain's area postrema and nucleus of the solitary tract, and this effect is inhibited by GFRAL blockade, indicating that the interaction between GDF15 and GFRAL is essential for achieving the reduction in food intake.[8,33,36] Furthermore, when challenged with a high-fat diet, GFRAL null mice gained substantially more weight compared to wild-type mice.[8,33,36]

Administration of GDF15 analogs consistently led to weight loss by reducing food intake. Therefore, GDF15 represents an attractive option in combating the current global obesity epidemic.[16] Furthermore, GDF15 influences body weight by altering dietary preferences, delaying gastric emptying, improving insulin resistance, promoting fat breakdown, and protecting β cells from apoptosis.[17,32] Therefore, GDF15 is a promising therapeutic target in the treatment of not only obesity, but also conditions such as diabetes.[17] Male mice without GDF15 exhibited poorer glucose tolerance, lower locomotor activity, and reduced metabolism compared to wild-type mice.[32]

In another study, a fusion protein of GLP-1 (glucagon-like peptide-1) and GDF15 labeled as QL1005 was developed, examining its potential for reducing body weight in animals. QL1005 demonstrated higher efficacy than semaglutide in *in vitro* studies. In obese mice, it led to a reduction in body weight, food intake, levels of insulin, fasting glucose, and triglycerides. These effects were attributed to the balanced impact of GLP-1 and GDF15 on metabolic pathways. The long-acting, dual protein GLP-1/GDF15 appears promising in the development of new metabolic drugs.[37]

Studies indicate that metformin increases the levels of GDF15 in the blood by stimulating its synthesis in the kidneys. Focusing on the kidneys as the site of metformin action and its regulation of GDF15 may be crucial for understanding the drug's impact on energy homeostasis. Silencing the expression of GDF15 in the kidneys or GFRAL in specific areas of the medulla abolished metformin's ability to reduce food intake and weight gain.[38]

The mechanisms by which the body responds to the availability of fatty acids are less understood than those controlling glucose levels. GDF15 inhibits the consumption of high-fat diets, but paradoxically, its levels increase in obese mice on such a diet. Studies have shown that fatty acids, especially linolenic acid, increase GDF15 levels in a dose-dependent manner. GDF15 mRNA expression was significantly higher in the kidneys than in the gastrointestinal tract. Linolenic acid reduced food intake and body mass in wild-type mice, but not in mice lacking the GFRAL receptor. These findings suggest that GDF15 acts as a fatty acid sensor, protecting cells from fatty acid overload.[39]

The flip side of harnessing the influence of GDF15 on nutrition and metabolism is also revealed in the topic of cachexia/anorexia. The nutritional deficiencies associated with diseases such as cancer, are common and often fatal. It occurs most frequently in the advanced stages of cancer and is likely a result of molecules released by cancer cells. The GDF15, produced in large quantities by cancer cells, plays a significant role by influencing feeding centers in the brain, leading to anorexia and weight loss.[40] The associations between GDF15 levels and nutritional indicators confirm the potential of this cytokine as a target for cancer-associated cachexia therapy.[40] Neutralizing antibodies targeting GDF15 and GFRAL, such as NGM120, are currently being clinically tested in the treatment of cancer and cancer-related anorexia-cachexia syndrome.[31]

GDF15 in aging and mitochondrial diseases

GDF15 is emerging as a significant participant in the field of aging research, as it is associated with various physiological processes and age-related conditions.

A cross-sectional study involving a group of 120 healthy individuals of different ages revealed a positive correlation between GDF15 levels and age, while also noting a negative correlation with telomere-related parameters. The results suggest that GDF15 may serve as

a potential biomarker for the aging process, influencing the risk of age-related disorders.[41,42] However, another study on the impact of GDF15 on the proliferation of old chondrocytes found higher levels of this factor in young adults compared to older individuals. The addition of GDF15 increased chondrocyte proliferation, indicating a role for GDF15 in processes related to cartilage aging, possibly through the activation of the TGF-β pathway.[43] Both studies shed light on the complex role of GDF15 in aging processes, serving as both a biomarker and an activator of cellular processes, which may have implications for understanding and potentially modifying aging processes and related conditions. However, the results inconsistency highlights the need for more comprehensive longitudinal studies to determine whether GDF15 is a reliable aging biomarker.

GDF15 plays a significant role in healthy aging, influencing mitochondrial function, cellular vitality, and preventing chronic diseases. Maintaining mitokine homeostasis through lifestyle can impact life extension.[44] The influence of GDF15 on mitochondrial function has led to its recognition as a diagnostic marker in mitochondrial diseases. A moderate positive correlation was found between GDF15 levels and the severity of mitochondrial disease in carriers of the m.3243A>G mutation. Higher GDF15 levels were associated with the presence of diabetes, cardiomyopathy, and kidney disorders.[45] Cell lines with a mutation causing MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes), treated with lactic acid or pyruvate, showed increased expression and secretion of GDF15. Serum GDF15 levels were also significantly higher in patients with mitochondrial diseases than in those with other conditions. These results suggest that GDF15 may be a promising biomarker for the diagnosis and evaluation of the therapeutic effectiveness of pyruvate in mitochondrial diseases.[46] The results of another study suggest that measuring GDF15 is the most useful first-line test for identifying patients with mitochondrial respiratory chain deficiency. In a comparative study of biomarker levels in patients with mitochondrial disease and healthy control individuals, it was found that GDF15 was significantly higher in mitochondrial disease patients (on average six times higher). Additionally, GDF15 measurement showed greater effectiveness in diagnosing mitochondrial disease than other studied biomarkers.[47]

GDF15 is one of the most active proteins associated with aging and various age-related diseases. Although GDF15 plays a protective role in many tissues during stress and aging processes, there are reports that its chronic elevation in old age may lead to harmful effects.[48]

GDF15 in gynecology

Research has shown a significant increase in GDF15 levels in the placenta and circulation during pregnancy.[49,50] The protein, often secreted by the placenta and abdominal organs, plays a role in nutritional stress.[50-53] The human trophoblast appears to produce a significant amount of GDF15 already in early pregnancy.[51]

The increase in GDF15 levels in the blood is associated with vomiting, weight loss, and cachexia, underscoring the potential therapeutic use of GDF15 as a target in the context of nausea and vomiting in pregnancy (NVP) and hyperemesis gravidarum (HG).[50,54,55] The discovery of GFRAL receptor in the brain sheds light on mechanisms related to nausea and confirms the role of GDF15 in NVP and HG.[50,56] Furthermore, genetic studies, particularly genome-wide association studies (GWAS), have demonstrated that genes within the GDF15-GFRAL axis are associated with the risk of NVP and HG.[50,57-59]

Decreased levels of GDF15 in the serum and trophoblast tissue of pregnant women have been strongly associated with miscarriages. Immunohistochemistry and enzyme-linked immunosorbent assay (ELISA) studies show that women who miscarried had significantly lower levels of GDF15 compared to those who had live births.[60] In mice, GDF15 knockout was related to increased embryo resorption and reduced migration and invasion abilities of extravillous trophoblast cells, facilitated by the upregulation of the TGF-β/Smad1/5 pathway and by inhibition of the Jagged-1 (JAG1)/NOTCH3/HES1 pathway.[60,61] The embryonic resorption could be reversed with the administration of recombinant GDF15. These findings suggest that sufficient levels of GDF15 are crucial for trophoblast invasion and proper placental development, indicating that GDF15 supplementation could potentially help maintain early pregnancy and reduce the risk of miscarriage.[61]

Increased levels of GDF15 are significantly associated with gestational diabetes mellitus (GDM) during the third trimester of pregnancy. However, GDF15 levels did not show a clear correlation with GDM-related adverse perinatal outcomes. These findings indicate that GDF15 could serve as a biomarker for GDM, though further research is needed to confirm its clinical utility and significance.[62]

GDF15 in neurology

A meta-analysis comprising eight studies revealed significantly higher levels of GDF15 in patients with neurodegenerative diseases compared to healthy control individuals.[63] This is further supported by another study that aimed to investigate the association between GDF15 levels and cognitive impairment without dementia (CIND) or Alzheimer's disease (AD), taking into account the presence of cerebrovascular disease (CeVD). Elevated GDF15 levels were significantly associated with disease groups, especially in patients with CeVD.[64] These findings suggest that serum GDF15 lev-

els may serve as a promising diagnostic biomarker for neurodegenerative diseases.

Relationships between GDF15 and ischemic stroke and its consequences were also demonstrated. In a study focused on the Chinese population, an analysis of single nucleotide polymorphisms (SNPs) in the GDF15 gene explored the association with susceptibility to ischemic stroke. The study suggests that the rs1804826G/T polymorphism of the GDF15 gene and sGDF-5 levels are associated with the development of ischemic stroke in the Chinese population, highlighting the role of the GDF15 gene in this context.[65] In another investigation, the association between GDF15 levels and three-month mortality in patients treated with revascularization therapy following ischemic stroke was assessed. GDF15 levels in serum were measured at admission and subsequent time points. Deceased patients had higher GDF15 levels at the beginning of the study. The analysis indicated that GDF15 levels at admission were independently associated with mortality after 3 months. This suggests that GDF15 concentration at admission may serve as a potential prognostic marker for patients with ischemic stroke treated with revascularization therapy.[66] To integrate GDF15 as a diagnostic or prognostic biomarker in clinical practice, algorithms incorporating GDF15 levels with clinical parameters and imaging findings need to be developed and validated. The cost-effectiveness of incorporating GDF15 measurement into routine clinical practice should be evaluated to ensure it provides a tangible benefit to patient management and outcomes.

Impact on liver and metabolic disorders

A correlation has been demonstrated between GDF15 concentrations and the development of liver diseases and metabolic disorders. One study aimed to investigate the role of GDF15 in liver fibrosis progression. It was found that GDF15 expression is reduced in patients with liver fibrosis. GDF15 deficiency exacerbated fibrosis, while GDF15 overexpression alleviated the process. GDF15 acts by reprogramming macrophage metabolic pathways, resulting in an anti-inflammatory effect. Transplanting GDF15-treated macrophages mitigated inflammation and liver fibrosis progression. The results suggest that GDF15 could be a potential therapeutic target for treating liver fibrosis by modulating liver macrophages.[67]

Another study suggests that GDF15 also plays a significant role in non-alcoholic fatty liver disease (NAFLD).[68] In the pathogenesis of NAFLD, mitochondrial dysfunction and inflammasome activation are crucial. GDF15 is essential for regulating this process. The study showed that GDF15 expression is decreased in the liver tissues of NAFLD patients and cell models of steatosis. GDF15 overexpression in transgenic mice alleviated obesity, liver steatosis, and AIM2 (absent in melanoma 2) inflammasome activation. Additionally, GDF15 limited oxidative stress, mitochondrial damage, and dsDNA (double-stranded deoxyribonucleic acid) accumulation, potentially contributing to weakening AIM2 inflammasome activation. These results suggest that GDF15 could be a potential therapeutic target for NAFLD by suppressing oxidative stress and inflammation.[68]

In another study, it was found that in non-alcoholic steatohepatitis (NASH), the expression of ARRB1 (Arrestin beta 1) is decreased. ARRB1 was found to interact with GDF15 and facilitate the transport of GDF15 precursor (pro-GDF15) to the Golgi apparatus for processing and maturation.[69] Recombinant GDF15 treatment reduced lipid accumulation in the absence of ARRB1 both in vitro and in vivo. Re-expression of ARRB1 in NASH models improved liver disease, and this effect was enhanced in the presence of excessive pro-GDF15 expression. Conversely, the standalone effect of excessive pro-GDF15 expression was weakened in models lacking ARRB1.[69]

The role of GDF15 is, however, more complex, as indicated by the inconsistencies among sources. GDF15 can exert both protective and harmful systemic effects, playing a role in the mitochondrial unfolded protein response (UPRmt) and may even be elevated in metabolic diseases such as obesity and NASH.[70]

Sepsis

Mitochondria are crucial organelles regulating various cellular processes, and mitochondrial stress, associated with electron transport chain defects and proteostasis disruptions, is linked to numerous diseases. Sepsis, a life-threatening condition, involves metabolic disturbances and impaired immune response. Mitochondrial stress is anticipated to play a role in sepsis pathogenesis. Cells activate homeostasis maintenance systems in response to mitochondrial stress, potentially leading to the activation of genes associated with cell survival and death. GDF15 has been identified as a key secreted protein in response to mitochondrial dysfunction.[71] GDF15 shows elevated levels in sepsis, correlating with inflammatory markers and organ damage indicators involved in SOFA (sequential organ failure assessment) score. It has high diagnostic value in sepsis, especially when combined with other markers. In vitro studies indicate that GDF15 may regulate macrophage inflammation, inhibit M1 (classically activated macrophages) polarization, support M2 (alternatively activated macrophages) polarization, enhance macrophage phagocytic and bactericidal functions. Additionally, GDF15 exhibits protective effects by inhibiting the JAK1/STAT3 (Janus Kinase 1/signal transducer and activator of transcription 3) pathway activation and NF-κB p65 subunit nuclear translocation. Dynamic monitoring of GDF15 levels may be crucial in sepsis assessment and prognosis.[72]

GDF15 in pulmonology

GDF15, secreted by tracheal epithelial cells, shows therapeutic potential by inhibiting excessive fibroblast activity and promoting epithelial repair. In a rat model with tracheal stenosis, the addition of GDF15 alleviated the degree of narrowing, suggesting its potential efficacy as a therapy for benign tracheal and bronchial stenosis.[73] Furthermore, research on mice lacking the GDF15 gene and exposed to ricin toxin demonstrated that the absence of GDF15 intensified lung injury, resulting in weight loss, decreased survival, and elevated levels of inflammation-related cytokines. These findings highlight a critical role for GDF15 in modulating the immune response in acute lung injury, suggesting potential avenues for new research and anti-inflammatory therapies in lung diseases.[74]

GDF15 is proposed as a potential biomarker in lung diseases such as bronchopulmonary dysplasia in newborns, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and pulmonary hypertension, aiding in diagnosis and prognosis.[75]

Study by Husebo et al. explored GDF15's role in COPD. High plasma GDF15 levels correlated with higher exacerbation rates, increased mortality, and greater declines in FEV1 and FVC. Increased GDF15 levels also predicted more frequent exacerbations and higher mortality independently. The study indicated that GDF15 acts as a fatty acid sensor, potentially protecting cells from fatty acid overload.[76] Elevated levels of GDF15 were also found in the sputum and lung tissue of smokers and COPD patients compared to non-smokers. Experiments showed that cigarette smoke exposure increases GDF15 expression in human bronchial epithelial cells and mouse lungs. Importantly, GDF15 deficiency reduced cigarette smoke-induced pulmonary inflammation in mice. These findings suggest that GDF15 contributes significantly to the inflammatory processes in the lungs caused by cigarette smoke, implicating its potential role in the pathogenesis and progression of COPD.[77]

Elevated GDF15 levels are associated with increased subclinical coronary atherosclerosis in COPD patients who are free of clinical cardiovascular disease. This relationship holds true even after adjusting for baseline cardiovascular disease risk, co-morbidities, severity and impact of COPD, markers of cardiac stress, and inflammation. These findings suggest that GDF15 independently contributes to subclinical coronary atherosclerosis in ever-smokers with COPD, highlighting its potential importance in the cardiovascular health of these patients.[78]

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has led to a pandemic affecting the respiratory and cardiovascular systems. Cytokine storms in COVID-19 patients contribute to vascular dysfunction, leading to severe complications such as acute respiratory distress syndrome (ARDS). GDF15 serves as a strong predictor of poor prognosis in critically ill patients, playing a central role as a tissue tolerance mediator in response to inflammation.[79]

Thrombosis

The relationship between GDF15 and thrombosis is a topic of interest in medical research. The study explores the interplay between GDF15 and deep vein thrombosis (VTE). Elevated GDF15 levels in VTE patients and mouse models of thrombosis prompt an investigation into how GDF15 influences the development of deep vein thrombosis. The study suggests that inhibiting GDF15 could offer therapeutic implications for improving the anticoagulant and fibrinolytic functions of endothelial cells in the context of venous thrombosis.[80]

Systemic autoimmune diseases

GDF15 is linked to acute and chronic inflammation, particularly in autoimmune diseases like Type I diabetes and rheumatoid arthritis. However, its role in systemic autoimmune diseases is not well understood. Studies on GDF15-deficient mice show that its absence contributes to lymphoproliferation, T, B, and plasma cell expansion, and elevated anti-DNA antibodies, leading to accelerated kidney inflammation. GDF15 deficiency also enhances in vitro lymphoproliferative responses and induces type I interferon in spleen cells exposed to toll-like receptor (TLR) stimuli. In individuals with lupus nephritis (LN), reduced GDF15 expression and increased type I interferon in the kidneys suggest GDF15's regulatory role in suppressing lymphocyte activation and proliferation, while negatively influencing Toll-like receptor-driven type I interferon signaling.[81]

A study by Xu et al. demonstrated the involvement of GDF15 in the pathogenesis of systemic lupus erythematosus (SLE). The results indicated that GDF15 levels are higher in SLE patients compared to the healthy population. To further investigate this finding, recombinant GDF15 was administered to pristane-induced lupus mice, which resulted in reduced histological scores and decreased percentages of CD8+, CD11b+, CD19+, and CD11C+ cells, as well as TH2 cells and pro-inflammatory cytokines (IL-1β, IL-2, IL-4, IL-21, and IL-22). These findings suggest that GDF15 is associated with the pathogenesis of lupus and may help reduce the activity of the disease.[82]

The activity of GDF15 has also been studied in patients with rheumatoid arthritis (RA) and idiopathic inflammatory myopathies (IIM). It has been shown that the serum concentration of GDF15 in patients with RA or IIM is higher compared to a healthy population.[83,84] Moreover, in RA patients, significantly higher levels of this factor were observed in individuals with active disease. Serum GDF15 levels showed a positive correlation

with erythrocyte sedimentation rate (ESR), morning stiffness, disease activity score-28 (DAS28), tender joint count, and carotid intima-media thickness (CIMT).[83] In IIM, elevated levels of GDF15 were also detected in diseased skeletal muscle. GDF15 predominantly localizes to small regenerating or denervated muscle fibers. In patients with sporadic inclusion body myositis, GDF15 co-localizes with the characteristic protein aggregates found within affected muscle fibers.[84]

While current studies provide valuable insights into GDF15's potential roles, the precise molecular mechanisms through which GDF15 modulates immune responses are not fully elucidated. Further research is needed to explore these pathways in detail. The dual role of GDF15 in promoting and inhibiting inflammation in different contexts complicates its use as a biomarker or a therapeutic target.

GDF15 in dermatology

The multifaceted role of GDF15 underscores its significance in unraveling the complexities of skin conditions such as psoriasis and age-related pigmentation alterations, offering potential therapeutic avenues for these dermatological concerns.

Psoriasis, marked by excessive keratinocyte proliferation and inflammation, exhibits reduced GDF15 levels. In psoriasis, GDF15 is inhibited by TNF-α (tumor necrosis factor), exacerbating psoriasis symptoms. GDF15 deficiency intensifies psoriatic changes and increases skin inflammation. GDF15 regulates cytokine and chemokine synthesis, inhibits the TAK1/NF-κB (transforming growth factor-β activated kinase 1/NF-κB) pathway in keratinocytes, and directly influences neutrophil adhesion and migration by inhibiting Rap1 (Ras-related protein 1) activation. Recombinant mouse GDF15 administration alleviates psoriasis symptoms in a mouse model, suggesting therapeutic potential for treating this skin condition.[85]

In a study on aging skin pigmentation, increased levels of GDF15 expression were observed in aging fibroblasts exposed to UV (ultraviolet) radiation and in photoaged skin with hyperpigmentation. Experiments using human melanocytes showed that GDF15 stimulates the melanogenesis process by activating the β-catenin signaling pathway and increasing the expression of MITF/tyrosinase (Microphthalmia-associated transcription factor/tyrosinase). Studies on ex vivo skin culture and a reconstructed model of human skin confirmed the stimulatory effect of GDF15 on skin pigmentation, suggesting its potential role in age-related pigmentation.[86]

Conclusion

The review underscores GDF15's pivotal role across various biological processes and medical disciplines. GDF15 emerges not only as a crucial player in normal physiological regulation but also as a key factor in the pathophysiology of numerous diseases. Its involvement in inflammatory pathways, apoptosis, angiogenesis, cell repair, and growth highlights a multifunctional role, affecting a wide spectrum of organ systems and disease processes.

In the realm of cardiovascular disorders, GDF15 serves as both a protective agent and a biomarker for disease severity and prognosis. Its elevated levels are indicative of cardiovascular risk and correlate with the severity and mortality of heart diseases, positioning it as a promising tool for risk stratification and management in cardiology.

GDF15's role in oncology is equally significant. Its varied expression in different cancer types and its influence on tumor progression, metastasis, and resistance to therapies mark it as a potential biomarker for cancer prognosis and a target for therapeutic intervention. The GDF15-GFRAL axis, in particular, offers new insights into the management of cancer-related anorexia and cachexia, as well as cancer cell resistance to treatment.

In metabolic disorders, GDF15 has shown a profound impact on body weight regulation, appetite control, and energy homeostasis. Its role in obesity, diabetes, and cachexia underscores its potential therapeutic utilization in these prevalent global health challenges.

The review also highlights GDF15's emerging role in aging and mitochondrial diseases, where it could act as a biomarker for aging processes and mitochondrial dysfunction. Its regulatory role in autoimmune diseases, sepsis, and liver diseases further emphasizes its systemic impact.

GDF15's influence extends to gynecology, neurology, and dermatology, indicating its broad relevance in medical science. In these fields, it serves as a biomarker and potential therapeutic target, offering novel insights into disease mechanisms and treatment strategies.

Overall, GDF15 represents a potential biomarker and therapeutic target with wide-ranging implications in health and disease. The concise overview of the diverse roles and implications of GDF15 in various medical disciplines is presented in Table 1.

GDF15's complex role in various physiological and pathological processes demands further research to fully exploit its potential in clinical practice. Understanding the multifaceted nature of GDF15 will be crucial in developing novel diagnostic and therapeutic approaches for a multitude of diseases, potentially improving patient outcomes across various medical specialties.

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Conflicts of interest

The authors declare no competing interests

Data availability

No datasets were generated or analyzed during the current study.

Ethics approval

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written. The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.

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