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Advances in Research on GDF-15 in Heart Failure Patients with Concurrent Frailty

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Abstract: ***Growth differentiation factor-15 (GDF-15), a cytokine responsive to stress, has been recently validated as a pivotal molecule that bridges heart failure and frailty. Studies have shown that GDF-15 levels are significantly correlated with the degree of frailty and poor prognosis in patients with heart failure, making it a promising biomarker for risk stratification and individualized treatment in this population. This article systematically elaborates on the mechanism of action, related signaling pathways, and prognostic evaluation value of GDF-15 in the comorbidity of heart failure and frailty, aiming to provide new theoretical basis and research ideas for exploring intervention strategies targeting GDF-15, optimizing multidimensional management schemes for heart failure with frailty, and improving patient clinical outcomes in the future.***

Keywords: GDF-15, Heart failure, Frailty, Biomarker, Signaling pathway.

1. Introduction

Heart failure (HF) is a syndrome marked by ventricular filling or ejection impairment resulting from structural or functional cardiac abnormalities, which subsequently leads to a range of clinical manifestations including dyspnea, fatigue, and fluid retention. Epidemiological data indicate that the global prevalence of heart failure has surpassed 64 million cases. Owing to the accelerated aging of the population and advancements in the management of acute myocardial infarction, the incidence of this condition continues to rise [1].

Frailty is a geriatric syndrome defined by a progressive reduction in physiological reserve, resulting in an increased vulnerability to stressors among individuals. Clinically, it is manifested by a notably elevated risk of adverse outcomes, including falls, disability, and mortality. In 2019, the Heart Failure Working Group of the European Society of Cardiology highlighted that frailty significantly intensifies the stress sensitivity of patients with heart failure, with a bidirectional reinforcing effect between the two conditions, collectively influencing the overall frailty of patients [2]. Cohort studies have demonstrated that the risk of frailty in patients with HF is approximately twice that of age-matched individuals without HF [3], whereas the risk of HF in individuals with concurrent frailty is eightfold higher than in those without frailty [4].

The coexistence of HF and frailty not only extends the duration of hospitalization and elevates readmission rates but also significantly deteriorates patients' quality of life, thereby imposing a substantial burden on the public healthcare system [5,6]. In this context, identifying molecular biomarkers capable of early detection of frailty in HF patients assumes considerable clinical importance. A recently systematic review collated data from 14 pertinent studies (comprising 7 longitudinal and 7 cross-sectional investigations) [7], explicitly identifying Growth differentiation factor-15 (GDF-15) as a potential biomarker for frailty. Elevated GDF-15 levels exhibit a dose-response relationship with an augmented risk of subsequent frailty, particularly in individuals with cardiovascular and metabolic diseases. Building upon this foundation, this present review aims to elucidate the relationship between GDF-15 and the onset of frailty in HF patients, explore its underlying mechanisms and associated signaling pathways, and assess its potential utility in diagnosing and prognosticating HF complicated by frailty. The ultimate goal is to furnish theoretical underpinnings for the development of targeted therapeutics and the refinement of clinical treatment strategies.

2. General Overview of GDF-15

GDF-15 is a member of the transforming growth factor-β superfamily and functions as a stress-induced cytokine, also referred to as macrophage inhibitory cytokine-1 [8]. The gene encoding GDF-15 is situated at chromosome 19p13.11 and comprises two exons. Initially, it is synthesized as a 308-amino-acid precursor protein, which is subsequently cleaved by furin-like proteases to form a disulfide-linked homodimer of approximately 25 kDa, representing its biologically active form [9]. Under physiological conditions, GDF-15 is expressed at low levels in various tissues, however, under stress conditions, its expression is markedly upregulated in organs such as the heart, liver, adipose tissue, and skeletal muscle, followed by release into the blood circulation. Signal transduction of GDF-15 is contingent upon its binding to the brainstem-specific receptor GFRAL and the co-receptor RET [8,10]. Functional investigations have demonstrated that GDF-15 is involved in diverse physiological and pathological processes, encompassing appetite regulation and energy metabolism, suppression of inflammatory responses, oxidative stress response, tissue repair and modulation of fibrosis [8,10]. Elevated circulating levels of GDF-15 not only exert anti-inflammatory and anti-ferroptotic effects but also contribute to metabolic adaptation in disease states such as HF, diabetes, and cancer cachexia [11]. Given these properties, GDF-15 emerged as a significant biomarker for prognostic evaluation in cardiovascular diseases, diabetes, and various malignancies [12,13].

3. Mechanisms of GDF-15 in Heart Failure Complicated with Frailty

As a stress-responsive cytokine, GDF-15 plays a regulatory role in the comorbidity of HF and frailty via multiple interconnected signaling pathways. Recent research has unveiled that GDF-15 primarily participates in the pathological progression of HF with frailty through three core dimensions: energy metabolism and mitochondrial stress, inflammation and oxidative stress, and regulation of apoptosis.

3.1 Energy Metabolism Disorders and Mitochondrial Stress

GDF-15, as a key mediator of mitochondrial stress response, exerts central regulatory effects in HF with frailty through multiple energy metabolism pathways. Clinical metabolomics studies have revealed significant abnormalities in energy metabolism intermediates among patients with HF and frailty. Through untargeted plasma metabolomics analysis, Prokopidis et al. [14] found that plasma GDF-15 levels in the heart failure with frailty group (HF-Frail) were approximately 3.21 times higher than those in the non-HF and non-frailty group, accompanied by a significant increase in branched-chain amino acids (leucine, isoleucine, valine) and a decrease in glutamine, methionine, and tryptophan levels. This metabolic pattern reflects enhanced systemic catabolism, which, together with elevated GDF-15 levels, constitutes a vicious cycle of "mitochondrial stress-energy metabolism disorder". Animal experiments further confirm the central role of GDF-15 in energy metabolism regulation. Takaoka et al. [15] demonstrated in a mouse model lacking PPP1R15A (an integrin stress response-induced eIF2α phosphatase) that cardiac stress promotes weight loss and exacerbates cardiac dysfunction via a GDF-15-dependent pathway, whereas blockade of GDF-15 activity effectively prevents cachexia and delays HF progression. Zhang et al. [16] found in an isoproterenol-induced heart failure mouse model and primary cardiomyocyte culture that GDF-15 exerts an anti-apoptosis effects by improving mitochondrial fusion. Specifically, silencing GDF-15 exacerbates mitochondrial fusion disorders and oxidative stress, suggesting that this factor delays the progression of HF by maintaining mitochondrial functional homeostasis. At the central regulatory level, GDF-15 functions by binding to the brainstem-specific receptor GFRAL and co-receptor RET. Rochette et al. [17] noted that binding of GDF-15 to the GFRAL-RET complex activates downstream Ras and PI3K/Akt signaling pathways, acting on the brainstem appetite center to induce anorexia and lead to weight loss and muscle wasting, which significantly exacerbates the occurrence and development of frailty in HF patients. Ferreira et al. [18] further revealed, based on the EMPEROR study, that although GDF-15 can exert cardioprotective effects by inhibiting insulin-like growth factor-1 (IGF-1) signaling and enhancing adenosine monophosphate-activated protein kinase (AMPK) signaling, this metabolic regulation process is accompanied by an increase in systemic energy consumption, objectively accelerating the progression of frailty.

3.2 Inflammatory Response and Oxidative Stress

GDF-15 regulates oxidative stress and inflammatory responses through multiple signaling pathways, driving the occurrence and progression of HF with concomitant frailty. Clinical studies have shown that in patients with preserved ejection fraction (HFpEF) [19], GDF-15 levels are significantly positively correlated with C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), and negatively correlated with hemoglobin and estimated glomerular filtration rate (eGFR), suggesting that it can serve as a biomarker reflecting systemic stress states. In elderly patients with comorbidities and HFpEF, persistent oxidative stress and inflammation lead to long-term high expression of GDF-15, which, by acting on brainstem receptors, causes appetite loss, malnutrition, weight loss, and reduced physical activity, forming a vicious cycle. Guo et al. [20] explored the antioxidant mechanism of GDF-15 in a lipopolysaccharide (LPS)-induced septic cardiomyopathy mouse model. The study found that delivering recombinant human GDF-15 using macrophage membrane-coated PLGA nanoparticles significantly reduced superoxide anion production and alleviated myocardial oxidative stress injury. Mechanistically, GDF-15 binds to MYPT1, inhibiting AKT-mediated phosphorylation and nuclear translocation of YBX-1, allowing cytoplasmic-retained YBX-1 to inhibit NLRP3 inflammasome activation and IL-1β release, thereby reducing cardiac oxidative stress levels and slowing muscle damage and functional decline. Meng et al. [21] further validated the anti-inflammatory effect of GDF-15 in a rat model of HFpEF using gene silencing technology. Silencing GDF-15 expression led to significant upregulation of inflammatory markers such as IL-1β, IL-6, IL-8, TNF-α, and oxidative stress markers such as myeloperoxidase and oxidized low-density lipoprotein in myocardial tissue, exacerbating cardiac function deterioration, confirming that GDF-15 exerts myocardial protective effects by inhibiting oxidative stress and inflammatory responses.

3.3 Myocardial Fibrosis and Apoptosis Regulation

GDF-15 exerts a dual protective effect on myocardial remodeling and cell survival regulation. At the level of myocardial fibrosis, GDF-15 participates in regulating the ventricular remodeling process: on the one hand, it induces SMAD 2/3 phosphorylation, enhances left ventricular shortening fraction, and inhibits ventricular dilation [17]; on the other hand, Meng et al. [21] found in a rat model of HFpEF that GDF-15 silencing can significantly upregulate collagen I, collagen III, and α-SMA, leading to exacerbated myocardial fibrosis, indicating that GDF-15 protects cardiomyocytes by inhibiting the fibrosis pathway. Regarding apoptosis regulation, multiple studies have confirmed that GDF-15 can enhance the survival ability of cells under stress conditions. In human stem cell-derived cardiomyocytes, Fung et al. [22] observed that recombinant GDF-15 pretreatment can significantly reduce the cytotoxic effects induced by doxorubicin, decrease apoptosis and mitochondrial structural damage. Mechanism studies have shown [23] that GDF-15 inhibits pathological mitophagy by downregulating BNIP3, while activating lysosomal function to alleviate hypoxia-induced mitochondrial damage and cardiomyocyte apoptosis. Zou et al. [24] reported that GDF-15 engineered exosomes (GDF-15-EVs) can be effectively internalized by cardiomyocytes, reducing H_2O_2-induced cell damage. Furthermore, mRNA sequencing suggested that these exosomes can significantly upregulate telomerase reverse transcriptase (TERT) expression, activate the AMPK

signaling pathway, and exert anti-apoptotic and pro-autophagic effects. Liang et al. [25] explored the role of GDF-15 pretreated mesenchymal stem cells (MSCs) in the treatment of myocardial infarction and found that pretreatment with GDF-15 can improve the survival rate of MSCs, significantly inhibit apoptosis, and promote proliferation. Given that one of the core pathologies of HF is the progressive loss of cardiomyocytes, GDF-15 indirectly enhances myocardial repair capacity by protecting the survival of transplanted cells, maintaining the number of cardiomyocytes, and delaying the progression of HF.

4. Clinical Diagnostic and Prognostic Value of GDF-15

GDF-15 levels are closely related to the state of frailty in patients with HF and exhibit significant value in risk stratification and prognostic assessment. Prokopidis et al. [14] analyzed 25 patients with chronic HF and 29 controls, assessing frailty using physical activity levels, grip strength, and a 30-second chair stand test. They found that plasma GDF-15 levels were significantly elevated in the HF with frailty group, and were negatively correlated with the grip strength/BMI ratio and chair stand test scores. This suggests that GDF-15 may serve as a biomarker for identifying the frailty phenotype in HF patients. In terms of prognostic assessment, a systematic review by Dakota [26] included 12 studies with a total of 5696 patients with HFpEF. The results showed that elevated GDF-15 levels were closely associated with an increased risk of all-cause mortality and readmission for HF, and its overall diagnostic performance was slightly superior to traditional biomarkers. Sakamoto et al. [19] found in an elderly population with comorbidities and HFpEF that for each unit increase in log-transformed GDF-15, the risk of adverse outcomes increased by 12.67 times. And incorporating GDF-15 into the MAGGIC risk score significantly improved the model's predictive ability, indicating its incremental predictive value. In summary, GDF-15 plays a crucial role in the identification, risk stratification, and prognostic assessment of HF with frailty. In clinical practice, elevated GDF-15 levels suggest an increased risk of comorbid frailty and a higher likelihood of adverse outcomes. Therefore, GDF-15 is expected to become a complementary tool to traditional HF risk scores, providing a basis for individualized treatment decisions, while also facilitating early identification and timely intervention in high-risk populations. This is of significant clinical importance for delaying disease progression and preventing related complications.

5. Summary and Outlook

The significance of GDF-15 in assessing HF combined with frailty is increasingly recognized, and its association with these two pathological conditions has become a focal point of current research. With the continuous development of related science and technology, the specific mechanisms of GDF-15 in the pathogenesis and progression of HF with frailty, as well as the key signaling pathways involved, will be further elucidated. At the same time, the understanding of the pathophysiological basis and treatment strategies for HF complicated by frailty will also continue to deepen, laying a solid theoretical foundation for the future development of drugs targeting GDF-15 regulation. These advancements not only provide new research directions for the effective prevention and treatment of HF with frailty but also open up potential innovative paths for optimizing diagnostic methods, treatment approaches, and prognostic assessments for such patients, offering significant clinical guidance value.

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