Review

Discovery Medicine 2024; 36(181): 248–255
https://doi.org/10.24976/Discov.Med.202436181.23

Growth Differentiation Factor-15 Orchestrates Inflammation-Related Diseases via Macrophage Polarization

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Published: 20 February 2024

Macrophage polarization is a critical determinant of disease progression and regression. Studies on macrophage plasticity and polarization can provide a theoretical basis for the tactics of diagnosis and treatment for macrophage-related diseases. These include inflammation-related diseases, such as sepsis, tumors, and metabolic disorders. Growth differentiation factor-15 (GDF-15) or macrophage inhibitory cytokine-1, a 25 kDa secreted homodimeric protein, is a member of the transforming growth factor-β (TGF-β) superfamily that is released in response to external stressors. GDF-15 regulates biological effects such as tumor occurrence, inflammatory response, tissue damage, angiogenesis, and bone metabolism. It has been shown to exert anti-inflammatory and pro-inflammatory effects in inflammation-related diseases. Moreover, inflammatory stimuli can induce GDF-15 expression in immune and parenchymal cells. GDF-15 exhibits a feedback inhibitory effect by inhibiting tumor necrosis factor-α secretion during the macrophage activation anaphase, suggesting that there may be a close association between the two. GDF-15 directly induces $CD14^+$ monocytes to produce the M2-like macrophage phenotype, inhibits monocyte-derived macrophage for M1-like polarization, and induces monocyte-derived Mφ for M2-like polarization. This review summarizes the macrophage polarization mechanism of GDF-15 under the conditions of sepsis, colon cancer, atherosclerosis, and obesity. An improved understanding of the role and molecular mechanisms of action of GDF-15 could greatly elucidate the mechanism of disease occurrence and development and provide new ideas for targeted disease prevention and treatment. An advanced understanding of the function and molecular mechanisms of action of GDF-15 may be helpful in the assessment of its potential value as a therapeutic and diagnostic target.

Keywords: growth differentiation factor-15; molecular mechanism; macrophage polarization; sepsis; atherosclerosis; colon cancer

Introduction

Macrophages are the constituents of the mononuclear phagocyte system, serving as the first line of host defense. Diversity and plasticity are hallmarks of monocyte-macrophage lineage cells. Generally, macrophages can be divided into two subtypes: M1 macrophage (pro-inflammatory, activated by lipopolysaccharides [LPSs] or interferon-γ) and M2 macrophage (anti-inflammatory, activated by Interleukin ([IL]-4, IL-13, or IL-10) [1]. M2 macrophages are divided into four subtypes: M2a, M2b, M2c, and M2d. Macrophage polarization has been suggested to be a critical determinant of disease progression and regression. Moreover, studies on macrophage plasticity and polarization can provide a theoretical basis for diagnostic and therapeutic strategies for macrophage-related diseases.

Growth differentiation factor-15 (GDF-15), a 25 kDa secreted homodimeric protein, is a transforming growth factor-β (TGF-β) superfamily member. It is widely distributed in mammalian tissues but is usually highly expressed in the placenta and prostate and poorly in the kidney, liver, cerebral choroid plexus, digestive tract, and respiratory epithelium [2]. GDF-15 is part of a generic gene program activated in response to external stressors and induced under inflammatory or traumatic stress stimuli, such as inhibiting tumor necrosis factor-α (TNF-α), TGF-β, and Interleukin-1 (IL-1). It exerts anti-inflammatory and pro-inflammatory effects in inflammation-related diseases in return. Moreover, inflammatory stimuli can induce its expression in both immune and parenchymal cells [3]. It exhibits a feedback inhibitory effect by TNF-α secretion during the macrophage activation anaphase, suggesting that there may be a close association between the two [2]. Further studies have revealed that GDF-15 can directly induce

$CD14^+$ monocytes to produce the M2-like macrophage phenotype, inhibit monocyte-derived macrophage for M1-like polarization, and induce monocyte-derived Mφ for M2-like polarization [4].

In this review, we present recent data on the role of GDF-15 in the regulation of common inflammation-related diseases, including sepsis, atherosclerosis, colorectal cancer, and obesity. Further, we highlight the underlying molecular mechanisms of GDF-15 effects. A deeper understanding of its role and molecular mechanisms will help identify novel therapeutic targets for inflammation-related diseases.

Molecular Mechanisms of Macrophage Polarization

The molecular mechanisms underlying M1/M2 macrophage polarization remain unclear. The main related pathways known to date are the Janus kinase/Signal transducer and activator of transcription (JAK/STAT), interferon regulatory factor (IRF), Notch, and phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathways (Fig. 1) [5–16]. Studying the relevant signaling pathways and regulatory mechanisms regulating macrophage polarization is significant for the prevention, treatment, and prognosis of various diseases. Owing to the diversity of macrophage function, complexity of signal pathway transduction and regulation, and network connections of various signal pathways, there is uncertainty in the phenotype transformation of macrophages. Therefore, further research on the signal pathways and regulatory mechanisms of macrophage polarization is needed.

Sepsis

Sepsis is a life-threatening organ dysfunction caused by a dysregulation of the body's immune response to infection or oxidative stress. In the early phase of systemic inflammatory response in sepsis, macrophages polarize toward the M1 type and release large amounts of inflammatory factors (such as IL-1, IL-6, TNF-α, and inducible nitric oxide synthase) [17]. Large amounts of chemokines (such as CC-type chemokine ligands 2–4 and CXC-type chemokine ligands 8–11) can exert protective effects by negatively regulating the abnormal activation of macrophage, reducing the activation of inflammatory vesicles [18]. The chemokines release inflammatory factors and affect macrophage apoptosis. In contrast, in the late stage of sepsis, there is dramatic apoptosis of immune cells, including macrophages, leading to immunosuppression, immune paralysis, and endotoxin tolerance. Macrophages undergo impaired M1/M2 macrophage polarization in severe sepsis due to immunosuppression [19]. Hotchkiss *et al.* [20] and Jiang *et al.* [21] demonstrated that a prominent clinical feature of sepsis is the disruption of the body's immunosuppressive system, with a relative increase in the number of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs), which in turn reduces the body's defense against pathogens. The subsequent onset of secondary infection is the leading cause of death in patients with severe sepsis. Therefore, it is critical to explore macrophage activation and its polarization regulation in diagnosing and managing sepsis.

GDF-15 is elevated in LPS- and cecal ligation puncture-induced sepsis mouse models [22,23]. Recombinant GDF-15 intervention increases mouse survival, and GDF-15 overexpression prevents model death [22–25]. GDF-15 prevents LPS-induced liver injury in mice by blocking TGF-β-activated kinase 1 (TAK1) phosphorylation. GDF-15 knockdown in mice enhances LPS-induced inflammatory response and exacerbates kidney and heart injury, whereas GDF-15 overexpression has the opposite effect [26]. The study on the macrophage polarization process showed that GDF-15 promotes the polarization of M1 macrophage to M2 macrophage by activating the PI3K/Akt signaling pathway, reducing the migration of mononuclear macrophages to the heart [27]. It protects cardiac function while inhibiting LPS-induced systemic inflammatory responses and improving the survival rate [4]. The GDF-15 regulation of macrophage polarization may be a novel approach to treating sepsis and can be vital for improving survival.

Atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory disease that arises from dysregulation of lipid metabolism and a maladaptive immune response driven by the accumulation of cholesterol-laden macrophages in the arterial wall. Mononuclear macrophage is critical in the pathogenesis of AS [27]. The dysregulation of lipid metabolism changes the phenotype of macrophages and impairs vital immune functions. The ratio of M1/M2 macrophage is a determinant of atherosclerotic plaque progression and stability [28]. Studies regarding M1/M2 macrophage that have been polarized *in vitro* and mouse models of AS have confirmed that M1 macrophage promotes plaque inflammation and M2 macrophage resolves plaque inflammation [29]. An increased level of M1 macrophage leads to the secretion of inflammatory factors, causing endothelial cell dysfunction and diluting the fibrous cap [29]. However, an increased level of M2 macrophage prevents plaque rupture and inhibits AS [30]. Therefore, macrophage polarization provides the basis for studying inflammatory immunity in atherosclerotic plaques.

GDF-15 expression is significantly upregulated in the arterial wall of patients with early AS and co-localizes with macrophage infiltration in the plaque, promoting the formation of atherosclerotic lesions [31]. Moreover, a study showed that GDF-15 inhibited macrophage accumulation in the arterial wall of mice with advanced AS, thereby reducing the expression of adhesion molecules and atherosclerotic plaque enlargement [32].

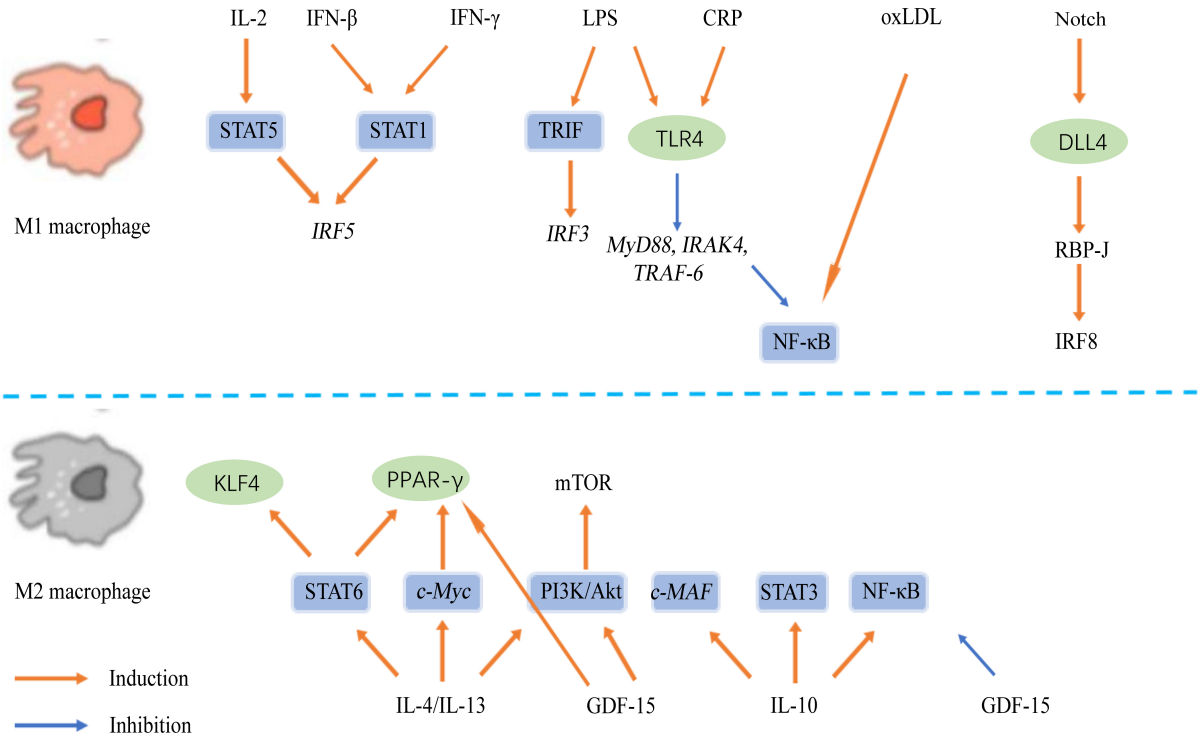

Fig. 1. Molecular Mechanisms of Macrophage Polarization. Image drawn using Adobe Illustrator 2022. The orangearrows represent promotion, while the blue arrows represent inhibition. The green ellipses represent the combination, while the blue boxes represent the main pathway. Janus kinase (JAK)/Signal transducer and activator of transcription (STAT) signaling pathway: ① Interleukin (IL)-2 binds to its receptor to phosphorylate STAT5, Interferon (IFN)-β, IFN-γ can activate the phosphorylation of STAT1, thereby regulating the expression of interferon regulatory factor 5 (*IRF5*) and promoting M1 type polarization; ② IL-10 activates STAT3 phosphorylation to promote M2-type polarization; ③ IL-4/IL-13 binds to its receptor, leading to receptor dimerization, activation of the JAK/STAT pathway, recruitment of STAT6, and phosphorylation into the nucleus. Conversely, phosphorylated STAT6 can interact with Kruppel-like factor 4 (KLF4) and peroxisome proliferator-activated receptor (PPAR)-γ, combining to promote M2-type polarization. At the same time, macrophages are phenotypically transformed via the PPAR-γ-retinoid X receptor (RXR)-growth differentiation factor (GDF)-15 axis; lipopolysaccharide (LPS): ① It can activate *IRF3* and increase the expression of M1 macrophages; ② LPS-stimulated primary macrophages activate musculoaponeurotic-fibrosarcoma oncogene homologue c (*c-MAF*) and specifically enhance the production of anti-inflammatory cytokine IL-10, thereby promoting M2 polarization; Phosphatidylinositol-3-kinase (PI3K)/(protein kinase B) Akt signaling pathway: GDF-15 promotes the polarization of M1 macrophage to M2 macrophage by activating the PI3K/Akt signaling pathway, reducing the migration of mononuclear macrophages to the heart. Notch pathway: Notch binds to Delta-like canonical 4 (DLL4) to form a complex, where the intracellular domain of Notch enters the nucleus and interacts with recombination signal binding protein for immunoglobulin kappa J region (RBP-J), promoting macrophage polarization towards M1 type and inhibiting M2 type expression; Cellular-myelocytomatosis viral oncogene (*C-Myc*): IL-4/IL13 activates macrophages to induce *C-Myc* expression, control PPAR-γ, skew monocytes toward an M2 phenotype, and down-regulate inflammatory pathways in mature macrophages. Nuclear factor-κB (NF-κB) pathway: C-reactive protein (CRP) and LPS bind to Toll-like receptor 4 (TLR4) expressed on macrophages, thereby downregulating the expression levels of myeloid differentiation primary response gene (*MyD*) *88*, Interleukin-1 receptor-associated kinase (*IRAK*)-*4*, and tumor necrosis factor receptor-associated factor (*TRAF*)-*6*, inhibiting the downstream NF-κB signaling pathway and LPS-induced TNF-α The expression of IL-6 in THP-1 cells; Oxidized low-density lipoprotein (ox-LDL) activates NF-κB pathway by increasing cytoplasmic localization in mice and human atherosclerotic samples. GDF-15 inactivates NF-κB signaling in Treg cells in ischemic myocardia, decreases apoptosis, and increases M2 polarization.

Peroxisome proliferator-activated receptor γ (PPAR-γ) is a metabolic sensor and regulator expressed in atherosclerotic lesions and all vascular wall epithelial cell types. It plays a key role in the pathogenesis of AS and serves as a promising therapeutic target for the treatment of cardiovascular complications [33–36]. It regulates various effector genes associated with macrophage polarization [37–39]. The epigenomic analyses of upstream regulators of GDF-15 expression by Patsalos *et al.* [40] revealed that it is under the control of nuclear receptors retinoid X receptor

(RXR)/PPAR-γ. Moreover, the macrophage is phenotypically transformed via the PPAR-γ-RXR-GDF-15 axis [40].

M2 macrophage mainly infiltrates early atherosclerotic plaques, but as the plaques expand, M1 macrophage infiltration gradually becomes dominant and may lead to acute atherothrombosis [41]. The residual risk in individuals with aortic stenosis remains high despite current preventive measures and increasingly effective revascularization procedures. In patients susceptible to sudden death and myocardial infarction, high secretion of pro-inflammatory factors (e.g., IL-6) by M1 macrophage is often associated with poor prognosis [42]. Clinical evidence suggests that GDF-15 levels are significantly elevated in patients with acute myocardial infarction [43]. In a model of ischemic heart disease, the nuclear factor-κB (NF-κB) signaling pathway was found to promote macrophage to M2-type polarization for a pro-arterial vasculogenic effect [44]. Furthermore, studies have shown that GDF-15 inactivates NF-κB signaling in Treg cells in ischemic myocardia, decreases apoptosis, and increases M2 polarization, thereby improving cardiac function after myocardial infarction [44].

A deeper comprehension of macrophage polarization regulation may provide valuable insight into pathways that could potentially manipulate macrophage behavior towards an atheroprotective state.

Colon Cancer

In most tumors, tumor-associated macrophage (TAM), which infiltrates tumor tissues, generally has an M2-like phenotype. TAMs secrete various growth factors to facilitate tumor angiogenesis and enzymes involved in matrix degradation to promote tumor invasion and metastasis, induce Treg cell differentiation to inhibit the cytotoxicity of $CD8^+$ T cells, and inhibit the proliferation and killer function of cytotoxic T lymphocytes and natural killer cells [45]. They also inhibit the activation, maturation, and antigen presentation functions of DC cells, thus participating in tumor immune escape and promoting the malignant progression of tumors [45].

TGF-β1, an immunosuppressive molecule, inhibits the proliferation and differentiation of various lymphocytes and plays a vital role in promoting tumor immune evasion [46]. A study found that GDF-15 regulates cellular-myelocytomatosis viral oncogene (*c-Myc*) at the transcriptional level by activating the K-Ras-the c-Jun N-terminal kinase (JNK)/ERK-c-Myc pathway and stabilizes c-Myc in a protein-modified manner, regulating TGF-β1 expression [47]. There are many contradictory results regarding the role of GDF-15 in cancer cells. Most studies have suggested that GDF-15 is a pro-apoptotic molecule that promotes tumor cell apoptosis [48–50], whereas other studies have suggested that GDF-15 may facilitate tumor progression [51–55].

For example, much clinical evidence has shown that serum GDF-15 levels are significantly elevated in patients with colon cancer and can be used as a predictor of tumor progression and recurrence [56]. Overexpression of GDF-15 in mouse colon cancer CT26 cells promotes tumorigenesis in vivo and induces the expression of Arg1, CD206, and TGF-β1 in peritoneal macrophages and TAMs, inhibiting M1-like polarization to M2-like in the tumor microenvironment. This provides a novel mechanism for tumor immune tolerance and describes new ideas and targets for blocking tumor escape and improving tumor immunotherapy effects [57]. Similarly, studies have shown that the expression of $CD206^+$ macrophage can significantly increase in human colon cancer tissues, while an M2-like TAM-conditioned medium can induce the migration of human colon cancer SW480 cells [58,59]. The inhibition of C-C motif chemokine receptor 2 (CCR2) and vascular endothelial growth factor (VEGF) signaling reduces pro-metastatic macrophage infiltration and counteracts tumor metastasis to target organs [58]. GDF-15 has been shown to activate the downstream hypoxia-inducible factor-1α (HIF-1α)/VEGF signaling pathway through the murine double minute 2 (*Mdm2*)/*p53* system, promoting endothelial cell proliferation and vascular lumen formation [60]. Nonetheless, whether GDF-15 can promote M2-like cell infiltration through the activation of VEGF signaling requires further investigation. Clarifying the mechanism can provide insights into how GDF-15 induces M2 macrophage, laying a solid foundation for exerting immune suppression function.

Obesity

Obesity is a chronic low-grade inflammatory disease [61]. Adipose tissues, composed of adipocytes, preadipocytes, endothelial cells, and immune cells (including macrophage and lymphocytes), are essential initiators of the inflammatory response. Studies have shown that CD11c-activated adipose tissue macrophage (ATMs) derived from obese mice exhibit overlapping profiles and increased transcription of related genes in M1/M2 macrophage [62,63]. During the development of obesity, adipose tissues exhibit elevated macrophage infiltration, with a predilection for pro-inflammatory M1 activation as opposed to the M2 phenotype in lean patients [64]. The ATMs, in turn, secrete pro-inflammatory factors, creating an inflammatory cycle that blocks the action of insulin on adipocytes, ultimately leading to insulin resistance [65]. Several intracellular pathways have been hypothesized to induce the pro-inflammatory activation of macrophages in ATMs, including the Toll-like receptor 4 (TLR4)/NF-κB, JNK, and caspase/NLRP3 inflammasome pathways [66–68]. A study showed that fibronectin type III domain-containing protein 5 (FNDC5) inhibits M1 macrophage polarization and inflammatory factor release through adenosine 5′-monophosphate-activated protein kinase (AMPK)

phosphorylation, thereby reducing adipose tissue inflammation and insulin resistance induced by high-fat diet in obese mice [69]. F4/80^{+}CD11c^{-}CD301^{+} macrophage, which has M2-type characteristics, has also been reported to increase adipose tissue macrophages during chronic weight loss. It is crucial in regulating lipolysis, maintaining tissue homeostasis, suppressing inflammation, and promoting insulin sensitivity [70]. These inflammatory pathways could be utilized as innovative therapy options for inflammation-related diseases.

Many clinical studies have indicated that GDF-15 is related to obesity, insulin resistance, anorexia, and weight loss induced by metabolic disorders [71,72]. GDF-15 can prevent the occurrence of obesity by controlling appetite, increasing heat production, and promoting lipid decomposition and oxidative metabolism [73,74]. Additionally, the metabolic benefits of GDF-15 may be attributed to its anti-inflammatory properties. Luan *et al*. [22] suggested that GDF-15 can improve the tolerance of the heart and liver to inflammation and improve survival rate by regulating triglyceride metabolism. Similarly, another study showed that GDF-15 transgenic mice with a high-fat diet exhibited reduced NLRP3 inflammasome activity, reduced pro-inflammatory macrophage infiltration into white adipose tissues, and lowered serum leptin and insulin levels [75]. Studies regarding GDF-15 treatment have often reported changes in body weight and adipose tissue mass, which may contribute to the observed anti-inflammatory effects. A study reported the direct anti-inflammatory effect of GDF-15 in macrophages. In that study, the anti-inflammatory cytokine IL-4 upregulated GDF-15 expression and induced M2-like macrophage polarization via enhancing oxidative metabolism [76]. These results indicate that GDF-15 may hold potential as a therapeutic target in metabolic disorders, particularly those related to energy metabolism.

Conclusion

Macrophage polarization plays an essential role in various biological and pathological processes. The former includes embryonic development and pregnancy, whereas the latter includes inflammation-related diseases such as sepsis, tumors, and metabolic disorders. The inducible factors, signaling pathways, and transcription factors involved in macrophage polarization intersect, forming a complex system. Under special conditions, M1/M2 can transform into each other, forming a dynamic change process. In some autoimmune, chronic inflammatory, and tumor diseases, precise regulation of the mutual transformation and proportion of M1/M2 macrophages has gradually become a new therapeutic target. However, research on the polarization mechanism and regulatory molecules of macrophages should be in-depth and systematic.

GDF-15 was identified and expressed for the first time in the cDNA library of macrophage activation-related genes from the human monocyte line U937; TGF-β members of the superfamily are involved in various physiological and pathological processes. The effects of GDF-15 on inflammation, cardiovascular disease, nerve injury, and tumors are also important and directly affect patients' prognosis and quality of life. Only a few studies have clearly reported on the effects of GDF-15 on immune cells.

In this review, we summarized the macrophage polarization mechanism of GDF-15 under the conditions of sepsis, colon cancer, AS, and obesity. The elucidation of the role and the molecular mechanisms of GDF-15 may help evaluate its potential as a diagnostic and therapeutic target in inflammatory-related diseases. Further research and validation are needed to effectively utilize GDF-15 for macrophage phenotype transformation to achieve the desired short-term therapeutic effect and long-term prognosis.

Author Contributions

JJH: investigated correlative literature and drafted the manuscript. XHD and YD: investigated correlative literature and handled funding and supervision; HYZ: conceived and designed the review, and made critical revision of the manuscript for key intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We would like to thank Editage (https://www.editage.cn/) for English language editing.

Funding

The corresponding author has applied research related to this study that was funded by [China National Key Research and Development Program] (Grant number [2019YFC0119600]), and [Major Science and Technology Project of Hainan Province] (Grant number [ZDKJ202004]).

Conflict of Interest

The authors declare no conflict of interest.

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