Review and Monograph

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Abstract

Type 2 diabetes has become a major global public health challenge. Its onset and progression involve not only disorders of glucose metabolism but also the persistent presence of chronic low-grade inflammation. Recent studies suggest that inflammation resolution is an important biological process through which the body actively regulates inflammatory responses, and that impaired inflammation resolution may be one of the key mechanisms underlying the sustained chronic inflammatory state in type 2 diabetes, potentially playing an important role in the development of cardiovascular and renal complications. In addition to their classical glucose-lowering effects, some antidiabetic drugs have been reported, to varying degrees, to regulate the process of inflammation resolution through multiple pathways, thereby influencing local and systemic inflammatory microenvironments, including mechanisms such as modulating levels of specialized pro-resolving mediators and affecting macrophage polarization states. These effects may contribute, to some extent, to their cardiorenal protective benefits; however, the specific molecular mechanisms and their causal relationships with clinical endpoints remain to be further elucidated. This article systematically reviews the mechanisms of inflammation resolution and its potential role in type 2 diabetes and related complications, explores the potential regulatory effects of existing antidiabetic drugs on the process of inflammation resolution, and discusses future research directions. An in-depth analysis of the regulatory network of inflammation resolution in type 2 diabetes and the association between antidiabetic drugs and inflammation resolution may help provide new clinical perspectives and practical approaches for the comprehensive prevention and treatment of type 2 diabetes.

Full Text

Review and Monograph

Research Progress in Inflammation Resolution for the Prevention and Treatment of Type 2 Diabetes Mellitus

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【Abstract】 Type 2 diabetes mellitus has become one of the major public health challenges worldwide. Its onset and progression involve not only disorders of glucose metabolism but also the persistent presence of chronic low-grade inflammation. Recent studies suggest that inflammation resolution is an important biological process through which the body actively regulates inflammatory responses. Impaired inflammation resolution may be one of the key mechanisms leading to the persistent chronic inflammatory state in type 2 diabetes mellitus, and may play an important role in the development of cardiovascular and renal complications. In addition to their classic glucose-lowering effects, some hypoglycemic agents have been reported, to varying degrees, to regulate the process of inflammation resolution through multiple pathways, thereby influencing local and systemic inflammatory microenvironments. These mechanisms include affecting the levels of specialized pro-resolving mediators and modulating macrophage polarization. Such effects may contribute, to some extent, to their cardio-renal protective benefits; however, the specific molecular mechanisms and the causal relationships between these effects and clinical endpoints remain to be further clarified. This article systematically reviews the mechanisms of inflammation resolution and its potential roles in type 2 diabetes mellitus and related complications, explores the potential regulatory effects of existing hypoglycemic agents on inflammation resolution, and discusses future research directions. In-depth elucidation of the regulatory network of inflammation resolution in type 2 diabetes mellitus and the relationship between hypoglycemic agents and inflammation resolution will help provide new clinical ideas and practical pathways for the comprehensive prevention and treatment of type 2 diabetes mellitus.

【Keywords】 diabetes mellitus, type 2; inflammation resolution; hypoglycemic agents; specialized pro-resolving mediators; macrophages

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Research Progress in Inflammation Resolution for the Prevention and Treatment of Type 2 Diabetes Mellitus

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【Abstract】 Type 2 diabetes mellitus (T2DM) is a major global health challenge. Its onset and progression not only involve glucose metabolic disorders but are

also associated with the persistence of chronic low-grade inflammation. Evidence indicates that the inflammation resolution is an active and highly coordinated biological process. However, the non-resolving inflammation may correlate with the pathogenesis of insulin resistance, β-cell dysfunction, and the progression of diabetes and its complications, including cardiovascular disease and nephropathy. In addition to classical glucose-lowering effects, some antidiabetic drugs have been reported to regulate the resolution of inflammation through various pathways, thereby influencing both local and systematic inflammatory microenvironments. These mechanisms include affecting the production of specialized pro-resolving mediators and regulating macrophage polarization. Such effects may underlie the cardioprotective and renal protective benefits of antihyperglycemic drugs, although the specific molecular mechanisms and the relationships with clinical outcomes remain incompletely understood. This review systematically summarizes the mechanisms of inflammation resolution and their roles in type 2 diabetes mellitus and its complications, and discusses the potential molecular regulatory mechanisms of antidiabetic

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agents in inflammation resolution, which may provide novel clinical insights for the treatment of type 2 diabetes.

【Key words】 Diabetes, type 2; Inflammation resolution; Hypoglycemic drugs; Specialized pro-resolving mediators; Macrophages

Type 2 diabetes has become one of the major public health problems worldwide. At present, more than 530 million adults worldwide have type 2 diabetes, and the number of affected patients is expected to approach 800 million by 2045[1]. A chronic inflammatory state is one of the key pathological bases for the occurrence and progression of type 2 diabetes, participating in the development of insulin resistance and the progressive decline of β-cell function[2]. This view is also supported by epidemiological studies: multiple chronic low-grade inflammatory diseases, such as periodontitis, are closely associated with the risk of developing type 2 diabetes and with disease prognosis[3]. In addition, chronic inflammation is also extensively involved in the occurrence and progression of

common comorbidities of type 2 diabetes, such as hypertension and dyslipidemia, as well as complications, including cardiovascular disease and kidney disease[4].

Over the past 30 years, research on the mechanisms of chronic inflammation in type 2 diabetes has continued to deepen. However, existing intervention strategies have largely focused on suppressing inflammatory initiation or blocking pro-inflammatory signaling pathways; therapeutic exploration truly based on the entire dynamic process of inflammation regulation, especially the mechanism of inflammation resolution, remains relatively limited. Inflammation is a protective immune response generated by the body in response to injury or pathogen stimulation. Its dynamic process usually includes stages such as injury recognition, recruitment and activation of immune cells, and inflammation resolution and repair[5]. Among these, inflammation resolution is not the result of passive dilution of inflammatory mediators, but rather a highly programmed process actively regulated by a series of specialized pro-resolving mediators (SPMs)[6]. This process is of vital importance for clearing inflammatory stimuli, removing apoptotic cells, and initiating tissue repair.

In the context of type 2 diabetes, the body often presents a state in which persistent low-grade inflammatory activation coexists with impaired inflammation resolution, that is, a "pro-inflammatory–pro-resolving imbalance." Impaired inflammation resolution may lead to persistence of the inflammatory response, further aggravating insulin resistance and pancreatic β-cell decline, and may be associated with the occurrence and progression of multisystem complications involving the heart, kidneys, and blood vessels[7]. Therefore, shifting from simply inhibiting inflammatory activation to promoting inflammation resolution may provide a new theoretical basis and direction for prevention and treatment of type 2 diabetes and its complications. This article aims to systematically elucidate the molecular and cellular mechanisms of inflammation resolution, summarize its association with type 2 diabetes and its complications, and explore the potential role of current commonly used hypoglycemic drugs in targeting inflammation resolution.

1 Mechanisms of Inflammation Resolution and the Association between Impaired Inflammation Resolution and Disease

Inflammation resolution is an active, finely regulated, and highly coordinated stage of the inflammatory response. Its core goals are to terminate the immune response, restore immune microenvironmental homeostasis, and promote tissue repair[8] (Figure 1). The process of inflammation resolution includes multiple stages, such as clearance of stimuli, attenuation of pro-inflammatory signals, apoptosis and clearance of inflammatory cells, macrophage phenotypic switching, and tissue repair.

During the stage of clearing inflammatory stimuli, neutrophils, as the earliest immune cells recruited to the inflammatory site, jointly participate in the clearance

of pathogens and damage-associated molecules through multiple effector mechanisms, including phagocytosis of pathogens, release of reactive oxygen species, myeloperoxidase, and antimicrobial peptides, and formation of neutrophil extracellular traps[9–10]. As the stimulus burden decreases, the inflammatory response gradually transitions from the amplification phase to the resolution phase.

Attenuation of pro-inflammatory signals is a core stage linking stimulus clearance and tissue repair. It involves coordinated mechanisms such as regulation of the nuclear factor κB (nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB) pathway and the neutralization and clearance of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)[11]. At the same time, the number of inflammatory cells is regulated through multiple pathways, which may include anti-infiltration effects[12], egress of immune cells from tissues[13–14], and clearance and apoptosis of neutrophils[15–16]. However, the specific mechanisms by which each pathway regulates inflammatory-cell numbers are context-dependent.

Macrophages play a key regulatory role in the later stages of inflammation. On the one hand, they phagocytose residual pathogens and tissue debris, and clear apoptotic neutrophils through efferocytosis, thereby preventing apoptotic cells from rupturing and releasing pro-inflammatory substances[17]. If efferocytosis is impaired, apoptotic cells may undergo secondary necrosis, with loss of membrane integrity and release of intracellular contents, thereby prolonging or aggravating the inflammatory response[18]. On the other hand, macrophages undergo phenotypic switching under regulation by the microenvironment. According to functional status, macrophages can be classified into pro-inflammatory M1-type macrophages and repair-associated M2-type macrophages. M1-type macrophages can release large amounts of pro-inflammatory factors such as TNF-α, interleukin-1β (IL-1β), and IL-6, participating in inflammatory amplification; whereas M2-type macrophages suppress excessive inflammatory responses and promote tissue repair by producing anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β)[19–20]. During the stage of inflammation resolution, macrophages gradually shift from a predominantly M1-like phenotype to a predominantly M2-like phenotype, which helps suppress the inflammatory response and avoid excessive inflammatory injury[21].

During inflammation resolution, SPMs are key endogenous regulatory factors driving the programmed termination of inflammation. SPMs do not merely suppress the inflammatory response; rather, they actively initiate the inflammation-resolution program and regulate immune-cell function through multiple targets and pathways, terminating the amplification effect of inflammation and promoting tissue repair[22]. SPMs are generated from essential polyunsaturated fatty acids in the human body, such as Omega-3 and Omega-6, through multiple enzyme-catalyzed reactions, and mainly include four major classes: lipoxins, resolvins, protectins, and maresins[23]. Functionally, SPMs exert pro-resolving

effects through multiple molecular mechanisms. For example, SPMs can effectively inhibit the chemotaxis and infiltration of inflammatory cells such as neutrophils and monocytes toward inflammatory sites, induce macrophage switching from the M1 type to the M2 type, enhance macrophage "efferocytosis,"inhibit Th1 and Th17 cells, and enhance the activity of regulatory T cells (Treg)[24–27]. Abnormal SPM levels during the inflammation-resolution stage may impair the inflammation-resolution process and thereby promote the persistence of chronic inflammation; this phenomenon may be diabetes mellitus···

and other chronic diseases.[28]

Impaired resolution of inflammation may prevent inflammatory responses from being terminated in a timely manner, placing the body in a persistent state of chronic low-grade inflammation and inducing a series of shared pathophysiological changes in multiple tissues and organs, including imbalance of the tissue microenvironment, impairment of cellular function, and remodeling of tissue structure, which may further lead to fibrosis and organ dysfunction. Long-standing impairment of inflammatory resolution may also affect the function of key metabolic organs such as adipose tissue, the liver, skeletal muscle, and pancreatic islets, thereby disrupting systemic energy-metabolic homeostasis.[29–31] During the occurrence and progression of metabolic diseases, impaired resolution of inflammation may be one of the important mechanisms linking obesity with metabolic abnormalities. In the obese state, activation of inflammatory responses in adipose tissue accompanied by impaired inflammatory resolution can lead to persistent infiltration of inflammatory cells and increased release of pro-inflammatory factors; these changes may be associated with disordered glucose and lipid metabolism.[32] In addition, inflammatory resolution may be related to abnormal hepatic metabolism. A case–control study found that circulating levels of the SPM member MaR1 were decreased in patients with metabolic dysfunction–associated steatotic liver disease (MASLD), and that the occurrence of MASLD was negatively correlated with serum MaR1 concentration, suggesting that impaired inflammatory resolution reflected by reduced MaR1 levels may participate in the occurrence and progression of MASLD.[33–34]

In-figure text: vasodilation; neutrophil infiltration; cytokine release; inflammatory onset phase; inflammatory response; inflammatory development phase; macrophage activation; chemokine aggregation; persistent inflammation; immune-cell infiltration; tissue fibrosis; organ dysfunction; impaired inflammatory resolution; inflammatory resolution phase; release of anti-inflammatory mediators; immune-cell clearance; tissue repair.

Note: This figure was drawn based on the Biomedical General Drawing Platform (BioGDP, https://biogdp.com/).[34]

Figure 1 Biological Processes of Inflammatory Response and Nonresolving Inflammation

2 Pathological Mechanisms of Impaired Inflammatory Resolution in the Occurrence and Progression of Type 2 Diabetes

Type 2 diabetes is a metabolic disease centered on insulin resistance and β-cell failure, and chronic low-grade inflammatory responses accompany its occurrence and progression.[2] Impaired inflammatory resolution is considered one of the important mechanisms underlying the persistence of chronic inflammation in type 2 diabetes. Its essence is an imbalance between the body' s mechanisms of inflammatory initiation and resolution, mainly involving core processes such as abnormal SPM levels and imbalance of macrophage polarization.

2.1 Abnormal SPM Levels

Circulating SPM levels are associated with the capacity for inflammatory resolution. Existing studies indicate that insufficient supply of substrates for SPM synthesis and decreased activity of key synthetic enzymes, among other factors, lead to SPM deficiency, which may be one of the important mechanisms by which obesity-related adipose-tissue inflammation occurs and persists. This inflammation can further induce insulin resistance and β-cell dysfunction, thereby promoting the occurrence and progression of type 2 diabetes.[35]

Animal models have provided direct evidence for the above mechanisms. Compared with littermate control mice, obese diabetic mice with leptin-receptor gene mutations (db/db) showed significantly reduced levels of the SPM precursor docosahexaenoic acid (DHA) and its downstream metabolites —17-hydroxydocosahexaenoic acid (17-HDHA), 14-hydroxydocosahexaenoic acid, and 4-hydroxydocosahexaenoic acid—in dorsal skin wounds.[36] In a diet-induced obese mouse model, mRNA expression of 12/15-lipoxygenase in adipose tissue was downregulated; this enzyme is a key enzyme for 17-HDHA biosynthesis in mice, and its deficiency led to reduced generation of 17-HDHA.[37–39]

n-3 polyunsaturated fatty acids are precursors of SPMs, and dietary intervention with n-3 polyunsaturated fatty acids promotes inflammatory resolution. Obese diabetic mice (db/db) and lean controls (db/+) received three different high-fat dietary interventions: a diet rich in saturated/monounsaturated fatty acids (HF/S), a diet rich in n-6 polyunsaturated fatty acids (HF/6), and an HF/S diet containing long-chain n-3 polyunsaturated fatty acids (HF/S3). After 6 weeks of intervention, endogenous SPM biosynthesis was found to be significantly increased in the HF/S3 group, accompanied by alleviation of adipose-tissue inflammation and improvement in insulin resistance. In a wild-type mouse model fed a high-fat diet, exogenous 17-HDHA treatment increased the protein level of nuclear factor κB inhibitor α (Inhibitor of kappa B α, IκBα) in adipose tissue. As the principal endogenous inhibitor of NF-κB signaling, accumulation of IκBα effectively restrained the pro-inflammatory cascade and promoted the phenotypic transition of macrophages from M1 to M2, ultimately reducing in-

flammation in adipose tissue.[35] Similarly, in male db/db mice, intervention with resolvin D1 (RvD1) improved glucose tolerance and reduced fasting blood glucose.[40]

Findings from human studies are similar to those from animal experiments. Studies have shown that levels of multiple key SPM precursors and SPMs in obese individuals are lower than those in lean controls. Compared with healthy controls, patients with type 2 diabetes have significantly reduced serum resolvin E1 levels.[41] In addition, an analysis of 96 patients with type 2 diabetes with or without diabetic foot ulcers found that, regardless of whether diabetic foot ulcers were present, mean plasma MaR1 levels were lower than those in non-diabetic controls, with the most pronounced decrease occurring in patients complicated by diabetic foot ulcers. Reduced plasma MaR1 concentration was associated with obesity, abnormal glucose and lipid metabolism, decreased first-phase insulin secretion, and aggravated insulin resistance.[42]

At present, liquid chromatography–tandem mass spectrometry is the mainstream technique for quantitatively detecting SPMs.[43] By contrast, although enzyme-linked immunosorbent assays are convenient to perform, they are limited by the complex isomers of SPMs; their specificity is poor and cross-reactions readily occur, so positive results often require independent validation.[44–46] It is worth noting that substantial controversy remains in the current literature regarding the true concentration levels of SPMs in vivo. This is mainly attributable to the extremely low abundance of endogenous SPMs,

and can readily generate false mass-spectrometric signals through non-enzymatic autoxidation during sample processing; moreover, the analytical workflows and criteria for determination used in different studies have not yet formed universally accepted standards.[46] These methodological limitations jointly compromise the reliability of the data. Therefore, the clinical significance of changes in existing SPM levels should be interpreted objectively and cautiously, and a standardized quantitative detection system urgently needs to be established in the future.

2.2 Imbalance in Macrophage Polarization

During the occurrence and progression of type 2 diabetes mellitus, macrophages are key effector cells that regulate inflammation. In particular, macrophages residing in adipose tissue play an important role in maintaining metabolic homeostasis. Taking adipose tissue as an example, under physiological conditions adipocytes are relatively small, the adipose-tissue microenvironment is dominated by anti-inflammatory signals, and macrophages mainly exhibit an M2-like phenotype characterized by tissue repair and immune regulation. However, obesity-induced adipocyte hypertrophy and hyperplasia disrupt this balance and drive macrophage transition toward a pro-inflammatory phenotype through several mechanisms. First, hypertrophic adipocytes secrete chemokines, such as monocyte chemoattractant protein-1, leukotriene B4,

macrophage inflammatory protein, macrophage migration inhibitory factor, and monocyte chemoattractant protein-3, recruiting circulating monocytes with pro-inflammatory properties (Ly6C^hi) to infiltrate adipose tissue and polarize into M1-like macrophages.[47] Second, adipocyte hypertrophy and hyperplasia can also lead to local tissue hypoxia and activate hypoxia-inducible factor-1α (HIF-1α), promoting a shift in cellular energy metabolism from oxidative phosphorylation to glycolysis, thereby further promoting macrophage polarization toward the M1 phenotype and monocyte recruitment.[48–49] In addition, enlarged adipose tissue releases excessive free fatty acids; excessive uptake of these fatty acids by adipose-tissue macrophages can induce lipotoxicity and directly promote the generation of M1 macrophage phenotypes.[50–52]

This polarization shift can activate the IKK/NF-κB pathway, c-Jun N-terminal kinase, and mitogen-activated protein kinases through inflammatory cytokines released by macrophages, such as IL-1β and TNF-α, thereby aggravating insulin resistance and forming a vicious cycle of "obesity—chronic low-grade inflammation—insulin resistance," which drives the occurrence and progression of type 2 diabetes mellitus.[21,53–54]

In type 2 diabetes mellitus, persistent hyperglycemia can further amplify inflammatory responses. On the one hand, hyperglycemia can induce macrophage transition toward an M1-like phenotype by upregulating the expression of acetyl-CoA synthetase 1, thereby exacerbating pancreatic β-cell dysfunction and insulin secretion impairment.[55–56] In addition, accumulation of advanced glycation end products activates the RAGE/NF-κB pathway and promotes macrophage differentiation toward a pro-inflammatory M1 phenotype.[57]

The sustained inflammatory state associated with impaired inflammation resolution may participate in the occurrence and progression of multiple complications of type 2 diabetes mellitus, including diabetic nephropathy and cardiovascular complications. Long-standing impairment of inflammation resolution may promote sustained activation of renal inflammatory responses, which may in turn induce renal fibrosis and accelerate the decline of renal function.[58–59] A randomized controlled trial found that the baseline plasma level of the SPM member 15-epi-lipoxin A4 was significantly reduced in patients with diabetic nephropathy, suggesting that impaired inflammation-resolution function may be involved in the development and progression of diabetic nephropathy.[60] Impairment of inflammation resolution may likewise participate in the formation of diabetes-related myocardial injury. Studies have found that, in myocardial tissue of diabetic mice, there is marked myocardial fibrosis, cardiomyocyte apoptosis, and hypertrophy; at the same time, the ratio of M1- to M2-type macrophage markers in cardiac tissue is imbalanced, suggesting that disruption of the inflammation-resolution process may be involved in diabetes-related myocarditis and cardiac remodeling.[61] In addition, under diabetic conditions, metabolic disturbances such as hyperglycemia, insulin resistance, and dyslipidemia may participate in chronic inflammatory responses through impaired inflammation resolution, thereby potentially affecting vascular endothelial-cell function and being asso-

ciated with the occurrence and progression of atherosclerotic plaques. In vitro experiments have found that high-glucose culture induces increased differentiation of mouse bone-marrow–derived macrophages and monocytes toward a pro-inflammatory phenotype (M1), thereby inhibiting the inflammation-resolution process; meanwhile, high-glucose culture can also enhance the adhesion of monocytes to activated endothelial cells and increase macrophage uptake of oxidized LDL and foam-cell formation, thereby accelerating atherosclerotic lesion formation.[62]

However, the traditional M1/M2 binary classification makes it difficult to comprehensively capture the heterogeneity of macrophages in vivo. In complex metabolic microenvironments, macrophage polarization is not static and dichotomous; rather, it presents a continuous spectrum and mixed phenotypes dynamically regulated by local signals.[63-64] In recent years, the application of technologies such as single-cell omics has enabled researchers to resolve the characteristic subpopulations of macrophages and their dynamic developmental trajectories at higher resolution, providing strong technical support for elucidating the complex mechanisms by which macrophages participate in inflammation resolution in type 2 diabetes mellitus and for identifying potential intervention targets.[66]

3 Regulatory Effects of Glucose-Lowering Drugs on Impaired Inflammation Resolution in Type 2 Diabetes Mellitus

Glucose-lowering drugs are core interventions in the treatment of type 2 diabetes mellitus. Their main objectives are to improve hyperglycemia and reduce the risk of diabetes-related complications. In recent years, studies have found that, in addition to exerting classic glycemic-control effects, some glucose-lowering drugs can improve impaired inflammation resolution through multiple pathways, alleviating chronic low-grade inflammation; this may be one of the important mechanisms by which they confer cardiovascular, renal, and other target-organ protection. However, evidence supporting this mechanism at the present stage mostly comes from in vitro experiments, animal models, or indirect clinical indicators. Human interventional evidence using inflammation-resolution–related biomarkers as the primary study endpoints remains lacking. Therefore, current evidence is still insufficient to constitute high-level evidence-based medical support, and evaluation of the effects of drugs in regulating inflammation resolution remains exploratory, awaiting further validation in prospective clinical studies. Among the currently mainstream glucose-lowering drugs, the mechanisms by which metformin, SGLT2 inhibitors, GLP-1 receptor agonists, and thiazolidinediones promote inflammation resolution already have clear support in the literature. By comparison, other agents such as insulin, sulfonylureas, and dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors have only a small number of reports describing anti-inflammatory effects, with relatively limited evidence or unclear mechanisms. Therefore, this article focuses on the following four classes

of drugs (Table 1).

3.1 Metformin

As a first-line glucose-lowering drug for the treatment of type 2 diabetes mellitus, the classic glucose-lowering mechanisms of metformin mainly include inhibiting gluconeogenesis, reducing hepatic glucose output, improving insulin resistance in peripheral tissues, and regulating intestinal glucose metabolism, etc.[67-

[^68] In recent years, studies have shown that, in addition to regulating metabolism, metformin may have the potential to promote inflammation resolution, possibly by improving defects in inflammation resolution and thereby participating in target-organ protection.

Table 1. Summary of the mechanisms and clinical significance of four classes of glucose-lowering drugs in promoting inflammation resolution

Drug class	Main mechanism promoting inflammation resolution	Clinical significance
Metformin	Promotes macrophage polarization toward the M2 phenotype	Improves insulin resistance and vascular endothelial protection
SGLT-2 inhibitors	Upregulates M2-type markers	Reduces inflammatory burden in the heart and blood vessels
GLP-1 receptor agonists	Promotes macrophage polarization toward the M2 phenotype	Synergistically promotes long-term protection of the cardiovascular and cerebrovascular systems and the kidneys
Thiazolidinediones	Increases SPMs levels	Promotes resolution of tissue inflammation

Note: SGLT-2 = sodium-glucose cotransporter 2; GLP-1 = glucagon-like peptide-1; SPMs = specialized pro-resolving mediators.

At the molecular level, metformin can reduce inflammatory responses by activating the AMP-activated protein kinase pathway and inhibiting activation of the NOD-like receptor family pyrin domain-containing protein 3 inflammasome. At the same time, metformin can induce macrophage polarization, suppress the M1-like phenotype, and promote transition toward the M2-like phenotype, thereby facilitating inflammation resolution[^69-^71]. In a high-fat-diet-fed C57/6J male mouse model, metformin intervention improved the inflammatory state of adipose tissue and increased M2-type macrophages. In vitro,

after metformin intervention in palmitic acid-induced macrophages, the proportion of M1-type macrophages decreased, whereas the proportion of M2-type macrophages increased, suggesting that metformin can improve obesity-related chronic low-grade inflammation[^69]. These mechanisms provide a biological basis for its potential protective effects in metabolic diseases such as insulin resistance, atherosclerosis, and chronic kidney disease, although the causal relationships and its overall contribution remain to be verified.

3.2 SGLT-2 inhibitors

Sodium–glucose cotransporter 2 (sodium-dependent glucose transporters 2, SGLT-2) inhibitors are a new class of glucose-lowering drugs that reduce blood glucose by inhibiting glucose reabsorption in the proximal renal tubules and promoting urinary glucose excretion[^72]. SGLT-2 inhibitors not only have favorable glucose-lowering effects but also exert cardiovascular and renal protective effects independent of glycemic control; one potential mechanism may be related to improvement of defects in inflammation resolution.

SGLT-2 inhibitors can regulate the inflammatory microenvironment by affecting macrophage infiltration and polarization. In a normoglycemic rabbit model of atherosclerosis, SGLT-2 inhibitor intervention reduced macrophage infiltration in the vascular wall, downregulated the expression of inflammatory markers such as TNF-α, IL-1β, and IL-6, and simultaneously upregulated the expression of M2-type macrophage markers such as arginase 1, suggesting that it may enhance the process of inflammation resolution by promoting phenotypic transition from M1- to M2-like macrophages[^73]. During myocardial infarction, infiltrating macrophages play a key role in cardiac remodeling, and delayed phenotypic conversion from M1- to M2-like macrophages is considered one of the major factors leading to adverse ventricular remodeling. In a rat model of myocardial infarction, SGLT-2 inhibitor intervention was found to activate the reactive oxygen and nitrogen species-mediated signal transducer and activator of transcription 3 (STAT3) signaling pathway, enhance the activation of M2-like macrophages, and may thereby facilitate formation of a microenvironment conducive to inflammation resolution, reducing fibroblast infiltration and collagen accumulation and attenuating cardiac fibrosis[^74].

In patients with type 2 diabetes, dapagliflozin treatment can reduce C-reactive protein levels and is accompanied by improvement in left ventricular systolic function[^75]. Clinical studies such as EMPA-REG OUTCOME have shown that SGLT-2 inhibitors can reduce the risk of heart failure and cardiovascular death. Although these benefits involve multifactorial mechanisms, inflammation regulation may be an important component[^76].

With respect to renal protection, macrophage polarization status may be associated with renal inflammation and fibrosis. In a mouse model of type 2 diabetes, dapagliflozin intervention reduced infiltration of M1-type macrophages in renal tissue, regulated the local inflammatory microenvironment, and promoted

transition of inflammation toward the resolution phase, suggesting that its renoprotective effect may be related to mechanisms of inflammation regulation[^77].

3.3 GLP-1 receptor agonists

GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonist, GLP-1 RA) are a class of incretin-based glucose-lowering drugs. By activating the GLP-1 receptor, they enhance glucose-dependent insulin secretion, inhibit glucagon secretion, improve glucose uptake by peripheral tissues, and suppress hepatic gluconeogenesis, thereby exerting glucose-lowering effects[^78]. In addition to their classical metabolic regulatory actions, increasing evidence suggests that GLP-1 RAs may have effects that promote inflammation resolution.

Mechanistically, some in vitro and animal studies suggest that activation of the GLP-1/GLP-1R signaling pathway is associated with activation of inflammation-related signaling molecules such as STAT3. In an in vitro study examining the effect of exenatide on activation of human monocyte-derived macrophages, exenatide was found to regulate macrophage functional status, inhibit the expression of proinflammatory factors, and promote transition toward an M2-type anti-inflammatory phenotype, thereby contributing to inflammation resolution to a certain extent[^79]. For example, in an animal model of Alzheimer' s disease, semaglutide intervention promoted the transition of microglia from the M1 to the M2 phenotype, accompanied by decreases in inflammatory-factor levels and neuroprotective effects. In metabolism-related diseases, the inflammation-resolution-promoting potential of GLP-1RAs has also received some support. Clinical studies have shown that liraglutide can reduce serum CRP levels in adults with type 2 diabetes and improve chronic low-grade inflammation[^80]. In a high-fat-diet-induced mouse model, an increased proportion of M2-like macrophages in liver tissue was observed after liraglutide treatment, suggesting that it may promote inflammation resolution by regulating the hepatic immune microenvironment[^81].

Multiple large randomized controlled trials have shown that GLP-1RAs may improve the prognosis of cardiovascular disease, stroke, and kidney disease in patients with type 2 diabetes[^82–^84]. Although the above cardioprotective and renoprotective benefits involve multiple mechanisms, such as weight loss, blood pressure improvement, and glycemic control, their inflammation-resolution-promoting effects may play a synergistic role.

3.4 Thiazolidinediones

Thiazolidinediones (TZDs) are a class of drugs that act by···

···oral glucose-lowering agents that exert their effects by activating peroxisome proliferator-activated receptor γ. Clinical studies have found that TZDs improve insulin sensitivity and lower blood glucose, but their long-term use in major cardiovascular endpoints such as cardiovascular disease remains controversial [85]. This controversy may be related to the dual mechanisms of action of TZDs: on

the one hand, in addition to improving insulin resistance and regulating lipid metabolism, TZDs may also modulate inflammatory responses and promote the process of inflammation resolution, thereby potentially improving the cardiovascular risks associated with atherosclerosis; on the other hand, these drugs can cause sodium retention and increase the risk of heart failure, which to some extent offsets their potential cardiovascular benefits. Animal experiments have found that pioglitazone can increase the level of the anti-inflammatory mediator 15-epi-lipoxin A4 in mouse myocardium [86]. In a randomized controlled trial, after patients with type 2 diabetes were treated with different doses of pioglitazone, blood 15-epi-lipoxin A4 levels increased, suggesting that pioglitazone may exert a pro-resolution effect by elevating SPMs levels [87].

4 Summary and Outlook

Type 2 diabetes is a metabolic disease characterized by persistent activation of chronic low-grade inflammation and impaired inflammation-resolution capacity. Existing research has focused on the role of chronic low-grade active inflammatory responses in the occurrence and progression of type 2 diabetes and its complications. However, inflammation resolution, as the normal turning point of inflammation, may—like metabolic dysfunction—also become one of the important pathological links in type 2 diabetes, mainly manifested as tissue fibrosis, abnormalities in innate immune cells, and abnormal SPMs phenotypes. At the same time, inflammation resolution and its regulation may also explain, to some extent, the clinical benefits of existing diabetes therapies. Routine monitoring of biomarkers related to inflammation resolution would help interpret the clinical benefits of type 2 diabetes treatment, and further exploration of the role of inflammation resolution in the prevention and treatment of type 2 diabetes would be useful, thereby enabling deeper clinical and basic research to further investigate causal relationships.

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