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REVIEW

Role of metformin in inflammation

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Abstract

Background Metformin has good anti-hyperglycemic effectiveness, but does not induce hypoglycemia , is very safe, and has become the preferred drug for the treatment of type 2 diabetes. Recently, the other effects of metformin, such as being anti-inflammatory and delaying aging, have also attracted increased attention.

Methods and Results The relevant literatures on pubmed and other websites for reading, classification and sorting, and did not involve any animal experiments.

Conclusion Metformin has anti-inflammatory effects through multiple routes, which provides potential therapeutic targets for certain inflammatory diseases, such as neuroinflammation and rheumatoid arthritis. In addition, inflammation is a key component of tumor occurrence and development ; thus, targeted inflammatory intervention is a significant benefit for both cancer prevention and treatment. Therefore, metformin may have further potential for inflammation-related disease prevention and treatmen. However, the inflammatory mechanism is complex; various molecules are connected and influence each other. For example, metformin significantly inhibits p65 nuclear translocation, but pretreatment with compound C, an AMPK inhibitor, abolishes this effect, and silencing of HMGB1 inhibits NF-κB activation . SIRT1 deacetylates FoxO, increasing its transcriptional activity . mTOR in dendritic cells regulates FoxO1 via AKT. The interactions among various molecules should be further explored to clarify their specific mechanisms and provide more direction for the treatment of inflammatory diseases, as well as cancer.

Keywords Metformin · Anti-inflammation · Inflammatory cytokine · Mechanisms

Introduction

Metformin has been used since 1957 for the treatment of type 2 diabetes due to its good anti-hyperglycemic effectiveness, but does not induce hypoglycemia,high safety, low cost, and low rate of adverse reactions, and has become the medication of choice for first-line treatment. In addition, it can reduce the complications caused by diabetes and has several benefits unrelated to blood-sugar control, such as prolonged life and reduced risk for cancer and cardiovascular events [1–6]. It inhibits the occurrence and progression of colorectal cancer [7, 8], improves the survival rate of endometrial cancer patients [9], and reduces the incidence of breast cancer [10]. Regarding inflammatory diseases, metformin can target oxidative stress to downregulate transcription factor NF-κB-mediated pro-inflammatory signaling and reduce mucosal damage in inflammatory bowel disease [11], improve rheumatic disease [12, 13], and inhibit the expression of pro-inflammatory factors in neuroinflammation [14]. Inflammation is a key component of tumorigenesis. For example, chronic inflammation is considered the underlying mechanism causing DNA damage in gastric cancer [15]. However, the specific mechanisms of inflammation need further exploration. The possible relevant mechanisms of the anti-inflammatory effects of metformin are reviewed below (Fig. 1).

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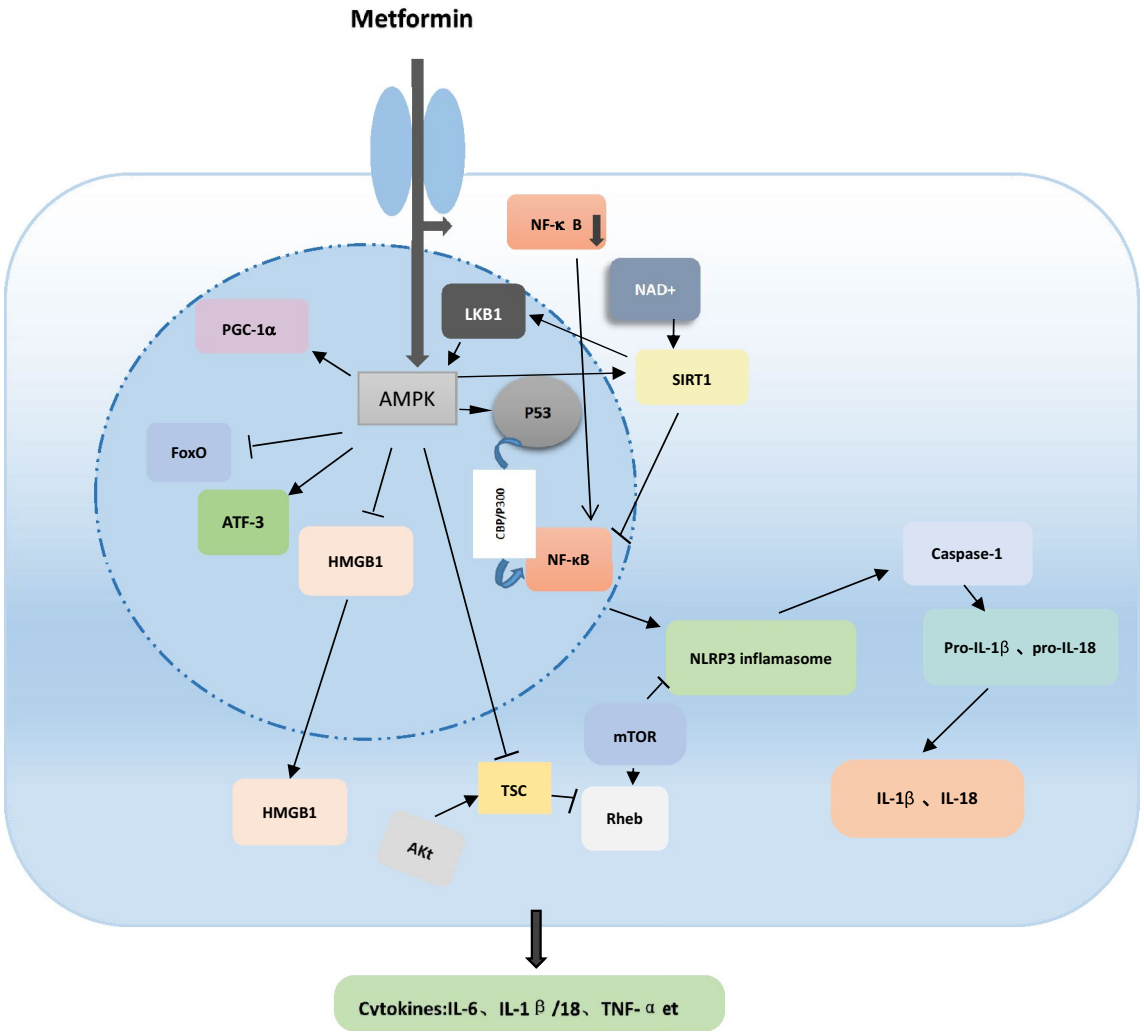

Fig. 1 Anti-inflammatory mechanism of metformin

Suppression of pro-inflammatory cytokine release

Pro-inflammatory cytokines are present at all stages of the inflammatory response and play important roles in the occurrence and development of inflammation. Metformin inhibits pro-inflammatory cytokine release to have anti-inflammatory effects [16–21]. A study in rats of the potential protective effect of metformin on depression-like behavior and neuroinflammation induced by oxandrolone (OXA) showed that metformin reversed the upregulation of the pro-inflammatory factors interleukin 1 (IL-1) mRNA, IL-6 mRNA, and tumor necrosis factor alpha (TNF-α) mRNA in the hypothalamus and hippocampus [16]. Another study found that metformin inhibited IL-1-induced release of IL-6 and IL-8 and NF-κB activity, thereby hindering human blood-vessel-wall inflammation [22]. It has been found to reverse the increased expression of the pro-inflammatory cytokines IL-17, IL-18, and IL-6 in mouse models of aldosterone-induced myocarditis [20], and to inhibit the extracellular signal-regulated kinase 1/2-early growth response factor-1 (ERK1/2-Egr-1) pathway in human monocytes, thereby suppressing lipopolysaccharide (LPS)-induced TNF and tissue factor (TF) production and thus alleviating the induction effect of TNF on chemotaxis proteins and interleukins [23]. In a TBI model, metformin reduced ERK1/2 and p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation levels [24], indicating that it may inhibit the inflammatory response induced by microglial activation via the NF-κB-MAPK signaling pathway.

The release of NF-κB is a crucial initial step in inflammation. NF-κB is an important nuclear transcription factor in cells that is involved in inflammatory, immune, and stress responses, as well as apoptosis regulation. Its overactivation is associated with many human diseases, such as rheumatoid arthritis, as well as inflammatory changes in heart

and brain diseases [22, 24]. Metformin inhibits the phosphorylation and nuclear translocation of the NF-κB subunit p65 and suppresses the degradation of its inhibitory protein I καB, causing NF-κB to be sequestered in the cytoplasm and unable to translocate to the nucleus to participate in inducing an inflammatory response [17, 18, 24, 25]. Most studies have shown that metformin promotes the synthesis of the anti-inflammatory factor IL-10 [16, 26]; however, one study [27] found that it and its analogues had no effect on IL-10 secretion, but reduced IL-12 p40 and IL-6 secretion. In addition, that study found that metformin significantly inhibited five plasma cytokines (CCL11, CCL22, IL-2, IL-4, and stromal-cell-derived factor 1). CCL11 is independent of BMI and diabetes, however, BMI is associated only with CCL22 and stromal-cell-derived factor 1αβ, indicating that the anti-inflammatory effect of metformin is partly independent of its comprehensive control of blood sugar, lipids, and body weight.

Activation of adenosine 5′-monophosphate-activated protein kinase

Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) is a highly conserved serine/threonine protein kinase that is closely associated with bioenergy metabolism regulation and is widely expressed in various cells. AMPK is a heterotrimeric serine/threonine kinase composed of three subunits, one catalytic subunit and two regulatory subunits. The metformin-activated AMPK pathway mainly reduces the expression of inflammatory cytokines and chemokines, including CCL2, CXCL10, and CXCL11, by acting on various downstream proteins such as histone deacetylase (HDAC) and peroxisome-proliferator-activated receptor co-activation factor 1α (PGC-1α) [21, 28].

HDAC activation

Silent information regulation 2 homolog 1 (SIRT1) is an NAD^+-dependent deacetylase with histone protein/protein as a substrate, and is a key enzyme associated with energy metabolism and lifespan signaling. Immunohistochemistry results have confirmed that AMPK activation increases p-SIRT1 expression levels, and knockdown of AMPK or use of the AMPK inhibitor compound C abolishes metformin activity [29]. This is consistent with numerous studies that found that metformin activates AMPK to upregulate SIRT1 and has an anti-inflammatory effect [29–33]. SIRT1 inhibits transcriptionally active NF-κB [34, 35]. After pretreatment with the SIRT1 activator, TNF-α-induced cellular NF-κB transcription is reduced. By contrast, pretreatment with SIRT1 inhibitor or HDAC I and II inhibitors increases TNF-α-induced NF-κB activity. Co-transfection experiments that used p300 to acetylate RelA/p65 in vivo have revealed that SIRT1 directly deacetylates RelA/p65 lysine 310 to act with the p65 subunit rather than p50 to repress NF-κB gene expression [34]. SIRT1 also positively activates AMPK. Lan et al. expressed the AMPK upstream kinase LKB1, wild-type SIRT1, and catalytically inactive SIRT1 in HEK293T cells. After wild-type SIRT1 activation with an activator, LKB1 acetylation was significantly reduced, however, inactive SIRT1 and shRNA knockout SIRT1 increased LKB1 acetylation several fold, with different LKB1 fragments interacting with SIRT1, showing that SIRT1-mediated Lys-48 is a key site for upstream kinase LKB1 activation, phosphorylation, and cytosolic localization by AMPK [36]. In a study of the endotoxin-induced endothelial pro-inflammatory response [35], pretreatment of human umbilical vein endothelial cells (HUVECs) with metformin and the AMPK activator AIRCA phosphorylating AMPKα at threonine 172 and serine 498 of HDAC5 induced nuclear export of phosphorylated HDAC5. Thus, metformin inhibited the upregulation of vascular cell adhesion molecule-1 (VCAM1) adhesion molecules induced by LPS and TNF-α and downregulation of Krupp-like factor 2 (KLF2), thus improving the endotoxemia-induced endothelial pro-inflammatory response. However, after AMPK knockdown, the inhibitory effect of metformin on inflammation was abolished.

PGC-1α activation

PGC-1α is a class of nuclear co-activators and its expression is regulated by various factors. It interacts with multiple transcription factors to regulate the transcription efficiency of target genes and participates in activities including multiple mitochondrial metabolic pathways, immunity, and inflammation. Metformin activates the AMPK-PGC-1α pathway [37, 38]. Increasing or restoring PGC-1α inhibits inflammatory cytokines [37, 39–41]. Hang et al. [37] found that pAMPK/AMPK ratios varied in different regions of the mouse brain, being significantly higher in the ventral midbrain regions than in the cortex and other regions. They also found that levels of PGC-1α, a downstream target of AMPK, were well correlated with AMPK activity levels in different brain regions. In their study, PGC-1α significantly reduced the normally higher ventral midbrain pAMPK/AMPK ratio caused by parkin defects in the Parkinson's disease (PD)-related gene, and Paris, a negative regulator of PGC-1α, was upregulated. Metformin treatment significantly restored the pAMPK/AMPK ratio and PGC-1α levels in the ventral brain of deficient mice.

Metformin also restores the nuclear translocation level of PGC-1α [42]. Immunofluorescence and histochemical analyses have demonstrated that PGC-1α expression levels in microglia in the brains of humans and mice that have suffered an ischemic stroke are altered in a time-dependent manner and peak on the first day. To further determine the

role of PGC-1α in microglia, investigators have performed transient middle cerebral artery occlusion (tMCAO) surgery after inducing PGC-1α overexpression in PGC-1α mice (mPGC-1α) and PGC-1αf/f mice (littermate control mice carrying the PGC-1α allele) and found that PGC-1α mediates neuroprotection after stroke. Quantification of 40 cytokines/chemokines in microglia using protein-array analysis and verified by FACS analysis revealed that the levels of many pro-inflammatory cytokines such as IL-1, CCL5, IL-6, IL-17, and TNF-α, were significantly decreased and IL-1 maturation and release were mainly regulated by NLRP3, consistent with the suppression of NLRP3 activation in mPGC-1αmice. ChIP-Seq analysis and plasmid transfection experiments have confirmed that PGC-1αand ERR jointly regulate ULK1 expression in microglia and reduce the expression of pro-inflammatory factors, thus inhibiting neuroinflammation [39].

Activation of the tumor suppressor gene p53

p53 is a tumor suppressor gene that normally monitors or slows cell division to keep it in the normal range. When it undergoes a mutation resulting in an altered spatial conformation, it loses its regulatory effect and transforms into an oncogene. Recent studies have shown that p53 also plays a role in inflammation [43–47]. Metformin activates AMPK acting at p53 serine 15 and serine 20, enhancing p53 activity and having an anti-inflammatory effect [43]. Treatment of SKM-1 cells with metformin results in increased AMPK phosphorylation and p53 expression. Metformin-induced upregulation of p53 expression is attenuated after AMPK knockdown [48]. When comparing cytokine concentrations in streptomycin-induced diabetic mice without the p53 gene and in wild-type mice, IL-6, IL-11, IL-12, and other pro-inflammatory factors are significantly increased in p53 gene-deficient mice than in control mice. Knockout of the p53 gene in mice results in neutrophils and macrophages responding more frequently to LPS stimulation, showing stronger pro-inflammatory cytokine induction and NF-κB DNA binding activity [44]. The above studies showed that p53 expression is inversely associated with pro-inflammatory factors [44, 45] and the regulation by metformin is inseparable from AMPK. Furthermore, p53 inhibits the activity of three different NF-κB binding sites, slowing its mediated transcription; NF-κB-induced cytokine-encoding gene expression is enhanced upon p53 failure [47]. In addition, it inhibits the transcriptionally active NF-κB by competing for a complex of limited p300 and CREB-binding protein (CBP) coactivating proteins [46].

FoxO1 inhibition and FoxO3a activation

Both FoxO1 and FoxO3 are important members of the Forkhead box protein (FoxO) family. Their activity is regulated by various modification processes such as phosphorylation and acetylation and both participate in a variety of physiopathological processes. Recently, several studies have shown that FoxO plays an important role in inflammation and immune cells [49–51]. However, FoxO family expression is mainly regulated by the AMPK signaling pathway [52–54]. After knockdown of FoxO1, the expression levels of pro-inflammatory factors such as TNF-α, IL-1β, MIP2, and IFN-β significantly decreased [55] but significantly increased with FoxO1 overexpression, leading to macrophage activation and promotion of the inflammatory response [56, 57]. In terms of macrophage apoptosis, inhibiting FoxO1 activity promotes macrophage apoptosis and suppresses the inflammatory response [58]. FoxO1 activation promotes macrophage proliferation and the inflammatory response [59, 60]. FoxO3a directly enhances its own transcriptional activity by phosphorylating AMPK. Knockdown of FoxO3a results in significantly increased NF-κB activity and inflammatory factors [61, 62]. FoxO3a also reduces the pro-inflammatory cytokine TNF-α and promotes the production of anti-inflammatory cytokines such as IL-10 through protein–DNA interactions directly regulating transforming growth factor 1 (TGF-β1) and indirectly controlling TGF-β1 [63].

Transcription factor 3 (ATF-3) activation

ATF-3 has a leucine zipper structure and belongs to the ATF/CREB family of transcription factors. It is a key regulator in the stress response and involved in various physiopathological processes. It negatively regulates the expression of pro-inflammatory genes [66, 67]. Expression of pro-inflammatory factors IL-6 and IL-8 is significantly upregulated in human bronchial epithelioid cells when lacking ATF-3, and nuclear expression of NF-κB p65 and p-p-p65 protein increase the degradation of p65 repressor IkBa and increase the levels of p-IkBa protein, indicating that ATF-3 plays a role in regulating p65 phosphorylation status [66]. Furthermore, ATF-3 directly binds to NF-κB p65 and inhibits the expression of inflammatory response cytokines induced by the NF-κB signaling pathway [64], or directly binds to the promoter regions of IL-6 and IL-12b to regulate the inflammatory response [67].

In LPS-induced inflammation in mouse macrophages, metformin increases ATF-3 expression and suppresses pro-inflammatory factors in a dose-dependent manner. After treatment with metformin, LPS-induced enrichment of NF-κB at the IL-6 and TNF-α promoter is replaced by

ATF-3. Furthermore, ATF-3 competes with NF-κB for the promoter binding of TNF-α and IL-6 to inhibit NF-κB signaling. Knockdown of ATF-3 results in the inhibition of the phosphorylation of pro-inflammatory cytokines and abolishes MAPK activity. Phosphorylation of threonine 172 is very important for AMPK activity; however, after knockdown of AMPK, the effect of metformin on ATF-3 and pro-inflammatory factors is attenuated. In one study [65], leptin-deficient mice were used to model obesity and type 2 diabetes. The mice were treated with oral metformin for 3 weeks and the levels of pro-inflammatory cytokines and ATF-3 in plasma and tissues were analyzed. Significantly increased AMPK and significantly decreased plasma pro-inflammatory cytokine levels were observed in treated mice compared to control mice. The above studies confirm that metformin has anti-inflammatory effects, at least in part, through AMPK-ATF-3-dependent mechanisms.

NLRP3 inflammasome inhibition

The NLRP3 inflammasome contains three domains: NYD, NACHT, and LRR. The inflammasome has a high-molecular-weight multiprotein cytosolic assembly composed of receptors and sensors, an important component of innate immunity, and is closely associated with many diseases such as rheumatoid arthritis [68]. When stimulated by agonists, the NLRP3 inflammasome can activate caspase-1, thus promoting the maturation of cellular interleukins and other cytokines. Metformin affects the NLRP3 inflammasome mainly through the AMPK-dependent and AMPK-independent pathways. Yang et al. [69] found that metformin acts on the NLRP3 inflammasome through the AMPK/mTOR pathway and inhibits the recruitment and activation of the pro-inflammatory protein caspase-1 by NLRP3 inflammasome, thus preventing the conversion of IL-1 and IL-18 precursors into mature cytokines. Furthermore, AMPK can activate autophagy-negative regulation to inhibit the NLRP3 inflammasome [70]. In addition, the inhibition of the NLRP3 inflammasome can be independent of the metformin-activated AMPK pathway, reduce DNA polymerase (DNA POL) activity by reducing the ATP content and inhibiting mitochondrial DNA (mt-DNA) synthesis, reduce the cytosol of oxidized mt-DNA (Ox-mtDNA), and inhibit NLRP3 inflammasome activation as well as caspase-1 and IL-1β cleavage and release [71].

Mammalian target of rapamycin signaling pathway inhibition

Mammalian target of rapamycin (mTOR) is a class of filament/threonine kinase and has an important role in eukaryotic cell signaling. Cytokine expression in T cells is affected by mTOR stability. mTOR participates in immune suppression, affecting transcription and protein synthesis, and is an important regulator of cell growth, proliferation, and the immune response, mainly acting through the formation of the mTORC1 and mTORC2 complexes. Metformin has been widely recognized as an anti-inflammatory agent that acts through the AMPK-mTOR pathway [69, 72–74]. It directly modulates mTOR [75, 76] independently of the AMPK pathway, but may be dependent on the ability of Rag GTPases to induce the transfer of mTORC1 to the intracellular lumen occupied by Rheb. Therefore, direct inhibition of mTORC1 signaling inhibits inflammation [75].

High-mobility group box 1 protein inhibition

High-mobility group box 1 (HMGB1) contains three major functional domains: an A-box domain at the N-terminal, a B-box domain with cytokine activity at the middle, and the C-terminal, an acidic tail domain composed of 30 acidic amino acids [77]. Horiuchi et al. [78] studied metformin in vitro and in vivo using a compound containing a metformin-like structure for affinity chromatography; mass spectrometry showed that the HMGB1 protein bound to metformin. Furthermore, full-length HMGB1, three functional domains, A-free junction and acid-free HMGB1 recombinant protein were obtained for pulldown experiments. The HMGB1 mutants containing an acidic tail structure clearly bound to the compound whereas mutants lacking the acidic tail did not. The association between recombination of full-length HMGB1 and the compound was concentration-dependently inhibited only in the presence of the acidic tail mutants. The results confirm that metformin binds directly to the acidic tail of the C terminal end of HMGB1, thereby inhibiting p38 phosphorylation and the cytokine-like activity of HMGB1.

The high-mobility family protein B1, a multifunctional protein jointly involved with DNA in the regulation of gene expression, is also an alarm protein for cellular inflammation that induces the inflammatory response through its cytokine-like activity [78–81]. In one study [82], the development of neuroinflammatory responses was monitored using magnetic resonance imaging (MRI) and immunohistochemistry after injecting a single redox isoform of HMGB1 directly into the cerebral cortex. The results indicated that disulfide HMGB1 (ds-HMGB1) and complete reduction of HMGB1 (fr-HMGB1) acted as pro-inflammatory mediators that promoted blood–brain barrier disruption and a local inflammatory response. Targeting HMGB1 can alleviate a variety of disease injuries [78, 83–85] such as sepsis-induced acute liver, kidney, and lung injuries. The use of anti-HMGB1 monoclonal antibodies inhibits the activation of parkinsonian microglia and the expression of inflammatory cytokines such as IL-1 and IL-6 [80], alters murine sepsis models and

early inflammatory factor profiles, improves the sepsis survival rate [86], and blocks the activation of NF-κB, p38, and Erk1/2 [81]. HMGB1 is associated with toll-like receptor (TLR) [79, 87–89], late glycosylation end product receptor (RAGE) [90], C-X-X motif chemokine receptor 4 (CXCR4), and *N*-methyl-d-aspartate receptor (NMDAR), which play important roles in inflammation [91]. HMGB1 also binds to the complement system C1q to activate the classical pathway in an antibody-independent manner, exacerbating the sterile inflammatory environment [92]. Furthermore, metformin inhibits HMGB1 mRNA expression and nuclear translocation to hinder the associated inflammatory response [93, 94]. In rabbit AF stem cells, LPS-induced HMGB1 release from the nucleus to the cytoplasm causes increased release of inflammatory cytokines, and treatment with metformin inhibits HMGB1 nuclear translocation and the expression of inflammatory factors TNF-α, IL-6, IL-1, and I L-1β [93].

Oxidative stress pathway inhibition

Oxidative stress and inflammation are interrelated processes; oxidative stress is an imbalance between oxidation and antioxidant effects in the body. When the antioxidant system cannot adequately act on reactive oxygen clusters, a large number of oxidation intermediates emerge, such as leukotriene (LT), thromboxane A2 (TXA2), and other pro-inflammatory mediators. Reactive oxygen clusters degrade the inhibitory subunit IκBα of NF-κB leading to increased release of NF-κB to promote inflammation [94–96]. Metformin has anti-inflammatory effects through antioxidants [20, 79, 97]. Alhaider et al. [79] found that metformin restores the mRNA levels of antioxidant genes such as GST, NQO1, and CAT in a streptomycin-induced rat diabetic nephropathy model, thus inhibiting the expression of TNF-α and IL-6 pro-inflammatory genes. Metformin inhibits the aldosterone-induced oxidative stress response, silences the cytoplasmic adaptor molecule TRAF31 interacting protein 2 (TRAF3IP2) in the oxidative stress response, and inhibits the expression of pro-inflammatory factors such as IL-6, IL-17, and IL-18 [20]. Metformin reduces the production of reactive oxygen species and pro-inflammatory factors caused by multiple pathways,such as hyperglycemia-triggered mitochondrial dysfunction, generation of advanced glycation end-products(AGEs) and the activation of protein kinases (PKC), improves endothelial dysfunction and cardiac function, and slows down diabetes-related cardiovascular events[4, 5].

Conclusion

Metformin has anti-inflammatory effects through multiple routes, which provides potential therapeutic targets for certain inflammatory diseases, such as neuroinflammation and rheumatoid arthritis. In addition, inflammation is a key component of tumor occurrence and development [98–102]; thus, targeted inflammatory intervention is a significant benefit for both cancer prevention and treatment. Therefore, metformin may have further potential for inflammation-related disease prevention and treatmen. However, the inflammatory mechanism is complex; various molecules are connected and influence each other. For example, metformin significantly inhibits p65 nuclear translocation, but pretreatment with compound C, an AMPK inhibitor, abolishes this effect, and silencing of HMGB1 inhibits NF-κB activation [77, 85]. SIRT1 deacetylates FoxO, increasing its transcriptional activity [103]. mTOR in dendritic cells regulates FoxO1 via AKT [104]. The interactions among various molecules should be further explored to clarify their specific mechanisms and provide more direction for the treatment of inflammatory diseases, as well as cancer.

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Declarations

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Research involving human and/or animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

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