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Review article

Unraveling the immunometabolism puzzle: Deciphering systemic sclerosis pathogenesis

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ABSTRACT

The article delves into the pathogenesis of systemic sclerosis (SSc) with an emphasis on immunometabolism dysfunctions. SSc is a complex autoimmune connective tissue disorder with skin and organ fibrosis manifestation, vasculopathy, and immune dysregulation. A growing amount of research indicates that immunometabolism plays a significant role in the pathogenesis of autoimmune diseases, including SSc. The review explores the intricate interplay between immune dysfunction and metabolic alterations, focusing on the metabolism of glucose, lipids, amino acids, the TCA (tricarboxylic acid) cycle, and oxidative stress in SSc disease. According to recent research, there are changes in various metabolic pathways that could trigger or perpetuate the SSc disease. Glycolysis and TCA pathways play a pivotal role in SSc pathogenesis through inducing fibrosis. Dysregulated fatty acid β-oxidation (FAO) and consequent lipid metabolism result in dysregulated extracellular matrix (ECM) breakdown and fibrosis induction. The altered metabolism of amino acids can significantly be involved in SSc pathogenesis through various mechanisms. Reactive oxygen species (ROS) production has a crucial role in tissue damage in SSc patients. Indeed, immunometabolism involvement in SSc is highlighted, which offers potential therapeutic avenues. The article underscores the need for comprehensive studies to unravel the multifaceted mechanisms driving SSc pathogenesis and progression.

1. Introduction

Systemic Sclerosis (SSc), known as scleroderma, is a complex autoimmune connective tissue disorder with unknown etiology that is characterized by fibrosis of the skin and internal organs, vasculopathy, and immune system dysregulation. Scleroderma affects multiple organs, including the skin, lungs, heart, gastrointestinal (GI) tract, and kidneys [1,2]. Despite its relatively low prevalence, the burden of disease associated with SSc is substantial [3]. SSc significantly affects the quality of life and life expectancy [4]. Among all

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rheumatic diseases, SSc exhibits the highest mortality rate [3]. Young or middle-aged females constitute the majority of the SSc patients. The female-to-male ratio ranges from 3:1 to 8:1, and this disproportion is particularly heightened during the childbearing years [5,6]. SSc has a profound impact on life expectancy, with a mortality ratio of 3.5 [7]. Prevalence and incidence for SSc were divergent in different regions of the world. The lower incidence and prevalence rates are in Japan [8] and northern Europe [9,10], with incidence of <10 per 1 million per year and prevalence of <150 per 1 million. The higher incidence and prevalence rates are in Australia [11], southern Europe [12–15], the USA [16], and Canada [17] with incidence of >10 per 1 million per year and prevalence of >150 per 1 million. According to these data, geographical factors could be implicated in the incidence and prevalence of SSc [18,19].

Scleroderma can be categorized into two main subtypes, which are determined by the extent of skin involvement: localized scleroderma and systemic scleroderma. Localized scleroderma is a disease that is limited to the skin and subcutaneous tissue leading to the development of thickened patches on the skin [20,21]. Diffuse cutaneous systemic sclerosis (dcSSc) is characterized by widespread skin involvement alongside internal organ manifestations [20,22]. A significant amount of research has been conducted on the pathogenesis of SSc and deepened our knowledge of the underlying causes of the disease and various clinical manifestations, but the exact mechanisms remain unclear [23]. Studies have demonstrated that genetic susceptibility and environmental factors play a significant role in the pathogenesis of the disease [2,24]. An essential characteristic of SSc is the presence of a pathophysiological triad, which includes increased ECM and collagen disposition within tissues, immune dysregulations, microvascular damage, and dysfunctions [25]. The hallmarks of this disease are autoimmunity, chronic inflammation, structural changes in the microvasculature, and fibrosis in the skin and internal organs [26].

Immunometabolism is a set of changes in the metabolic pathways of immune cells that alter their functions [27]. A close relationship exists between immune responses and changes in metabolic processes [28]. Metabolic pathways can directly regulate immune responses. Indeed, alterations in the metabolic pathways of immune cells are associated with changes in immune responses [27]. Altered cell metabolism has been linked to several autoimmune diseases including, rheumatoid arthritis (RA) [29,30], systemic lupus erythematosus (SLE) [28], and SSc [31]. It has also been shown that immunometabolism plays a crucial role in SSc pathogenesis [32]. In SSc, immune cells undergo glycolytic deregulation, which is linked with a high level of aerobic glycolysis and acidosis [33]. Additionally, it has been demonstrated that changes in the tricarboxylic acid cycle (TCA) metabolic pathway are associated with dysfunction of immune cells and inflammatory responses.

Further analysis revealed that TCA dysfunction can lead to elevated fibroblast differentiation due to succinate accumulation [31]. Moreover, there are several reports of modifications in lipid metabolic pathways in SSc patients that have regulatory effects on endothelium and immune responses [32]. It is also reported that immune cells produce pro-inflammatory cytokines due to dysregulated FAO, which leads to chronic inflammation and fibrosis in SSc patients [34]. In addition, altered glutamine metabolism plays a significant role in autoimmune and fibrotic conditions [35]. Moreover, alterations in the pentose phosphate pathway (PPP) lead to the accumulation of ROS, inducing fibrosis and promoting inflammation in SSc patients [36]. A disturbance in metabolism pathways is associated with the upregulation of transforming growth factor β1 (TGF-β1) in immune cells, which leads to fibrosis induction in immune cells [35].

As mentioned earlier, immunometabolism has gained considerable attention in recent decades. Systemic and cellular metabolism of immune cells uncovers new aspects of novel therapies. A growing number of investigations indicate that immunometabolism plays a significant role in the pathogenesis of autoimmune diseases including SSc. In this review, we aim to summarize the intricate interplay between immune system dysfunction and changes in metabolic pathways such as glycolysis, the TCA, the PPP, FAO, fatty acid synthesis, and amino acid metabolism in SSc disease. Finally, the study aims to clarify underlying mechanisms linking immune dysregulation with metabolic pathways, thereby the potential role of immunometabolism in the pathogenesis, progression, and treatment of SSc patients.

2. Glucose metabolism in SSc

Glycolysis plays a significant role in the activation and cytokine production of immune cells [37]. In response to their specific functions, immune cells undergo metabolic modifications to fulfill their needs [38,39]. When immune cells are in resting status, they obtain their energy primarily from oxidative phosphorylation of glucose, and during their activation, the metabolic pathway shifts toward aerobic glycolysis to fulfill phenotypic and functional demands [40]. Metabolic reprogramming is essential for the differentiation, proliferation, and effector function of immune cells, which may potentially disrupt immune homeostasis in autoimmune diseases [41]. In autoimmune diseases including SSc, bioenergetic metabolism increases due to considerable energy consumption [42]. Glucose metabolism is the critical component of all biological activities due to its role in energy production for cellular functions [28,43]. Adenosine triphosphate (ATP), the source of energy for cells, is produced mainly through two biochemical pathways: glycolysis in the cytosol and oxidative phosphorylation in mitochondria [44]. Glucose metabolism not only provides energy for cell functions but also has various biological functions [45].

Glycolysis and glycolytic enzymes are dysregulated in autoimmune diseases [30,37]. Recently, it has been documented that glycolysis is dysregulated and plays a significant role in fibrosis development in SSc [42]. Specifically, glycolysis is increased in SSc fibroblasts compared to normal fibroblasts. Moreover, a high level of glycolysis in SSc fibroblasts was associated with the accumulation of lactic acid and low pH [33,37]. Keloid scar fibroblasts, which share characteristics with SSc fibroblasts, predominantly utilize aerobic glycolysis as their source of energy [33,42,46]. It was discovered that lung tissue and myofibroblasts from idiopathic pulmonary fibrosis (IPF) underwent a shift to glycolysis as their primary metabolic pathway [47,48], which was associated with high levels of lactic acid [49]. In the presence of lactic acid, endothelial cells are transdifferentiated into myofibroblasts through the activation of TGF-β [50,51]. Enhanced glycolytic metabolism and acidic extracellular microenvironment contribute to the inhibition of

angiogenesis and induction of myofibroblasts, thereby promoting the fibrotic process in SSc [33] (Fig. 1). According to recent studies, glycolysis has an essential role in SSc pathogenesis by inducing fibrosis. Further studies are needed to reveal the various aspects of glycolysis and introduce potential therapeutic targets for the management of SSc patients.

3. TCA cycle in SSc

The TCA cycle, known as the citric acid or Krebs cycle, is the major metabolic pathway for providing energy for cell demands. The TCA cycle is a series of chemical reactions that occur in cells and involves the breakdown of glucose to produce energy. Studies have shown that this cycle undergoes significant changes in autoimmune diseases such as SSc [52]. Itaconate is a by-product of the TCA cycle that is created through immune-responsive gene 1 (IRG1) by the decarboxylation of *cis*-aconitate. Emerging evidence suggests that itaconate has anti-inflammatory and immunomodulatory functions and inhibits succinate dehydrogenase (SDH) in SSc. Recent research has shown that 4-octyl itaconate (4-OI), a cell-permeable derivative of itaconate, can reduce collagen in dermal fibroblasts in SSc patients [53]. Another derivative of itaconate has been shown to reduce liver fibrosis. Studies have shown that the TCA pathway products such as acetate, succinic acid, and fumaric acid are increased in SSc patients due to TCA pathway impairment. Additionally, there is a significant reduction of phosphoglycerate dehydrogenase (PHGDH) in plasmacytoid dendritic cells (PDCs) of SSc patients [54]. The conversion of isocitrate by the isocitrate dehydrogenase (IDH) can result in elevated levels of succinate in SSc patients, which can bind to G protein-coupled receptor 91 (GPCR91) and increase α-SMA and TGF-β. Succinate has also been shown to induce HIF-1a production in lung myofibroblasts in IPF by overexpression of TGF-1 [55]. All these findings suggest that itaconate could play a crucial role in decreasing fibrosis and could be a potential therapeutic target in SSc patients. A significant portion of the coenzymes are provided by this pathway, which are then oxidized by the mitochondrial electron transport chain to produce ATP [52]. It has been demonstrated that the TCA pathway plays a significant role in epigenetic modifications, regulating cell proliferation and maintaining normal functions of cells [56]. It is noteworthy to mention that resting immune cells and anti-inflammatory cells, such as M2 macrophages can produce ATP through the TCA. Moreover, the TCA pathway is responsible for providing the intermediate metabolites necessary for modulating inflammatory functions by regulating the activity of epigenetic enzymes [57].

The TCA cycle has been shown to undergo significant alterations in autoimmune diseases, including SSc [56]. Itaconate, a by-product of the TCA cycle, is an unsaturated dicarboxylic acid and is synthesized from the decarboxylation of *cis*-aconitate in the TCA cycle through immune-responsive gene 1 (IRG1) [57–59]. Emerging evidence indicates that itaconate has immunomodulatory and anti-inflammatory functions [59] and inhibits succinate dehydrogenase (SDH) in SSc [60]. Data obtained from these studies suggest that itaconate could play a significant role in decreasing fibrosis and could be a potential therapeutic target in SSc patients. ROS level is upregulated, and the Nrf2/HO-1 signaling pathway is diminished in SSc patients especially in SSc fibroblast. Due to increased levels of ROS and decreased level of Nrf2, the anti-fibrotic mechanisms could be impaired in SSc disease [53]. Furthermore, Nrf2-KO mice have exacerbated fibrosis in the animal model of skin fibrosis [61]. Animal model studies revealed that the 4-OI, derivate of itaconate, could reduce both the pro-inflammatory molecules such as IL-6 and MCP-1 and also ROS levels [62]. Therefore, pharmacological strategies such as 4-OI that restore the decreased level of Nrf2, would be a useful therapeutically for decreasing fibrosis in SSc disease [53].

The concept of metabolic reprogramming and immunometabolism is a potential therapeutic strategy. The TCA pathway and its products, itaconate, have gained considerable attention in the field of immunometabolism in recent years. Recent studies in patients with SSc have demonstrated the dysregulated TCA pathway could be implicated in fibrosis induction. The focus of future studies should be on discovering new aspects of SSc treatment by targeting the dysregulated TCA cycle. More data is needed regarding the role of the TCA cycle in SSc disease, and further research should be conducted on a large scale in different ethnicities to clarify the role of the TCA cycle in the pathogenesis and treatment of SSc patients.

4. Lipid metabolism in SSc

Immune cells use lipid metabolism to maintain their energy sources for cell function and signaling. It is also known that lipids serve as precursors for cellular membrane components and they regulate multiple significant processes in the body, such as signal transduction, gene expression, and cell activation [63]. Within the lipid family, fatty acids are the most common form of stored and circulating energy. Fatty acids/triacylglycerol can be produced by different metabolic pathways such as de novo lipogenesis, triacylglycerol storage in the cytoplasm, and triacylglycerol-derived fatty acids from lipoprotein remnants [64].

Several studies have shown that M1 macrophages produce inflammatory mediators through lipid biosynthesis [65]. Fatty acid synthase (FAS) has been shown to play a major role in inducing M1 macrophages [66]. Saturated fatty acids have been shown to activate inflammasomes [65]. Increasing evidence has suggested that metabolic reprogramming in activated fibroblasts is a key feature of fibrosis [67].

In 1970, it was demonstrated that subcutaneous lipids of SSc patients were replaced with collagen-enriched fibrotic tissue [68]. Altered concentrations of fatty acids, acyl glycine, and carnitine derivatives in plasma indicate altered lipid metabolism in SSc patients [32]. Furthermore, skin lesions of SSc patients have been reported to have reduced levels of peroxisome proliferator-activated receptor-γ (PPAR-γ), fatty acid binding protein, and adiponectin [31]. It has also been demonstrated that PPAR-γ is involved in the regulation of fatty acid metabolism by integrating different signaling pathways [64]. It is noteworthy to mention that PPAR-γ plays a significant role in anti-inflammatory responses [69]. Recent studies suggest that endogenous activation of PPAR-γ is associated with the activity of the FAS enzyme [70]. PPAR-γ is the major regulator of adipogenesis. Studies have shown that PPAR-γ activation in bleomycin-induced skin fibrosis mice results in enhanced levels of adipogenesis and reduced inflammation and dermal fibrosis [31, 69]. Dysregulated FAO and consequent lipid metabolism result in dysregulated ECM breakdown and fibrosis induction. Decreased

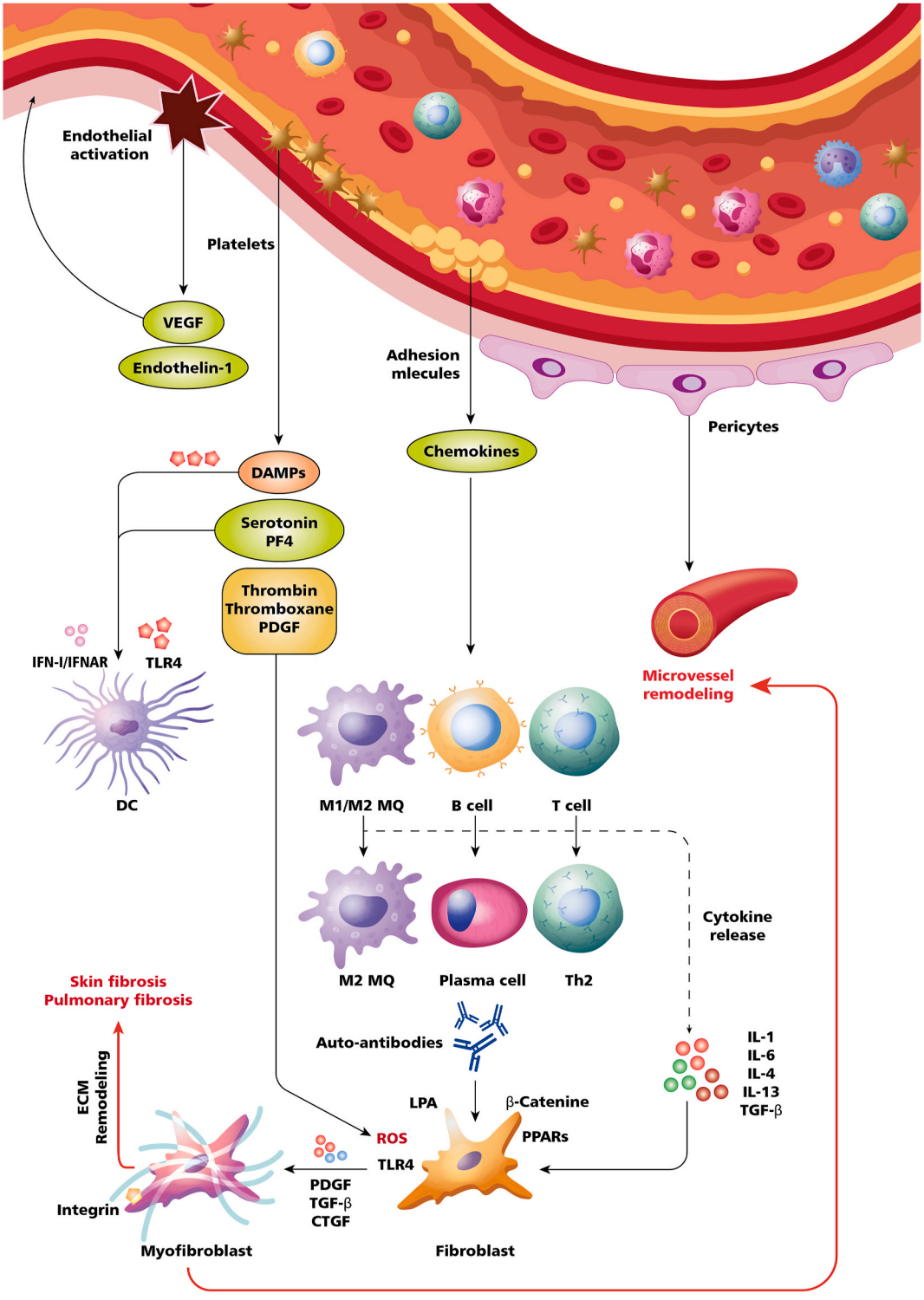

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Fig. 1. Interplay of endothelial activation and immunometabolic pathways in systemic sclerosis: Activated endothelial cells lining the blood vessels become leaky, facilitating the infiltration of immune cells into healthy tissues. Immune cell activation is initiated by damage-associated molecular patterns (DAMPs) released by stressed/damaged cells. DAMPs bind to Toll-like receptors (TLRs) on immune cells, further fueling inflammation and even influencing their metabolic state. Immune cells, including T cells, B cells, and macrophages, become activated and undergo metabolic reprogramming, switching to a more energetically active state to fuel their aggressive inflammatory response. The target of this immune attack are fibroblasts, the cell type responsible for tissue repair. However, in systemic sclerosis, these fibroblasts become hyperactivated and transition to a profibrotic state, characterized by excessive collagen production, the main building block of scar tissue. This relentless collagen deposition ultimately leads to the fibrosis that disrupts organ function and causes the debilitating symptoms of systemic sclerosis.

PPAR-γ levels are associated with FAO inhibition, which leads to lipid accumulation through the downregulation of carnitine palmitoyl transferase 1 (CPT1) and acyl-CoA oxidase (ACOX) that finally leads to fibrosis induction in fibroblasts [67]. Emerging evidence suggests that altered PPAR-γ expression in normal fibroblasts may result in TGF-β-induced collagen gene expression, blocking myofibroblast differentiation and impairing the normal function of fibroblasts in SSc [69]. Carnitine transports FA as acyl-carnitine into the mitochondria for oxidation. Alterations in FA metabolism may lead to changes in the acyl-carnitine level. Palmitoyl-carnitine plays a key role in the transfer of long-chain FA inside the mitochondria. A decrease in palmitoyl-carnitine levels may negatively impact FA balance. Altered energy metabolism in immune cells of SSc patients could be due to dysregulated FA and carnitine profiles [34].

According to the mentioned data, lipid metabolism is closely related to SSc and its complications, which suggests new potential therapeutic targets for the treatment of SSc patients. The field of immunometabolism improves our understanding of major changes in cellular lipid metabolism. However, there is a lack of data on the exact role of lipid metabolism in SSc pathogenesis. Further studies should be conducted to elucidate various aspects and the exact mechanism behind the role of lipid metabolism in SSc. Targeted modulation of the FAO metabolism could be helpful in inhibiting inflammation in SSc and, therefore might offer a novel therapeutic target.

5. Amino acid metabolism in SSc

Amino acids (AAs) are fundamental nutritional elements for immune cells and for organ development, tissue homeostasis, and immunological reactions [27,71]. Acting as signaling molecules in cells, AA also plays a pivotal role in governing gene expression [72]. AAs are essential nutrients for immune cells, organ development, tissue homeostasis, and immunological responses. They also function as signaling molecules in cells. They can be utilized in various biochemical reactions such as glucose metabolism, ATP production, and fatty acid synthesis. Furthermore, they can also serve as metabolic precursors for a variety of biomolecules, including nucleotide components and signaling molecules [73]. AA holds a crucial place in immune reactions, participating in the activation of immune cells such as B and T lymphocytes, natural killer cells, and macrophages. They also contribute to maintaining cellular redox equilibrium, regulation of gene expression, facilitating lymphocyte proliferation, and supporting the production of antibodies, cytokines, and cytotoxic agents [74]. It has been demonstrated that AAs play a critical role in the production of intermediate molecules, building blocks of proteins [75].

Immune cells metabolize AAs in various ways for proliferation and effector functions [76]. Emerging data have shown that AA metabolism plays a significant role in immune cells. AA metabolism in granulocytes could be linked with autoimmune rheumatic diseases (AIRDs) [77] and inflammatory diseases [78]. It is noteworthy to mention that impaired AA metabolism is also associated with vascular endothelial dysfunction, methylation process, and immune responses [75]. Arginine metabolism is related to different aspects of the immune system and can induce pro-inflammatory or anti-inflammatory responses [79].

Recent studies have paid considerable attention to different AAs and their altered metabolism in SSc pathogenesis. Homocysteine (Hcy), a non-essential AA, has higher plasma concentrations in patients with SSc compared with healthy subjects. It has been demonstrated that higher levels of Hcy worsen the pulmonary stage of SSc disease [80,81]. The Hcy interferes with the integrity of the vascular system and endothelial function and is also linked to Renynod's phenomenon [81,82]. Hydroxyproline, hydroxylysine, and proline are involved in collagen biosynthesis [83]. The upregulation of metabolites such as glutamine, proline, citrulline, and ornithine can lead to impaired collagen synthesis and fibrosis of the skin and internal organs [55]. The hydroxyproline content of mucosal esophageal has been used as a collagen deposition index in the progressive form of SSc patients [84]. Arginine, which has a high correlation with inflammation, is metabolized via two different pathways: the nitric oxide (NO) and the arginase pathway [76]. Arginine and homoarginine are associated with endothelial dysfunction in SSc patients [85]. Lymphocytes prefer glutamine as a source of energy [76], and glutaminolysis has been pointed out as a significant factor in the metabolism of AA and lipids, providing energy and substrates for fibroblasts in ECM synthesis. Additionally, it has been considered a vital factor in the development of fibrosis in SSc fibroblasts. Inhibition of glutaminolysis leads to decreased levels of α-KG and, subsequently, less production of ECM in the fibrosis process [67]. Proline is required for collagen production [86,87]. It was found that SSc patients have higher concentrations of proline compared to healthy individuals [75]. TGF-β effects on fibroblasts lead to increased levels of proline, which enhances collagen deposition and fibrosis induction [88]. Prolinase, a metalloproteinase enzyme, targets dipeptides that end with proline or hydroxyproline [89,90]. The broad tissue distribution of prolinase suggests that serum prolinase activity (SPA) could be implicated in the progression of many diseases [91]. At the initial phases of SSc, increased collagen turnover might lead to an elevated proline level due to catabolism of proline-containing iminopeptides or hydroxyproline [92]. Studies show that elevated proline levels have an inhibitory effect on SPA. This inhibition could potentially worsen SSc severity due to increased proline levels [75,92,93]. Therefore, decreased SPA in SSc and increased proline are evidence for impairment in collagen tissue [94]. It was found that scleroderma was linked to reduced concentrations of proline, which is an indication of accelerated protein synthesis [75]. Consequently, a deficiency in proline,

an essential AA, in patients with scleroderma may indicate a poor prognosis [95]. The metabolic pathway of glutamine, recognized as glutaminolysis, has emerged with potential significance as an important mediator in autoimmune and fibrotic conditions [96–98]. Glutamine metabolism is implicated in the proliferation and differentiation of myofibroblast by providing energy and biosynthetic precursors. It also plays a pivotal role in fibrosis through α-ketoglutarate, which is an essential substituent of collagen I in ECM, contributing to the progression of fibrotic conditions [35]. A study conducted by John Henderson et al., they found that glutaminase was consistently upregulated in fibroblasts of SSc patients. Therefore, altered glutamine metabolism could be an important factor in the fibrosis of SSc patients [35]. Glutaminolysis also plays a critical role in the fibrosis of IPF [99].

As mentioned earlier, impaired AA metabolism and protein synthesis have been reported in SSc patients [55]. Recently, a significant number of studies have been conducted on different AAs and their role in the fibrotic processes of SSc patients. Accordingly, there have been several reports that documented altered metabolism of AAs could play significant roles in SSc pathogenesis through various mechanisms. A more specific and efficient treatment for SSc patients may be achieved through these alterations. Although adequate data about the role of AAs metabolism in SSc are available, more comprehensive studies are required to investigate different aspects of these changes and their interactions with other factors that ultimately lead to SSc development and its progression.

6. Oxidative stress in SSc

The rate of production and removal of ROS in normal conditions is equal, and it is well compensated, but when there is an overproduction or lack of anti-oxidant enzyme activity, vascular lesions could be the outcome [100]. ROS is a chemically active molecule with an oxygen atom that can damage cells by oxidizing them [101]. ROS are essential elements in various actions including immune responses, cytokine production, microbial clearance, cell proliferation, and cell death [29,101]. ROS can induce a variety of apoptotic and non-apoptotic mechanisms through different biological activities in different cell types and organs [102]. Emerging evidence has suggested that ROS is involved in the pathogenesis of cancer and autoimmune diseases [101].

It has been demonstrated that SSc patients show elevated levels of ROS production in the skin, fibroblasts, and endothelial cells [101]. Increased levels of ROS in SSc, which contains superoxide anion (O_2), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), nitric oxide (NO), peroxynitrite (ONOO), and hypochlorous acid (HOCL), can induce production of pro-inflammatory and pro-fibrotic cytokines such as TGF-β and platelet-derived growth factor (PDGF) resulting in the activating and proliferating of fibroblasts, increased synthesis of type I collagen, and promoting vascular damage [103]. Furthermore, ROS can increase TGF-β production through the MAPK pathway and SMAD phosphorylation [104,105]. The released TGF-β can induce ROS production in non-phagocytic cells through the NADPH oxidase 4 (NOX4) [102]. It has also been demonstrated that ROS may be produced by different cell types that lead to chronic oxidative stress in SSc patients. Neutrophils in SSc patients produce ROS and are involved in tissue fibrosis and endothelial cell dysfunction. Moreover, monocytes contribute to the development of fibrosis in the skin [102]. As a result of increased ROS production, type I collagen is produced at a higher rate in fibroblasts of patients with SSc [103]. Oxidants may directly or indirectly cause fibroblast activation or involvement in fibrosis by changing the balance between protease and anti-protease activity. Exceeding ROS production from antioxidant defense results in fibroblast activation, which leads to ECM deposition and fibrosis [102]. It has also been indicated that SSc patients exhibit elevated levels of free radicals alongside diminished antioxidative potential. It is also shown that the level of plasma superoxide dismutase, the main part of the antioxidative defense, is higher in SSc patients compared with healthy subjects. Decreased ascorbic acid levels due to vitamin C deficiency have been reported in SSc patients [106]. PDGF has been suggested to be involved in increased ROS production via activation of NOX1-based oxidases. Additionally, significant amounts of TGF-β receptors have been reported in skin lesions of SSc patients compared with healthy subjects. Overexpression of TGF-β receptors and release of TGF-β in SSc patients through PDGF receptor signaling lead to skin abnormalities in SSc patients [105]. ROS induces heightened permeability in endothelial cells, consequently triggering the deposition of ECM and fostering the development of fibrosis [106]. ROS may cause different modifications to molecules such as nucleic acid, lipids, and proteins [100]. It has been reported that SSc patients have higher levels of oxidative stress, which results in elevated lipid peroxidation [105]. Oxidized LDL leads to the recruitment of monocytes, induces cytotoxic effects on endothelial cells, and the formation of connective tissue. Oxidative stress resulting from hypoxia/ischemia may lead to changes in the immune response of SSc patients. Collectively, ROS production has a crucial role in tissue damage of SSc patients and is a potential therapeutic target [106]. Further large-scale studies need to be conducted to investigate the therapeutic significance of oxidative stress inhibition in SSc patients.

7. Therapeutic approaches targeting immunometabolism in SSc

Understanding the intricate interplay between immunometabolism and SSc pathogenesis has paved the way for the development of novel therapeutic approaches. Here, we discuss the emerging tactics aimed at modulating immunometabolism dysfunctions to mitigate SSc progression.

7.1. Metabolic modulators

Targeting metabolic pathways, aberrantly dysregulated in SSc, holds promise for therapeutic intervention [107]. Drugs such as metformin, which primarily acts on cellular metabolism by activating AMPK, have shown potential therapeutic effects in ameliorating fibrosis and inflammation in SSc in preclinical studies [108]. Small molecules targeting glycolysis, fatty acid metabolism, or mitochondrial function may offer avenues to explore therapeutic options [109]. The inhibition of glycolysis by 2-deoxy-D-glucose (2-DG) and shikonin, naphthoquinone extracted from Lithospermum is a traditional Chinese herb, significantly reduces renal fibrosis in mice

with SSc. Disrupted glycolysis in renal fibroblasts leads to a decrease in the expression of fibrosis markers such as α-smooth muscle actin (α-SMA) and fibronectin, along with an increase in intracellular pH and a reduction in lactate accumulation [110]. Intervention in these dysregulated metabolic pathways could offer potential therapeutic options in SSc patients in near future.

7.2. Immunomodulatory agents

Given the intimate connection between immunometabolism and immune cell function, immunomodulatory agents represent another promising avenue for SSc therapy [111]. For instance, inhibitors targeting the mammalian target of rapamycin (mTOR), a key regulator of cellular metabolism and immune responses, have shown efficacy in preclinical models of SSc by dampening aberrant fibrotic and inflammatory processes [112]. Furthermore, modulators of immune checkpoints, such as programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), may hold the potential to restore immune homeostasis in SSc [113,114]. Targeting specific metabolic pathways or metabolites holds promise as a therapeutic strategy for autoimmune disorders. For instance, inhibiting mTOR with rapamycin has shown safety and efficacy in small-scale clinical trials. By inhibiting mTORC1, rapamycin has the potential to restore normal T cell lineage distribution and decrease disease activity in systemic lupus erythematosus (SLE). Clinical studies have also indicated the therapeutic potential of rapamycin in RA, SSc, and Sjogren's syndrome by modulating the immune system. The N-acetylcysteine, acting as a stable cysteine analog, replenishes cysteine and glutathione (GSH) levels, thereby reducing oxidative stress. Additionally, N-acetylcysteine has been shown to inhibit mTORC1 in double-negative T cells. Combining N-acetylcysteine with rapamycin could, therefore, present a promising therapeutic approach for autoimmune diseases. Interestingly, it has been observed that various immunomodulatory drugs commonly used in autoimmune diseases may exert their therapeutic effects by modulating the metabolism of the immune cells [115]. Further studies should be conducted to reveal the efficacy of this method in patients with SSc.

7.3. Nutritional interventions

Emerging evidence suggests that dietary interventions targeting specific metabolic pathways could influence the course of SSc [116]. For instance, supplementation with antioxidants or nutrients that regulate mitochondrial function, such as coenzyme Q10 or L-carnitine, may help alleviate oxidative stress and mitochondrial dysfunction observed in SSc patients [117]. Moreover, dietary modifications aimed at modulating the gut microbiota composition could indirectly influence immunometabolism balance and hold promise as adjunctive therapies for SSc [118]. Nutritional metabolism significantly influences immune responses in both malignant and infectious diseases. Obesity-induced by diet and increased extracellular lipid availability reprogram the cellular metabolism of natural killer cells, resulting in diminished anti-tumoral activity in both animal models and human patients. A ketogenic diet enhances the survival of the influenza model via increasing mucus production by epithelial cells in the lung. Intermittent fasting disrupts nutritional metabolism, promotes the localization of pro-inflammatory monocytes and memory T cells to the bone marrow, and thereby enhances persistence during infection. Additionally, dietary restriction of the methionine has been shown to be beneficial in a model of autoimmune disease by suppressing epigenetic remodeling and the effector functions of TH17 cells through reduced intracellular S-adenosyl-methionine (SAM) levels [119].

7.4. Cellular therapies

Cell-based therapies represent a burgeoning field in SSc research, with the potential to modulate immunometabolism and promote tissue regeneration [120]. Mesenchymal stem/stromal cells (MSCs), owing to their immunomodulatory and regenerative properties, have garnered attention as a potential therapeutic option for SSc [121]. MSCs exert their effects, in part, by modulating immunometabolism pathways within the microenvironment, thereby attenuating fibrosis and inflammation [122].

7.5. Personalized medicine approaches

As our understanding of the heterogeneity underlying SSc pathogenesis continues to evolve, personalized medicine approaches tailored to individual immunometabolism profiles may hold promise in optimizing therapeutic outcomes [123]. Biomarkers indicative of specific immunometabolism dysfunctions could guide treatment selection and monitor response to therapy, facilitating a more targeted and effective approach to SSc management [123,124].

Collectively, therapeutic interventions targeting immunometabolism represent a promising frontier in the treatment of SSc patients. By modulating metabolic pathways intertwined with immune dysregulation, these approaches hold the potential to mitigate fibrosis, inflammation, and vascular abnormalities characteristic of SSc, ultimately improving patient outcomes and quality of life. Further translational research and clinical trials are warranted to validate the efficacy and safety of these strategies in the management of SSc.

8. Concluding remarks

In conclusion, the pathogenesis of SSc is a multifaceted process involving complex interactions between immune dysregulation and metabolic dysfunction. SSc, characterized by fibrosis, vasculopathy, and immune system dysregulation, poses significant challenges due to its impact on various organs and high mortality rates, particularly among young or middle-aged females [125].

Recent research has shed light on the emerging field of immunometabolism, revealing its pivotal role in SSc. The dysregulation of metabolic pathways, including glycolysis, TCA, lipid metabolism, and amino acid metabolism, has been implicated in immune cell dysfunction and the development of fibrosis (Table 1 and Fig. 2). These metabolic alterations contribute to the pathophysiological triad of increased extracellular matrix, microvascular damage, and immune activation in SSc [110]. Specifically, glycolytic deregulation leading to aerobic glycolysis and acidosis, TCA dysfunction associated with elevated fibroblast differentiation, and altered lipid pathways affecting endothelium and the immune system are key features of SSc immunometabolism [34]. Additionally, disturbances in amino acid metabolism, such as elevated levels of homocysteine and proline, further contribute to the autoimmune and fibrotic conditions seen in SSc [75]. Oxidative stress, characterized by an imbalance in ROS production and removal, plays a crucial role in SSc pathogenesis. Elevated ROS levels contribute to pro-inflammatory and pro-fibrotic cytokine production, fibroblast activation, and collagen synthesis [126]. Targeting oxidative stress may hold therapeutic potential for mitigating tissue damage in SSc. Considering these findings, understanding the intricate interplay between immune dysfunction and metabolic perturbations provides valuable insights for potential therapeutic strategies. Targeting specific metabolic pathways, such as glycolysis or the TCA cycle, could offer new avenues for intervention [35,127]. However, further comprehensive studies are needed to unravel the exact mechanisms and interactions between these metabolic alterations and their role in SSc development and progression. Ultimately, the exploration of immunometabolism in SSc opens avenues for more tailored and effective treatments, offering hope for improved outcomes in patients with this challenging autoimmune disorder.

Ethics approval

This study was reviewed and approved by Abadan University of Medical Sciences with the approval number: IR.ABADANUMS.REC.1402.146, dated February 23, 2024.

Consent for publication

All co-authors have read and agreed with the content of the manuscript.

Table 1
Changes in metabolic pathways in SSc disease.

Metabolic pathway	Metabolic Changes	Its effects on SSc	Ref(s)
Glucose metabolism	Dysregulation of glycolysis and glycolytic enzymes like LDH	Increase in bioenergetic metabolism due to considerable energy consumption.	[1]
	Increased glycolysis in fibroblasts	Effect on fibrosis development and accumulation of lactic acid and low pH	[2,3]
	The primary metabolic pathway for lung tissue and myofibroblasts in IPF becomes glycolysis	Increased level of lactic acid	[4,5]
Amino Acid metabolism	Increased concentration of Homocysteine	Increased pulmonary complications in SSc Promotion of atherogenic process by elevating the oxidation of LDL Interfering with integrity of the vascular system and endothelial function Association with Reynold's phenomenon	[6,7]
	Upregulation of glutamine, proline, citrulline and ornithine	Impaired collagen synthesis and fibrosis of the skin and internal organs	[8]
	Elevated levels of Proline in SSc patients	Enhanced collagen formation and contribution to fibrosis Inhibition of SPA and potentially worsen SSc severity	[9–12]
	Autoantibodies against MMP-1 and MMP-3	Inhibition of the collagen destruction	[13, 14]
Lipid metabolism	Dysregulation of FAO	Dysregulation of ECM breakdown and fibrosis pathogenesis	[15]
	Decreased PPAR-γ and downregulation of CPT1 and ACOX	Fibrosis	[15]
	Altered PPAR-γ expression in normal fibroblast	TGF-β-induced collagen gene expression Blockage of myofibroblast differentiation Impaired function of normal fibroblasts	[16]
TCA cycle	Elevation in the levels of the TCA pathway products including acetate, succinic acid or fumaric acid	Inhibition of succinate dehydrogenase (SDH), reduction of the collagen in dermal fibroblasts	[17, 18]
	Elevation in the levels of succinate	Increased levels of GPCR91, α-SMA and TGF-β, inducing HIF-1a production in lung myofibroblasts and IPF by increasing the expression of TGF-1	[8,19]
Oxidative Stress	Increased ROS production	Higher rate production of type I collagen in fibroblasts, extra-cellular matrix deposition and fibrosis and promotion of vascular damage.	[20, 21]
	Higher levels of oxidative stress and elevated lipid peroxidation	Induction of cytotoxic effects on endothelial cells and connective tissue formation	[22, 23]

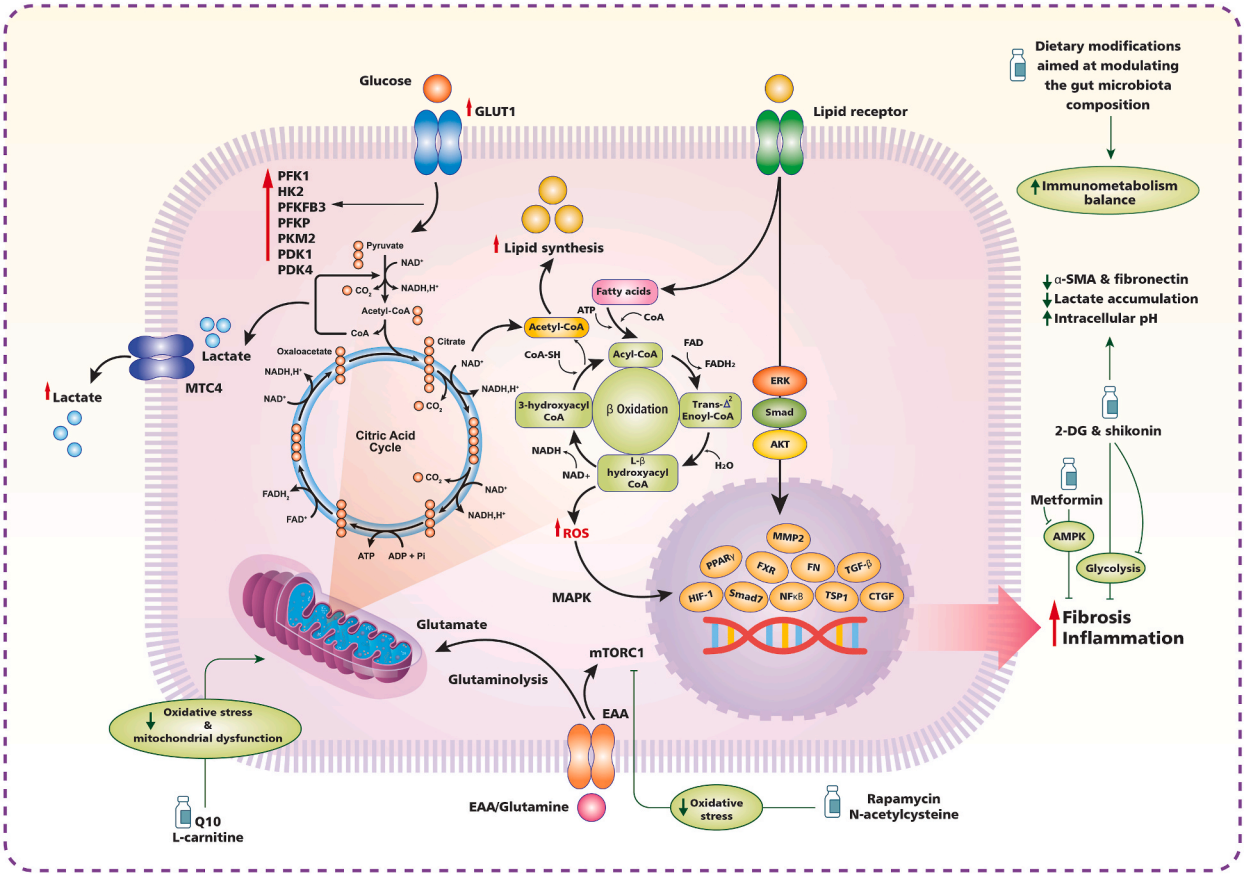

Fig. 2. Dysregulated metabolic pathways in SSc: As depicted in the figure, various metabolic pathways are dysregulated in SSc patients. Impaired metabolic pathways, including glycolysis, TCA cycle, beta-oxidation, lipid synthesis, and ROS production led to production of high levels of some intermediate molecules. Excessive amount of these molecules could affect cell fate, which is generally associated with aggressive phenotype and inflammatory state of these cells. Chronic inflammatory state due to metabolic disturbance is associated with fibrosis induction, an important clinical presentation of SSc patients. Finally, this picture depicts the dysregulated metabolic pathways that are associated with SSc pathogenesis.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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