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REVIEW
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Metabolic Syndrome and Psoriasis: Mechanisms and Future Directions

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Psoriasis is an immune-mediated systemic disease with associated comorbidities, including metabolic syndrome (MetS) which contributes substantially to premature mortality in patients with psoriasis. However, the pathological mechanisms underlying this comorbidity are unclear. Studies have shown that the pathological parameters of psoriasis mediate the development of MetS. We reviewed the potential mechanisms which mediate the association between psoriasis and MetS, including endoplasmic reticulum stress, pro-inflammatory cytokine releases, excess production of reactive oxygen species, alterations in adipocytokine levels and gut microbiota dysbiosis. Here, we highlight important research questions regarding this association and offer insights into MetS research and treatment.

Keywords: psoriasis, metabolic syndrome, gut microbiota, insulin resistance, autoimmunity, obesity

INTRODUCTION

Psoriasis, one of the most common chronic, recurrent, and inflammatory skin diseases, affects 2~3% of the total world population (1). There are several clinical cutaneous manifestations of psoriasis. The disease most commonly presents as chronic, symmetrical, erythematous, scaling papules and plaques (2). Pathologically, epidermal hyperproliferation and parakeratosis are the main histological features of psoriasis. Notably, increased release of pro-inflammatory cytokines and the chronic activation of innate and adaptive immune systems result in long-term damage to multiple tissues and organs of patients with psoriasis (3). Psoriasis is a systemic disease that is associated with multiple comorbidities, such as psoriatic arthritis, Crohn's disease, cancer, depression, cardiovascular disease (CVD) (4), and metabolic syndrome (MetS). Among these, MetS is one of the most common and important comorbidities (5–8). An increasing number of clinical studies have confirmed that psoriasis is often related with MetS, such as obesity, hypertension, diabetes mellitus, hyperlipidemia, and obesity-associated non-alcoholic fatty liver disease (NAFLD) (**Figure 1**) (9–15). Another study views that compared to patients with milder psoriasis, those

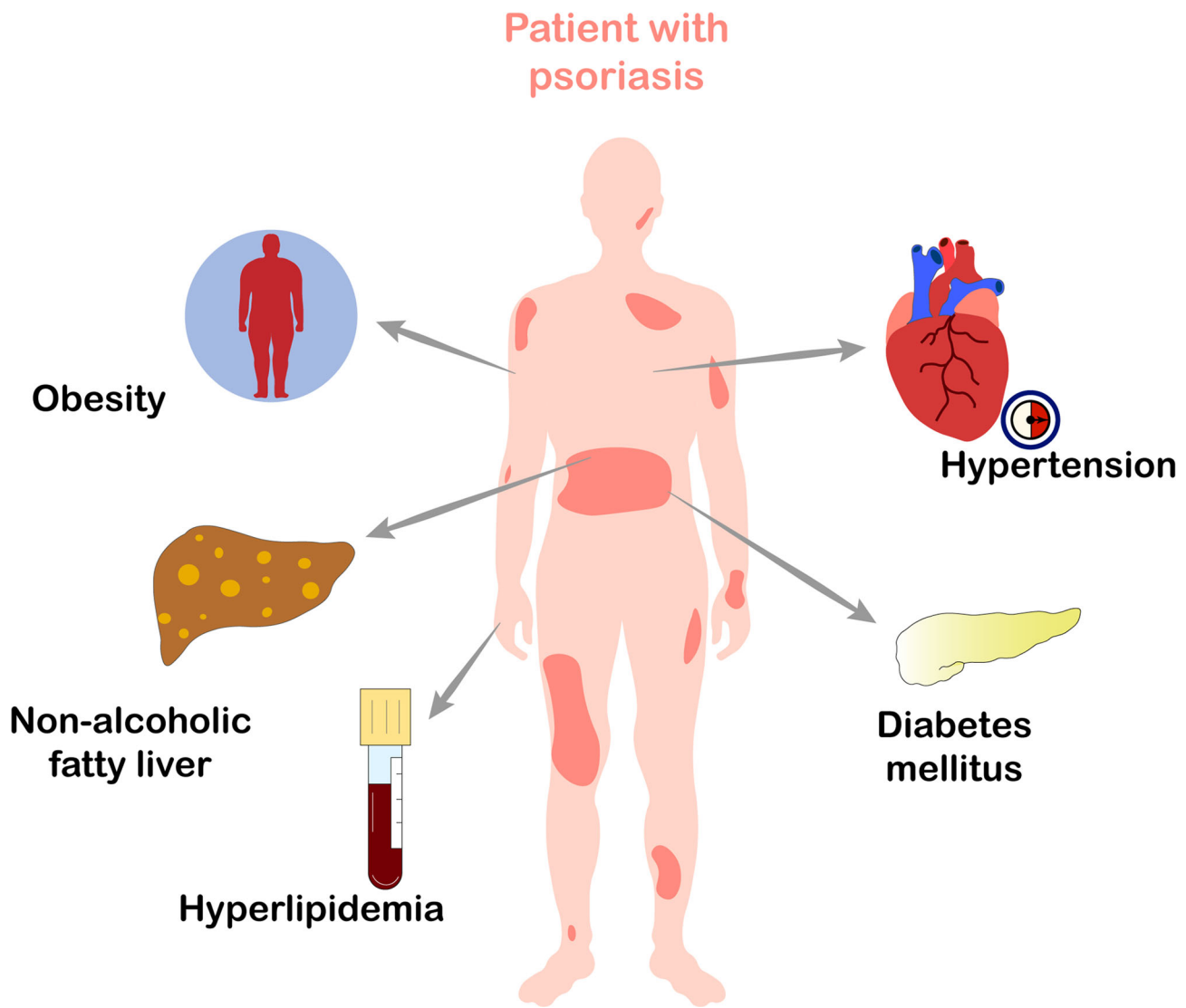

FIGURE 1 | Metabolic diseases which frequently occur in patients with psoriasis. Psoriasis is often associated with obesity, hypertension, diabetes mellitus, hyperlipidemia, and obesity-associated non-alcoholic fatty liver disease, all of which belong to metabolic syndrome.

with more severe psoriasis have greater hazard of MetS (16). MetS directly increases the risk of CVD and premature mortality in patients with psoriasis (17), thus substantially reducing their life expectancy. Therefore, it is critical to understand the exact mechanisms underlying the relationship between psoriasis and MetS.

Recently, the prevalence of MetS in patients with psoriasis has attracted the attention of researchers. The precise mechanisms underlying the association between psoriasis and MetS remain unknown. Therefore, in this review, we have discussed these mechanisms, particularly, the pathogenic factors possibly involved, including endoplasmic reticulum (ER) stress in multiple cells, pro-inflammatory cytokine profiles, excess production of reactive oxygen species (ROS), alterations in adipocytokine levels, and gut microbiota dysbiosis. This review highlights the previously established and the emerging important mechanisms that link psoriasis with MetS.

PRO-INFLAMMATORY CYTOKINES LINKING PSORIASIS AND METS

The hallmark of psoriasis is sustained inflammation (18). The pathogenesis of psoriasis has involvement of dynamic interactions between multiple cell types and cytokines (19). Th17 cells produce several cytokines, such as IL-17 (IL-17A/IL-17F), tumor necrosis factor-α (TNF-α), and IL-22 (4), which induce altered differentiation and hyperproliferation of keratinocytes. Therefore, Th17 cells play a predominant role in the pathogenesis of psoriasis and are indicators of an increased

risk of psoriasis. Moreover, pro-inflammatory cytokines are implicated in many diseases, including obesity, diabetes mellitus, hypertension, NAFLD, and hyperlipidemia (20–23). It is well-known that tissue inflammation plays a critical role in insulin resistance (IR) (24–26). IR is the key primary defect underlying the development of type 2 diabetes (T2D), and it is also a central component of MetS (27).

IL-17 plays a crucial role in inflammation, IR, and T2D, indicating that it is a potential mediator linking MetS and psoriasis (28). It promotes a vascular inflammatory response and plays a critical role in angiotensin II-induced hypertension and vascular dysfunction (29). Previous studies reported that serum IL-17 levels were significantly elevated in subjects with MetS and Type 1 diabetes compared to health group (30, 31). Secukinumab, anti-IL-17A monoclonal antibody, is an effective biological agent for the treatment of plaque psoriasis. In patients with higher response for secukinumab, mean body weight, waist circumference, and BMI consistently decreased (32). Furthermore, combined administration of anti-IL-17A monoclonal antibody (secukinumab and ixekizumab) reduced fasting glucose levels in imiquimod treated mice and improved hyperglycemia in patients with psoriasis (33), suggesting that IL-17 may be a key cytokine linking psoriasis and hyperglycemia (34).

TNF is also closely associated with the pathogenesis of psoriasis. The Food and Drug Administration has approved efficacious TNF inhibitors for the treatment of moderate and severe plaque psoriasis, including infliximab, adalimumab, and etanercept (35). Patients with psoriasis who have administration of anti-TNF drugs often show an improvement in MetS. For patients with psoriasis, it has been demonstrated that the treatment with etanercept or adalimumab improved metabolic parameters including blood lipid and glucose levels and systolic and diastolic blood pressure (36). Another study further confirmed that anti-TNF treatment improves the metabolic profile of patients with psoriasis by downregulating their total cholesterol and low-density lipoprotein (LDL) levels (37). Mechanistically, TNF-α inhibits THP-1 cell uptake of oxidized LDL, thus increasing the extracellular accumulation of oxidized LDL (38). Additionally, the treatment with adalimumab significantly improves insulin sensitivity in patients with moderate-to-severe plaque psoriasis (39). TNF-α directly contributes to IR (40, 41) by activating stress kinases, such as IκB kinase, c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase in muscle and fat cells, thereby blocking insulin signal transduction (42, 43). In some views, anti-TNF-α antibody is supposed as the first-line treatment for psoriasis with metabolic syndrome (44). In contrast, a view points out that the treatment with anti-TNF (infliximab and adalimumab) leads to no significant changes in insulin sensitivity or fasting glucose levels, but increased body fat (45). This may be due to the limited studied population, and only men were included.

Moreover, serum IL-1β, IL-6, and IL-22 levels were significantly upregulated in patients with T2D (46) and obese individuals (47, 48). Notably, deletion of IFN-γ improves IR and metabolic parameters in diet-induced obesity models (49). The above-mentioned studies have demonstrated that the immune system is closely linked to metabolic disorders. Pro-inflammatory cytokines may link psoriasis with MetS (**Figure 2**).

ADIPOCYTOKINES LINKING PSORIASIS AND METS

Adipose tissues secrete adipocytokines that modulate organ functions and lipid metabolism. Leptin and adiponectin, two classical adipokines, are well-established endocrine hormones that act on specific receptors of remote target organs (50). Adiponectin is an insulin sensitizer that ameliorates IR and regulates glucose and lipid metabolism by binding to its receptors, AdipoR1 and AdipoR2 (51). This might be due to reduction in ectopic lipids in the liver and muscle (52). Adiponectin induces an increase in serum high-density lipoprotein (HDL) and down-regulates serum triglycerides through enhanced catabolism of triglyceride-rich lipoproteins (53). Adiponectin ameliorates obesity-induced NAFLD by interacting with hepatic peroxisome proliferator-activated receptors (54).

Several studies have demonstrated that low adiponectin concentrations in patients with psoriasis may contribute to the development of MetS. Of note, the serum adiponectin level is negatively associated with the TNF-α and IL-6 levels (55). TNF-α can impair adiponectin multimerization, consequently decreasing adiponectin secretion (56, 57). This might be a reasonable explanation for the lower adiponectin concentrations in patients with psoriasis compared to those of controls. Moreover, multiple studies postulate that adiponectin links the pathological processes of psoriasis and obesity (58). A meta-analysis has shown that patients with psoriasis exhibit low levels of adiponectin (59). Compared to patients with psoriasis without metabolic abnormalities, patients with psoriasis and MetS or high body mass index have significantly lower adiponectin levels. The psoriasis area and severity index (PASI) score (60) are negatively correlated with adiponectin levels (61, 62). Overall, low serum adiponectin levels in patients with psoriasis may be the link to MetS.

Leptin is a critical hormonal regulator of metabolism, and leptin concentrations are directly associated with the subsequent development of metabolic disorders such as IR, T2D, and CVD (63, 64). The reduction of plasma leptin levels in obese individuals can restore hypothalamic leptin sensitivity, then effectively enhancing insulin sensitivity, reduces weight gain (65). Increased leptin levels are observed in obese people and in patients with psoriasis (66), and are positively correlated with severity of psoriasis (67). The systemic anti-inflammatory drug, acitretin, used to treat psoriasis, reduces leptin levels (68). In addition, leptin is an important signaling transducer which may link obesity and psoriasis (69). One study reported that leptin levels were higher in obese patients with psoriasis than those of normal-weight patients (70). Moreover, leptin level is affected by IL-17 (71), which might explain the higher leptin concentrations observed in patients with psoriasis than controls. These studies

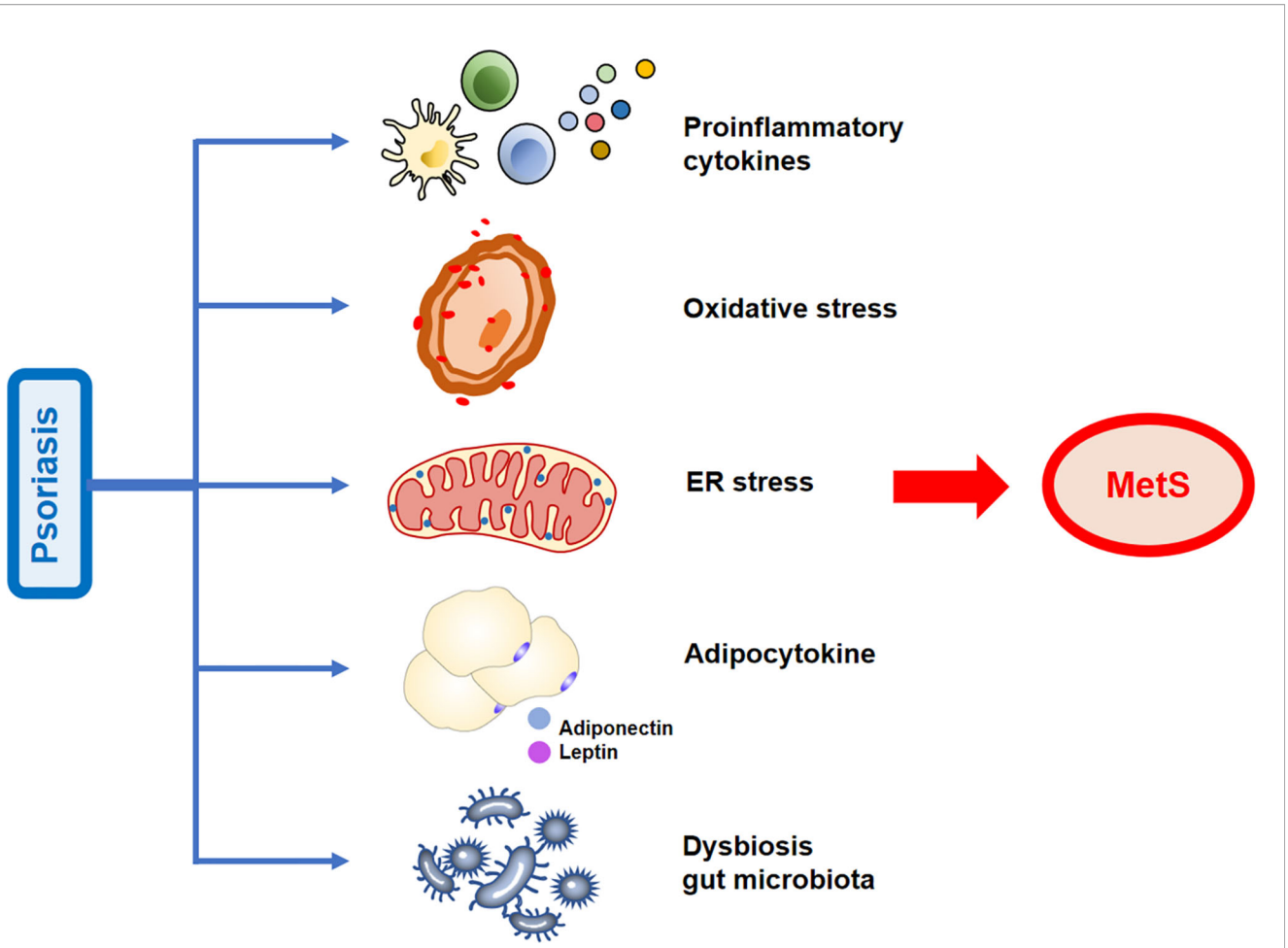

FIGURE 2 | Possible mechanisms linking psoriasis and metabolic syndrome (MetS). The increased release of pro-inflammatory cytokines, adipose tissue secretory adipocytokines, activation of oxidative stress states, increased endoplasmic reticulum (ER) stress, and gut microbiota dysbiosis observed in psoriasis contribute to the development of MetS.

suggest that high leptin levels may be an important factor in psoriasis-associated metabolic diseases.

Moreover, recent studies have hypothesized that several other important adipokines, such as retinol-binding protein 4, fetuin-A, and lipocalin-2 are mediators of obesity in psoriasis (58). Adipokines could serve as a crucial link in the causal relationship between psoriasis and MetS (**Figure 2**) and may serve as biomarkers for determining the risk of developing psoriasis comorbidities.

OXIDATIVE STRESS STATUS IN PATIENTS WITH PSORIASIS AND THE ASSOCIATION WITH METS

Oxidative stress is the dysregulation between the production of ROS and endogenous antioxidant defense mechanisms, which causes protein and lipid peroxidation, DNA damage, and cellular dysfunction, eventually leading to cell death (72). Increased oxidative stress in adipocytes is one of pathological mechanisms of obesity-associated metabolic diseases (73, 74). Thus, reducing ROS production can increase insulin sensitivity and alleviate hyperlipidemia, hepatic steatosis, and IR (75, 76). Additionally, a positive correlation has been established between oxidative stress and low HDL levels (77). Furthermore, LDL-related dyslipidemia and impaired fasting glucose are associated with increased oxidative stress (78). Quantitative combination of natural antioxidants (vitamins C and E) prevents MetS by reducing oxidative stress (79). These results indicate that a pro-oxidant/antioxidant imbalance plays an important role in MetS development (80).

Numerous evidences support that increased ROS production and oxidative stress status are implicated in the progression of psoriasis. Studies have revealed that in the serum/plasma and blood cells of patients with psoriasis, oxidative damage markers increased (81–87). In addition, oxidative stress markers and PASI score have a positive correlation (88). The salivary total oxidative status and oxidative stress index may serve as potential diagnostic biomarkers for plaque psoriasis (89). Of note, the activated neutrophils/monocytes that generate oxidative damage

may be the main source of oxidative stress in psoriasis. Increased oxidative stress in psoriasis may be caused by an insufficient antioxidant system (90). These evidences suggest that oxidative stress may contribute to the development of MetS in patients with psoriasis (**Figure 2**).

ENDOPLASMIC RETICULUM STRESS LINKS PSORIASIS WITH METS

ER is an important organelle with a vast membranous network in eukaryotic cells (91, 92). The ER has many cellular functions, including protein synthesis, folding, and transport, lipid and steroid synthesis, carbohydrate metabolism and calcium storage (93–96). The altered functions of ER can result in the accumulation of unfolded or misfolded proteins, which is a cellular condition named ER stress (97). Prolonged ER stress is a critical factor in the pathogenesis of MetS (98, 99). Inositol-requiring enzyme 1, an ER stress sensor, induces malfunction in both brown and beige fat, eventually leading to obesity (100). Treatment with the ER stress inhibitor (tauroursodeoxycholate) can improve metabolic parameters in MetS rat and mitigate the MetS-induced cardiovascular complications (101). Reducing ER stress can alleviate IR (102–105). Specifically, the interfered transport of newly synthesized insulin proreceptors from ER to the plasma membrane can inhibit the proteolytic maturation of insulin proreceptors. Consequently, the insulin signaling was broken by consuming the insulin receptors on cell surface (106).

Studies have shown that pro-inflammatory mediators such as TNF-α, IL-1β, IL-17A, and IFN-γ contribute to the induction of ER stress in multiple immunocytes such as macrophages and T cells (107–110). ER stress can be found in patients with psoriasis. Moreover, the over-expressed ER stress-associated proteins, including binding immunoglobulin heavy-chain protein, C/EBP homologous protein, and X-box binding protein 1 in the epidermis of patients with psoriasis vulgaris suggests that ER stress is increased in the keratinocytes of these patients (111). One study reported increased expression of ER stress marker GRP78/BIP in the subcutaneous fat tissues of imiquimod-induced psoriasiform in diabetic obese mice (112). Above evidences show increased ER stress is involved in psoriasis.

Overall, due to the common emergence of ER stress in both MetS and psoriasis, we may speculate that ER stress mediates their frequent co-occurrence (**Figure 2**). However, there is less evidence on ER stress in the association between MetS and psoriasis. The ER stress in psoriasis that promotes MetS is expected to elucidate in further research.

GUT MICROBIOTA IN PATIENTS WITH PSORIASIS AND ITS ASSOCIATION WITH METS

In the bodies of adult mammals, skin, oral mucosa and gastrointestinal tract are heavily colonized by microbiota, with the largest population found in the colon. Microorganisms have variable relationships with their hosts and exist as mutualists, symbionts, or pathobionts (113). The gut microbiome plays important roles in host immunity, metabolism, and the production of numerous compounds that influence the host (114, 115). There is an emerging interest in metabolic health and gut microbiome dysbiosis. After the transplantation of metformin-treated human microbiome into germ-free mice with glucose intolerance, the glucose defects were corrected (116). Moreover, gut microbiota specifically controlled the expression of microRNAs in white adipocytes, controlling adiposity and insulin sensitivity in mice (117). Overall, these studies suggest that the gut microbiota regulates host metabolism and obesity.

Numerous studies have demonstrated the role of *Akkermansia muciniphila* in preventing obesity-associated metabolic disorders in both humans and animal models (118–121). Importantly, the intestinal microbes of patients with psoriasis show significant differences from those of healthy subjects (122–124). Notably, a previous study found that the abundance of *A. muciniphila* was significantly decreased in patients with psoriasis (125). Overall, compared with healthy controls, patients with psoriasis have a different specific intestinal microbiome. Therefore, we hypothesize that MetS in patients with psoriasis may be related to changes in the richness of specific flora (**Figure 2**).

The intestinal microbiota plays critical roles in preserving epithelial barrier integrity, forming a mucosal immune system to battle with exogenous pathogens (126, 127). There are differences in intestinal permeability between individuals with and without T2D (128, 129). The disruption of barrier integrity is closely related with the emergence of metabolic disorder, such as obesity and T2D (127–130). Alleviated metabolic endotoxemia and enhanced intestinal barrier function causes significant weight loss and improves IR in diet-induced obese mice (131). The loss of intestinal barrier can cause the bacteria translocation and produce endotoxins or harmful metabolites, then induce systemic inflammation and aggravate MetS (132). For instance, elevated bacterial lipopolysaccharides in the circulation and organs activate the transcription of cytokines *via* toll-like receptor 4, promoting IR and metabolic diseases (133). Thus, the injured mucosal barrier induced by the gut microbiota involves in the development of MetS.

It has been found that barrier integrity injury and bacterial translocation are involved in the development of psoriasis (134). Bacterial DNA was detected in the peripheral blood of patients with psoriasis (135). In patients with moderate-to-severe psoriasis, serum markers of intestinal barrier integrity injury increased (136). For example, intestinal fatty acid binding protein, a biomarker of intestinal barrier damage, significantly elevated in patients with psoriasis compared to that in controls (137). From these studies, bacterial translocation may occur in psoriasis (138). Therefore, intestinal barrier impairment and bacterial translocation caused by dysbiosis of the gut microbiota may explain pathologically metabolic diseases in patients with psoriasis. Dysregulated gut microbiota in patients with psoriasis may be a novel therapeutic target in MetS.

PERSPECTIVE

Accumulating evidence suggests there is a relationship between psoriasis and increased risks of MetS. However, major gaps in understanding of MetS in patients with psoriasis remain. In this review, we summarized numerous studies that links psoriasis and MetS. We assume that the emergence of some factors, including ER stress, pro-inflammatory cytokine releases, excess production of ROS, alterations in adipocytokine levels and gut microbiota dysbiosis, may be predictors of MetS in patients with psoriasis.

Specifically, it seems that the pathogenic pathways in psoriasis and MetS have considerable overlap. Thus, there is a possible interaction between the psoriasis and MetS. Psoriasis and MetS both show the chronic inflammatory state (139). Notably, some inflammatory factors, such as IL-17 and TNF, can both mediate the occurrence of psoriasis and MetS. Besides, adipocytokine, a vital meditator of MetS, can regulate body metabolism meanwhile contribute to the development of a pro-inflammatory state. Subsequent studies should focus on the causal relationship between the common pathogenic factors and psoriasis with MetS. Furthermore, the role of Th17-derived cytokines in the pathogenesis of psoriasis and MetS is both increasingly recognized. Anti-IL-17 agents or TNF inhibitors improved the metabolic disorder when treat psoriasis. Thus, further long-term and large-scale studies are warranted to identify whether anti-IL-17 agents or TNF inhibitors have benefits on psoriasis with MetS. Despite the pathological mechanism of MetS remains incompletely understood, oxidative stress and ER stress are considered as leading causes and can be therapeutically targeted (140, 141). In order to underly the pathophysiological mechanisms psoriasis and MetS, more connections from the complex molecular regulatory network should be established through muti-omics analysis. Future investigations should aim to determine the elaborate upstream and downstream signaling pathways that activate ER stress and oxidative stress in psoriasis complicated with MetS. What's more, the dysregulated gut microbiota may become a novel therapeutic target in patients with psoriasis. The oral supplementation with *A. muciniphila* should be applied to investigate the effects on metabolic abnormalities in patients and or animal models with psoriasis. In addition, other possible targeted microbiotas should be screened in psoriasis and MetS through genomics and metabolomics. These selected microbiotas could be used as a biological marker for monitoring the MetS in psoriasis.

Collectively, our review implies that administration of MetS is of importance in clinical management of patients with psoriasis in the future. Elucidating the mechanisms linking MetS and psoriasis could provide potential new therapeutic targets and specific strategies to combat MetS in psoriasis, even other autoimmune disease, such as systemic lupus erythematosus and psoriatic arthritis.

AUTHOR CONTRIBUTIONS

YH collected and reviewed the literature and wrote the manuscript. SZ and Y-jZ wrote and revised the manuscript. PZ rechecked the manuscript and put forward meaningful comments on it. Q-xZ and Y-wH assisted in drawing. Y-wH, L-nG and H-zZ revised the manuscript. ZW and JL designed the main study and reviewedthis manuscript. All authors have read and approved the final submitted manuscript.

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