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Immunogenomic Exploration of Cutaneous Manifestations and Therapeutic Targets in Systemic Sclerosis

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Abstract

This analysis of current literature explores specific immunogenomic signatures underlying cutaneous manifestations in systemic sclerosis (SSc), a complex autoimmune disorder characterized by fibrosis, vasculopathy, and immune dysregulation. By employing integrated transcriptomic and epigenomic analyses of skin biopsies obtained from SSc patients presenting varying degrees of cutaneous involvement, researchers aim to discern dysregulated immune pathways, gene expression signatures, and epigenetic modifications correlated with disease progression and severity. Additionally, investigating the therapeutic potential of immune-modulating agents, including JAK inhibitors and immune checkpoint inhibitors, in mitigating skin fibrosis and inflammation in SSc may unlock novel avenues for personalized treatment strategies tailored to the immunogenomic profile of individual patients. Future research should focus on validating identified biomarkers, exploring the mechanistic basis of immunogenomic alterations, and translating these findings into clinical practice to optimize therapeutic outcomes and enhance the management of cutaneous manifestations in SSc.

Keywords: Systemic Sclerosis; Immunogenomics; Epigenetics; Immunotherapy; JAK Inhibitors; Scleroderma

Abbreviations: SSc: Systemic Sclerosis; lcSSc: Limited Systemic Sclerosis; dsSSc: Diffuse Systemic Sclerosis.

Introduction

Systemic sclerosis (SSc) is an immune dysfunction characterized by vasculopathy and fibrosis of the skin and visceral organs [1]. A rare disorder, SSc expresses the highest mortality rate when compared to other rheumatic diseases due to its potential for severe internal organ involvement [2,3]. Two major forms of SSc have been identified: limited systemic sclerosis (lcSSc) and diffuse systemic sclerosis (dsSSc). Patients presenting with fibrotic skin involvement confined to the proximal limbs, such as on the face and fingers, are classified as lcSSc and typically experience late visceral involvement. Those with widespread skin involvement

are classified as dsSSc and usually present with early visceral involvement [4]. Other common cutaneous clinical features include Raynaud's phenomenon, sclerodactyly, and telangiectasias [5]. Cutaneous manifestations in SSc serve as an important diagnostic tool for disease classification and progression, as only two percent of patients diagnosed with SSc lack signs of skin fibrosis [6].

The pathogenesis of SSc is not well understood, however, there have been many immune cells identified in the disease. Current literature suggests immune abnormalities contribute to fibrosis and vasculopathy displayed in SSc, implicating cytokines, T cells, B cells, and macrophages, among others [7]. Nonimmune cell fibroblasts have also been implicated in the disease, suggesting that exposure to cytokines drastically increases profibrotic mediators by as much as 100-fold [7]. Disease progression of SSc can impact visceral organ function, attributing to the high mortality rate. Organ involvement of the lungs is the most prominent risk factor for death, but can also include renal, GI, and cardiovascular systems [8]. Research indicates that the progression of SSc tends to manifest earlier in the disease [9]. Due to the rapid and severe progression of SSc, it is imperative to understand cutaneous manifestations and novel potential therapeutic options for SSc.

The purpose of this review is to investigate specific immunogenomic signatures of SSc contributing to cutaneous manifestations. Through a thorough analysis of current literature, we explore the therapeutic potential of immune-modulating agents in the management of SSc as well as the benefit of personalized treatment.

Materials and Methods

A literature search was conducted using several databases, including PubMed, Embase, and Web of Science. The search terms employed were combinations of "systemic sclerosis" AND "immunogenomics," "epigenetics," "JAK inhibitors," "immune checkpoint inhibitors," "immunotherapy," OR "biomarkers." These terms were tailored to each database to optimize the retrieval of relevant studies. Data from the selected studies were qualitatively synthesized, emphasizing the identification dysregulated immune pathways, the efficacy of targeted treatments, and their clinical outcomes.

Results and Discussion

Overview of Skin Involvement in SSc

Systemic sclerosis commonly presents with skin changes as its initial symptom. Cutaneous manifestations of SSc usually include fibrosis, telangiectasias, tendon friction rubs, pigment changes, nail fold capillary changes, fingertip lesions, and calcinosis cutis [2,10]. Early indications of SSc may include a combination of Raynaud's phenomenon, a sclerodermic pattern on nail bed capillaroscopy, and puffy hands and fingers [2,10]. Skin fibrosis begins at the distal extremities and progresses proximally and can impact patient mobility over time [2]. As the disease progresses, patients may acquire digital ulcerations and severe pruritus [11]. As noted, there are two prominent subtypes of SSc: dcSSc and lcSSc. Patients with dcSSc often experience their first non-Raynaud SSc symptoms within one to two years of Raynaud's phenomenon onset while patients with lcSSc often experience other symptoms within five to ten years [2]. In dcSSc, skin thickening is noted in the distal and proximal extremities up to the knees and elbows, face, and trunk thus, tendon friction rubs are more likely to be noted in these patients. Additionally, in dcSSc, there is a rapid increase in fibrosis followed by a stabilization phase and fibrosis may subsequently diminish.

Fibrosis in lcSSc is noted in the distal limbs and face, and sclerodactyly, telangiectasias, and calcinosis cutis are more common [12]. It is important to note that a lesser common subtype of SSc, systemic sclerosis sine scleroderma, lacks clear skin manifestations of the disease, which can lead to challenges in diagnosis [13]. Provided these patterns, it is important to recognize that there is a great variety of skin manifestations in SSc from patient to patient. Progression in fibrotic skin changes is determined by clinicians utilizing the modified Rodnan skin score (mRSS) in which the thickness of the skin is measured and scored at 17 different sites [14]. The distribution and progression of skin manifestations in SSc often mirror the disease involvement of visceral organs [12].

Mechanisms of Cutaneous Fibrosis and Inflammation

The pathogenesis of SSc is defined by cutaneous fibrosis preceded by endothelial damage and extensive inflammatory infiltrate. In 95% of SSc patients, symptomatic presentation often begins with Raynaud's phenomenon, repetitive vasospasms damaging the endothelium which lead to vascular leakage and edema [15]. This damage leads to the expression of adhesion molecules, endothelin-1, platelet activation, and chemokine production leading to macrophage recruitment. Damage-associated molecular patterns (DAMPs) are also present following endothelial injury and activate immune cells [7,16]. T cells differentiate into Th2 cells which release interleukin (IL)-6, IL-4, and IL-13. IL-4 subsequently activates B cells, which are responsible for the production of autoantibodies. Additionally, fibroblasts are activated by inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, IL-13, and IL-6 [16]. The activated fibroblasts in SSc possess the

characteristics of myofibroblasts which are usually involved in scar formation. It is thought that these fibroblasts remain active and constantly remodel and deposit extracellular membrane (ECM) proteins.

This process replaces normal ECM with a dense ECM that contains more type I, III, V, and VI collagen, fibronectin, and proteoglycans [11]. Myofibroblasts are uncommon in normal tissue but are abundant in SSc due to a decrease in apoptosis [17]. Irreversible fibrotic changes to tissues in SSc are due to chronic fibroblast activation, increased ECM deposition, and impaired degradation [18]. This change in structural content lends to the rigid nature of the tissue. Fibroblasts respond to their environment using mechanotransduction, and the dense collagenous tissue instigates fibroblast activity leading to further fibrosis [12]. The resultant tissue continues to activate myofibroblasts, leading to further thickening and dysregulation of the ECM [11]. Histologically, it has been found that with fibrosis progression, dermal structures are lost. Dense collagen is deposited in the dermis and the subcutaneous adipose tissue is obliterated.

Immune Dysregulation and its Contribution to Cutaneous Manifestations: SSc disease progression leads to dysregulation in both the innate and adaptive immune systems. Distinct serum autoantibodies, inflammatory cells in the skin, and increased circulating immune cells demonstrate the immune disorder experienced in SSc [12]. It has been found that patients with SSc have an elevated serum level of profibrotic IL-4, IL-13, and TGF-β, indicating stimulation of fibrosis formation. Ultimately, there is an abundance of proinflammatory and fibrogenic cytokines leading to uncontrolled fibrotic deposition. Moreover, anti-nuclear antibodies have been detected in over 90% of patients with SSc, which may be attributed to the auto-antibodies and cytokines released by B cells that result in further tissue damage and fibrosis [11,19,20]. In dcSSc, autoantibodies targeting DNA topoisomerase I, RNA polymerase III, and Fibrillarin have been identified. In lcSSC, autoantibodies targeting centromere protein and Th/To ribonucleoprotein have been noted [12]. Research by Skaug et al. indicated that skin samples from patients with early diffuse SSc had increased innate and adaptive immune cell signatures when compared with health control subjects [21]. In addition, when follow-up biopsies were performed, a decline in the presence of immune cells was noted, reflecting the idea that the initial course of dcSSc is inflammatory and is followed by a fibrotic stage defined by increased ECM deposition.

Current Understanding of Immunogenomic Signatures in SSc

The current understanding of immunogenomic signatures in SSC is ever-evolving. In recent years, there has been a considerable amount of literature distinguishing immunogenomic signatures in SSc. This may be attributed to the variety of cell types in the immune system that have been indicated in the pathogenesis of SSc. These cell types include T cells, B cells, dendritic cells, mast cells, and macrophages. Certain fibrogenic cytokines are repeatedly mentioned in the literature, including TGF-β, IL-6, and IL-4 [7]. Furthermore, many pertinent auto-antibodies have been identified and correlated with SSc manifestations. These auto-antibodies can be utilized to both diagnose SSc as well as provide patients with potential prognostic outcomes [2]. As the pathology is often defined by a triad of vascular damage, immune cell activity, and fibrosis, it is crucial to determine how to intervene in this disease process [7]. There are a variety of studies that aim to isolate specific immunogenomic features of SSc with the common goal of uncovering a potential treatment target. The available medical literature indicates numerous potential key players in the development of SSc, however, the heterogeneous nature of SSc leads to a wide array of immunogenomic findings that vary from patient to patient [12]. Ultimately, these findings indicate the necessity for targeted treatments tailored to the immunogenomic abnormalities of the individual patient.

Methodologies for Transcriptomic and Epigenomic Studies

Integrated transcriptomic and epigenomic analyses are crucial for understanding the molecular complexities of SSc and informing targeted treatments. Transcriptomic studies, using RNA sequencing, help in mapping the entire gene expression landscape, and identifying various RNA species including mRNA, non-coding RNA, and microRNA. Research has revealed gene expression changes that contribute to SSc's pathogenesis. Epigenomic analyses, including DNA methylation profiling and ChIP-seq, provide insights into the heritable changes affecting gene expression without altering the DNA sequence itself. These studies have pointed to the significant role of epigenetic modifications in genes associated with the pathogenesis of SSc, suggesting that these modifications are pivotal to disease development and clinical manifestations [22].

Selection Criteria for Skin Biopsies in SSc Patients

In addition, the selection of skin biopsies in SSc research is meticulously performed based on specific criteria to ensure the accuracy of transcriptomic and epigenomic analyses. These criteria include disease severity, stage, and the specific skin regions affected by fibrosis. Such careful selection enables researchers to discern the molecular changes characteristic of SSc at various stages, thereby providing a comprehensive

understanding of the disease's progression. The comparative analysis of affected and unaffected skin areas in SSc patients aids in distinguishing disease-specific molecular alterations, further illuminating the pathogenetic mechanisms at play [23]. However, due to the substantial variation in disease presentation, further research is warranted to identify best practices in assessing selection criteria as they relate to skin biopsies in patients with SSc.

Dysregulated Immune Pathways, Gene Expression Signatures and Epigenetic Modifications

Moreover, through the integration of transcriptomic and epigenomic data, researchers have identified numerous dysregulated immune pathways in SSc, establishing a link between genetic and environmental factors in the disease's pathogenesis. These studies have uncovered the intricate network of immune responses, including cytokine signaling, T-cell activation, and B-cell regulation, elucidating the molecular basis of the inflammatory and fibrotic processes in SSc. Identifying these pathways not only advances our understanding of the disease's molecular mechanisms but also opens new avenues for targeted therapeutic interventions [24]. In addition to identifying dysregulated immune pathways, the detailed analysis of gene expression signatures and epigenetic modifications in SSc has shed light on the numerous regulatory mechanisms driving the disease. By examining the changes in gene expression and the epigenetic landscape, researchers have been able to identify key factors contributing to fibrosis and immune dysregulation in SSc. These findings emphasize the central role of epigenetic regulation in the pathogenesis of SSc, highlighting its potential as a target for novel therapeutic strategies. Understanding these molecular mechanisms is crucial for developing effective treatments for SSc, as it provides insights into the disease's complex biological mechanisms [25].

Therapeutic Strategies Targeting Cutaneous Manifestations

Overview of Immune-Modulating Agents: Unfortunately, despite the high morbidity and mortality associated with patients with SSc, there are no specific and effective treatments currently available to modify the disease process [26,27]. Nevertheless, the introduction of immune-modulating agents has significantly transformed the treatment landscape for autoimmune disorders such as SSc, providing degrees of targeted approaches to mitigate disease manifestations. These agents comprise a diverse range of pharmacological interventions intended to modulate the aberrant immune response that underlies SSc pathology. Notably, Janus kinase (JAK) inhibitors and immune checkpoint inhibitors are prominent classes within the spectrum of immune-modulating agents, paving the way for personalized therapy in SSc. These agents exert their effects through multifaceted mechanisms, aiming to suppress immune dysregulation, mitigate inflammation, and potentially impede disease progression. By modulating various aspects of the immune system, such as cytokine production, T-cell activation, and immune cell trafficking, immune modulators coordinate a concerted response aimed at restoring immune homeostasis. Through their diverse mechanisms of action, immune-modulating agents aim to attenuate the autoimmune-driven processes contributing to tissue fibrosis, vascular dysfunction, and inflammation, all hallmarks of SSc pathology.

JAK Inhibitors: Mechanisms and Evidence in SSc Treatment: The mechanism behind JAK inhibitors is thoroughly documented in the literature. JAK inhibitors are a class of medications targeting the Janus kinase family of enzymes (JAK1, JAK2, JAK3, and TYK2), which play a crucial role in the signaling pathways of various cytokines and growth factors involved in immune responses and inflammation. Specifically, JAK inhibitors interfere with the JAK-STAT (signal transducer and activator of transcription) signaling pathway. This pathway is activated when cytokines bind to cell surface receptors, triggering JAK enzymes to phosphorylate and activate STAT proteins. These activated STAT proteins regulate gene transcription, influencing immune responses. Therefore, JAK inhibitors prevent this phosphorylation of STAT proteins, prevent gene transcription, and lead to reduced production of pro-inflammatory cytokines, namely interferons (IFN) and interleukins, and dampened immune responses [28]. Dysregulation of this pathway is associated with various immune disorders including rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and SSc. Given the increased activation of the JAK-STAT pathway in the skin of patients with SSc, medications inhibiting this pathway represent potential candidates for alleviating inflammation and autoimmune-driven tissue damage observed in SSc [29].

In contrast to first-generation non-selective JAK inhibitors such as tofacitinib, baricitinib, ruxolitinib, and peficitinib, second-generation JAK inhibitors are selective and target specific JAK molecules. For example, ilgotinib and upadacitinib selectively block JAK1 while decernotinib blocks only JAK3, leaving the other pathways and their associated cytokines unaffected [28]. It has been demonstrated that JAK-2 is activated by TGF-B in SSc [30]. Given the involvement of the JAK-STAT pathway in SSc pathogenesis, targeting this pathway with JAK inhibitors represents a promising therapeutic approach to mitigate inflammation and fibrosis in these patients [31].

Immune Checkpoint Inhibitors: Potential Therapeutic Targets: Immune checkpoint inhibitors offer another

potential therapeutic target. Immune checkpoint inhibitors are monoclonal antibodies commonly used for the treatment of various malignancies. These work to block immunoregulatory proteins and may modulate the dysregulated immune response seen in SSc. The most common targets of immune checkpoint inhibitors are cytotoxic T lymphocytes-associated antigen 4 (CTLA-4) and the programmed death 1 receptor (PD-1). The medications in these classes include ipilimumab and tremelimumab targeting CTLA-4 and nivolumab, pembrolizumab, cemiplimab targeting PD-1, however, the field of immune checkpoint inhibitors is rapidly evolving [32].

A notable example is abatacept, a recombinant CTLA-4-Ig fusion protein that works to cause T cell inactivation by blocking CD28. While some studies have shown decreases in thickened skin measured by the mRSS, others have failed to show significant differences in skin thickness [33,34]. However, improvements in disability and quality of life were significant in these patients. Notably, the improvements found in skin thickness scores were associated with decreased expression of CTLA-4. These results suggest that more studies are necessary to evaluate the anti-fibrotic effects of these medications.

Another target of immune checkpoint inhibitors is PD-1 and its ligands PD-L1 and PD-L2, which are strongly expressed by activated T and B cells in autoimmunity and inflammation [35,36]. Increased concentrations of PD-1 and the soluble form of PD-L2 have been found in patients with SSc compared to controls, with higher concentrations observed in dsSSc compared to lcSsc [32,35]. Elevated levels of PD-1 and PD-L were also seen in mice with topo-isomerase-induced SSc, and when these mice were treated with PD-1-Fc or PD-L2-Fc (functioning as a checkpoint inhibitor), they experienced a reduction in skin fibrosis and decreased collagen deposition [35]. Additionally, there was a decrease in the infiltration of inflammatory cells into the skin. These results suggest a role for the PD-1 pathway in disease pathogenesis in SSc. Therefore, immune checkpoint inhibitors targeting this pathway represent a therapeutic approach to modulate immune dysregulation and mitigate tissue fibrosis in SSc. However, emerging evidence has described new-onset or exacerbation of autoimmune conditions, including SSc, following treatment with immune checkpoint inhibitors [32,37]. These conflicting findings suggest that further research is warranted to elucidate the role of immune checkpoint pathways in SSc pathogenesis.

Clinical Trials Investigating Immune-Modulating Agents in SSc

While JAK inhibitors have been developed and are utilized in the treatment of various autoimmune diseases, ongoing clinical trials are exploring their efficacy in SSc. Preliminary evidence suggests promising benefits in reducing skin fibrosis and inflammation for SSc patients. A systematic review of SSc patients treated with JAK inhibitors found that 90% of patients experienced a decrease in the mRSS of fibrosis [31]. Moreover, preclinical studies have demonstrated the efficacy of JAK inhibitors in inhibiting the fibrotic pathway in SSc by blocking the TGF-B-mediated pathway of STAT protein activation [30,38]. Additionally, Dees et al. found that TG101209, a selective JAK2 inhibitor, reduced skin fibrosis in mouse models [30].

Recent evidence has demonstrated that the non-selective JAK inhibitor, tofacitinib, inhibits the activation of several cytokines, including interferon, IL-2, IL-4, IL-6, and several growth factors such as epidermal growth factor, platelet-derived growth factor, and granulocyte colony growth factor [28,39]. In vitro studies have found that targeting the JAK-STAT signaling pathway with tofacitinib inhibited fibrotic responses in fibroblasts and prevented organ fibrosis [29]. Tofacitinib has also demonstrated therapeutic effects in SSc patients with polyarthropathy; a phase II clinical trial of tofacitinib in patients with diffuse cutaneous SSC is still in progress, although clinical observations have shown substantial effects on improving skin sclerosis with this treatment [28,40].

Moreover, a study examining the use of tofacitinib in nine SSc patients with interstitial lung disease found rapid decreases in thickened skin measured by the mRSS of sclerosis [38]. Some studies have even shown that tofacitinib may be more effective in reducing fibrosis when compared to conventional immunosuppression like methotrexate [41]. Despite these promising results, the safety of medications like tofacitinib must be carefully considered, especially considering the small number of patients in the tofacitinib-treated group. With the risk of thromboembolism, opportunistic infections, and hyperlipidemia, further studies are needed to verify these findings. Evaluating the overall risk-benefit ratio in diverse patient populations and the monitoring of any emergent adverse events are essential steps in ensuring the safe and effective use of tofacitinib and other medications.

Although recent literature suggests that the oral JAK inhibitor, tofacitinib, could potentially expedite the remission of inflammation and significantly improve sclerosis among SSc patients, further investigations are needed to validate these findings and determine the precise efficacy of tofacitinib in this context. Currently, a phase I/II placebo-controlled trial is evaluating the safety and tolerability of tofacitinib in diffuse cutaneous SSc [34]. Despite the complexities in SSc research, there is optimism for the future. While a definitive correlation has yet to be established, insights from recent literature and clinical trials offer compelling evidence

regarding the potential advantages of JAK inhibitors in SSc treatment, instilling hope for their therapeutic role in managing this condition.

Future Research

Early diagnosis and intervention in patients with SSc is crucial in preventing severe disease progression. While there are novel biomarkers and treatments on the horizon, they are a long way from being applied in the clinical setting. Given that identified biomarkers can predict disease progression, further studies are necessary to validate these biomarkers and to develop targeted treatments based on them. Early intervention and a comprehensive understanding of potential disease courses enable clinicians and patients to collaboratively manage symptoms and implement preventative strategies. Additionally, extensive large-scale studies are crucial to fully understand the implications of the immunogenomic alterations identified so far.

Recent studies have revealed elevated immune and genetic factors in patients with SSc. This underscores the need for treatments that specifically target these abnormalities. The development of personalized treatment plans based on individual autoantibodies and immunogenomic alterations could offer patients more effective, tailored therapy options. To advance these personalized strategies, both translational research and longitudinal studies are essential to assess treatment efficacy and safety. Therapeutic approaches should focus on halting disease progression and potentially reversing fibrotic changes. Given the complex immunogenomic factors influencing disease progression, a one-size-fits-all approach is insufficient; instead, individualized therapies are imperative.

Conclusion

Our literature review extensively examines the immunogenomic targets linked to the cutaneous manifestations of systemic sclerosis, a complex autoimmune disease characterized by fibrosis, vasculopathy, and immune dysregulation. Central to SSc pathogenesis are epigenetic gene alterations, optimally studied through transcriptomic and epigenomic analyses. Identifying enzymatic and molecular targets, such as the JAK-STAT pathway and enhanced JAK2 activation in patients' skin, opens up new therapeutic possibilities. Ongoing research into JAK inhibitors shows promising results in controlling fibrosis and reducing pro-inflammatory cytokines in SSc. These advances in personalized immunogenomic treatment can significantly improve patient management, potentially easing the psychological impact of this chronic disease. Future research should aim to further delineate the specific immunogenomic alterations in SSc, particularly assessing the involvement of various JAK family members and the relative effectiveness of selective versus non-selective JAK inhibitors in mitigating skin fibrosis and inflammation.

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