International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
www.dermatologypaper.com
Derma 2024; 7(2): 115-118
Received: 16-07-2024
Accepted: 22-09-2024

Alshaimaa Anas Ibrahim Farahat
Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Egypt

Dareen Abd El-Aziz Mohammed
Department of Pathology, Faculty of Medicine, Tanta University, Egypt

Doaa Salah Hegab
Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Egypt

Abeer Abd El-Hakam Hodeib
Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Egypt

Iman Hamed El_Maadawy
Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Egypt

Corresponding Author:
Latha P
Associate Professor, Department of OBG, Narayana College of Nursing, Nellore, Andhra Pradesh, India

Role of JAK-STAT in pemphigus vulgaris

Alshaimaa Anas Ibrahim Farahat, Dareen Abd El-Aziz Mohammed, Doaa Salah Hegab, Abeer Abd El-Hakam Hodeib and Iman Hamed El_Maadawy

DOI: https://doi.org/10.33545/26649411.2024.v7.i2b.211

Abstract
Pemphigus vulgaris is a subtype of autoimmune bullous diseases (AIBDs) that are characterized by flaccid blisters and erosions of skin and mucous membranes with dysregulated immune activity. Autoantibodies binding to desmosomal proteins which is desmogleins (Dsg) 1 and 3 lead to intraepidermal acantholytic blisters in pemphigus diseases. Different factors play a role in immunpathogensis of PV. The complicated mechanisms of immune dysregulation deserve a special attention to study the process and contributors of immune response. The Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway is essential for numerous growth factors (GFs) and cytokines. This signalling pathway is linked to the pathophysiology of several autoinflammatory and autoimmune disorders.

Keywords: Autoimmune bullous diseases, pemphigus vulgaris, JAK-STAT

Introduction
Autoimmune bullous diseases (AIBDs) are uncommon, tissue-specific auto-immune disorders of the skin, characterized by pathogenic auto-antibodies that induce mucocutaneous lesions [1].
Pemphigus vulgaris (PV) constitutes one of common AIBDs. Diverse disease-related variables, such as genetic and environmental influences, operate independently or synergistically to modulate the immunopathogenesis of PV. The intricate pathways of immunological dysregulation in PV need focused study to investigate the processes and factors influencing immune response [2].
The JAK-STAT pathway is essential for immunological control, cellular apoptosis, differentiation, and proliferation, influencing several cytokines and GFs. This signalling pathway is linked to the pathogenesis of numerous autoinflammatory and autoimmune disorders [3].

Genetics
Although most instances of PV lack a familial history, data indicates that genetics significantly influence the occurrence, severity, and prognosis of PV. An elevated prevalence of human leucocytic antigen (HLA) - DQB1*05:03 in Caucasian people has been noted [4].
These data indicate that certain major histocompatibility complex (MHC) class II alleles are essential for T-cell detection of autoantigens in PV individuals, resulting in autoantibodies synthesis via interactions of T cell-B cell [5].

Etiopathogenesis
The generation of autoantibodies targeting desmosomal components is regarded as the primary mechanism in the pathogenesis of pemphigus. The literature has additionally emphasised the significant function of cellular alongside humoral immunity [6].

Antigens in pemphigus vulgaris
The antigens implicated with pemphigus vulgaris are desmoglein 1 (Dsg1) and 3 (Dsg3), both of that are transmembrane glycoproteins. The fundamental pathogenesis of PV involves the disruption of the adhesive properties of Dsgs via autoantibodies, resulting in

development of blisters [7].

Cadherins are inter-cellular adhesive molecules that rely on calcium crucial for maintaining the integrity of tissues. They may be categorised into two groups: conventional cadherins (P and N) and desmosomal cadherins (Dsgs and desmocollins (Dscs)). Structurally, they possess 5 extracellular domains which are identical across the groups, along with intracellular and transmembrane domains that vary between desmosomal and classical cadherins. The distal extracellular domain of the cadherin molecule interacts with the homologous distal region of the neighbouring cell molecules [8].

Desmogleins has 4 isoforms; Dsg1 and Dsg3 have sole expression in the squamous stratified epithelium, the site of PV bullous lesions. Dsg2 can be detected in all tissues containing desmosomes, such as simple myocardium and epithelium. Dsg4 has been detected in hair follicles and may be involved in lesions of the scalp, often seen in PV. Dscs are a category of transmembrane-glycoproteins which, alongside Dsgs, constitute the desmosomes [9].

Pathogenic autoantibodies in pemphigus vulgaris

PV is induced by IgG autoantibodies targeting Dsg1 and/or Dsg3, leading to the disruption of intercellular adherence and subsequent blister development [10].

Nonetheless, the mechanism whereby the binding of autoantibodies to Dsgs induces acantholysis continues to be ambiguous. Potential explanations for this occurrence include (i) modifications in intracellular transduction signalling and disruption of the cytoskeleton, leading to keratinocyte contraction, and (ii) spatial obstruction for Dsg adhesion and the development of Dsg-deficient desmosomes [10].

Link between pathogenic factors in pemphigus vulgaris and its relation to JAK-STAT pathway

After exposure to different stimuli in susceptible patient, dendritic cells presenting Dsg antigens to naive T cell then differentiate to different T cell subsets. Cytokines from Th2 cells (e.g., IL-4) are markedly elevated in individuals with PV, suggesting a dysregulation between Dsg3-reactive Th2 and Th1 cells in the disease's development (11). IL-4 generating Th2 cells may stimulate B cells to produce anti-Dsg antibodies. Acantholysis observed in PV is triggered by a humoral autoimmune reaction. Autoreactive Treg cells further secrete IL-10. IL-10 has intricate impacts, as it may facilitate immunoglobulin class shift to IgG4, the primary sub-class of anti-Dsg antibody while exerting distinct impacts throughout various stages of disease development (Figure 1) [12].

These aforementioned cytokines and also another different cytokines (e.g. IL-15, IL-17 and IL-21) released in PV individuals by different inflammatory cells utilize JAK-STAT pathway to mediate their intracellular effects. The JAK-STAT signalling pathway is a crucial mediator in the transmission of various cytokine-induced signals. Various cytokines may selectively activate certain proteins of JAK and STAT, resulting in a wide array of cellular reactions [13].

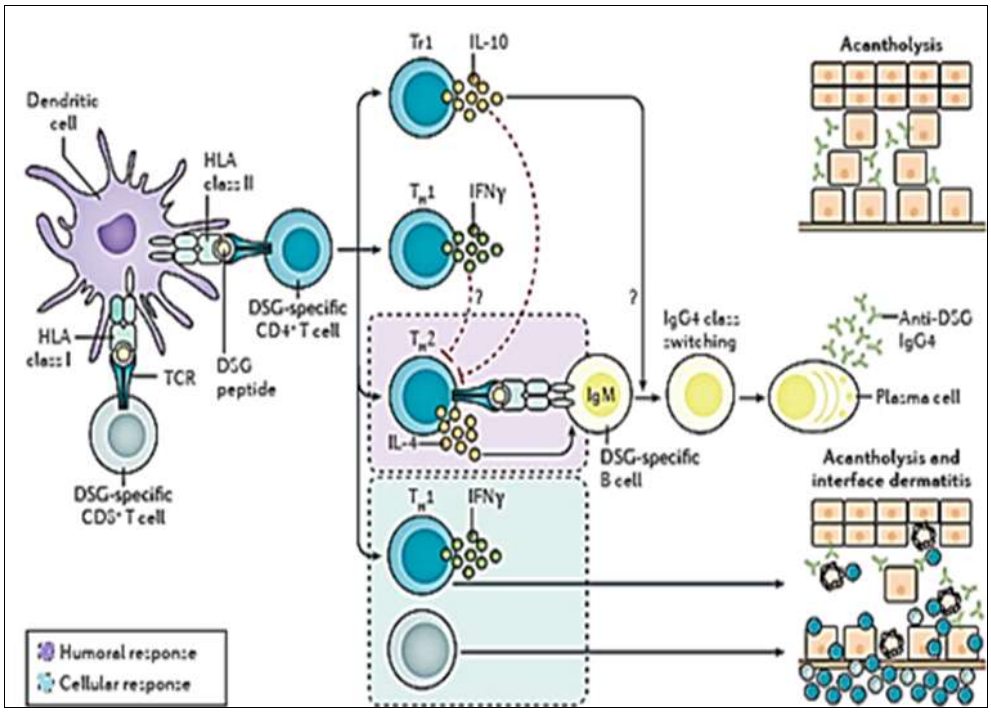

Fig 1: Immune pathway in pemphigus vulgaris (12)

JAK-STAT signal pathway

Janus kinases are considered non-receptor tyrosine kinases (TK), which are intracellular TK with no direct communication with extracellular environment (14). Several cytokines and GFs utilize it for expressing genes that govern cell activation, differentiation, and proliferation. It is a fundamental relay mechanism in the population of circulating monocytes and lymphocytes, including several cytokines and their receptors [15].

They are linked to receptors of cytokine, facilitate tyrosine phosphorylation of receptors, and attract ≥ one STAT proteins. Tyrosine-phosphorylated STATs undergo dimerization [16] and then translocate into the nucleus via the nuclear membrane to modulate particular genes. The absence or mutation of JAK-STAT components is associated with several human illnesses [17]. Consequently, the inhibition of the JAK-STAT pathway has potential for the treatment of several illnesses [18] (Figure 2) [19].

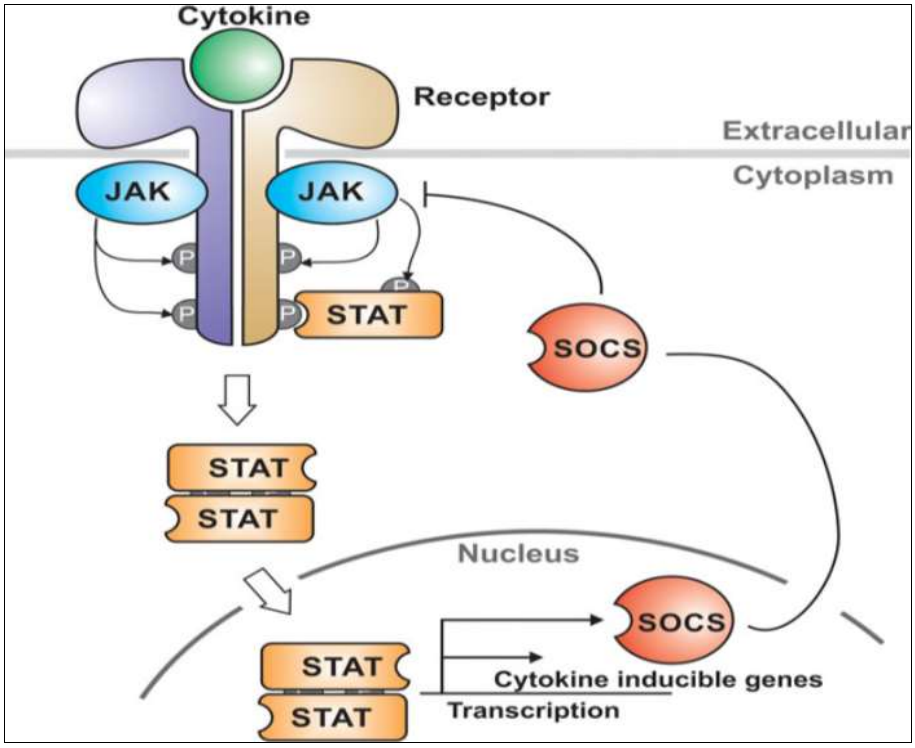

Fig 2: JAK-STAT pathway [19]

Possible role of JAK1 and STAT3 in pemphigus vulgaris

JAK1 and JAK3 are used by some cytokines as members of the IL-2 family, that involves IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. Some cytokines like IL-4 and IL-21 have an impact in the development of PV by drive pathogenic Th cells and developing autoreactive B cells. Additionally, IL-7 and IL-9 facilitate the induction and control of autoantibody synthesis in PV through improving B cell responses and are related with several autoimmune disorders that use JAK-family kinases [20]. IL-15 is implicated in the enhancement and functionality of CD8+ cells in PV [21, 22]. Consequently, JAK inhibitors provide a potential alternative therapy for PV by obstructing these pathways [22].

Immunoglobulin G4 is the predominant subtype of autoantibodies in PV and is recognized for its restricted capacity to activate complement. Anti-Dsg3 IgG directly induced breakdown of desmosomes by facilitating the internalization of Dsg3 [23] and disrupting desmosome turnover [24]. Transcription of Dsg3 is negatively controlled by STAT3 in keratinocytes, and corticosteroid therapy enhances expression of Dsg3 through STAT3 inhibition via an unidentified mechanism which might involve JAKs. Furthermore, STAT3 interacts with and modulates several genes that influence the Th17 phenotype and its differentiation [25]. Serum concentrations of Th17-related cytokines (IL-17 and IL-23) are markedly elevated in individuals with PV [26]. The findings indicate that targeted JAK-STAT pathway inhibition might be advantageous without the recognized side impacts of steroids [27].

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Farahat ANI, Abd El-Aziz Mohammed D, Hegab DS, Abd El-Hakam Hodeib A, El_Maadawy IH. Role of JAK-STAT in pemphigus vulgaris. International Journal of Dermatology, Venereology and Leprosy Sciences. 2024; 7(2): 115-118.