REVIEW

Pathergy: a review of potential mechanisms and novel therapeutic targets

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Abstract

Pathergy reaction is the phenomenon of formation of non-healing skin lesions or ulcers following minor injuries. Although conceptually similar to the isomorphic reaction (Koebnerisation), these are two separate phenomena that should be distinguishable to treating clinicians. The underlying pathomechanisms of pathergy are not yet fully understood and subsequently therapy is lacking. Recent advances in the understanding of wound healing through keratinocyte and fibroblast cross-talk and mesenchymal stem cell (MSC) may hopefully foster the development of novel targeted therapies for pathergy-associated wounds and diseases in the near future.

Keywords pathergy, isomorphic phenomenon, Behçet's disease, pyoderma gangrenosum, wound healing

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Introduction

Pathergy is a term used to describe hyper-reactivity of the skin that occurs in response to minimal trauma[1,2]. It is a reaction characterised by non-specific pustules or papules, or enlargement of pre-existing wounds, developing on sites of minor trauma, including blunt trauma. Pathergy is characteristic for pyoderma gangrenosum (PG) and other neutrophilic skin conditions such as Behçet's disease (BD) and Sweet's syndrome. Development of a monocytic and neutrophilic cell infiltrate without true vasculitis can be seen on histopathology. It can be elicited via a pathergy test, which leads to the production of an erythematous papule at the site of a skin prick and intradermal injection of saline solution[1]. The lesions arising from pathergy tend to be non-specific papules or pustules that ultimately may develop in skin ulcers[1]. This review focuses on the potential underlying mechanisms involved in pathergy and examines novel mesenchymal stem cell (MSC)-based therapy to successfully treat non-healing chronic wounds.

Characteristics

Comparing Koebner phenomenon and pathergy

Koebner phenomenon and pathergy are conceptually similar yet completely separate entities. Koebner phenomenon is the appearance of new skin lesions on previously unaffected skin secondary to trauma, for example in psoriasis. These new lesions are both clinically and histologically identical to the patient's underlying cutaneous disease[3,4]. The lesions seen in Koebner phenomenon adopt the same clinical and histological features as the patients' original skin disease, hence why this condition is also termed the isomorphic response (from Greek: 'equal shape'). Mechanisms are thought to be related to the presence of T resident memory cells (TRM) in previously affected sites of cutaneous disease.

Disease associations and clinical significance of pathergy

Pathergy is seen in a range of chronic cutaneous diseases across the dermatology specialty. It is therefore imperative for all practising dermatologists, as well as clinicians involved in wound care, to be aware of the pathergy response and understand the proposed underlying pathomechanisms involved. A greater understanding of pathergy and pathergy-associated reactions is of essential importance for initiating treatment and minimising occurrence of painful chronic wounds which may become necrotic or secondarily infected or may scar. Pathergy-associated diseases such as PG have an increased morbidity and mortality rate when

compared to the general population and this, coupled with the unpredictability and chronic nature of the disease, may place a burden on the healthcare system[5]. A comparison of the aetiologies, clinical presentation, proposed pathogenesis and diagnosis of these pathergy-associated diseases can be seen in Table 1.

Pyoderma gangrenosum (PG)

PG is a rare, chronic inflammatory skin disease characterised by rapidly progressing painful pustules which progressively break down, forming larger ulcers with violaceous undermined borders. The incidence of disease ranges from 0.3–5.8 per 100,000 individuals, with an increased mortality rate when compared with the general population[5,10]. Pathergy is seen in 25–50% of patients with PG and is more common in PG associated with systemic disease[11]. Pathergy may be triggered by incidental or iatrogenic trauma. Examples of pathergy-induced PG include wound infection, surgical procedures that include caesarean section, breast reduction, central line insertion and stoma formation[12,13].

Behçet's disease (BD)

BD is universally recognised as a multisystemic inflammatory disease of unknown aetiology with chronic course and unpredictable exacerbations; its clinical spectrum varies from pure vasculitic manifestations with thrombotic complications to inflammatory involvement of multiple organs and tissues, including orogenital mucosa, skin and eyes[14].

Although the pathergy phenomenon is seen in various disease entities, pathergy testing is only indicated in establishing the diagnosis of BD. A positive skin pathergy test (SPT) or skin pathergy reaction (SPR) is a hyper-reactivity response to needle-induced trauma, characterised by papule or pustule formation within 24–48 hours after sterile needle prick. The aim of the SPT is the generation of pathergy lesions in BD patients by administration of a minimal skin puncturing trauma. Positive SPT is the only diagnostic test for BD and is one of the minor criteria for BD diagnosis; it has been derived by the International Study Group of Behçet's Disease[15]. Several studies have shown higher positive SPT rates in those with active disease[16–18].

Sweet's syndrome

The development of pathergy lesions has also been reported in other neutrophilic dermatoses, including Sweet's syndrome. The syndrome is characterised by a constellation of clinical symptoms, physical features and pathologic findings which include fever, neutrophilia, tender erythematous cutaneous lesions and a diffuse infiltrate consisting predominantly of mature neutrophils typically located in the upper dermis[19]. Cutaneous pathergy at sites of trauma have been reported in the literature and include sites where procedures such as biopsies, intravenous catheters placement, vaccination and venepuncture have been performed, as well as at locations of animal scratches and insect bites[20–22].

Pathomechanisms of pathergy

Despite being well-known to dermatologists since its first description in 1937, the mechanisms underlying the pathergy phenomenon and its aetiology is not yet fully understood. It has been suggested that pathergy may be driven by either a non-specific hyperinflammatory response to traumatic insult, an exaggerated response to microbial antigens, or interaction between genetic and environmental factors.

Normal wound healing versus pathergy

Wound healing, as a normal biological process in the human body, is achieved through a number of precisely and highly programmed phases: 1) rapid haemostasis; 2) appropriate inflammation; 3) mesenchymal cell differentiation, proliferation and migration to the wound site; 4) suitable angiogenesis; 5) prompt re-epithelialisation (re-growth of epithelial tissue over the wound surface); and 6) proper synthesis, cross-linking and alignment of collagen to provide strength to the healing tissue[23]. This process involves a continuous sequence of signals and responses in which platelets, fibroblasts, epithelial, endothelial and immune cells come together outside their usual domains to orchestrate a very complex event that results in tissue repair. These signals, which are mainly growth factors and cytokines, orchestrate the initiation, continuation and termination of wound healing[24,25].

After epidermal injury, there is an immediate release of inflammatory mediators from damaged cells and the induction of an acute inflammatory response (Figure 1:1). Degranulating platelets, resident tissue macrophages and mast cells also release mediators into the tissue milieu causing arteriolar dilatation, resulting in increased blood flow to the area[1,26].

In response to specific chemo-attractants, monocytes also infiltrate the wound site and become activated macrophages that release growth factors such as platelet-derived growth factor and vascular endothelial growth factor which initiate the formation of granulation tissue[27]. These events are the normal prerequisites of the repair of the wound. The heightened or abnormal inflammatory activity occurring in the pathergy reaction can be regarded as a deviation from the normal course of events in the cutaneous wound healing response to the minimal trauma of the SPT provocation. Whilst specific mechanisms which lead directly to pathergy are not well understood, any deviation along this wound healing pathway may hold the potential to induce a pathergy-like response.

Inflammatory cells and mediators

The main histopathological findings in BD-associated pathergy is a mixed dermal inflammatory cell infiltration with lymphocytes, neutrophils and sparse eosinophils, condensed at perivascular sites[28]. The density and severity of inflammatory cells range from perivascular mononuclear cell infiltration with minimal neutrophil infiltration, to dense perivascular and interstitial mixed cells infiltration with predominantly neutrophils. The difference in histopathological findings can be explained by the diversity of individual immune

Table 1. Comparison of pathergy-associated disease

Pyoderma gangrenosum	Behçet's disease	Sweet's syndrome
Epidemiology		
Female preponderance. Typically onset occurring in middle-age.	Both genders equally affected by the disease. Higher incidence in the middle and far-east.	Female preponderance of 4:1. Typical age of onset is between 30–60 years of age. No observed racial predilection.
Clinical presentation		
Inflammatory papule/pustule progressing to a painful ulcer with violaceous border, undermined border and purulent base.	Chronic remitting and relapsing inflammatory disorder characterised by recurrent oral aphthous ulcers, genital ulcerations, ocular manifestation and other systemic involvement.	Acute-onset tender plaques or nodules, fever, arthralgia, ophthalmologic manifestations, headaches and rarely oral/genital lesions
Pathogenesis		
Involves genetic mutations, neutrophil dysfunction and immune/inflammatory dysregulation. Abnormal cytokine signalling by T cells and macrophages. PG lesions found to have increased levels of inflammatory mediators (e.g. IL-23 + IL-17). Both are important in activating neutrophils and stimulating mediated inflammation.	Cell-mediated immunity plays a significant role. Type 1 helper T cell activation leads to increased circulating T-lymphocytes. Pro-inflammatory cytokines, including IL-1, IL-8, IL-12, IL-17, IL-37 and TNF, are increased. Increased macrophage activation, neutrophil chemotaxis and phagocytosis have been observed in BD lesions. Circulating immune complexes such as anti-endothelial cell antibodies play a role in the neutrophilic vascular reaction.	Theories include hypersensitivity to bacterial, viral or tumour antigens that may trigger neutrophil activation and infiltration. Also, the role of increased levels of cytokines/chemokines such as G-CSF, GM-CSF, IL-1 and interferon-gamma. Genetic factors such as HLA-B54 in the Japanese population, MEFV gene mutation in familial Mediterranean fever patients, and chromosome 3q abnormalities have been observed.
Diagnostic criteria		
Delphi Consensus[6]: A diagnosis of PG can be met if patient meets one major and (at least) four minor criteria. *Major criteria:* • Biopsy of ulcer edge with neutrophilic infiltrate *Minor criteria:* • Exclusion of infection • Pathergy phenomenon • History of IBD or inflammatory arthritis • History of papule, pustule or vesicle rapidly ulcerating • Peripheral erythema, undermining border and tenderness • Multiple ulceration, at least one on anterior lower leg • Cribriform scars at healed ulcer sites • Decreased ulcer size after 1 month of immunosuppression	**Revision of International Criteria for Behçet's disease[7]:** A diagnosis is reached if three or more points are met. *1 point:* • Positive pathergy test • Vascular manifestations • Neurological manifestations • Skin manifestations (pseudofolliculitis, skin apthosis) *2 points:* • Oral aphthosis • Genital aphthosis • Ocular lesions	**Revised criteria[8,9]:** A diagnosis of Sweet's syndrome can be met if patient meets both major criteria and two of the four minor criteria. *Major criteria:* • Sudden onset of tender erythematous plaques/nodules • Dense infiltrate on biopsy *Minor criteria:* • Fever >38˚C • Association with an underlying haematological malignancy, inflammatory disease or pregnancy. • Or preceded by upper respiratory tract infection or gastrointestinal infection • Positive response to corticosteroids • Elevated white cell count with neutrophil predominance and elevated inflammatory markers

response to the stimulating agents[2]. Immunohistochemical examination of pathergy site revealed Human Leukocyte Antigen-DR isotype (HLA-DR) expression of keratinocytes and inflammatory cells, Intracellular Adhesion Molecule (ICAM) and e-selectin expression by endothelial cells[28]. Inflammatory infiltrate had a dominance of CD3(+), CD4(+), CD45Ro(+) cells and small collections of neutrophil elastase positive cells were detected.

When compared with normal skin, sites of pathergy in BD show significant increases in the messenger RNA expression of interleukin-8, monocyte chemoattractant protein 1, interferon-g, IL-12 and IL-10[29] (Figure 1:1). BD patients also have increased numbers of mature dendritic cells, monocytes, lymphocytes, chemokines and cytokines (including IFN-γ, IL-10, IL-12 and IL-15)[30].

Non-specific hyperinflammatory response theory

Injured epidermal and dermal cells produce various chemokines, cytokines, growth factors, antimicrobial peptides altogether leading to an inflammatory reaction in response to trauma[31]. Specifically, TLR and nucleotide-binding oligomerization domain (NOD)-like receptors expressed by keratinocytes activate intracellular pathways and the release of cytokines IL-6, TNF-α and IL-1β. These cytokines activate dendritic cells in the dermis which triggers the release of IL-12, IL-23 and interferons. Keratinocytes also release chemokines which attract neutrophils, mature dendritic cells and T-lymphocytes to the dermis which leads to the polymorphonuclear cells and mixed inflammatory infiltrate seen in the dermis on histopathology[28,30]. One study hypothesised that immune processes triggered at the site of nonspecific trauma may provide insights into a dysregulated immune system, triggering a pathergy response in BD patients; it demonstrated an exaggerated Th-1-type immune response in BD patients[30]. Other studies showed that minimal mechanical skin trauma causes healthy individuals' uninvolved skin to induce proinflammatory cytokines, including IL-1β, IL-6, IL-8 and IL-12/23[32,33], suggesting that skin damage from trauma activates an innate cutaneous response which may be amplified due to genetic and environmental factors in pathergy-related diseases such as PG and BD.

Genetic implications in pathergy

Genetic factors have also been implicated in the activation of both the innate and adaptive immune systems in both BD and PG, and therefore may play a role in the mechanism of pathergy. HLA-b51 is a genetic marker that has been highly associated with BD in patients from many different ethnic groups, including European, Mediterranean and Asian peoples[34].

The reactivity of the 'pathergy test' is suggested to be correlated with HLA-B51 in Mediterranean countries[35,36]. In PG patients, a number of genes including Signal Transducer And Activator Of Transcription 1 (STAT1), IAA-Leu-resistant1 (ILR1), Mitogen-Activated Protein Kinase (MAPK8), interferon regulatory transcription factor 3 and 7 (IRF3, IRF7), Nuclear Factor Kappa B Subunit 1 (NFKB1), MX Dynamin Like GTPase 1 (MX1), Testicular Receptor 4 (TR4), Cluster of differentiation – 40 (CD40), CD40 ligand, Integrin Subunit Alpha M (ITGAM), TLR6 and HLA-A were upregulated in lesions caused by pathergy[31]. Many of these genes play a role in wound healing. This supports the notion that genetic factors play a role in the pathogenesis of pathergy-related diseases.

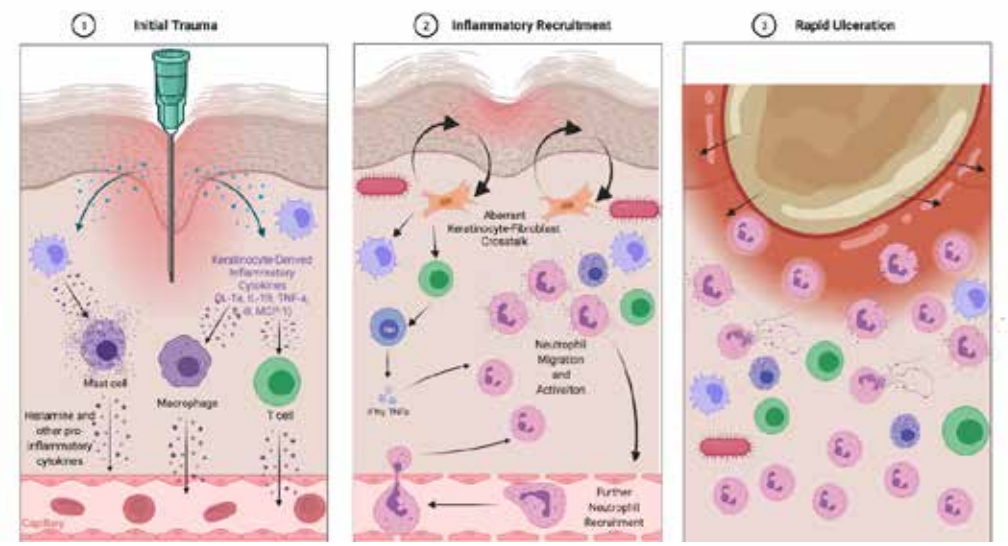

Figure 1. Schematic representation of the proposed pathogenesis of pathergy and deviations from the normal process of wound healing
1=initial trauma results in the release in keratinocyte-derived inflammatory cytokines which lead to stimulation and activation of a variety of resident inflammatory cells. These then signal via other chemokines including histamine to promote inflammation. An increase or aberration in the type of inflammation present is the first potential step which may produce a pathergy-like response
2=inflammatory recruitment from the circulation into the tissue primarily consists of neutrophils which interact with T cells, macrophages and fibroblasts to promote a persistent pro-inflammatory response. The presence of bacteria may also contribute to the ongoing inflammatory response via mediators such as TLR5 leading to a pathergy-type response. Aberrant fibroblast–keratinocyte interactions are proposed to be associated with the resultant ulceration, possibly through promoting breakdown of the basement membrane and again represent another potential cause of pathergy
3=the self-perpetuating inflammatory cascade then results in the characteristic inflammatory and histological findings of pathergy-associated diseases such as BD and PG. All these potential deviations from normal wound healing require further mechanistic investigations and may represent novel therapeutic targets for pathergy-related diseases

Exaggerated response to microbial antigens theory

This hypothesis is founded on the notion that bacterial or microbial elements may induce a pathergy response. Several studies have shown that the proportion of *Streptococcus sanguinis (S. sanguinis)* was significantly high in the oral bacterial flora of BD patients in comparison with healthy

controls[37–39]. It has been proposed that many BD patients tend to acquire a hypersensitivity against streptococci in their original oral bacterial flora, as demonstrated by a much stronger positive pathergy-type reaction when tested with their own streptococcal antigen compared with those by the 'pathergy test'[35,40]. Microbial antigens that have been linked to pathergy-associated conditions include herpes simplex virus, streptococci, staphylococci or Escherichia species[37]. This theory is supported by reduction in the inflammatory and pathergy response when skin was surgically cleansed with an aseptic epithelial barrier, such as by chlorhexidine or povidone iodide[41]. It is also supported by reports of a pathergy reaction at injection site in BD patients who had recently received a pneumococcal vaccination[42]. Another study showed that pathergy-positive BD patients had upregulated TLR5 expression which suggests that microbial or damage-associated signalling may trigger the exaggerated immune response that is characteristic for the pathergy phenomenon[43]. Similar to the previous theory of a non-specific hyper-inflammatory response, the insertion of an undefined microbial antigen into the skin triggers a cascade of events ending with inflammation in pathergy sites.

Role of keratinocyte–fibroblast interactions in aberrant wound healing

Keratinocytes express numerous growth factors and cytokines which increase wound epithelialisation and ultimately promotes wound healing[44]. To close the defect in the epidermis, keratinocytes at the wound edge must loosen their adhesion to each other and to the basal lamina and need to develop the flexibility to support migration over the freshly deposited matrix.

Throughout the mid- and late phase of wound healing, cellular interactions become dominated by the interplay of keratinocytes with another critical player involved in wound healing – fibroblasts. The cross-talk between these two cells progressively shifts the microenvironment away from inflammatory to a synthesis-driven granulation tissue[45]. Mesenchymal–epithelial interactions play a critical role as autocrine/paracrine regulators of fibroblasts and keratinocytes, influencing growth, function and differentiation of these cells and ultimately skin homeostasis[24]. Apart from paracrine growth factor regulation, the formation of a new basement membrane zone is another example where interaction between keratinocytes and fibroblasts are crucially involved[45]. Any aberration of these processes may be association with wound breakdown, expansion or the inhibition of re-epithelialisation.

Additionally, scRNA-seq investigations have revealed the dynamic nature of fibroblast identities during wound healing and the powerful wound-induced plasticity of myeloid lineage cells[46–49]. scRNA-seq analysis infer several pathways fibroblasts follow during wound healing, including contractile and regenerative functions[50]. Inflammatory cells can directly modulate fibroblast function and contribute directly to pathways involved in wound healing.

Therapies for pathergy-associated diseases

Until recently, therapies for pathergy-associated diseases have focused upon broad immunosuppression with oral steroids or modulation of neutrophil function through therapies such as dapsone and colchicine. In recent years, a number of biological therapies have been used in the treatment of pathergy-associated disease such as PG and BD (Table 2). Through targeting inflammatory mediators such as IL-1α and IL-1β, this antagonises inflammation derived both from the keratinocyte 'alarming' response as well as inflammation mediated by monocytes, macrophages and neutrophils. Additional targets such as IL-17 and C5a are involved in the downstream keratinocyte response to neutrophil trafficking and activation. Larger clinical trials will reveal whether these strategies result in clinically significant alterations in vivo.

Mesenchymal stem cells (MSC)

Treating ulcers or wounds caused by pathergy may prove difficult. In PG which has a known pathergy association there is no gold standard of treatment and this can prove challenging for both clinician and patient alike. Most treatment regimens involve topical and systemic immunosuppressants with appropriate wound care and pain management. Recently, the benefits of using human placental tissues in wound regeneration have been documented; one study has shown a 64% wound closure of a PG ulcer after nine weekly applications using this technology[27,51].

MSC are key to regenerative wound healing. MSC have spatial memory and respond to local environment. MSC orchestrate wound repair through structural repair via: cellular differentiation; immune-modulation; secretion of growth factors that drive neovascularisation and re-epithelialisation; and mobilisation of resident stem cells[52]. Viable cryopreserved

Table 2. List of biological agents tested for PG and BD in the literature

Mechanism of action	Therapy	Evidence for therapy	
		PG	BD
TNF-α *inhibitor*	Infliximab	✔	✔
	Adalimumab	✔	✔
	Etanercept	✔	✔
IL-1α *inhibitor*	Xilonix	✔	×
IL-1β inhibitor	Canakinumab	✔	✔
	Gevokizumab	✔	✔
IL-1RA inhibitor	Anakinra	✔	✔
IL-17 inhibitor	Secukinumab	✔	✔
IL-12 + IL-23 inhibitor	Ustekinumab	✔	✔
IL-6 inhibitor	Tocilizumab	✔	✔
C5a inhibitor	IFX-1	✔	×

human placental membranes (vCHPM) is an MSC-based therapy which is a promising strategy in successfully treating non-healing chronic wounds. It contains a combination of growth factors and extracellular matrices as well as viable MSC, fibroblasts and epithelial cells. These components have been shown to decrease inflammation, lower microbial loads and promote tissue regeneration[53,54]. vCHPM is also a rich source of high molecular weight hyaluronic acid (HC-HA) and pentraxin 3 (PTX3). The HC-HA/PTX3 has a unique ability to promote the death of activated macrophages while downregulating pro-inflammatory cytokines and upregulating anti-inflammatory cytokines[55–59]. The majority of studies have focused primarily on vCHPM and its role in treating diabetic foot ulcers and venous leg ulcers as opposed to PG or other pathergy-associated diseases.

Conclusion

Pathergy is a result of complex interactions between genetic background, immune-related and environmental factors. Further investigations are needed to understand the pathogenic mechanisms of pathergy to identify novel therapeutic targets for pathergy-associated diseases. Novel monoclonal antibody therapies may provide additional tools to help treat pathergy in the context of diseases such as BD and PG, and the knowledge gained through investigations into the mechanisms of pathergy will have direct relevance to other research in chronic wounds.

Conflict of interest

JWF has conducted advisory work for Janssen, Boehringer-Ingelheim, Pfizer, Kyowa Kirin, LEO Pharms, Regeneron and UCB, participated in trials for UCB, Pfizer and Eli Lilly, and received research support from Ortho Dermatologics.

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Ethics statement

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