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Immune response patterns in non-communicable inflammatory skin diseases

Running title: immune patterns in ncISD

Kilian Eyerich[1], Stefanie Eyerich[2]

[1] Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

[2] ZAUM – Center of Allergy and Environment, Technical University and Helmholtz Center Munich, Munich, Germany

Corresponding author:

Kilian Eyerich, MD, PhD

Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany

email: kilian.eyerich@tum.de

phone: +49-89-41403471

fax: +49-89-41403453

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Abstract

Non-communicable inflammatory skin diseases (ncISD) such as psoriasis or atopic eczema are a major cause of global disease burden. Due to their impact and complexity, ncISD represent a major challenge of modern medicine. Dermatology textbooks describe more than 100 different ncISD based on clinical phenotype and histological architecture. In the last decades, this historical description was complemented by increasing molecular knowledge – and this knowledge is now being translated into specific therapeutics. Combining the enormous advances made in lymphocyte immunology and molecular genetics with clinical and histological phenotyping reveals six immune response patterns of the skin – type I immune cells cause the lichenoid pattern characterized by immune-mediated cell death of keratinocytes; type II immune cells underlie the eczematous pattern with impaired epidermal barrier, infection, and eosinophils as well as the bullous pattern with loss of epithelial integrity; Th17 cells and ILC3 mediate the psoriatic pattern characterized by acanthosis, high metabolic activity, and neutrophils; dysbalance of regulatory T cells cause either the fibrogenic pattern with rarefication of cells and dermal thickening or the granulomatous pattern defined by formation of granulomas. With more and more specific therapeutic agents approved, classifying ncISD also according to their immune response pattern will become highly relevant. This review defines the six immune response patterns of ncISD and highlights therapeutic strategies targeting key lymphocyte mediators.

An immunologic view at inflammatory skin diseases

Non-communicable inflammatory skin diseases (ncISD) are frequent, affected individuals suffer from a devastating loss of quality of life, and socio-economic costs are enormous. The complex pathogenesis of ncISD is based on genetic predisposition and environmental influences that result in impaired epithelial function and altered immunity. Historically, disease classification in dermatology relies on precise clinical description in combination with histological description of microscopic tissue alterations and infiltrating immune cells. This classification is complex, and at times misleading. At the same time, insights into mechanisms how distinct lymphocyte subsets terminally orchestrate the inflammatory response and how these lymphocytes interact with resident skin cells[1] resulted in a

translational revolution leading to more and more specific therapeutics[2]. To acknowledge these recent advances made in design and approval of specific immune-mediating therapeutics, a classification of ncISD according to their immune-response patterns is required (figure 1, table 1, 2). This review summarizes what is known about immunology, histo-pathology, and clinical phenotype for each of the immune response patterns. It further describes limitations of the classification, early pathogenic events, and focuses on therapeutic consequences and future developments.

Lichenoid pattern (pattern 1)

The major physiologic role of the lichenoid pattern is disposal of keratinocytes that are potentially infected with intracellular microbes or are (pre-)carcinogenic due to DNA damages beyond repair. It is characterized by a cytotoxic immune response against keratinocytes of the basal layer ("interface dermatitis") that is mediated by killer T cells (Tc1), Th1 cells, ILC1, NKT, and NK cells (type 1 lymphocytes). This cytotoxic reaction is driven by the master regulator of type 1 lymphocytes, IFN-γ, and cytotoxic granules such as granulysin[3], perforin[4], granzyme B[5], and Fas/FasL[6]. In line with that observation, transcriptional network comparison of lesional lichen planus and lupus erythematosus with non-interface skin diseases revealed that differentially expressed genes are attributable to type 1 lymphocytes as well as to the effect of IFN-γ on keratinocytes, including apoptosis and necroptosis (unpublished data). Furthermore, interface dermatitis is induced in murine models of xenotransplantation or adoptive transfer of keratinocyte-reactive cytotoxic T cells[7]. In cell culture models, FasL induces the characteristic hypergranulosis while IFN-γ causes keratinocyte apoptosis with cytoid body formation, and ICAM-1 expression[8]. Increasing evidence suggests an additional and important role for plasmacytoid dendritic cells and IFN-α in the pathogenesis of lichenoid diseases, possibly via recruitment and amplification of interface dermatitis[9].

These molecular alterations have direct consequences that can be observed histologically: type 1 lymphocytes form a band along the basal membrane that is called "lichenoid infiltrate". Keratinocytes show signs of cell death, and cytoid bodies are present. Clinically, this results in flattened, polygonal papules with shiny desquamation; maximum clinical variants are erosions or bullae.

Eczematous pattern (pattern 2a)

The major physiologic role of the eczematous pattern is defence against extracellular parasites. Furthermore, recent evidence suggests a role in protection against toxins[10]. Skin lesions are dominated by Th2 and ILC2 cells (type 2 lymphocytes) secreting IL-4, IL-5, IL-13, and IL-31. These cytokines affect the epidermis in two ways: IL-4 and IL-13 downregulate genes of the epidermal differentiation complex, thus impairing the epidermal barrier and resulting in dry skin[11]. Furthermore, IL-4 and IL-13 inhibit cutaneous innate immunity[12,13] which explains why most patients affected from eczematous diseases suffer from skin colonization with *S. aureus* or other microbials[14]. Th2-derived IL-31 also impacts epidermal barrier and is a critical mediator of itch, a leading symptom of most diseases grouped into the eczematous pattern[15,16]. IL-5 is a strong activator of eosinophil and basophil granulocytes as well as mast cells[17]. The release of a plethora of mediators from these cells leads to edema and influx of further immune cells into the skin.

The type 2 immune deviation results in histological hallmarks such as spongiosis, serum crusts, and a mixed cellular infiltrate composed of lymphocytes and eosinophil granulocytes in the acute phase and irregular acanthosis in the chronic phase characterize the eczematous pattern. Clinically, the phenotype eczema presents as epidermo-dermatitis with co-occurrence of vesicles, papules, erythema, erosions and desquamation as well as dry skin.

Bullous pattern (pattern 2b)

A distinct pathology mediated by type 2 lymphocytes results in the bullous pattern, whose physiologic role is neutralization of extracellular microbes. Type 2 lymphocytes instruct B cells and plasma cells to form the antibody subclasses IgE, IgG1, and IgG4 via secretion of IL-4 and IgA via secretion of IL-5. The contribution of other lymphocytes such as follicular helper T cells to pathogenic antibody formation in bullous skin diseases is currently under debate[18]. IgG, IgA, or IgE[19] antibodies directed against structural proteins of the skin elicit the bullous pattern. They may either directly lead to keratinocyte apoptosis and loss of cellular adhesion, a concept called apoptolysis[20], or bind to their target and cause secondary inflammation via opsonisation[21].

Histological hallmark of type 2 lymphocyte-mediated auto-antibody formation is destruction of the skin integrity as a result of acantholysis, a gap between epidermis and dermis, or dermal split. An inflammatory infiltrate composed of lymphocytes, eosinophil or neutrophil granulocytes is always observed. Using immune-fluorescence, antibody deposits of distinct patterns are disease-defining. Clinically, the primary resulting lesion is a blister with surrounding erythema; depending on the thickness of the epidermal roof and manipulation, also erosions and crusts are frequently observed. Circulating specific antibodies are typical and represent biomarkers of bullous skin diseases[22]. Of note, diseases of the lichenoid or eczematous pattern may show a bullous clinical variant; those variants are not regarded as bullous pattern diseases, but rather as maximal variants of interface dermatitis or spongiosis, respectively, due to their distinct primary pathology.

Psoriatic pattern (pattern 3)

The psoriatic pattern is mediated by a group of lymphocytes comprised of Th17, Tc17, ILC3, and Th22 cells (type 3 lymphocytes) that share the physiologic role to warrant homeostasis at barrier organs such as the skin and mucous membranes of lung and gastrointestinal tract[23]. The pattern is caused by increased epidermal metabolism as well as by activation of innate immune signals. IL-21 and IL-22 increase keratinocyte proliferation and migration and inhibit their differentiation, thus contributing to acanthosis and parakeratosis[24,25]. IL-17A and IL-17F induce keratinocyte secretion of several antimicrobial peptides as well as of CXCL8, a chemokine recruiting neutrophils to the epidermis, and VEGF that stimulates vascularization[23,26].

Collectively, this results in histological hallmarks such as regular acanthosis with hyper-parakeratosis, (micro)-abscesses in the upper layers of the epidermis, dilated dermal capillaries and a lymphocytic dermal infiltrate. Clinically, a type 3 lymphocyte response is reflected by sharply demarcated plaques with thick desquamation. Sterile pustules are a further hallmark of the psoriatic pattern. IL-36 proteins and inducible nitric oxidase (NOS2)[27] in the skin and the antimicrobial peptide HBD-2 in the serum[28] are valid biomarkers of the psoriatic pattern.

Fibrogenic pattern (pattern 4a)

The fibrogenic pattern is a consequence of prolonged lymphocyte anti-inflammatory activity, usually a counter-regulation of a preceding inflammatory response. Lead cytokines of causative regulatory T cells (Tregs) such as iTreg, Th3, and Tr1 (type 4 lymphocytes) are IL-10 and TGF-β. The fibrogenic pattern is mediated via TGF-β that induces numerous pro-fibrotic genes in distinct tissue cells[29]. Furthermore, it is central in endothelial-to-mesenchymal transition to pro-fibrotic myofibroblasts[30]. The consequence is excessive extracellular matrix production, deposition, and tissue remodelling (fibrosis).

Alterations in the regulatory T cell department histologically lead to fibrosis that is observed as thickened collagen bundles and diminished number of cells. The lymphoid infiltrate is typically mild and located in deeper skin layers. The epidermis is normal or atrophic. This is reflected by clinical hallmarks such as well-demarcated thickening of the whole skin and a shiny, atrophic epidermis that may be surrounded by erythema in active lesions.

Granulomatous pattern (pattern 4b)

Granuloma formation is a general mechanism of the immune system after identification of a potentially harmful molecule that cannot be eliminated. In the skin, such molecules may be of infectious nature or degenerated extracellular matrix[31]. Recently, the term "Immunocompromised districts" (ICD) has been proposed for a localized immune dysbalance in the skin after trauma. Interestingly, granulomatous skin diseases occur frequently in ICD predilection sites[32]. As compared to the other patterns, level of evidence for a dominating role of a single lymphocyte subset is low for the granulomatous pattern. Both pro-inflammatory and regulatory T cells[33] are involved. The balance of TNF-α and type 4 lymphocyte-derived IL-10 expression seems to be critical for granuloma development and sustainability[34]. Interestingly, Tregs decrease after therapy with TNF-α blocking antibodies, indicating a functional link of Tregs and Th1/Th17 cells via TNF receptor 2[35].

The histological architecture of a granuloma is comprised of a center of epitheloid cells and histiocytes that may melt to giant cells or die and leave a cell-free mass (caseating granuloma). This center is surrounded by lymphocytes to a varying degree. In the skin, granulomas develop in the dermis, the

epidermis is typically non-involved or atrophic. Clinically, granulomatous diseases present as brownish papules of sharp demarcation with or without epidermal desquamation. Figurated or annular manifestation is regularly observed.

Concept limitations

The pattern principle deciphers only inflammatory skin diseases with a marked interaction of epithelia and inflammatory infiltrate. This excludes inflammation at deeper layers of the skin such as panniculitis and vasculitis and it excludes also primary dyskeratotic diseases without marked inflammation such as monogenetic keratinization disorders (ichthyosis), acantholytic dyskeratosis, or keratosis pilaris. Furthermore, the current concept is focused on terminal lymphocyte-mediated molecular events, because these are shared by different ncISD and they can be targeted therapeutically. The concept does not integrate the more heterogeneous early pathogenic events mediated by non-lymphoid immunity, though innate signals may influence the clinical course of ncISD. Typical examples are type 1 interferons that mediate lichenoid diseases[36] and psoriasis[37], alterations in the inflammasome causing autoinflammatory diseases[38], and Toll like receptor-induced activation of acute phase proteins that alter eczematous diseases[39].

Pattern interactions

ncISD are usually dominated by one immune response pattern, but their complexity and heterogeneity may be reflected by a mixture of patterns, especially in chronic disease situations. This holds e.g. true for atopic eczema, where type 2 lymphocytes are causative despite a mixed infiltrate of lymphocytes reflected by morphologic changes in the course of the disease[14]. Also contact dermatitis is not exclusively mediated by type 2 immunity, even though it is clinically and histologically to be attributed to the eczematous pattern. Other examples are bullous variants of lichenoid or eczematous diseases or granuloma formation that may occur in the course of several ncISD such as lichen planus,

lichen nitidus or lichen striatus. Furthermore, early lichenoid pattern responses may ultimately transform into the fibrogenic pattern, as frequently observed in scleroderma.

Evidence for the relevance of a lymphocyte subset balance is given by side effects observed after therapeutic intervention. Specific treatment of one lymphocyte subset causing an immune response pattern might cause imbalance towards another immune response pattern. The most evident example is treatment of psoriatic pattern diseases with molecules inhibiting TNF-α. A side effect is dryness of the skin and eosinophilia[40] – hallmarks of the eczematous pattern. In general, so-called paradoxical effects after treatment with biologics acting specifically on lymphocyte subsets comprises two phenomena. On the one hand, a spatial shift of lymphocytes, e.g. from the gastrointestinal system to the skin, results in development of psoriasis-like skin inflammation in patients treated for inflammatory bowel diseases. On the other hand, a shift in immune response patterns might result in lupus-like, lichenoid, eczematous, or granulomatous cutaneous immune responses[41].

Trigger factors and early events

The concept of lymphocyte-driven inflammatory patterns in the skin is further supported by insights into the biochemistry of antigens and mechanisms by which they stimulate lymphocytes. Although for the majority of ncISD the primary antigen remains unknown, recent evidence suggests that different types of antigens exist. A first group consists of common self-antigens in the skin such as DNA, collagens, antimicrobial peptides, and desmosomal components. Several of these antigens are proposed to play a role in psoriasis, namely the antimicrobial peptide LL-37[42], the melanocytic protease ADAMTSL5[43], and the phospholipase PLA2G4D[44]. Depending on the underlying lymphocyte reaction, self-antigens cause different immune response patterns. Desmoglein 3 (Dsg3) may stand exemplatory: Dsg3-specific type 2 lymphocytes are causative for pemphigus vulgaris[45], but a type 1 dominated immune response results in interface dermatitis[46] and type 3 lymphocytes specific for Dsg3 cause a psoriasis-like inflammation in mice[47].

In contrast to self-antigens, exogenous antigens frequently influence the resulting immune response in the skin. One example are birch or grass pollen that carry lipid mediators (PALMs) inducing a type 2

immune response[48]. In line with that observation, lymphocytes reacting to common aeroallergens in early patch test reactions are almost exclusively Th2 cells[13]. In contrast, microbial antigens derived from candida or staphylococci preferentially induce Th17 cells[49]. Guttate psoriasis is induced by molecular mimicry after infection with streptococci[50]. Lichen planus is associated with HCV infection[51].

Lessons learned for specific therapy

The current complex disease classification of ncISD results in the fact that clinical studies leading to drug approval are undertaken only in a small minority of diseases, while for most diseases an off-label use of biologics is common practice[52]. Grouping ncISD according to their molecular pathogenesis gives a rationale for the use of specific therapies. One example is the rare disease pityriasis rubra pilaris (PRP) that is grouped in the psoriatic pattern. Despite missing approval, biologics used for psoriasis are also effective in PRP[53]. Specific therapeutics targeting type 3 lymphocytes, more recently type 2 lymphocytes and finally first evidences for type 1 or type 4 targeting molecules strengthen the concept of immune response patterns in the skin.

No satisfying specific therapy is available for lichenoid (pattern 1) skin diseases (table 2). Despite the fact that Belimumab, a monoclonal antibody targeting the B lymphocyte stimulator bLys, is approved for systemic lupus erythematosus[54], efficacy at cutaneous lesions is limited. Also for lichen planus, established biologics failed[55]. Thus, there is a high unmet medical need to define cutaneous endpoints in skin autoimmune diseases, and to identify new therapeutics[56]. In line with the pathogenic concept of the lichenoid pattern, early studies investigating antibodies targeting either IFN-α or IFN-γ are encouraging[57].

More advanced are therapeutics targeting type 2 lymphocytes mediating the eczematous (pattern 2a) and the bullous (pattern 2b) patterns. Dupilumab inhibits effects of IL-4 and IL-13 via targeting the IL-4 receptor α. Phase III studies in atopic eczema show a clinical efficacy superior to all previous therapeutic attempts[58]. Neutralising the IL-4 induced antibody subtype IgE using Omalizumab is an approved and efficient therapy for chronic urticaria[59]. In contrast to type 2-targeted therapies,

conflicting evidence exists regarding efficacy of TNF inhibitors or Ustekinumab in eczematous diseases. While some case series are encouraging[12,60], others report lack of long-term evidence[61] or paradoxical eczematous reactions after therapy with TNF inhibitors[62].

An established therapy for diseases following the bullous pattern (pattern 2b) is Rituximab that eliminates B cells by targeting CD20[63]. Furthermore, it is speculated that blocking of IL-4 might be effective in bullous diseases such as pemphigus[64].

The translational revolution in ncISD started when therapies specifically inhibiting type 3 lymphocytes and the psoriatic pattern (pattern 3) became available (table 2). Today, several antibodies targeting TNF-a (Infliximab, Adalimumab, Golimumab, Etanercept), IL-12p40 (Ustekinumab), and IL-17A (Secukinumab, Ixekizumab) are approved for psoriasis with enormous clinical efficacy[65]. Recently, adalimumab was also approved for hidradenitis suppurativa (HS)[66]. Also Ustekinumab seems to be effective in HS[67]. A lot of evidence exists for efficacy of type 3 targeting therapies in other diseases grouped in the psoriatic pattern, e.g. Pityriasis rubra pilaris[68].

Therapies neutralising regulatory T cells and with that the fibrogenic (pattern 4a) or eventually the granulomatous (pattern 4b) pattern are in early clinical studies. Namely, Fresolimumab, an antibody targeting TGF-β, had positive effects in a small clinical study with patients affected from sclerosis[69]. Other specific therapies did not significantly improve skin symptoms in scleroderma, including a recently published study on Tocilizumab, an antibody targeting IL-6[70] (table 2).

For the granulomatous reaction pattern, best evidence exists for therapies targeting TNF-α or IL-12p40. While case series report conflicting evidence on efficacy[71], TNF-α inhibitors may also induce granulomas in a paradoxical manner[72]. A similar situation is reported for Rituximab[73]. Thus, no fully convincing therapeutic option to treat granulomatous skin diseases exists to date.

Technological advances drive both a better understanding of lymphocyte-mediated down-stream events in the pathogenesis of ncISD as well as development of therapeutics specifically interfering

with lymphocyte subpopulations. That is why a downstream-oriented molecular classification of ncISD as proposed in this review is reasonable and why the current classification based on clinical picture and histology needs revision. A challenge of the future will be to standardize diagnostics of ncISD and to define adequate endpoints for clinical studies beyond the diseases psoriasis and atopic eczema. Although it may not be obvious at first glance, grouping ncISD according to their immune response pattern is the first step towards individualized (also called precision) medicine. It may be speculated that the future of defining and treating ncISD will be a combination of the immune response pattern at disease-level with early pathogenic triggers at the individual patient´s level. Specifically, an individual patient will be classified into one of the six immune response patterns to determine the ideal symptomatic therapy, and in parallel specific early events – e.g., environmental trigger factors, stress, or infections – will be identified to combine the symptomatic therapy with individualized disease prevention.

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Table 1

	1	2a	2b	3	4a	4b
	lichenoid	eczematous	bullous	psoriatic	fibrogenic	granulomatous
Clinical phenotype	Polygonal papules, sharply demarcated livid plaques, fine and shiny desquamation	Vesicles, papules, erythema, erosion, crusts, desquamation, sebostasis	Bullae with surrounding erythema, erosions, crusts	Pustules, thick desquamation, sharply demarcated plaques	Skin thickening, epidermal atrophy, teleangiectasia, papules without desquamation	Brownish/ yellowish papules, without desquamation
Histological phenotype	Interface dermatitis, hypergranulosis, lymphocyte infiltration till deeper layers, cytoid bodies	Spongiosis, serum crusts, eosinophils, edema	Acantholysis/ epidermolysis with cellular infiltration	(micro)-abscess/ neutrophils, regular acanthosis, dilated capillaries	Presence of mucin/ amyloid, thickening of fibers, cellular rarefication, normal or atrophic epidermis	Presence of Granulomas, normal or atrophic epidermis
Patho-mechanism/ molecular phenotype	Apoptosis, necroptosis	Downregulation of epithelial innate immunity, Epithelial barrier impairment, Eosinophil recruitment, mast cell activation	Direct lysis of antibody, Opsonization	Recruitment of neutrophils, Activation of epithelial innate immunity, Migration of epithelial cells, Downregulation of epithelial differentiation, vascularization	Extracellular deposit of peptides/ peptidoglycans / mucins, growth factors	Granuloma formation
Major cytokines	IFN-γ	IL-4, IL-5, IL-13, IL-31	IL-4, IL-5	IL-17A, IL-17F, IL-21, IL-22	TGF-β, IL-10	IL-10, TNF-α (non Treg)
Biomarkers	Skin: CXCL10, RIP-3, Fas/FasL, Caspase 3	Blood and skin: CCL17, CCL22	Blood and skin: Specific antibody levels	Blood: HBD-2 Skin: IL-36, NOS2	Skin: Foxp3, COMP	Skin: Adipophilin[74]

Table 1. Hallmarks of immune response patterns in ncISD

Table 2

1	2a	2b	3	4a	4b
lichenoid	eczematous	bullous	psoriatic	fibrogenic	granulomatous
Alopecia areata	Atopic eczema/ dermatitis	Adult linear IgA bullous dermatosis	Acne vulgaris	Amyloidosis (Ear amyloid; nodular)	Actinic granuloma
Ashy dermatosis (Erythema dyschronicum perstans)	Childhood granulomatous periorificial dermatitis*	Brunsting-Perry cicatrical pemphigoid	Acne keloidalis (Folliculitis keloidalis nuchae)	Atrophoderma (Pierini-Pasini)	Annular elastolytic giant cell granuloma
Benign lichenoid keratosis	Chronic urticaria (cholinergic, idiopathic, physical)	Bullous pemphigoid (IgG, IgE type)	Acne fulminans	Eosinophilic fasciitis (Shulman)	Cheilitis granulomatosis (Miescher/ Melkersson-Rosenthal)
Contact dermatitis*, allergic/ photo-allergic/ photo-toxic/ irritant/ systemic	Chronic actinic dermatitis	Chronic bullous dermatosis of childhood	Acne inversa (Hidradenitis suppurativa)	Graft-versus-host disease, sclerodermatous*	Childhood granulomatous periorificial dermatitis*
Dermatomyositis	Chronic superficial dermatitis/ small plaque parapsoriasis*	Cicatrical pemphigoid	Acrodermatitis continua suppurativa (Hallopeau)	Lichen amyloidosus	Drug reaction, interstitial granulomatous
Drug eruption (lichenoid, fixed)	Contact dermatitis*, allergic/ photo-allergic/ photo-toxic/ irritant/ systemic	Dermatitis herpetiformis (Duhring)	Acute febrile neutrophilic dermatosis (Sweet)	Hyalinosis cutis et mucosae (Urbach-Wiethe)	Facial aseptic granuloma
Erythema multiforme	DRESS syndrome	Epidermolysis bullosa acquisita	Acute generalized exanthematous pustulosis	Keloid	Foreign body granuloma
Graft-versus-host disease, lichenoid	Dishydrotic eczema	Lichen planus pemphigoides*	Acute generalized pustular bacterid (Andrews)	Lichen myxedematosus	Granuloma annulare
Graft-versus-host disease, sclerodermatous*	Drug eruption, spongiotic	Pemphigoid gestationis (Herpes gestationis)	Chronic superficial dermatitis/ small plaque parapsoriasis*	Lichen sclerosus et atrophicus	Interstitial granulomatous dermatitis
Graham-Little-Piccardi-Lasseur syndrome	Eosinophilic cellulitis (Wells syndrome)	Pemphigus foliaceus	Dissecting cellulitis of the scalp	Morphea/ scleroderma (linear/ profunda)	Necrobiosis lipoidica
Keratosis lichenoides chronica*	Eosinophilic annular erythema	Pemphigus erythematosus (Senear-Usher)	Drug eruption, psoriasiform	Mucinosis (acral persistent popular; popular)	Palisaded neutrophilic granulomatous dermatitis
Lichen nitidus	Eosinophilic folliculitis (Ofuji)	Pemphigus herpetiformis	Folliculitis decalvans	Nephrogenic fibrosing dermopathy	Rosacea*
Lichen striatus	Erythema toxicum neonatorum	Pemphigus, IgA type	Impetigo herpetiformis	Parry-Romberg syndrome	Sarcoidosis
Lichen (planus, planopilaris)	Gianotti-Crosti syndrome	Pemphigoid vegetans	Infantile acropustulosis	Pretibial myxedema	
Lichen planus pemphigoides*	Granuloma gluteale infantum	Pemphigus vulgaris	Keratosis lichenoides chronica*	Reticular erythematous mucinosis (REM)	
Lupus erythematosus (discoid, subacute, chilblain, tumid)	Ichthyosis, acquired		Palmoplantar pustulosis	Scleromyxedema	
Lymphocytic infiltration (Jessner-Kanof)	Lichen simplex chronicus		PAPA syndrome	Striae distensae	
Pityriasis lichenoides et varioliformis acuta Mucha-Habermann	Nummular eczema/ dermatitis		Pityriasis rubra pilaris	Systemic sclerosis	
Pityriasis lichenoides chronica	Patchy pityriasiform lichenoid eczema		Prurigo pigmentosa*		
Polymorphic light eruption*	Perioral dermatitis		Psoriasis (plaque type, inverse, palmopantar, guttate)		
Postmenopausal frontal fibrosing alopecia (Kossard)	Pityriasis alba		Psoriasis pustulosa (palmoplantar, generalized)		
Toxic epidermal necrolysis	Polymorphic eruption of pregnancy		Reiter´s syndrome		

Vitiligo	Polymorphic light eruption*	Rosacea*	
	Prurigo nodularis	SAPHO syndrome	
	Prurigo pigmentosa*	Sebopsoriasis	
	Seborrheic dermatitis		
	Stasis dermatitis (eczema craquelé)		
	Zoon´s balanitis		

Table 2. ncISD grouped into immune response patterns. * shows more than one pattern, dominant pattern unresolved.

Figure legends

Figure 1. Lymphocyte subsets drive distinct response patterns in the skin. Distinct lymphocyte subgroups differentiate out of common naïve precursor cells under specific micro-environmental stimuli. Lymphocyte subsets are characterized by lineage-defining transcription factors as well as secreted cytokines. These cytokines elicit six distinct cutaneous response patterns. Shown are representative histological and clinical pictures of each response pattern.

Figure 2. Efficacy of specific therapeutics in index diseases of each immune response pattern. Level of evidence is indicated by size, level of efficacy by colour of circles.