General introduction

IMMUNE SYSTEM

The human immune system is comprised of a complex network that involves lymphoid organs, cells, humoral factors and cytokines. The essential function of the immune system in host defense is to protect against invading pathogens, including bacteria and viruses, and foreign bodies. The immune system can be divided in two categories; the innate or nonspecific immunity and the adaptive or specific immunity. The innate immune response forms the host's first line of defense and consists of physical and chemical barriers (skin and mucosa), effector cells (e.g. granulocytes, macrophages and dendritic cells), antimicrobial peptides (e.g. defensins and cathelicidins), soluble mediators (e.g. cytokines and complement) and cellular receptors (e.g. Toll-like receptors (TLRs)) that can provide immediate and non-specific response to a wide array of pathogens.[1] The adaptive or acquired immune response forms the second line of defense and consists of antigen-specific reactions through highly specialized T lymphocytes and B lymphocytes.[2] Whereas the innate response is rapid, the adaptive response may take days to weeks to develop. Moreover, after an initial pathogen encounters, adaptive immune cells can persist in the host for life, providing immunological memory and the capacity for rapid response in the event of re-exposure.

Primary immunodeficiency diseases (PIDs) are characterized by a compromised or entirely absent function of a part of the immune system, which makes people vulnerable for infections. In patients with a PID, the types of infections depend on the underlying immunological defects. For example, patients with a humoral immunodeficiency due to a defect in B lymphocyte function are at increased risk for recurrent infections predominantly caused by extracellular, encapsulated bacterial pathogens, mainly of the upper and lower respiratory tract and gastrointestinal tract. On the other hand, patients with a cellular immunodeficiency, i.e. defect in T lymphocyte function, have an increased risk of infections caused by intracellular pathogens, including Herpes simplex virus, *Mycobacterium*, *Listeria* and intracellular fungal infections.

PRIMARY IMMUNODEFICIENCY DISEASES

PIDs encompass a heterogeneous group of more than 430 inheritable defects of immunity caused by variants in genes encoding functional proteins of human immune cells.[3-5] However, with the increasing power of next-generation sequencing the number of recognized genetic disorders is even expanding.[5] The incidence of symptomatic PIDs is estimated at 1 in 2,000 live births with a prevalence of 1 in 10,000-12,000 in the general population, of which the majority is due to highly consanguineous populations in the Middle East/Northern African region.[4,6,7] PIDs are clinically typically characterized by an increased risk of

recurrent and/or severe infections. In addition, patients may suffer from autoimmune and autoinflammatory complications and have an increased risk of development of (hematological) malignancies and allergic disorders.[8-10] Autoimmune disorders, such as type 1 diabetes mellitus, rheumatoid arthritis and psoriasis, are the result of an immune response directed against normal bodily constituents, called auto-antigens. In autoinflammatory disorders, like familiar mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS), the innate immune system is abnormally activated, leading to recurrent episodes of fever and inflammation.[11] Autoimmune as well as autoinflammatory conditions are characterized by disruption of the normal function of the immune system, also called immune dysregulation. Interestingly, various forms of immune dysregulation, both as primary or as accompanying symptoms next to the immunodeficiency, occur in many PIDs and, therefore, PIDs could be considered as immune dysregulation syndromes.[12]

Currently, PIDs are classified into ten main groups of PID according to the predominant immunological mechanisms that are disrupted and their most relevant clinical features.[3] These groups include (i) immunodeficiencies affecting cellular and humoral immunity; (ii) combined immunodeficiencies with associated or syndromic features; (iii) predominantly antibody deficiencies; (iv) diseases of immune dysregulation; (v) congenital defects of phagocyte number, function or both; (vi) defects in intrinsic and innate immunity; (vii) autoinflammatory disorders; (viii) complement deficiencies; (ix) bone marrow failure; and (x) phenocopies of PID. The primary humoral immunodeficiencies are categorized within the predominantly antibody deficiencies (PADs) and are characterized by B lymphocyte abnormalities that result in decreased numbers or impaired function of B lymphocytes, low immunoglobulin (Ig) levels or both. On a global scale, PADs form the largest PID phenotype as more than 60% of the PIDs diagnosed in clinical practice consist of a humoral immunodeficiency.[13-18]

One of the clinical hallmarks of PIDs is an increased susceptibility to infections. Therefore, a PID should be considered when a patient has recurrent, severe, prolonged and/or difficult-to-treat infections. Based on these clinical findings, ten general warnings signs of PID have been composed by the European Society for Immunodeficiencies (ESID), mainly focusing on the presence of infectious complications, to raise the suspicion of a PID.[19] These warning signs include (i) four or more new ear infections within one year; (ii) two or more serious sinus infections within one year; (iii) two or more months on antibiotics with little effect; (iv) two or more pneumonias within one year; (v) failure of an infant to gain weight or grow normally; (vi) recurrent, deep skin or organ abscesses; (vii) persistent thrush in mouth or fungal infection of the skin; (viii) need for intravenous antibiotics to clear infections; (ix) two or more deep-seated infections including septicemia; and (x) a family history of PID. In case of presence of two or more warning signs, the suspicion for a PID should be raised.

However, despite use of these warning signs to improve earlier recognition of an underlying PID, diagnosis of PIDs is still delayed. The diagnostic delay, i.e. the time between onset of the first symptoms and diagnosis, of PIDs in the Netherlands may be up to 14.5 years for defects in innate immunity.[13] As a consequence, these inherited PIDs are diagnosed at a median age of 19.0 years.[13]

Diagnostic delay in PIDs results in persistence of symptoms, irreversible organ damage and dysfunction, recurrent hospitalizations, and functional limitations of patients, which all contribute to a lower quality of life for both mental and physical components as compared with healthy controls and patients with other chronic diseases.[20-24] Therefore, early recognition of PIDs is crucial and the identification of new PID-characteristic symptoms as early warning signs for suspicion of PIDs could aide earlier diagnosis.

Skin disorders in primary immunodeficiency diseases

It has been well recognized that a wide spectrum of both infectious and noninfectious skin disorders are common in PIDs and may be among the presenting clinical manifestations.[25-30] Overall, *Staphylococcus* (*S.*) *aureus*-induced skin infections, such as folliculitis and skin abscesses, are the most common infectious skin disorders reported in PIDs, like leukocyte adhesion defects (LADs), chronic granulomatous disease (CGD), severe congenital neutropenia and hyper IgE syndrome (HIES).[31-33] Known noninfectious skin disorders include autoimmune, autoinflammatory, malignant and allergic manifestations, which could all be attributed to immune dysregulation. Dermatitis is described as one of the most prominent noninfectious skin manifestations in PIDs.[30]

The relation between skin disorders and PIDs has been investigated in few studies. Studies in PID cohorts from Iran and Mexico have demonstrated that skin manifestations preceded and were the basis for PID diagnosis in 31.8% and 78.9% patients, respectively.[26,27] In addition, Aghamohammadi *et al.* have shown that in patients with severe and/or therapy refractory dermatitis an underlying PID could be detected in 8% of the patients, including HIES and Wiskott-Aldrich syndrome (WAS).[34] Although skin conditions seem to be frequently occurring in PIDs and may even precede the diagnosis of a PID, they are currently not considered as one of the warning signs for PIDs.

Atopic manifestations in primary immunodeficiency diseases

Atopic manifestations consist of atopic dermatitis (AD), food allergy (FA), asthma and allergic rhinitis (AR). In general, patients with severe dermatitis frequently have an atopic constitution and tendency towards development of other atopic manifestations.[35,36] The atopic manifestations encompass allergic disorders, which are already known as prevalent comorbidities in various PIDs.[4,30,37] Nonetheless, a narrative review reported occurrence of

these manifestations mainly in immunodeficiencies affecting cellular and humoral immunity, like DOCK8 deficiency, and combined immunodeficiencies (CIDs) with associated or syndromic features, such as Comèl Netherton syndrome.[30] Other original studies reported atopic manifestations most commonly in CIDs and, albeit in lower frequencies, in PADs, like selective IgA deficiency.[38-54] However, original data on atopic manifestations in PIDs are limited, mainly based on small numbers of PID patients and the diagnosis of atopic manifestations is generally not based on diagnostic tests.

ATOPIC SYNDROME

Atopy is the genetic predisposition to produce specific IgE following exposure to allergens. This predisposition results in the development of AD, FA, asthma and AR: the atopic syndrome.[55] The worldwide prevalence of these manifestations in children varies between 15-20%, 1-10%, 3-29% and 9-15%, respectively, and in adults between 1-3%, 3-4%, 2-12% and 7-42%, respectively.[56-60] The atopic march characterizes the course of atopic manifestations over time, generally starting with AD in infancy and followed by FA, asthma and AR later in childhood.[61] However, it is known that the atopic march not always follows the classic sequence and may occur at any age.[62,63] Furthermore, not all atopic patients will develop the complete spectrum of atopic manifestations.[61]

Subgroups of the atopic phenotype, termed endotypes, are possibly responsible for the heterogeneous presentation of the atopic syndrome. These endotypes are the result of variations in physiological, biological, immunological and/or genetic mechanisms, as involved in the multifactorial pathogenesis of atopic manifestations.[64] Various genetic loci associated with multiple atopic manifestations have been identified in recent years based on genome-wide association studies showing common genetic mechanisms involved.[65-74] Additionally, immune dysregulation plays an important role in the pathogenesis of the atopic syndrome. The major immunological abnormality consists of enhanced IgE production against environmental antigens triggering the release of inflammatory mediators, including histamine, in the skin, gastrointestinal tract, lungs and nose.[75] The abnormal regulation of antigen-specific IgE production in patients with atopic manifestations seems to be the result of a preferential presence of CD4+ T lymphocytes producing interleukin (IL)-4 and IL-5, but not interferon γ (IFN-γ), which suppresses IgE synthesis.[76-78]

Interestingly, atopic manifestations are prevalent comorbidities in various (monogenic) PIDs, which may be due to overlapping pathogenic pathways. Therefore, current insights in the pathways involved in PIDs could be used to define the endotypic profile of atopic patients in more detail, contributing to determination of more homogeneous subclasses of

these patients. Subsequently, pathway-targeted or even gene-targeted treatment strategies could be developed to personalize treatment regimens for the atopic syndrome based on endotype profiles.

ATOPIC DERMATITIS

AD is an important cutaneous manifestation within the atopic syndrome and one of the most common chronic inflammatory diseases. It is characterized by intense itch, erythema and scaling. Symptoms generally start in infancy with a relapsing-remitting course, but may occur at any age.[79] Based on genetic and epidemiological data, AD is found to be associated not only with the atopic syndrome but also with systemic immune-mediated inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease. This suggests that AD should be considered as manifestation of systemic inflammation rather than being inflammation limited to the skin.[80,81]

AD has a multifactorial pathogenesis characterized by three major pathophysiological changes consisting of (i) abnormalities of the skin barrier; (ii) changes in the immune response; and (iii) alterations in the skin microbiome.

Abnormalities of the skin barrier

The healthy skin forms the first line of defense of the body against harmful stimuli from the environment, like irritants, allergens, antigens and microorganisms. Furthermore, it prevents the body from excessive water loss. The impaired barrier function in AD enables environmental stimuli to penetrate into the skin and subsequently provoke an immune reaction. Various abnormalities in the skin barrier function, including an increased skin pH, reduced expression of antimicrobial peptides and a breach in epidermal lipids resulting in increased skin permeability, have been associated with development of AD.[82-85] Additionally, a filaggrin deficiency, which is involved in skin hydration and water retention within the epidermis, was found as most important genetic risk factor for AD.[83,86]

Changes in the immune response

Exposure to microorganisms through an impaired skin barrier initiates a rapid innate immune response preventing further invasion of these microorganisms. Both skin tissue damage and invading microorganisms stimulate TLRs, which are expressed by keratinocytes and antigen-presenting cells in the skin.[87] This leads to a release of inflammatory mediators that enhances the strength of tight junctions to limit penetration of allergens and microorganisms. Patients with AD, however, were shown to have decreased function of TLR2 and TLR9, which leads to alterations in the skin microbiome, increased penetra-

tion of microorganisms and more severe inflammation.[87,88] Accordingly, a genome-wide association study in AD identified candidate genes involved in regulation of the innate host defense and T lymphocyte function. This emphasizes the contribution of immunological processes in the pathogenesis of AD.[65]

In AD, the nonlesional skin shows increased numbers of T helper (Th) lymphocytes, like Th2, Th17 and Th22, representing in a pro-inflammatory state.[80] Enhanced penetration of environmental stimuli through the impaired skin barrier stimulates additional Th2 cell migration into the skin and subsequent acute inflammation.[89] These AD lesions are predominated by production of pro-inflammatory cytokines, including IL-4, IL-13 and IL-31, which further modulate the skin barrier function, amongst others, by suppressing filaggrin expression and inhibiting the production of antimicrobial peptides. Chronic inflammation promotes a shift towards a Th1 cell immune response controlled by IL-12 production by dendritic cells, possibly stimulated by *S. aureus*.[90] The Th1 cells in chronic AD lesions produce IFN-γ, which inhibits keratinocyte differentiation resulting in skin hyperplasia.

The humoral immune response is also involved in AD. Penetration of allergens through the skin leads to Th2 cytokine production. These cytokines stimulate IgE production by B lymphocytes. Many patients with AD show high IgE levels against specific allergens, like food allergens or inhalant allergens.[91-93] Moreover, some patients with AD also have increased IgE against microbial antigens, suggesting that microbes act as allergens instead of antigens.[94-99] In addition to the increased IgE levels in AD, IgG antibody production was found to be stimulated in response to contact with food antigens, leading to a pro-inflammatory response and phagocytosis of the antigen.[100] Furthermore, IgG levels against microbial antigens on the skin of AD patients are found to be higher than in controls.[101] Further identification of antibody responses against microbial antigens could help us to better understand how microbes interact with the immune system and potentially induce inflammation in AD.

Alterations in the skin microbiome

Multiple studies have described alterations of the skin microbiome in patients with AD, predominantly consisting of an overgrowth of *S. aureus* on both the lesional and nonlesional skin accompanied by reduced diversity of commensal bacteria.[102,103] Moreover, *S. aureus* colonization was found to be positively correlated with AD severity, with patients having a higher *S. aureus* load during flares.[102,104] A birth cohort study, which aimed to identify the role of the skin microbiome in AD, found that *S. aureus* colonization and lower number of commensal *Staphylococcus* species at the age of two to three months were correlated with development of AD later in life.[105] These findings suggest that cutaneous dysbiosis, including abundance of *S. aureus*, plays a role in initiation of AD. However, a

systematic review found that not only *S. aureus* is involved in the dysbiosis in AD, but also other species, including *S. epidermidis*, *Propionibacterium* and *Malassezia*.[106]

Some mechanisms by which *S. aureus* interacts with the skin barrier and immune system have been unraveled. For example, *S. aureus* can aggravate skin inflammation via the production of enterotoxins that stimulate the release of pro-inflammatory cytokines.[90,102,104,107] Furthermore, *S. aureus* produces α-toxin that induces keratinocyte damage.[108] However, the importance of *S. aureus* colonization in the complex pathogenesis of AD, as compared with the other involved genetic and immunological factors, remains poorly understood.[106]

Interaction between skin barrier, immune system and skin microbiome

The above described pathophysiological components within the multifactorial pathogenesis of AD seem to interact in a multidirectional way. Pro-inflammatory cytokines cause skin barrier impairment, while, on the other hand, an increased skin permeability results in environmental stimuli penetrating through the skin and provoking an immune reaction.[109,110] Both alterations in the immune system and skin barrier impairment might favor *S. aureus* colonization and staphylococcal antigens contrarily seem to interact with the immune system and skin barrier.[103,108,111] However, studies on the interaction between the immune system and *S. aureus* are still scarce. Further evaluation of the antibody response against antimicrobial antigens could provide insights in the antigens that are expressed by the skin microbiome *in vivo* and will reveal how the immune system of AD patients counteracts these antigens. Thereby, the contribution of each of the three factors to the AD phenotype is still unknown.

As previously described, *S. aureus* is abundant in the skin microbiome of AD patients, which could therefore be a target for treatment in AD. Current long-term anti-staphylococcal treatment strategies, like antibiotics, have the disadvantages of affecting the commensal microbiota and inducing bacterial resistance.[112-114] In this context, it would be interesting to study the effect of an endolysin selectively targeting *S. aureus* on AD symptoms in a randomized controlled trial (RCT).

AIMS OF THE THESIS

- To evaluate whether skin disorders and atopic manifestations are prognostic warning signs for PIDs in order to shorten the diagnostic delay.
- To define homogeneous endotypes within the atopic phenotype based on known pathological pathways in PIDs in order to improve patient stratification for future pathway-targeted treatment strategies.

- To provide an overview of the antibody responses against *S. aureus* antigens, as most abundant microorganism in patients with AD, in order to gain insight into the interaction between the immune system and skin microbiome in the pathogenesis of AD.
- To study the effect of a targeted intervention against *S. aureus* on AD symptoms in order to elucidate the contribution of the microbiome within the multifactorial pathogenesis of AD.

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