



Human hyper-IgE syndrome: singular or plural?

Qian Zhang¹ · Bertrand Boisson^{1,2,3} · Vivien Béziat^{2,3} · Anne Puel^{1,2,3} · Jean-Laurent Casanova^{1,2,3,4,5}

Received: 28 April 2018 / Accepted: 2 August 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Spectacular progress has been made in the characterization of human hyper-IgE syndrome (HIES) over the last 50 years. HIES is a primary immunodeficiency defined as an association of atopy in a context of very high serum IgE levels, characteristic bacterial and fungal diseases, low-level clinical and biological inflammation, and various non-hematopoietic developmental manifestations. Somewhat arbitrarily, three disorders were successively put forward as the underlying cause of HIES: autosomal dominant (AD) STAT3 deficiency, the only disorder corresponding to the original definition of HIES, and autosomal recessive (AR) DOCK8 and PGM3 deficiencies, in which atopy and high serum IgE levels occur in a context of manifestations not seen in patients with typical HIES. Indeed, these three disorders disrupt different molecular pathways, affect different cell types, and underlie different clinical phenotypes. Surprisingly, several other inherited inborn errors of immunity in which serum IgE levels are high, sometimes almost as high as those in HIES patients, are not considered to belong to the HIES group of diseases. Studies of HIES have been further complicated by the lack of a high serum IgE phenotype in all mouse models of the disease other than two *Stat3* mutant strains. The study of infections in mutant mice has helped elucidate only some forms of HIES and infection. Mouse models of these conditions have also been used to study non-hematopoietic phenotypes for STAT3 deficiency, tissue-specific immunity for DOCK8 deficiency, and cell lineage maturation for PGM3 deficiency. We review here the history of the field of HIES since the first clinical description of this condition in 1966, together with the three disorders commonly referred to as HIES, focusing, in particular, on their mouse models. We propose the restriction of the term “HIES” to patients with an AD STAT3-deficiency phenotype, including the most recently described AR ZNF341 deficiency, thus excluding AR DOCK8 and PGM3 deficiencies from the definition of this disease.

Introduction

Hyper-IgE syndrome (HIES) has a rich history, but no universal definition. Three disorders were successively designated as HIES. Job’s syndrome was first described in 1966 (Davis et al. 1966), shown to be autosomal dominant (AD) in 1999 (Grimbacher et al. 1999), and shown to be due to monoallelic loss-of-function (LOF) *STAT3* mutations in 2007

(Minegishi et al. 2007). Autosomal recessive (AR) forms of HIES were described in 2004 (Renner et al. 2004), with biallelic mutations of *DOCK8* described in 2009 (Zhang et al. 2009; Engelhardt 2009) and of *PGM3* in 2014 (Sassi et al. 2014; Stray-Pedersen et al. 2014; Zhang et al. 2014a, b, c). However, many other inborn errors of immunity leading to high serum IgE levels and severe infections, including Wiskott–Aldrich syndrome (*WAS* or *WIPF1* mutations), DiGeorge Syndrome (22q11.2DS), Omenn Syndrome (hypomorphic mutations in genes for which null alleles underlie SCID), immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX, *FOXP3* mutations), and Netherton/Comèl-Netherton syndrome (*SPINK5* mutations), have never been considered to belong to the HIES group. AD STAT3, AR DOCK8, and AR PGM3 deficiencies are currently considered to be *bona fide* forms of HIES by some investigators (Engelhardt 2009; Wu et al. 2016; Picard et al. 2018; Yang et al. 2014), but not others (Zhang et al. 2009, 2016; Picard et al. 2018; Peanne 2017; Lundin et al. 2015). Only Job’s syndrome and PGM3 deficiency are recognized

✉ Qian Zhang
qzhang02@rockefeller.edu

¹ St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA

² Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Paris, France

³ Paris Descartes University, Imagine Institute, Paris, France

⁴ Pediatric Hematology-Immunology Unit, Necker Hospital for Sick Children, AP-HP, 75015 Paris, France

⁵ Howard Hughes Medical Institute, New York, NY, USA

as HIES in the International Union of Immunological Societies 2018 classification, which considers DOCK8 deficiency to be a combined immunodeficiency (CID) (Picard et al. 2018). These three disorders have related, but different immunological and clinical phenotypes, with only a modest overlap. We review here the history of HIES, and what is currently known about its three proposed genetic forms, and we discuss the contribution of the corresponding mouse models to studies of the pathogenesis of this disease. Like other investigators (Lundin et al. 2015; Zhang et al. 2016), we suggest that the term “HIES” best applies to patients with a phenotype of AD STAT3 deficiency.

The history of IgE and HIES in human diseases

The definition of “HIES” has been revised and extended on many occasions over the years. Paradoxically, HIES was first described before the discovery of IgE. In May 1966, Ralph J. Wedgwood and coworkers described two red-haired girls with recurrent “cold” staphylococcal abscesses, eczema, and respiratory infections (Davis et al. 1966). They named the disease “Job’s syndrome,” based on the skin boils of the patients. A month later, Robert A. Good and coworkers discovered that X-linked chronic granulomatous disease (CGD) was caused by an inborn error of phagocytic cells resulting in a failure to destroy the bacteria taken up by phagocytosis (Holmes et al. 1966). At the time, some argued that Job’s syndrome was a variant of CGD (Bannatyne et al. 1969), but this view was overturned in 1969, when Wedgwood demonstrated normal nitroblue tetrazolium (NBT) reduction, indicating that superoxide anion production in phagocytes was normal after phagocytosis in the leukocytes of patients with Job’s syndrome, at odds with the characteristic features of CGD (White et al. 1969). Job’s syndrome was subsequently recognized as a distinct condition, different from CGD. IgE was discovered 2 months after the first description of Job’s syndrome in 1966 (Ishizaka et al. 1966a, b) and it was not until 1971 that serum IgE levels were first reported to be high in patients with Job’s syndrome (Pabst et al. 1971). In 1972, Buckley and coworkers described “hyper-IgE syndrome with recurrent infections,” a new syndrome consisting of recurrent cutaneous, pulmonary, and joint abscesses, growth retardation, coarse facies, chronic dermatitis, and extremely high serum IgE levels (Buckley et al. 1972). Between 1972 and 1980, Job’s syndrome and “hyper-IgE syndrome with recurrent infections” were considered to be different conditions, although similarities between them, including high serum IgE levels and specificity, anti-staphylococcal IgE antibodies, and leukocyte chemotaxis, were recognized and analyzed (Clark et al. 1973; Hill et al. 1974, 1976; Hill and Quie 1974; Pincus et al. 1975; Van Scoy et al.

1975; Dahl et al. 1976; Witemeyer and Epps 1976; Paslin and Norman 1977; Weston et al. 1977; Buckley and Becker 1978; De Cree et al. 1978; Stanley et al. 1978). At the start of the 1980s, researchers in the field finally agreed that Job’s syndrome was not restricted to red-haired females and was identical to “hyper-IgE syndrome with recurrent infections” (Buckley and Becker 1978; Stanley et al. 1978; Gammon 1979; Schopfer et al. 1979; Berger et al. 1980; Donabedian and Gallin 1983; Dreskin et al. 1985). The term and the acronym HIES emerged in 1983 (Donabedian and Gallin 1983; Dreskin et al. 1985; Donabedian et al. 1982; Garraud et al. 1999).

Before Job’s syndrome and “hyper-IgE syndrome with recurrent infections” were combined under the same umbrella as HIES, other conditions had been shown to be associated with high serum IgE levels. Between 1966 and 1980, extremely high serum IgE levels were observed in patients with several other PIDs, including Wiskott–Aldrich syndrome, DiGeorge syndrome, and Omenn syndrome. These conditions were rightly seen to be very different from both Job’s syndrome and “hyper-IgE syndrome with recurrent infections,” and were, therefore, not included in the definition of HIES. Following the recognition of HIES as a single disorder, efforts were made to evaluate its clinical phenotypes by a scoring system and to define its mode of inheritance and map the genetic defect (Donabedian and Gallin 1983; Grimbacher et al. 1998, 1999a, b). HIES was first shown to be autosomal dominant in 1999 (Grimbacher et al. 1999). Its clinical features were characterized and found to include recurrent skin and pulmonary abscesses, extremely high serum IgE levels, and facial and skeletal features (Grimbacher et al. 1999). In 2004, Grimbacher and coworkers proposed the classification of HIES into two subgroups: the AD form as classical Job’s syndrome, and the AR form, which lacks skeletal and dental abnormalities but includes recurrent viral and fungal infections (Renner et al. 2004). Soon after this report, mutations of *TYK2* (AR, 2006) (Minegishi et al. 2006), *STAT3* (AD, 2007) (Minegishi et al. 2007; Holland et al. 2007; Renner et al. 2007), *DOCK8* (AR, 2009) (Zhang et al. 2009; Engelhardt 2009), and *PGM3* (AR, 2014) (Sassi et al. 2014; Stray-Pedersen et al. 2014; Zhang et al. 2014a, b, c) were sequentially reported as genetic causes of disease in patients enrolled in “HIES” cohorts. STAT3 deficiency has since been universally recognized as the major AD form of HIES (Kumanovics et al. 2010; Chandris et al. 2012). By contrast, the suggestion that DOCK8 deficiency is the major AR form of HIES has remained controversial (Freeman and Holland 2010; Heimall et al. 2010; Zhang and Su 2011). Indeed, DOCK8 deficiency has also been categorized as a combined immunodeficiency (CID) (i.e., a T- and B-cell deficiency) by one of the two groups that discovered it (Zhang et al. 2009) and by the International Union of Immunological Societies (Picard et al.

2018). PGM3 deficiency is very rare and its classification as a form of HIES has not been contested (Yang et al. 2014). Finally, TYK2 deficiency, which has been shown to underlie HIES in two families (Minegishi et al. 2006; Fuchs et al. 2016), has been tentatively redefined as a cause of mycobacterial and viral diseases in a context of normal serum IgE levels, based on its identification in multiple families with this phenotype (Picard et al. 2018; Kreins et al. 2015). The meaning of the term “HIES” has thus evolved considerably over the last 50 years. Before reviewing STAT3, DOCK8, and PGM3 deficiencies in humans and mice, and discussing their relevance to HIES, we will begin by briefly reviewing the current state of knowledge regarding IgE.

IgE and its production

IgE was first isolated in 1966 (Ishizaka et al. 1966a, b; Lyons and Milner 2018; Johansson and Bennich 1967), in the same year as Job’s syndrome was first described. The existence of IgE was actually suspected 45 years before its physical discovery (Ishizaka and Ishizaka 2016). In 1921, Prausnitz and Küstner found that allergies could be transferred to previously unaffected individuals by the transfer of serum from allergic patients. Erythema-wheal assays were used to test for this serum fraction, which was named “reagin.” IgG, IgM, IgA, and IgD were discovered sequentially between the 1930s and 1960s. However, the name IgE (“E” for the erythema-wheal assays) was coined by Ishizaka and coworkers, who eventually isolated it from human serum in 1966. Mouse IgE was identified a couple of years later (Prouvost-Danon et al. 1972). Its low abundance probably accounts for IgE being the last human Ig isotype to be discovered. In the general population, serum IgE concentrations are at least three orders of magnitude lower than those of any other type of Ig. Despite this low abundance, IgE typically exerts rapid, potent, and broad effects on a wide range of cell types, through FcεRI/FCER1 and CD23/FCER2 (Oettgen 2016). Abnormally high serum IgE levels are, therefore, an alarming trait. It is not rare for Job’s syndrome patients to have serum IgE levels as high as 10,000 IU/ml, a thousand times higher than the upper limit of the normal range and almost in the range normally recorded for IgM. Nevertheless, the diagnostic cutoff for HIES is > 1000 IU/ml, which can overlap with atopic diseases and parasitic infections (Cooper et al. 2008; Davila et al. 2015). The name “HIES” may have contributed to the setting of this diagnostic cutoff. Most HIES patients have extremely high IgE levels, but a small proportion of patients with clear genetic diagnoses present with relatively low IgE levels (see below for further discussion). “HIES” therefore requires a relatively low cutoff point, resulting in some overlap with other common diseases, to prevent the exclusion of patients with the

same genetic defects but lower levels of IgE. The situation is rendered even more complicated by the normal serum IgE concentrations observed in some HIES patients later in life (Grimbacher et al. 1999). Thus, high IgE levels are very good indicators, but are not absolutely required for the diagnosis of HIES.

The molecular and cellular basis of IgE production in humans remains poorly understood due to a number of technical challenges. Most of what we know has been gleaned from mouse models, even though mouse IgE was not discovered until 1972, 6 years after the discovery of human IgE (Prouvost-Danon et al. 1972). We now understand that the *Iε* promoter is activated by IL-4, acting in synergy with IL-13 and CD40-CD40L signaling (Oettgen 2016; Pene et al. 1988; Punnonen et al. 1993). The origin of IgE-producing B cells and plasma cells remains unclear. In antibody responses involving other isotypes, germinal center B cells undergo clonal expansion, somatic hypermutation (SHM), and class switch recombination (CSR), and long-term memory B cells are generated. The process appears to be different for IgE-producing B cells. Following their activation and initial expansion, IgE-expressing B cells are either rapidly becoming plasma cells at the expense of memory B cells, or immediately undergo apoptosis. High-affinity IgE is generated through a unique process, in which B cells first undergo IgM to IgG CSR, and then IgG to IgE CSR, also known as sequential CSR (Oettgen 2016; Xiong et al. 2012; Looney et al. 2016; He et al. 2017; Zhang and Seppanen 2018). Any abnormality of these processes could potentially lead to the unregulated production of IgE, and thus to hyper-IgE, with or without allergic manifestations. Given the complexity of these processes, the difficulties involved in studies of the synthesis of IgE and pathogenesis of HIES in humans might best be overcome by the use of new emerging mouse models. Conversely, the discovery of genetic causes of HIES, or perhaps eventually of isolated IgE deficiency, may shed light on the mechanisms controlling human IgE production. A very elegant review on inborn errors of atopic disorders and their relationship to abnormal IgE production was recently published (Lyons and Milner 2018).

Job’s syndrome

Most patients with Job’s syndrome suffer from infections, atopic disease, and abnormalities of the joints, skeletal, dental, and vascular systems. The clinical features of Job’s syndrome have been reviewed extensively in more than 200 patients worldwide (Donabedian and Gallin 1983; Chandris et al. 2012; Paulson et al. 2008; Woellner et al. 2010; Vogel et al. 2015). Two related scoring systems, the “NIH score” and the “STAT3 deficiency score” (Grimbacher et al. 1999a, b; Woellner et al. 2010), have been proposed to assist

clinical diagnosis, because many of the early manifestations are non-specific and the penetrance of each phenotype is both age-dependent and incomplete. The early signs of Job's syndrome are mostly atopic disorders, including neonatal rash and chronic atopic dermatitis. Patients with Job's syndrome are susceptible to two key pathogens: *Staphylococcus aureus* and *Candida albicans*. The typical "cold" skin and lung abscesses are mostly caused by *S. aureus* or, more rarely, *Streptococcus pneumoniae*, whereas lung infections, particularly if secondary, can also be caused by *Aspergillus* and *Pseudomonas* (Chandesris et al. 2012). Typically, patients also display chronic mucocutaneous candidiasis (CMC) (43–85%). Although severe, the fungal infections are usually limited to mucocutaneous surfaces and the lungs. A hallmark of STAT3-deficient patients is poor or delayed clinical and biological inflammation, as best exemplified by the cold abscesses observed in these patients (Chandesris et al. 2012). Non-hematopoietic abnormalities include dental abnormalities (retention of the primary teeth), facial abnormalities (coarse appearance), osteopenia (resulting in multiple fractures), and various vascular malformations (including coronary artery aneurysms). About 7–9% of the patients also develop malignancies, especially various types of lymphoma, including Burkitt, non-Hodgkin, histiocytic lymphoma, peripheral T-cell, and other B-cell lymphomas.

The immunological phenotypes include high IgE levels, eosinophilia, low levels of Th17 cells, and memory B cell lymphopenia. Almost all patients have extremely high total IgE levels accompanied with eosinophilia. However, patients with normal IgE levels have occasionally been reported (Grimbacher et al. 1999; Chandesris et al. 2012). Serum IgE levels decline with age, particularly in adult patients (Grimbacher et al. 1999). T-cell differentiation, particularly for Th17 cells (de Beaucoudrey et al. 2008; Ma et al. 2008; Milner et al. 2008; Renner et al. 2008; Minegishi et al. 2009), is disrupted; T-cell activation and proliferation in patients are normal overall, distinguishing this condition from SCID or CID. Despite the wide range of immunological and non-immunological phenotypes (Deenick et al. 2013; Wilson et al. 2015), around 80% of patients live to an age of at least 50 years (Chandesris et al. 2012). Minegishi and coworkers, as well as several other groups, discovered that Job's syndrome is caused by heterozygous, LOF, and dominant-negative (DN) *STAT3* mutations (Minegishi et al. 2007; Holland et al. 2007; Renner et al. 2007). About 90 different mutations of *STAT3* have been reported, the vast majority of which are missense (Vogel et al. 2015). No more than ten mutations have been demonstrated experimentally to be dominant-negative. However, no stop-gain mutations have been proven to cause Job's syndrome, suggesting that the underlying mechanism in Job's syndrome is not one of haploinsufficiency. Three individuals are heterozygous for a mutation that creates a premature stop, which has however

not been proven to underlie haploinsufficiency and Job's syndrome (Abolhassani et al. 2018). Interestingly, three families with mosaic mutations in multiple tissues have been described. The mosaic carriers presented intermediate phenotypes when compared with their heterozygous offspring family members (Spielberger et al. 2012; Hsu et al. 2013). The complexity of STAT3 signaling and the broad expression of *STAT3* in many tissues have made it harder to understand the mechanism of disease, but both human cells and mouse models have recently been used to elucidate this mechanism.

The complexity of Job's syndrome is not surprising, because STAT3 is pleiotropic (O'Shea et al. 2015). There are seven STATs (signal transducer and activator of transcription, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6), and four JAKs (Janus kinase, JAK1, JAK2, JAK3, TYK2) in humans and mice. More than 50 different cytokines and their receptors make selective use of a combination of JAKs and STATs to transmit signals regulating tissue development, organism homeostasis, and host defense (Deenick et al. 2013; Wilson et al. 2015; O'Shea et al. 2015; Villarino et al. 2015). STAT3 is ubiquitous and involved in many cytokine responses, including IL-6. The canonical transcriptional activity of STAT3 has been studied intensively for over 20 years. Following cytokine binding to the receptors, the Y705 residue at the C-terminus of STAT3 is phosphorylated by JAK tyrosine kinases. Phosphorylated STAT3 (p-STAT3) molecules then form homodimers or heterodimers with other STATs via the SH2 domain and are translocated to the nucleus, where they bind directly to DNA and promote transcription. S727 phosphorylation further increases the transcriptional activity of the molecule (O'Shea et al. 2015). Unphosphorylated STAT3 was recently shown to bind to DNA and to exert transcriptional activities not normally associated with tyrosine kinase-mediated signaling (Hillmer et al. 2016; Yang et al. 2005, 2007a, b; Yang and Stark 2008). Moreover, STAT3 has been shown to have non-transcriptional functions in mitochondria, including electron transport chain regulation, gamma-glutamyl cycle control, and reactive oxygen species (ROS) regulation (Hillmer et al. 2016; Wegrzyn et al. 2009; Garama et al. 2015). Mitochondrial STAT3 has also been implicated in Ras-mediated oncogenic transformation (Hillmer et al. 2016; Gough et al. 2009, 2013). However, it remains unclear whether these non-canonical functions of STAT3 are related to human disease.

The discovery of AD LOF *STAT3* deficiency paved the way for studies of the many defective pathways in Job's syndrome patients (Mogensen 2013). A patient with an AR deficiency of GP130 (also known as IL6ST), a receptor chain common to the receptors for IL-6, IL-11, IL-27, OSM, and LIF was recently shown to suffer from a disease resembling Job's syndrome, but with normal numbers of

Th17 cells (Schwerd et al. 2017). Meanwhile, defects in IL-11RA (Nieminen et al. 2011; Keupp et al. 2013; Miller et al. 2017) and LIFR (Kosfeld et al. 2017) have been discovered in patients with craniosynostosis and congenital anomalies of the kidneys and urinary tract (CAKUT), respectively. The GP130-deficient patient also presented with high IgE levels, susceptibility to bacterial infections, eczema, and skeletal abnormalities, suggesting that GP130 signaling through STAT3 is responsible for these defects, which are seen in patients with both these disorders. Inborn errors affecting specific cytokines and their receptors facilitated further dissection of the phenotypes seen in patients with Job's syndrome. The discovery of defective Th17 cell differentiation in patients with this syndrome (de Beaucoudrey et al. 2008; Ma et al. 2008; Milner et al. 2008; Renner et al. 2008; Minegishi et al. 2009), together with inborn errors of IL-12R β 1, IL-17A/F, and the IL-17RA/IL-17RC receptor complex, RORC, and ACT1 (Puel et al. 2010a, b, 2011, 2012; Liu et al. 2011; Cypowyj et al. 2012; Boisson et al. 2013; Ling et al. 2015; Levy et al. 2016; Ouederni et al. 2014; Okada et al. 2015), strongly suggested that IL-17 activity played a key role in attracting neutrophils to the tissues and controlling mucocutaneous fungal infections (Puel et al. 2010a, b, 2012). The recent discovery of an ERBIN-deficient family has bridged the gap between STAT3 and TGF- β signaling (Lyons et al. 2017). STAT3 promotes the expression of ERBIN, which impairs TGF- β signaling, thereby skewing CD4⁺ T-cell differentiation and impairing Treg functions. Two out of three ERBIN-deficient patients have slightly high serum IgE levels and allergic disease, implying that other STAT3 pathways contribute to the extremely high serum IgE concentrations in patients with Job's syndrome. LOF defects of IL-21 and IL-21R lead to inflammatory bowel diseases and cryptosporidial infections, respectively (Kotlarz et al. 2013, 2014; Salzer et al. 2014; Avery et al. 2010). Patients with these defects also display defective Ig class switching and slightly high serum IgE levels, suggesting that insufficient IL-21 signaling is not the only cause of hyper-IgE syndrome (Kotlarz et al. 2013, 2014; Salzer et al. 2014; Avery et al. 2010; Erman and Haematologica 2015; Ma et al. 2016). Other inborn errors have been used to analyze the non-hematopoietic phenotypes, which are much more difficult to study in patients, due to the lack of access to primary cells (Mogensen 2013). Studies of LIFR deficiency, a severe AR disease also known as Stuve-Wiedemann syndrome (SWS), have suggested that many of the skeletal abnormalities may be associated with insufficient LIF signaling (Kosfeld et al. 2017; Dagoneau et al. 2004; Gaspar et al. 2008; Yesil et al. 2014). Moreover, the features of patients with AR IL-11RA deficiency suggest that the craniosynostosis and supernumerary teeth seen in Job's syndrome patients may result from insufficient IL-11 signaling (Nieminen et al. 2011; Keupp et al. 2013;

Miller et al. 2017). These signaling pathways may interact and overlap in Job's syndrome patients, thereby contributing jointly to the various phenotypes. Studies in both Job's syndrome patients and patients with defects of the STAT3 pathways have begun to resolve the various functions of human STAT3 and the pathogenesis of the various phenotypes of Job's syndrome.

The only mouse model of Job's syndrome currently available was reported in 2013: a transgenic mouse reproducing some of the features of Job's syndrome in humans (Steward-Tharp et al. 2014; Siegel et al. 2013). The AD mode of inheritance for this disease was mimicked by introducing the V463del mutation, which is common in patients, into the mice via a BAC transgene. The mutant mouse carried two copies of wild-type *Stat3* (wt-Stat3) and two copies of the mutant *Stat3* gene (mut-Stat3). Total Stat3 (both wt-Stat3 and mut-Stat3) protein levels were similar to those in the parental mouse strain. The V463del mutation affects the DNA-binding domain. It impairs transcriptional activity but does not affect the normal phosphorylation of the Y705 residue on activation. This study did not report the levels of the mut-Stat3 protein in mice, but the mutation was dominant, as shown by the level of transcriptional activity upon stimulation with IL-6. The mouse reproduced several of the main features of Job's syndrome, including high IgE levels and a failure to generate Th17 cells. The mutant mouse also displayed impaired control of intestinal *Citrobacter* infection, and a higher mortality on challenge with LPS. More interestingly, bone marrow transplantation restored the production of IL-17 and IL-22 in the mutant mouse, whereas the control of *Citrobacter* infection was only partially rescued, suggesting that non-hematopoietic functions of STAT3 play an important role in host defense (Steward-Tharp et al. 2014). Studies in the same mouse model also demonstrated that the mast cell degranulation induced by IgE receptor cross-linking was impaired in mut-Stat3 mice, consistent with the low levels of food allergy and anaphylaxis in patients despite their high IgE levels (Steward-Tharp et al. 2014). Overall, this mouse model had a phenotype similar to that of patients, including high IgE levels, and is therefore promising for future studies of this multifaceted disease.

In addition to the attempts made to model AD Job's syndrome, murine recessive STAT3 deficiency models have taught us much about the functions of STAT3 (Table 1). Germline *Stat3* deletion is embryo-lethal (Hillmer et al. 2016). However, it is unclear whether heterozygous animals are entirely normal or harbor certain defects. Due to the lethality of the germline knockout in mice, four separate floxed mouse strains have been established with the cre-LoxP system. The canonical transcriptional activity of Stat3 is abolished in all four strains. Many tissue/cell-specific knockout strains have been generated from these four floxed strains and analyzed. Both the myeloid and lymphoid lineages of

Table 1 Various mouse strains modeling the human diseases of HIES

Human disease	Mouse strain	Modeling of human disease
AD, LOF, STAT3 deficiency (Job's syndrome)	Stat3 ^{wt,wt/V463del,V463del} (BAC transgene) Steward-Tharp et al. (2014), Siegel et al. (2013)	High IgE, low Th17 Impaired mast cell degranulation induced by IgE receptor cross-linking Impaired control of intestinal Citrobacter infection High mortality upon LPS challenge
	Germline knockout Hillmer et al. (2016)	Lethal
	TIE2-Cre-Stat3 Δ /flox Panopoulos et al. (2006), Nguyen-Jackson et al. (2010), Zhang et al. (2010)	Impaired G-CSF-induced emergency granulopoiesis Impaired neutrophil chemotaxis towards CXCR2 ligands
	CD11c-Cre-Stat3 ^{flox/flox} Melillo et al. (2010)	Selectively impaired pDC differentiation
	Mx1-Cre-Stat3 ^{flox/flox} , Lys2-Cre-Stat3 ^{flox/flox} , and TIE2-Cre-Stat3 Δ /flox Hillmer et al. (2016), Laouar et al. (2003), Cheng et al. (2008), Takeda et al. (1999)	Abnormal DC and macrophage maturation and differentiation
	CRE-ER-Stat3 ^{flox/flox} and TIE2-Cre-Stat3 Δ /flox Zhang et al. (2014)	Enhanced osteoclast development mediated by macrophages and osteoclast precursors
	Mx1-Cre-Stat3 ^{flox/flox} Chou et al. (2006)	Impaired Flt3L signaling in common lymphocyte progenitors
	CD19-Cre-Stat3 ^{flox/flox} Fornek et al. (2006), Kane et al. (2016)	Impaired IL-21 signaling in maturation of B and plasma cells Impaired B cell survival and elevated IgE
	TIE2-Cre-Stat3 Δ /flox Yang et al. (2007a, b)	Impaired IL-6 and TGF- β signaling in Th17 cell differentiation
AR, LOF, DOCK8 deficiency	<i>cpm, pri</i> , germline knockout (All LOF deficiency) Zhang et al. (2014), Randall et al. (2009), Harada et al. (2012), Lambe et al. (2011), Randall et al. (2011), Crawford et al. (2013), Janssen (2017), Singh (2017), Singh et al. (2014), Flesch et al. (2015), Krishnaswamy et al. (2015), Jin et al. (2016), Miyamoto et al. (2016)	Normal IgE Defective MZB Impaired affinity maturation and the persistence of IgG responses to T cell-dependent antigens Decreased survival in T, NKT, Tregs, ILCs Increased susceptibility to cutaneous HSV infection Loss of tissue-resident memory T cells in the skin Abnormal interstitial T cells and DCs migration
AR, hypomorphic, PGM3 deficiency	Pgm3 ^{mld1/mld1} (hypomorphic) Greig et al. (2007)	Low platelets Anemia Impaired B cell maturation Low T cell count Embryonic-lethal
	Pgm3 ^{gt/gt} (LOF) Greig et al. (2007)	
	Pgm3 ^{mld1/gt} Greig et al. (2007)	SCID-like phenotypes, extremely low peripheral T cell counts, absence of mature B cells Dysmorphic features; glomerulonephritis

the immune system have been studied, and these analyses have yielded intriguing results. It has long been debated whether neutrophils from patients with Job's syndrome display impaired chemotaxis (Clark et al. 1973; Hill et al. 1974, 1976; Hill and Quie 1974; Pincus et al. 1975; Van Scoy et al. 1975; Dahl et al. 1976; Wittemeyer and Epps 1976; Paslin and Norman 1977; Weston et al. 1977; De Cree et al. 1978; Church et al. 1976). Conflicting results have been obtained in human studies, whereas mouse studies have clearly shown that G-CSF-induced emergency granulopoiesis is defective in Stat3-deficient neutrophils, together with chemotaxis towards CXCR2 ligands (Panopoulos et al. 2006; Nguyen-Jackson et al. 2010; Zhang et al. 2010). During the acute

phase of infection, particularly in candidiasis, the endothelial cells produce G-CSF, triggering the immediate mobilization of neutrophils from the bone marrow and expansion of the immature granulocyte population to increase the neutrophil reserve. This results in a rapid increase in the number of circulating neutrophils. This G-CSF-mediated acute response is Stat3-dependent. A failure to mobilize neutrophils, together with the lack of Th17 cells in Job's syndrome patients (Milner et al. 2008), may contribute to their susceptibility to bacterial and fungal infections, especially at mucocutaneous surfaces (Cypowij et al. 2012).

Other functions of Stat3 have also been revealed by studies of conditional knockout mouse models (Table 1). Several

Stat3-dependent signaling pathways, including the Flt3, G-CSF, IL-6, and IL-10 pathways, govern the maturation and differentiation of dendritic cells (DCs) (Hillmer et al. 2016). DCs can be classified as conventional DCs (cDCs), which migrate into tissues to perform phagocytosis and present antigens, and plasmacytoid DCs (pDCs), which produce large amounts of type I interferon (IFN). Stat3 overexpression drives the development of hematopoietic progenitors into cDCs and pDCs. The Stat3-dependent Flt3 signal is particularly important for the differentiation of pDCs. The conditional deletion of Stat3 in CD11c-expressing cells selectively impairs pDC differentiation, with little effect on the cDC compartment (Melillo et al. 2010; Laouar et al. 2003). By contrast, Stat3-mediated IL-6 signaling and IL-10 signaling have been shown to suppress DC maturation and activation by reducing the expression of MHC II, costimulation molecules, SA100A9, and PD-L1, and by limiting TLR-induced pro-inflammatory responses (Hillmer et al. 2016; Melillo et al. 2010; Cheng et al. 2008; Kitamura et al. 2005; Wolffe et al. 2011; Takeda et al. 1999). Stat3 also restrains the RANK and TLR4 pathways by directly inhibiting the expression of a key E2 ubiquitin-conjugating enzyme, Ubc13, in these pathways (Zhang et al. 2014). Macrophages and osteoclast precursors from Stat3-deficient mice display enhanced osteoclast development following RANK stimulation, potentially accounting for the skeletal abnormalities seen in Job's syndrome patients. Lymphocyte counts are normal in Job's syndrome, but studies of mouse models have shown that Stat3-dependent signaling pathways are indispensable in many lymphoid lineages, including the Flt3L signaling pathway in common lymphocyte progenitors (Chou et al. 2006), IL-6 and TGF- β signaling in Th17 cell differentiation (Hillmer et al. 2016; Yang et al. 2007a, b), and IL-21 signaling in the expansion and maturation of B cells and plasma cells (Hunter and Jones 2015; Fornek et al. 2006). Intriguingly, B cell-specific deletion of Stat3 in mouse models challenged with antigen resulted in elevated IgE, suggesting that the hyper-IgE in Job's patients might be B cell-intrinsic (Kane et al. 2016). Studies of the conditional deletion of Stat3 in multiple lineages have improved our overall understanding of the mechanisms underlying the various phenotypes seen in Job's syndrome patients.

DOCK8 deficiency

Inherited DOCK8 deficiency was first reported in 2009 (Zhang et al. 2009; Engelhardt 2009). Years earlier, Bodo Grimbacher's group had already distinguished AR-HIES from Job's syndrome, and described AR-HIES as a condition characterized by susceptibility to viral and fungal infections rather than bacterial infections (Renner et al. 2004). We now know that a sizeable proportion of the AR-HIES patients

known at the time were actually DOCK8-deficient. Most patients present with severe allergy, chronic infections, and early-onset cancer. The clinical presentation and treatment of this condition were recently extensively reviewed; about 200 patients have been reported worldwide (Zhang et al. 2016; Aydin et al. 2015; Engelhardt et al. 2015). The first sign suggestive of DOCK8 deficiency is usually severe allergies, including atopic dermatitis soon after birth, asthma, multiple food, and respiratory allergies. However, despite this initial presentation of severe allergy in DOCK8-deficient patients, the hallmark of the disease is a broad spectrum of infections, including chronic cutaneous viral infections, recurrent respiratory infections, and mucocutaneous candidiasis. More than half the patients have been reported to have life-threatening infections, with an overall survival as low as 37% at 30 years of age (Aydin et al. 2015). It is, therefore, unsurprising that DOCK8 deficiency is increasingly considered to be a CID rather than a form of HIES, as proposed by Helen Su in her seminal paper (Zhang et al. 2009, 2016). The immunological phenotypes of DOCK8 deficiency include high serum IgE levels, eosinophilia, and T- and NK-cell lymphopenia. Serum IgE levels are high in almost all patients, with a median value of about 2000 IU/ml (Aydin et al. 2015). DOCK8, which is mostly expressed in hematopoietic cells, belongs to the dedicator of cytokinesis (DOCK) family. All 11 members of this family function as atypical guanine nucleotide exchange factors (GEFs), activating small Rho GTPases, such as RAC1, RAC2, and CDC42 (Zhang et al. 2014). DOCK8 was first isolated and cloned in 2004 as a CDC42-interacting protein of the DOCK family (Ruusala and Aspenstrom 2004). As a newly identified protein, the *in vivo* functions of DOCK8 were then characterized by studying human disease and the corresponding mouse models (Zhang et al. 2009; Engelhardt 2009; Ruusala and Aspenstrom 2004; Randall et al. 2009).

All the mutations identified in patients with DOCK8 deficiency to date are LOF, and heterozygous carriers are clinically healthy. AR DOCK8 deficiency has two specific genetic features. The first is the high frequency of large deletions (CNVs), which have been identified in more than half the patients. The mechanism for the unusually high frequency of deletions probably involves frequent homologous recombination between repetitive DNA sequence elements over a large stretch of the DOCK8 locus close to the telomere (Zhang et al. 2016). This high frequency of homologous recombination also accounts for the other specific feature of DOCK8 deficiency, including its unusually high frequency of somatic reversion. In DOCK8-deficient patients, homologous recombination may repair the mutant allele by gene conversion or intragenic single crossover. Five years after the first discovery of DOCK8 deficiency, reversion was detected in 17 of the 23 families followed at the NIH (Jing et al. 2014). Reversion has also been reported in other

PIDs, such as WAS (Wada and Candotti 2008; Davis et al. 2010; Trifari et al. 2010; Wada et al. 2003, 2004; Konno et al. 2004) and X-linked lymphoproliferative disease (XLP) (Palendira et al. 2012) in particular, in which reversion has been reported in up to 10–30% of patients. Nevertheless, the frequency of reversion in DOCK8 deficiency is unprecedented among PIDs. Careful investigations of different cell populations also revealed that T and NK cells in which DOCK8 defects were repaired were at a significant advantage in terms of growth. The clonal expansion of these cell populations eventually resulted in the reversion becoming clinically detectable (Jing et al. 2014). Reversion resulted in no particular growth advantage in the B cells of patients, but it has been shown that DOCK8 may also regulate the activation and IgE production triggered by TLR9-MYD88 signaling in a STAT3-dependent pathway, which might explain the B cell defects and hyper-IgE shared by DOCK8-deficient and Job's syndrome patients (Jabara et al. 2012; Massaad et al. 2017). Similar to Job's syndrome patients, DOCK8-deficient patients also presented with defective Th17 cell differentiation, which has been suggested to be caused by defective STAT3 phosphorylation and translocation (Keles et al. 2016). In addition to its role in the expansion of T- and NK-cell populations, DOCK8 has been shown to participate in NK cell effector functions, T-cell activation, Th1, and Th2 cell differentiation, although conflicting results have been obtained in different studies (Zhang et al. 2014; Keles et al. 2016; Ham et al. 2013, 2015; Kearney 2017; Mizesko et al. 2013; Janssen et al. 2016; Tangye et al. 2017). The high frequency of somatic reversion modifies the clinical presentation of the disease in an unpredictable, but often beneficial way. Conversely, somatic reversion does not occur in mouse models, which have nevertheless become a key tool for studies of the underlying mechanisms of disease.

Interestingly, Dock8-deficient mice were discovered independently through unbiased screening for antibody responses, a model for common variable immunodeficiency (CVID) rather than CID or HIES (Randall et al. 2009). Using *N*-ethyl-*N*-nitrosourea (ENU)-induced mutation in mice, the Goodnow group discovered two independent mouse pedigrees (*cpm* and *pri*) with LOF mutations of *Dock8* (Randall et al. 2009). Other total knockout mice were subsequently established (Zhang et al. 2014; Harada et al. 2012). All these mouse strains have LOF mutations and present similar phenotypes (Table 1). For the sake of clarity, we refer to all these mouse strains hereafter as “Dock8-deficient” mice. Unlike human patients, Dock8-deficient mice do not have high IgE levels. Instead, they fail to form or maintain marginal zone B (MZB) cells in germinal centers, resulting in impaired affinity maturation and failure to maintain IgG responses to T cell-dependent antigens (Randall et al. 2009). A similar phenotype has been described in human patients, with patients having low titers of antibodies against

T cell-dependent vaccines although their total IgG levels are often normal or even elevated (Zhang et al. 2009). In mice, this defect was not rescued by normal T cells, implying that it was intrinsic to Dock8-deficient B cells. The survival defect was found not only in Dock8-deficient MZB cells, but also in many other cell types, including T cells (Lambe et al. 2011; Randall et al. 2011), NKT cells (Crawford et al. 2013), Tregs (Janssen 2017; Singh 2017), and ILCs (Singh et al. 2014). Studies of these defects in mice have helped to explain the wide spectrum of pathogens to which DOCK8-deficient patients are susceptible. However, the mechanisms underlying the survival defect of these different cell types remain unclear.

By contrast, studies focusing on the migration defect of Dock8-deficient mice have clearly elucidated the mechanisms underlying susceptibility to cutaneous viral infections and the survival defect of DCs and T cells (Zhang et al. 2014; Harada et al. 2012; Flesch et al. 2015; Krishnaswamy et al. 2015; Xu et al. 2017). Another DOCK family member, DOCK2, has been shown to play a key role in Rho GTPase-mediated chemotaxis and to cause severe immunodeficiency in patients (Fukui et al. 2001; Dobbs et al. 2015). The group that first reported the chemotaxis defect of Dock2-deficient cells, discovered a different type of migration defect in Dock8-deficient DCs (Harada et al. 2012), with poor interstitial migration during immune responses, 10 years after their initial discovery. Coincidentally, this migration defect of Dock8-deficient DCs was confirmed by an incidental second mutation occurring in an unrelated mouse strain (Krishnaswamy et al. 2015). Several years later, similar migration defects were also discovered in DOCK8-deficient human and mouse T cells (Zhang et al. 2014; Flesch et al. 2015). The migration defects of both T cells and DCs have been linked to CDC42, suggesting that a specific DOCK8 pathway may operate during cell migration (Zhang et al. 2014; Harada et al. 2012). Interstitial cell migration is impaired in both DOCK8-deficient DCs and T cells, but the underlying mechanisms differ between these two cell types. Dock8-deficient DCs fail to transmigrate through the subcapsular sinus floor to the lymph nodes for T-cell priming. This deficiency therefore results in a general defect of T-cell responses during immune responses (Harada et al. 2012). Dock8-deficient T cells maintain their ability to migrate to infected tissues, but undergo catastrophic morphological changes and cell death when migrating in dense tissues, such as those of the skin. This results in a considerable loss of tissue-resident memory T cells in the skin, compromising the immunity of the skin to HSV (Zhang et al. 2014; Flesch et al. 2015). The tissue-specific defect of Dock8-deficient T cells provides clues to a new disease mechanism accounting for the prominent skin-tropism of viral infections in patients. The migration defects of DCs and T cells also suggest that similar migration defects may occur in other cell types, such as

B cells and NKT cells. In general, it is very difficult to study migration defects, particularly those concerning interstitial migration, directly in patients. Mouse models have proved highly useful for elucidating the disease mechanisms relevant to DOCK8 deficiency.

PGM3 deficiency

AR PGM3 deficiency was first reported in 2014, in patients with HIES or SCID/CID (Sassi et al. 2014; Stray-Pedersen et al. 2014; Zhang et al. 2014a, b, c). Shortly afterwards, more patients were reported from both types of cohort (Lundin et al. 2015; Bernth-Jensen et al. 2016; Ben-Khemis et al. 2017). To date, 29 patients from nine families (including 16 patients from 4 families carrying identical mutations) have been identified with HIES, and eight patients from five families with SCID/CID. Patients from these two cohorts have clinical features in common, including severe infections (recurrent respiratory infections, and, less commonly, abscesses, and candidiasis), glomerulonephritis (possibly due to autoimmunity), allergies and eczema, and multiple severe non-immunological phenotypes, including dysmorphic features, skeletal dysplasia, developmental delay, and neurological impairment. Common immunological phenotypes include neutropenia, lymphopenia, and eosinophilia (with or without high IgE levels), of variable severity. Serum IgE levels were normal in patients from the SCID/CID cohort, whereas they were high in most patients from the HIES cohort. Almost all patients from both these cohorts displayed impaired T-cell proliferation in response to stimulation with PHA/PMA or TCR (Sassi et al. 2014; Zhang et al. 2014a, b, c; Bernth-Jensen et al. 2016). This feature is also observed in DOCK8 deficiency but not Job's syndrome, providing strong support for the classification of PGM3 deficiency as a CID rather than a form of HIES. Moreover, the presentation of PGM3 deficiency varies among patients, ranging from SCID to HIES. Patients carrying the same mutation often present with similar phenotypes. For example, all 16 Tunisian patients from four families carrying the same homozygous E340del mutation presented with similar HIES phenotypes, and the two unrelated Tunisian patients carrying the same homozygous N246S mutation presented with similar SCID phenotypes and dysmorphic features. However, too few data are currently available to analyze the correlation of genotype with cellular and clinical phenotypes in patients. Surprisingly, measurements of residual PGM3 expression and function did not differentiate between the patients of these two cohorts (Sassi et al. 2014; Stray-Pedersen et al. 2014; Zhang et al. 2014a, b, c; Wu et al. 2016; Lundin et al. 2015; Bernth-Jensen et al. 2016; Ben-Khemis et al. 2017). It would, nevertheless, be very interesting to compare the deleteriousness of biallelic PGM3

genotypes with that of various cellular, immunological, and clinical phenotypes. Indeed, all patients identified to date carry hypomorphic mutations, which are likely to differ in severity, thereby resulting in immunological and clinical defects of different severities.

PGM3 deficiency has more features in common with other inherited glycosylation defects than with HIES (Lyons et al. 2015). PGM3 (phosphoglucomutase 3), also known as AGM1 (N-acetylglucosamine-phosphate mutase 1), is one of the five ubiquitously expressed hexose phosphate mutases identified in humans (Pang et al. 2002; Hopkinson and Harris 1968). Anecdotally, before the identification of PGM3 as a phosphoglucomutase, it was known for its polymorphism and used as a genetic marker in forensic science (Yoshida et al. 1979; Goldman et al. 1985). PGM3 is one of the key enzymes in glycosylation, a process that modifies proteins and lipids by adding glycans (Greig et al. 2007). About 50% of the proteins in our bodies are glycosylated, and there are hundreds to thousands of different types of glycans, forming a complicated network affecting almost all physiological processes in all living organisms (Ohtsubo and Marth 2006). An estimated 1–2% of the genome encodes proteins involved in glycosylation. It is therefore unsurprising that 105 of the genetic diseases identified to date, including PGM3 deficiency, have been shown to involve glycosylation defects, also known as congenital disorders of glycosylation (CDGs) (Peanne 2017; Ohtsubo and Marth 2006). These CDGs affect different steps of the glycosylation process in different tissues, resulting in a wide spectrum of phenotypes. In brief, when glucose enters the cell, it is mostly converted to fructose-6-phosphate and used for glycolysis to produce energy. However, a small amount of fructose-6-phosphate instead enters the hexosamine biosynthesis pathway (HBP), to produce uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc). PGM3, together with several other enzymes, such as GFPT, GNPAT1, and UAP1, is required for the HBP. PGM3 catalyzes the isomerization of GlcNAc-6-phosphate to GlcNAc-1-phosphate, which is followed by a final reaction to yield UDP-GlcNAc. The newly synthesized UDP-GlcNAc is then transferred to the Golgi apparatus and used as a substrate in various glycosylation processes, including *N*-glycosylation, *O*-glycosylation, and *O*-GlcNAcylation, or converted into UDP-GalNAc (Willems et al. 2016). PGM3 deficiency would therefore be expected to decrease cellular UDP-GlcNAc levels and to affect many downstream glycosylation processes.

Mouse models are of great potential value, given the diversity of hypomorphic mutations and biallelic genotypes in PGM3-deficient patients. Mice with hypomorphic and LOF mutations were generated years before the discovery of the human disease. In 2007, Kile's group discovered a *Pgm3*-deficient mouse strain through the screening of mice with ENU-induced mutations (Table 1). The mutation in this

mouse strain led to aberrant mRNA splicing and the production of Pgm3 proteins with less than 1% the wild-type level of enzyme activity. Mice homozygous for this mutation had a mild phenotype, consisting of smaller than normal numbers of lymphocytes, red blood cells, and platelets, and were therefore named *Pgm3^{mld1/mld1}*. The same group also generated mice with a LOF mutation of *Pgm3*, named *Pgm3^{gt/gt}*. Homozygosity for the LOF mutation is embryo-lethal. Both *Pgm3^{mld1/wt}* and *Pgm3^{gt/wt}* mice were apparently normal, indicating that most, if not all Pgm3 deficiency phenotypes are inherited in an AR manner. Interestingly, when the authors crossed the two mutant strains to generate *Pgm3^{mld1/gt}* mice, these mice had even less enzyme activity and a more severe phenotype than the *Pgm3^{mld1/mld1}* mouse, but they were nevertheless alive. Both *Pgm3^{mld1/mld1}* and *Pgm3^{mld1/gt}* mice display many of the phenotypes of human patients, including anemia, impaired B-cell maturation, and low T-cell numbers. Surprisingly, the *Pgm3^{mld1/gt}* mouse more closely resembles patients with a SCID phenotype, with only very small numbers of peripheral T cells and a total absence of mature B cells. The *Pgm3^{mld1/gt}* mouse also had other phenotypes in common with patients, such as dysmorphic features, and, more interestingly, glomerulonephritis. Overall, studies of mouse models have shown that incremental changes in Pgm3 activity lead to a graded series of pathological changes in different tissues (Greig et al. 2007). It is, therefore, possible that the different phenotypes seen in PGM3-deficient patients originate from residual enzyme activities. HIES patients with PGM3 deficiency probably have a T-cell disorder with Th2 bias, similar to that in DOCK8-deficient patients. It has been shown that the paucity of Th cells is often accompanied, by default, by a Th2 phenotype (Lyons and Milner 2018; Milner et al. 2007). Another clinical feature common to patients from HIES and SCID/CID cohorts was neutropenia, which probably contributes to the wide spectrum of infections found in these patients (Sassi et al. 2014; Stray-Pedersen et al. 2014; Zhang et al. 2014a, b, c; Bernth-Jensen et al. 2016). Pgm3-deficient mice had normal neutrophil numbers, but neutrophil defects are common in CDGs. Seven of the 10 CDGs classified as immunodeficiencies include either neutropenia or neutrophil trafficking/chemotaxis defects (Lyons et al. 2015). The hematopoietic defects in the mouse models were rescued by bone marrow transplantation, consistent with the encouraging results obtained for the few human patients to have undergone transplantation. Overall, the mouse models are promising and complementary to human research.

Other syndromes in which IgE levels are high

Several other PIDs from the CID category are also characterized by high IgE levels, at least in some patients. These syndromes, including Wiskott–Aldrich syndrome, DiGeorge Syndrome, and Omenn Syndrome, are all characterized by

large decreases in T-cell numbers and a severe impairment of T-cell function. The high serum IgE levels may result from the clonal expansion of certain T/B cells, weak TCR affinity and signaling, or an imbalance in the differentiation of Th1/Th2 cells (Milner et al. 2007). The more recent discovery of high IgE levels in IPEX patients suggests that the lack of functional Tregs, as observed in other CIDs, may trigger excessive IgE production (Verbsky and Chatila 2011). As IgE levels vary among patients with these diseases, it is not easy to establish mouse models that faithfully reproduce the phenotype. Recently, Ma et al. reported a new cohort of AD, hypomorphic CARD11 deficient patients, who presented with eczema, recurrent infections, and elevated IgE was found in 5/7 of the patients (Ma et al. 2017). The patients' T cells displayed defects in both NF-κB and mTORC1 activation, which might underlie their abnormal IgE production. Whether this disorder should be classified as CID or HIES is unclear. Defects other than T-cell defects may also result in high serum IgE levels. Comèl-Netherton syndrome is one such defect. It is caused by biallelic *SPINK5* mutations, leading to aberrant epidermal desquamation and an impairment of epidermal barrier function (Netherton 1958; Bitoun et al. 2002; Samuelov and Sprecher 2014; Chavanas et al. 2000). Patients suffer from congenital erythroderma, a specific hair-shaft abnormality (bamboo hair), and atopic manifestations, with high IgE levels. Some patients also experience severe sepsis and cutaneous infections with viruses such as HPV, presumably because of the skin lesions. The phenotype, genotype, and mouse models have all recently been reviewed (Samuelov and Sprecher 2014; Furio and Hovnanian 2014; Hernandez-Martin and Gonzalez-Sarmiento 2015; Kasperek et al. 2016; Sarri et al. 2017). In addition, filaggrin (*FLG*) deficiency can lead to impaired keratinization and defective skin barriers, which result in ichthyosis vulgaris and in some patients with elevated serum IgE (Smith et al. 2006; Enomoto et al. 2008; Johansson et al. 2017). It is usually categorized as an inherited disorder of keratinization.

Concluding remarks

The transformation of the definition of HIES over the last 50 years reflects continuing progress in biomedical research. From the first description of two red-haired girls with “cold abscesses” in 1966, to that of various inborn errors of immunity, the term “HIES” has taken on a completely new meaning. Many discoveries made thanks to the remarkable advances in molecular biology have shed light on the genetic causes of the disease. Syndromes are now defined by both their clinical characteristics and genetic causes, and molecular defects are more often incorporated into their names than was the case 50 years ago. In this respect, we believe that the two AR forms of HIES, DOCK8 and PGM3

deficiency, would be better classified as CIDs, due to the cytoskeletal and glycosylation defects of T cells, respectively, observed in these forms. The name “HIES” should be reserved for patients with AD STAT3 deficiency or other as yet unknown genetic defects resulting in diseases similar to Job’s syndrome, in terms of both clinical features and immunological defects. Surprisingly, the mouse models of DOCK8 and PGM3 deficiencies were established independently of or before the discovery of the corresponding human diseases. The mouse model of Job’s syndrome due to STAT3 deficiency is currently the only mouse model reproducing the high IgE levels of the three diseases discussed above. The mechanisms underlying these high levels of IgE remain unclear in these diseases. The DOCK8-deficient mouse reproduces the infectious phenotype well, although further studies are required to improve our understanding of the survival defects in a wide range of cell types and their connections to disease phenotypes. PGM3-deficient mouse models reproduce the incremental changes in enzyme activity. However, further studies are required to explain the allergic and infectious phenotypes in patients. Overall, we suggest that HIES should no longer be considered a mixture of different genetic disorders. The use of well-defined mouse models will improve our understanding of the unique disease mechanisms specific to each entity. We propose restriction of the term “HIES” to patients with AD STAT3 deficiency and phenocopies, and the exclusion from this group of patients with T-cell deficits displaying a Th2 bias, such as those with DOCK8 and PGM3 deficiencies. However, HIES may nevertheless turn out to be plural, rather than singular, despite the exclusion of DOCK8 and PGM3 deficiencies, if novel genetic etiologies of *bona fide* HIES that phenocopy AD STAT3 deficiency are discovered in the future. While this review was being revised, we and others reported patients with AR ZNF341 deficiency, which appears to be a phenocopy of AD STAT3 deficiency. This is understandable, as ZNF341 is a transcription factor that controls the expression, activation, and activity of STAT3 (Beziat 2018; Frey-Jakobs 2018). One can therefore use the plural when referring to HIES, not because of AR DOCK8 and PGM3 deficiency, but because of AR ZNF341 deficiency that closely mimics AD STAT3 deficiency.

Acknowledgement The funding was provided by Howard Hughes Medical Institute (NA; PI: JLC) and also by National Institute of Allergy and Infectious Diseases (Grant No. 5R01AI127564-02).

References

- Abolhassani H et al (2018) Clinical, immunologic, and genetic spectrum of 696 patients with combined immunodeficiency. *J Allergy Clin Immunol* 141(4):1450–1458
- Avery DT et al (2010) B cell-intrinsic signaling through IL-21 receptor and STAT3 is required for establishing long-lived antibody responses in humans. *J Exp Med* 207(1):155–171
- Aydin SE et al (2015) DOCK8 deficiency: clinical and immunological phenotype and treatment options—a review of 136 patients. *J Clin Immunol* 35(2):189–198
- Bannatyne RM, Skowron PN, Weber JL (1969) Job’s syndrome—a variant of chronic granulomatous disease. Report of a case. *J Pediatr* 75(2):236–242
- Ben-Khemis L et al (2017) A founder mutation underlies a severe form of phosphoglutamase 3 (PGM3) deficiency in Tunisian patients. *Mol Immunol* 90:57–63
- Berger M et al (1980) IgE antibodies to *Staphylococcus aureus* and *Candida albicans* in patients with the syndrome of hyperimmunoglobulin E and recurrent infections. *J Immunol* 125(6):2437–2443
- Bernth-Jensen JM, Holm M, Christiansen M (2016) Neonatal-onset T(–)B(–)NK(+) severe combined immunodeficiency and neutropenia caused by mutated phosphoglucomutase 3. *J Allergy Clin Immunol* 137(1):321–324
- Beziat V et al (2018) A recessive form of hyper-IgE syndrome by disruption of ZNF341-dependent STAT3 transcription and activity. *Sci Immunol* 3(24):eaat4956
- Bitoun E et al (2002) Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. *J Invest Dermatol* 118(2):352–361
- Boisson B et al (2013) An ACT1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. *Immunity* 39(4):676–686
- Buckley RH, Becker WG (1978) Abnormalities in the regulation of human IgE synthesis. *Immunol Rev* 41:288–314
- Buckley RH, Wray BB, Belmaker EZ (1972) Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. *Pediatrics* 49(1):59–70
- Chandesris MO et al (2012) Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine* 91(4):e1–e19
- Chavanas S et al (2000) Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 25(2):141–142
- Cheng P et al (2008) Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein. *J Exp Med* 205(10):2235–2249
- Chou WC, Levy DE, Lee CK (2006) STAT3 positively regulates an early step in B-cell development. *Blood* 108(9):3005–3011
- Church JA et al (1976) T lymphocyte dysfunction, hyperimmunoglobulinemia E, recurrent bacterial infections, and defective neutrophil chemotaxis in a Negro child. *J Pediatr* 88(6):982–985
- Clark RA et al (1973) Defective neutrophil chemotaxis and cellular immunity in a child with recurrent infections. *Ann Intern Med* 78(4):515–519
- Cooper PJ et al (2008) Environmental determinants of total IgE among school children living in the rural Tropics: importance of geohelminth infections and effect of anthelmintic treatment. *BMC Immunol* 9:33
- Crawford G et al (2013) DOCK8 is critical for the survival and function of NKT cells. *Blood* 122(12):2052–2061
- Cypowyj S et al (2012) Immunity to infection in IL-17-deficient mice and humans. *Eur J Immunol* 42(9):2246–2254
- Dagoneau N et al (2004) Null leukemia inhibitory factor receptor (LIFR) mutations in Stuve-Wiedemann/Schwartz-Jampel type 2 syndrome. *Am J Hum Genet* 74(2):298–305
- Dahl MV, Greene WH Jr, Quie PG (1976) Infection, dermatitis, increased IgE, and impaired neutrophil chemotaxis. A possible relationship. *Arch Dermatol* 112(10):1387–1390

- Davila I et al (2015) Relationship between serum total IgE and disease severity in patients with allergic asthma in Spain. *J Invest Allergol Clin Immunol* 25(2):120–127
- Davis SD, Schaller J, Wedgwood RJ (1966) Job's syndrome recurrent "cold" *Staphylococcal* abscesses. *Lancet* 1(7445):1013–1015
- Davis BR et al (2010) Somatic mosaicism in the Wiskott–Aldrich syndrome: molecular and functional characterization of genotypic revertants. *Clin Immunol* 135(1):72–83
- De Cree J et al (2013) Defective neutrophil chemotaxis and raised serum ige levels in a child with recurrent bacterial infections and eczema. Influence of levamisole. *Arch Dis Child* 53(2):144–149
- de Beaucoudrey L et al (2008) Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med* 205(7):1543–1550
- Deenick EK et al (2013) Naive and memory human B cells have distinct requirements for STAT3 activation to differentiate into antibody-secreting plasma cells. *J Exp Med* 210(12):2739–2753
- Dobbs K et al (2015) Inherited DOCK2 deficiency in patients with early-onset invasive infections. *N Engl J Med* 372(25):2409–2422
- Donabedian H, Gallin JI (1983) The hyperimmunoglobulin E recurrent-infection (Job's) syndrome. A review of the NIH experience and the literature. *Medicine* 62(4):195–208
- Donabedian H, Alling DW, Gallin JI (1982) Levamisole is inferior to placebo in the hyperimmunoglobulin E recurrent-infection (Job's) syndrome. *N Engl J Med* 307(5):290–292
- Dreskin SC, Goldsmith PK, Gallin JI (1985) Immunoglobulins in the hyperimmunoglobulin E and recurrent infection (Job's) syndrome. Deficiency of anti-*Staphylococcus aureus* immunoglobulin A. *J Clin Invest* 75(1):26–34
- Engelhardt KR et al (2009) Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol* 124(6):1289–1302
- Engelhardt KR et al (2015) The extended clinical phenotype of 64 patients with dedicator of cytokinesis 8 deficiency. *J Allergy Clin Immunol* 136(2):402–412
- Enomoto H et al (2008) Filaggrin null mutations are associated with atopic dermatitis and elevated levels of IgE in the Japanese population: a family and case-control study. *J Hum Genet* 53(7):615–621
- Erman B et al (2015) Combined immunodeficiency with CD4 lymphopenia and sclerosing cholangitis caused by a novel loss-of-function mutation affecting IL21R. *Haematologica* 100(6):e216–9
- Flesch IE et al (2015) Delayed control of herpes simplex virus infection and impaired CD4(+) T-cell migration to the skin in mouse models of DOCK8 deficiency. *Immunol Cell Biol* 93(6):517–521
- Fornek JL et al (2006) Critical role for Stat3 in T-dependent terminal differentiation of IgG B cells. *Blood* 107(3):1085–1091
- Freeman AF, Holland SM (2010) Clinical manifestations of hyper IgE syndromes. *Dis Markers* 29(3–4):123–130
- Frey-Jakobs S et al (2018) ZNF341 controls STAT3 expression and thereby immunocompetence. *Sci Immunol* 3(24):eaat4941
- Fuchs S et al (2016) Tyrosine kinase 2 is not limiting human antiviral type III interferon responses. *Eur J Immunol* 46(11):2639–2649
- Fukui Y et al (2001) Haematopoietic cell-specific CDM family protein DOCK2 is essential for lymphocyte migration. *Nature* 412(6849):826–831
- Furio L, Hovnanian A (2014) Netherton syndrome: defective kallikrein inhibition in the skin leads to skin inflammation and allergy. *Biol Chem* 395(9):945–958
- Gammon WR (1979) Phagocyte chemotaxis. *J Invest Dermatol* 73(6):515–520
- Garama DJ et al (2015) A synthetic lethal interaction between glutathione synthesis and mitochondrial reactive oxygen species provides a tumor-specific vulnerability dependent on STAT3. *Mol Cell Biol* 35(21):3646–3656
- Garraud O et al (1999) Regulation of immunoglobulin production in hyper-IgE (Job's) syndrome. *J Allergy Clin Immunol* 103(2 Pt 1):333–340
- Gaspar IM et al (2008) Long-term follow-up in Stuve-Wiedemann syndrome: a clinical report. *Am J Med Genet A* 146A(13):1748–1753
- Goldman D et al (1985) Twenty-seven protein polymorphisms by two-dimensional electrophoresis of serum, erythrocytes, and fibroblasts in two pedigrees. *Am J Hum Genet* 37(5):898–911
- Gough DJ et al (2009) Mitochondrial STAT3 supports Ras-dependent oncogenic transformation. *Science* 324(5935):1713–1716
- Gough DJ, Koetz L, Levy DE (2013) The MEK-ERK pathway is necessary for serine phosphorylation of mitochondrial STAT3 and Ras-mediated transformation. *PLoS ONE* 8(11):e83395
- Greig KT et al (2007) Agm1/Pgm3-mediated sugar nucleotide synthesis is essential for hematopoiesis and development. *Mol Cell Biol* 27(16):5849–5859
- Grimbacher B, Holland SM, Puck JM (1998) The interleukin-4 receptor variant Q576R in hyper-IgE syndrome. *N Engl J Med* 338(15):1073–1074
- Grimbacher B et al (1999a) Genetic linkage of hyper-IgE syndrome to chromosome 4. *Am J Hum Genet* 65(3):735–744
- Grimbacher B et al (1999b) Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med* 340(9):692–702
- Ham H et al (2013) Dedicator of cytokinesis 8 interacts with talin and Wiskott–Aldrich syndrome protein to regulate NK cell cytotoxicity. *J Immunol* 190(7):3661–3669
- Ham H et al (2015) HkRP3 is a microtubule-binding protein regulating lytic granule clustering and NK cell killing. *J Immunol* 194(8):3984–3996
- Harada Y et al (2012) DOCK8 is a Cdc42 activator critical for interstitial dendritic cell migration during immune responses. *Blood* 119(19):4451–4461
- He JS et al (2017) IgG1 memory B cells keep the memory of IgE responses. *Nat Commun* 8(1):641
- Heimall J, Freeman A, Holland SM (2010) Pathogenesis of hyper IgE syndrome. *Clin Rev Allergy Immunol* 38(1):32–38
- Hernandez-Martin A, Gonzalez-Sarmiento R (2015) Recent advances in congenital ichthyoses. *Curr Opin Pediatr* 27(4):473–479
- Hill HR, Quie PG (1974) Raised serum-IgE levels and defective neutrophil chemotaxis in three children with eczema and recurrent bacterial infections. *Lancet* 1(7850):183–187
- Hill HR et al (1974) Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent "cold" staphylococcal abscesses. *Lancet* 2(7881):617–619
- Hill HR et al (1976) Severe staphylococcal disease associated with allergic manifestations, hyperimmunoglobulinemia E, and defective neutrophil chemotaxis. *J Lab Clin Med* 88(5):796–806
- Hillmer EJ et al (2016) STAT3 signaling in immunity. *Cytokine Growth Factor Rev* 31:1–15
- Holland SM et al (2007) STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 357(16):1608–1619
- Holmes B et al (1966) Fatal granulomatous disease of childhood. An inborn abnormality of phagocytic function. *Lancet* 1(7449):1225–1228
- Hopkinson DA, Harris H (1968) A third phosphoglucomutase locus in man. *Ann Hum Genet* 31(4):359–367
- Hsu AP et al (2013) Intermediate phenotypes in patients with autosomal dominant hyper-IgE syndrome caused by somatic mosaicism. *J Allergy Clin Immunol* 131(6):1586–1593
- Hunter CA, Jones SA (2015) IL-6 as a keystone cytokine in health and disease. *Nat Immunol* 16(5):448–457
- Ishizaka K, Ishizaka T (2016) Identification of IgE. *J Allergy Clin Immunol* 137(6):1646–1650

- Ishizaka K, Ishizaka T, Hornbrook MM (1966a) Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity with gamma-E-globulin antibody. *J Immunol* 97(6):840–853
- Ishizaka K, Ishizaka T, Hornbrook MM (1966b) Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J Immunol* 97(1):75–85
- Jabara HH et al (2012) DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. *Nat Immunol* 13(6):612–620
- Janssen E et al (2016) A DOCK8-WIP-WASp complex links T cell receptors to the actin cytoskeleton. *J Clin Invest* 126(10):3837–3851
- Janssen E et al (2017) DOCK8 enforces immunological tolerance by promoting IL-2 signaling and immune synapse formation in Tregs. *JCI Insight* 2(19):e94298
- Jin S et al (2016) DOCK8: regulator of Treg in response to corticotropin-releasing hormone. *Allergy* 71(6):811–819
- Jing H et al (2014) Somatic reversion in dedicator of cytokinesis 8 immunodeficiency modulates disease phenotype. *J Allergy Clin Immunol* 133(6):1667–1675
- Johansson SG, Bennich H (1967) Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 13(4):381–394
- Johansson EK et al (2017) IgE sensitization in relation to preschool eczema and filaggrin mutation. *J Allergy Clin Immunol* 140(6):1572–1579 e5
- Kane A et al (2016) B-cell-specific STAT3 deficiency: insight into the molecular basis of autosomal-dominant hyper-IgE syndrome. *J Allergy Clin Immunol* 138(5):1455–1458 e3
- Kasperek P et al (2016) A viable mouse model for Netherton syndrome based on mosaic inactivation of the Spink5 gene. *Biol Chem* 397(12):1287–1292
- Kearney CJ et al (2017) DOCK8 Drives Src-dependent NK cell effector function. *J Immunol* 199:2118–2127
- Keles S et al (2016) Dedicator of cytokinesis 8 regulates signal transducer and activator of transcription 3 activation and promotes TH17 cell differentiation. *J Allergy Clin Immunol* 138(5):1384–1394 e2
- Keupp K et al (2013) Mutations in the interleukin receptor IL11RA cause autosomal recessive Crouzon-like craniosynostosis. *Mol Genet Genomic Med* 1(4):223–237
- Kitamura H et al (2005) IL-6-STAT3 controls intracellular MHC class II alphabeta dimer level through cathepsin S activity in dendritic cells. *Immunity* 23(5):491–502
- Konno A et al (2004) Differential contribution of Wiskott–Aldrich syndrome protein to selective advantage in T- and B-cell lineages. *Blood* 103(2):676–678
- Kosfeld A et al (2017) Mutations in the leukemia inhibitory factor receptor (LIFR) gene and Lifr deficiency cause urinary tract malformations. *Hum Mol Genet* 26(9):1716–1731
- Kotlarz D et al (2013) Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. *J Exp Med* 210(3):433–443
- Kotlarz D et al (2014) Human IL-21 and IL-21R deficiencies: two novel entities of primary immunodeficiency. *Curr Opin Pediatr* 26(6):704–712
- Kreins AY et al (2015) Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. *J Exp Med* 212(10):1641–1662
- Krishnaswamy JK et al (2015) Coincidental loss of DOCK8 function in NLRP10-deficient and C3H/HeJ mice results in defective dendritic cell migration. *Proc Natl Acad Sci USA* 112(10):3056–3061
- Kumanovics A et al (2010) Rapid molecular analysis of the STAT3 gene in Job syndrome of hyper-IgE and recurrent infectious diseases. *J Mol Diagn* 12(2):213–219
- Lambe T et al (2011) DOCK8 is essential for T-cell survival and the maintenance of CD8 + T-cell memory. *Eur J Immunol* 41(12):3423–3435
- Laouar Y et al (2003) STAT3 is required for Flt3L-dependent dendritic cell differentiation. *Immunity* 19(6):903–912
- Levy R et al (2016) Genetic, immunological, and clinical features of patients with bacterial and fungal infections due to inherited IL-17RA deficiency. *Proc Natl Acad Sci USA* 113(51):E8277–E8285
- Ling Y et al (2015) Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis. *J Exp Med* 212(5):619–631
- Liu L et al (2011) Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med* 208(8):1635–1648
- Looney TJ et al (2016) Human B-cell isotype switching origins of IgE. *J Allergy Clin Immunol* 137(2):579–586 e7
- Lundin KE et al (2015) Susceptibility to infections, without concomitant hyper-IgE, reported in 1976, is caused by hypomorphic mutation in the phosphoglucomutase 3 (PGM3) gene. *Clin Immunol* 161(2):366–372
- Lyons JJ, Milner JD (2018) Primary atopic disorders. *J Exp Med* <https://doi.org/10.1084/jem.20172306>
- Lyons JJ, Milner JD, Rosenzweig SD (2015) Glycans instructing immunity: the emerging role of altered glycosylation in clinical immunology. *Front Pediatr* 3:54
- Lyons JJ et al (2017) ERBIN deficiency links STAT3 and TGF-beta pathway defects with atopy in humans. *J Exp Med* 214(3):669–680
- Ma CS et al (2008) Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. *J Exp Med* 205(7):1551–1557
- Ma CS et al (2016) Unique and shared signaling pathways cooperate to regulate the differentiation of human CD4 + T cells into distinct effector subsets. *J Exp Med* 213(8):1589–1608
- Ma CA et al (2017) Germline hypomorphic CARD11 mutations in severe atopic disease. *Nat Genet* 49(8):1192–1201
- Massaad MJ et al (2017) DOCK8 and STAT3 dependent inhibition of IgE isotype switching by TLR9 ligation in human B cells. *Clin Immunol* 183:263–265
- Melillo JA et al (2010) Dendritic cell (DC)-specific targeting reveals Stat3 as a negative regulator of DC function. *J Immunol* 184(5):2638–2645
- Miller KA et al (2017) Diagnostic value of exome and whole genome sequencing in craniosynostosis. *J Med Genet* 54(4):260–268
- Milner JD et al (2007) Lymphopenic mice reconstituted with limited repertoire T cells develop severe, multiorgan, Th2-associated inflammatory disease. *Proc Natl Acad Sci USA* 104(2):576–581
- Milner JD et al (2008) Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* 452(7188):773–776
- Minegishi Y et al (2006) Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 25(5):745–755
- Minegishi Y et al (2007) Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 448(7157):1058–1062
- Minegishi Y et al (2009) Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. *J Exp Med* 206(6):1291–1301
- Miyamoto Y et al (2016) Dock8 interacts with Nck1 in mediating Schwann cell precursor migration. *Biochem Biophys Res* 6:113–123
- Mizesko MC et al (2013) Defective actin accumulation impairs human natural killer cell function in patients with dedicator of cytokinesis 8 deficiency. *J Allergy Clin Immunol* 131(3):840–848

- Mogensen TH (2013) STAT3 and the Hyper-IgE syndrome: Clinical presentation, genetic origin, pathogenesis, novel findings and remaining uncertainties. *JAKSTAT* 2(2):e23435
- Netherton EW (1958) A unique case of trichorrhexis nodosa; bamboo hairs. *AMA Arch Derm* 78(4):483–487
- Nguyen-Jackson H et al (2010) STAT3 controls the neutrophil migratory response to CXCR2 ligands by direct activation of G-CSF-induced CXCR2 expression and via modulation of CXCR2 signal transduction. *Blood* 115(16):3354–3363
- Nieminen P et al (2011) Inactivation of IL11 signaling causes craniosynostosis, delayed tooth eruption, and supernumerary teeth. *Am J Hum Genet* 89(1):67–81
- O'Shea JJ et al (2015) The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med* 66:311–328
- Oettgen HC (2016) Fifty years later: Emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. *J Allergy Clin Immunol* 137(6):1631–1645
- Ohtsubo K, Marth JD (2006) Glycosylation in cellular mechanisms of health and disease. *Cell* 126(5):855–867
- Okada S et al (2015) IMMUNODEFICIENCIES. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic RORC mutations. *Science* 349(6248):606–613
- Ouederni M et al (2014) Clinical features of Candidiasis in patients with inherited interleukin 12 receptor beta1 deficiency. *Clin Infect Dis* 58(2):204–213
- Pabst HF et al (1971) Immunological abnormalities in Job's syndrome. *Pediatr Res* 5:380
- Palendira U et al (2012) Expansion of somatically reverted memory CD8 + T cells in patients with X-linked lymphoproliferative disease caused by selective pressure from Epstein-Barr virus. *J Exp Med* 209(5):913–924
- Pang H et al (2002) Identification of human phosphoglucomutase 3 (PGM3) as N-acetylglucosamine-phosphate mutase (AGM1). *Ann Hum Genet* 66(Pt 2):139–144
- Panopoulos AD et al (2006) STAT3 governs distinct pathways in emergency granulopoiesis and mature neutrophils. *Blood* 108(12):3682–3690
- Paslin D, Norman ME (1977) Atopic dermatitis and impaired neutrophil chemotaxis in Job's syndrome. *Arch Dermatol* 113(6):801–805
- Paulson ML, Freeman AF, Holland SM (2008) Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3. *Curr Opin Allergy Clin Immunol* 8(6):527–533
- Peanne R et al (2017) Congenital disorders of glycosylation (CDG): Quo vadis? *Eur J Med Genet* <https://doi.org/10.1016/j.ejmg.2017.10.012>
- Pene J et al (1988) IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons gamma and alpha and prostaglandin E2. *Proc Natl Acad Sci USA* 85(18):6880–6884
- Picard C et al (2018) International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol* 38(1):96–128
- Pincus SH et al (1975) Defective neutrophil chemotaxis with variant ichthyosis, hyperimmunoglobulinemia E, and recurrent infections. *J Pediatr* 87(6 Pt 1):908–911
- Prouvost-Danon A et al (1972) Immunochemical identification of mouse IgE. *Immunology* 23(4):481–491
- Puel A et al (2010a) Inborn errors of mucocutaneous immunity to *Candida albicans* in humans: a role for IL-17 cytokines? *Curr Opin Immunol* 22(4):467–474
- Puel A et al (2010b) Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med* 207(2):291–297
- Puel A et al (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* 332(6025):65–68
- Puel A et al (2012) Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol* 12(6):616–622
- Punnonen J et al (1993) Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. *Proc Natl Acad Sci USA* 90(8):3730–3734
- Randall KL et al (2009) Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production. *Nat Immunol* 10(12):1283–1291
- Randall KL et al (2011) DOCK8 deficiency impairs CD8 T cell survival and function in humans and mice. *J Exp Med* 208(11):2305–2320
- Renner ED et al (2004) Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* 144(1):93–99
- Renner ED et al (2007) STAT3 mutation in the original patient with Job's syndrome. *N Engl J Med* 357(16):1667–1668
- Renner ED et al (2008) Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced T(H)17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. *J Allergy Clin Immunol* 122(1):181–187
- Ruusala A, Aspenstrom P (2004) Isolation and characterisation of DOCK8, a member of the DOCK180-related regulators of cell morphology. *FEBS Lett* 572(1–3):159–166
- Salzer E et al (2014) Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. *J Allergy Clin Immunol* 133(6):1651–1659 e12
- Samuelov L, Sprecher E (2014) Peeling off the genetics of atopic dermatitis-like congenital disorders. *J Allergy Clin Immunol* 134(4):808–815
- Sarri CA et al (2017) Netherton syndrome: a genotype-phenotype review. *Mol Diagn Ther* 21(2):137–152
- Sassi A et al (2014) Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity and increase serum IgE levels. *J Allergy Clin Immunol* 133(5):1410–1419, 1419 e1–13
- Schopfer K et al (1979) Staphylococcal IgE antibodies, hyperimmunoglobulinemia E and *Staphylococcus aureus* infections. *N Engl J Med* 300(15):835–838
- Schwerd T et al (2017) A biallelic mutation in IL6ST encoding the GPI30 co-receptor causes immunodeficiency and craniosynostosis. *J Exp Med* 214(9):2547–2562
- Siegel AM et al (2013) Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. *J Allergy Clin Immunol* 132(6):1388–1396
- Singh AK et al (2014) DOCK8 regulates protective immunity by controlling the function and survival of RORgammat + ILCs. *Nat Commun* 5:4603
- Singh AK et al (2017) DOCK8 regulates fitness and function of regulatory T cells through modulation of IL-2 signaling. *JCI Insight* <https://doi.org/10.1172/jci.insight.94275>
- Smith FJ et al (2006) Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 38(3):337–342
- Spielberger BD et al (2012) Challenges of genetic counseling in patients with autosomal dominant diseases, such as the hyper-IgE syndrome (STAT3-HIES). *J Allergy Clin Immunol* 130(6):1426–1428
- Stanley J et al (1978) Hyperimmunoglobulin E syndrome. *Arch Dermatol* 114(5):765–767
- Steward-Sharp SM et al (2014) A mouse model of HIES reveals pro- and anti-inflammatory functions of STAT3. *Blood* 123(19):2978–2987
- Stray-Pedersen A et al (2014) PGM3 mutations cause a congenital disorder of glycosylation with severe immunodeficiency and skeletal dysplasia. *Am J Hum Genet* 95(1):96–107

- Takeda K et al (1999) Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. *Immunity* 10(1):39–49
- Tangye SG et al (2017) Dedicator of cytokinesis 8-deficient CD4(+) T cells are biased to a TH2 effector fate at the expense of TH1 and TH17 cells. *J Allergy Clin Immunol* 139(3):933–949
- Trifari S et al (2010) Revertant T lymphocytes in a patient with Wiskott–Aldrich syndrome: analysis of function and distribution in lymphoid organs. *J Allergy Clin Immunol* 125(2):439–448 e8
- Van Scoy RE et al (1975) Familial neutrophil chemotaxis defect, recurrent bacterial infections, mucocutaneous candidiasis, and hyperimmunoglobulinemia E. *Ann Intern Med* 82(6):766–771
- Verbsky JW, Chatila TA (2011) T-regulatory cells in primary immune deficiencies. *Curr Opin Allergy Clin Immunol* 11(6):539–544
- Villarino AV et al (2015) Mechanisms of Jak/STAT signaling in immunity and disease. *J Immunol* 194(1):21–27
- Vogel TP, Milner JD, Cooper MA (2015) The Ying and Yang of STAT3 in Human Disease. *J Clin Immunol* 35(7):615–623
- Wada T, Candotti F (2008) Somatic mosaicism in primary immune deficiencies. *Curr Opin Allergy Clin Immunol* 8(6):510–514
- Wada T et al (2003) Second-site mutation in the Wiskott–Aldrich syndrome (WAS) protein gene causes somatic mosaicism in two WAS siblings. *J Clin Invest* 111(9):1389–1397
- Wada T et al (2004) Multiple patients with revertant mosaicism in a single Wiskott–Aldrich syndrome family. *Blood* 104(5):1270–1272
- Wegrzyn J et al (2009) Function of mitochondrial Stat3 in cellular respiration. *Science* 323(5915):793–797
- Weston WL et al (1977) A hyperimmunoglobulin E syndrome with normal chemotaxis in vitro and defective leukotaxis in vivo. *J Allergy Clin Immunol* 59(2):115–119
- White LR et al (1969) Leucocytes in Job's syndrome. *Lancet* 1(7595):630
- Willems AP, van Engelen BG, Lefeber DJ (2016) Genetic defects in the hexosamine and sialic acid biosynthesis pathway. *Biochim Biophys Acta* 1860(8):1640–1654
- Wilson RP et al (2015) STAT3 is a critical cell-intrinsic regulator of human unconventional T cell numbers and function. *J Exp Med* 212(6):855–864
- Witemeyer S, Van Epps DE (1976) A familial defect in cellular chemotaxis associated with redheadedness and recurrent infection. *J Pediatr* 89(1):33–37
- Woellner C et al (2010) Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol* 125(2):424–432 e8
- Wolfe SJ et al (2011) PD-L1 expression on tolerogenic APCs is controlled by STAT-3. *Eur J Immunol* 41(2):413–424
- Wu G et al (2016) Glycoproteomic studies of IgE from a novel hyper IgE syndrome linked to PGM3 mutation. *Glycoconj J* 33(3):447–456
- Xiong H et al (2012) Sequential class switching is required for the generation of high affinity IgE antibodies. *J Exp Med* 209(2):353–364
- Xu X et al (2017) LRCH1 interferes with DOCK8-Cdc42-induced T cell migration and ameliorates experimental autoimmune encephalomyelitis. *J Exp Med* 214(1):209–226
- Yang J, Stark GR (2008) Roles of unphosphorylated STATs in signaling. *Cell Res* 18(4):443–451
- Yang J et al (2005) Novel roles of unphosphorylated STAT3 in oncogenesis and transcriptional regulation. *Cancer Res* 65(3):939–947
- Yang XO et al (2007a) STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J Biol Chem* 282(13):9358–9363
- Yang J et al (2007b) Unphosphorylated STAT3 accumulates in response to IL-6 and activates transcription by binding to NFkappaB. *Genes Dev* 21(11):1396–1408
- Yang L, Fliegauf M, Grimbacher B (2014) Hyper-IgE syndromes: reviewing PGM3 deficiency. *Curr Opin Pediatr* 26(6):697–703
- Yesil G et al (2014) Stuve-Wiedemann syndrome: is it underrecognized? *Am J Med Genet A* 164(9):2200–2205
- Yoshida H, Abe T, Nakamura F (1979) Studies on the frequencies of PGM1, PGM3 and Es-D types from hair roots in Japanese subjects and the determination of these types from old hair roots. *Forensic Sci Int* 14(1):1–7
- Zhang Q, Seppanen MRJ (2018) Immunoglobulin E—an innocent bystander in host defense? *J Clin Immunol* 38:223–224
- Zhang Q, Su HC (2011) Hyperimmunoglobulin E syndromes in pediatrics. *Curr Opin Pediatr* 23(6):653–658
- Zhang Q et al (2009) Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med* 361(21):2046–2055
- Zhang H et al (2010) STAT3 controls myeloid progenitor growth during emergency granulopoiesis. *Blood* 116(14):2462–2471
- Zhang Y et al (2014a) Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and neurocognitive impairment. *J Allergy Clin Immunol* 133(5):1400–1409, 1409 e1–5
- Zhang H et al (2014b) STAT3 restrains RANK- and TLR4-mediated signalling by suppressing expression of the E2 ubiquitin-conjugating enzyme Ubc13. *Nat Commun* 5:5798
- Zhang Q et al (2014c) DOCK8 regulates lymphocyte shape integrity for skin antiviral immunity. *J Exp Med* 211(13):2549–2566
- Zhang Q, Jing H, Su HC (2016) Recent Advances in DOCK8 Immunodeficiency Syndrome. *J Clin Immunol* 36(5):441–449