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Invited Review Article

Hyper-IgE syndrome, 2021 update

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ABSTRACT

Clinically and pathologically, the patients with hyper-IgE syndrome present similar skin manifestations to common atopic dermatitis. The original hyper-IgE syndrome is characterized by diminished inflammatory response, in combination with *Staphylococcus aureus* skin abscess and pneumonia followed by pneumatocele formation. These immunological manifestations are frequently associated with skeletal and connective tissue abnormalities. We previously identified that major causal variants of the hyper-IgE syndrome are dominant negative variants in the *STAT3*.

In addition to the identification of new causative variants for the disorders similar to the original hyper-IgE syndrome, causative variants for new types of hyper-IgE syndrome centered only on atopy, high serum IgE levels, and susceptibility to infection, but not associated with diminished inflammatory response, pneumatocele formation, and connective tissue manifestations, have been identified. Recent discovery identified a novel zinc finger protein that regulates STAT3 transcription. Investigation of IL6ST variants disclosed that IL6ST/IL6R cytokine receptor plays a crucial role for the signal transduction upstream of STAT3 in the pathogenesis of the original hyper-IgE syndrome. Even if the same IL6ST variants are used for the signal transduction of IL-6 family cytokines, the signaling defect is more severe in IL-6/IL-11 and milder in LIF. The fact that the non-immune manifestations of the gain-of-function mutations of TGFBR1 and TGFBR2 are similar to the those of dominant negative mutations of STAT3 provide a clue to elucidate molecular mechanisms of non-immune manifestations of hyper-IgE syndrome. Research on this hereditary atopic syndrome is being actively conducted to elucidate the molecular mechanisms and to develop new therapeutic approaches.

Introduction

Hyper-IgE syndrome (HIES) is first described by Davis and Wedgwood in 1966, in two girls suffering from recurrent cold staphylococcal abscesses, pneumonia, and neonatal-onset eczema.[1] As this original report predated the identification of IgE,[2] a high serum concentration of IgE level was not recognized at this point. This syndrome was further characterized by Buckley *et al.*,[3] who found that recurrent staphylococcal abscesses and chronic eczema were associated with exceptionally high serum concentrations of IgE. They also showed that serum concentrations of the other immunoglobulins (IgG, IgA, IgM, and IgD) and IgG subclasses were normal in the patients. The non-immunological manifestations of HIES were established by Grimbacher, to extend to skeletal and connective tissue abnormalities, such as scoliosis, osteoporosis, fracture following minor trauma, hyper-extensive joints, and the retention of deciduous teeth.[4] In 2004, autosomal recessive (AR) form of HIES was reported in consanguineous families,[5] most of which is caused by the loss-of-function (LOF) mutations in the *Dedicator of cytokinesis 8* (*DOCK8*) gene.[6] In 2007, dominant-negative (DN) mutations in the signal transducer and activator of transcription 3 (STAT3) gene were identified as a major molecular etiology of classical HIES.[7] There are several review articles discussing this type of HIES.[8–11] Recently, it is postulated that HIES could include all the disorders presenting the three manifestations, i.e. atopic dermatitis, high serum IgE levels, and susceptibility to infections, in contrast to the narrow definition of the original STAT3-DN HIES.

At present, it is difficult to provide a definition of HIES that everyone is satisfied with. Based on the recent International Union of Immunological Societies (IUIS) PID classification [12,13] and Online Mendelian Inheritance in Man (OMIM) (https://www.ncbi.nlm.nih.gov/omim), I selected nine causative genes-function of mutations of the HIES, on the condition that at least two patients from two independent families were identified, i.e. (1) STAT3-DN, (2) Zinc Finger Protein 341 (ZNF341)-LOF, (3) Interleukin 6 Signal Transducer (IL6ST)-partial LOF, (4) IL6ST-DN, (5) IL6R-LOF, (6) Tyrosine

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kinase 2 (TYK2)-LOF, (7) Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)-LOF, (8) Transforming Growth Factor Beta Receptor (TGFBR) 1/2-GOF, (9) Caspase recruitment domain-containing protein 11 (CARD11)-DN. This has more information compared to classical autosomal dominant (AD) and AR classification, and easier to understand for non-specialists of PIDs. Because most of the patients with phosphoglucomutase 3 (PGM3)-partial LOF displayed impaired T-cell proliferation in response to PHA, anti-CD3, purified protein derivative (PPD), or tetanus toxoid (TT),[14,15] I classified this disorders into combined immunodeficiency (CID) category and will not discuss in this article.

STAT3-DN

STAT3 is a transcription factor that binds to the STAT3-responsive elements in the promoters of various genes, including acute-phase reaction proteins (Fig. 1).[16,17] STAT3 plays a critical role in responses to many cytokines and growth factors, including γc cytokines (IL-2, IL-7, IL-9, IL-15, and IL-21), GP130 cytokines (IL-6, IL-11, IL-27, IL-35, IL-39, cardiotrophin-1 (CT-1), cardiotrophin-like cytokine factor 1 (CLCF1), oncostatin M (OSM), and leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF)), type 1 and type 2 IFNs (IFNα, IFNβ, and IFNγ), IL-10 family cytokines (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29), receptor tyrosine kinases (epidermal growth factor (EGF), fibroblast growth factor (FGF), fms like tyrosine kinase 3 (Flt3) ligand, growth hormone (GH), insulin-like growth factor 1 (IGF1), macrophage colony-stimulating factor (M-CSF), and platelet-derived growth factor (PDGF), as well as IL-5, IL-12, IL-23, granulocyte-colony stimulating factor (G-CSF), leptin, and platelet activating factor (PAF). A null mutation in the STAT3 gene in mice demonstrated that STAT3 was essential for the survival of the embryo around the time of implantation.[18] The mice with tissue-specific deletions of STAT3 have shown STAT3 to play a crucial role in cell proliferation, survival, migration, apoptosis and inflammation in various tissues, organs and cells, including skin, respiratory epithelium, thymic epithelium, liver, mammary glands, neurons, lymphocytes, and macrophages.[19] It is considered that many of the clinical signs of STAT3-DN HIES likely reflect defects of the diverse functions of STAT3 *in vivo*.

Most of the patients with STAT3-DN HIES suffer from recurrent staphylococcal infections, beginning in infancy and predominantly involving the skin and lungs. *Staphylococcus aureus* is the bacterium most frequently isolated from the patients, but *Streptococcus pneumoniae, Haemophilus influenzae*, and enteric Gram-negative bacteria are occasionally isolated from the patients. Fungal infections, including mucocutaneous candidiasis and pulmonary aspergillosis, are also common in STAT3-DN HIES. Eczema usually begins during the neonatal period, earlier than the onset of common atopic dermatitis. Patients with HIES are usually free from other allergic manifestations, such as allergic rhinitis, asthma, food allergy, and anaphylaxis.

STAT3-DN HIES is associated with non-immunological manifestations, including characteristic facial appearance, pneumatocele formation, fracture due to minor external force (pathological fracture), osteoporosis, scoliosis, joint hyperextension, delayed loss of deciduous tooth. There is an increased rate of malignancy, predominantly malignant lymphoma. In most STAT3-DN HIES, the serum IgE levels are elevated, frequently higher than 2000 IU/μl. However, there are cases with only mildly elevated IgE and the IgE can fall into the normal range. Specific IgE against *S. aureus* and *Candida albicans* is elevated, and it is thus considered that antigen-specific IgE production is enhanced in this disorder. Eosinophilia is present in about 90% of the patients, and the number of eosinophils in the peripheral blood was mostly higher than 700/μl.

The other immunoglobulins levels are generally normal, and antibody responses to vaccination are impaired at least some of the HIES patients.[20,21]

STAT3 mutations are localized mostly to the DNA binding, SH2, and transactivation domain (Fig. 2). Mutations are in most part missense mutations and some small in-frame deletions. So far, there is no convincing report that STAT3 haploinsufficiency can cause this syndrome. STAT3 protein is present and can dimerize with wild type STAT3 protein, but inhibit STAT3 signaling of wild-type allele, i.e. function as dominant negative. The number of Th17 cells and memory B cells in peripheral blood is decreased. STAT3 signal

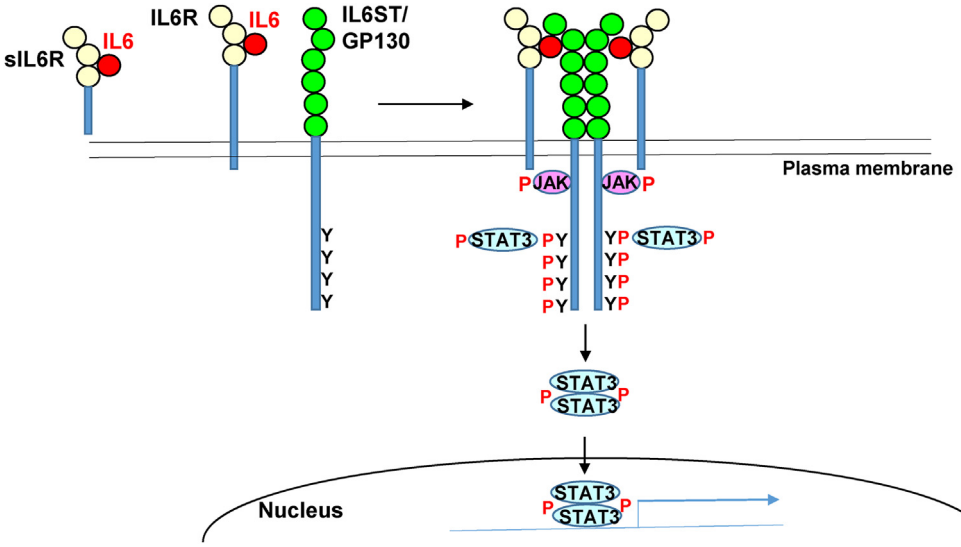

Fig. 1. Signal transduction of IL6-IL6R-IL6ST. IL6 binds to IL6R with low affinity, which is not sufficient for signal transduction. IL6-IL6R complex binds to IL6ST to initiate signaling. Soluble IL6R can be produced by alternative splicing or proteolytic cleavage, which can also initiate signaling. Hexameric IL6-IL6R-IL6ST complex induces phosphorylation of JAKs, then JAKs phosphorylate tyrosine residues in the cytoplasmic domain of GP130, leading to the recruitment and activation of STAT1, STAT3, and, STAT5. Phosphorylated STATs dimerize and translocated into the nucleus to the IL6-responsive elements identified in the promoters of various acute-phase protein genes. IL-6 signaling is disrupted by the mutations of the *IL6R, IL6ST, and STAT3 genes.*

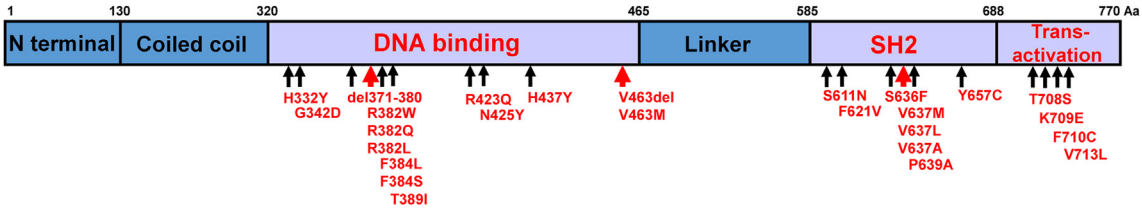

Fig. 2. Structure and mutations of STAT3. Structure and mutations of STAT3 is shown. Most of the mutations are located in the DNA binding, SH2, and transactivation domain. There are three hot spots for the mutations, i.e. R382, V463, and V637, shown with red arrows. Approximately 60% of the mutations are located in the hot spots.

dysfunction impairs IL-6 response in the liver, thus impairing elevated acute phase protein such as C reactive protein (CRP). Therefore, it is desirable to use an earlier marker such as IL-6 as a severity marker in the early stage of infection. In addition, when a child suffers from an early stages of severe infection, it is characteristic that the feeling of seriousness is lacking. Thus, it is necessary to pay close attention when you follow up this HIES patients, and it is recommended that the patients to be followed by PID specialists.

If suspected with newborn rash in combination with *S. aureus* infections and high serum IgE levels, in theory, we could diagnosis STAT3-DN HIES in newborn period. Early definitive diagnosis and start of prophylaxis might be able to prevent pneumatocele formation to improve quality of life of the HIES patient. But in practice, because of the rarity of this syndrome, it is difficult to diagnose this disorder in the neonatal period. Prophylactic antibiotics and antifungals are given in most cases of STAT3-DN HIES.[22,23] As an antibacterial agent against *S. aureus*, trimethoprim/sulfamethoxazole is generally used. It is relatively difficult to be resistance to the drug even when used for a long period of time. In addition, penicillinase-resistant penicillin antibiotic flucloxacillin and macrolide azithromycin may be administered. Since *S. aureus* is resident on the skin at a high rate, reduction of the amount of *S. aureus* by a bleach bath may improve atopic dermatitis. Prophylactic administration of anti-fungal agents such as itraconazole, voriconazole, and posaconazole, which are sensitive to Aspergillus, is also recommended. Long term use of these drug is associated with adverse effects.[24] Periodical blood chemistry and careful monitoring of drug serum levels are a critical component of this prophylaxis. In some patients with STAT3-DN HIES, surgical removal of the pneumatocele may be considered, but the frequency of complications is high, and it is necessary to carefully consider the surgical indication.[23] Immunoglobulin replacement therapy is recommended for children with this disease because of the deficiency in the production of specific antibodies.

As a curative treatment, hematopoietic stem cell transplantation (HSCT) has not been performed much because of the symptoms of non-hematopoietic tissues in STAT3-DN HIES, but impaired differentiation of Th17 cells is involved in the development of bacterial and fungal infections. Therefore, hematopoietic stem cell transplantation is being considered in cases where it is difficult to control lung infections with antibiotics. Application of HSCT to STAT3-DN HIES is still controversial and future studies are needed. Organic changes in the lungs (bronchiectasis and pneumatocele) are important factors in the prognosis of the patients, and regular follow-ups including chest computed tomography (CT) are recommended. Vaccination, including live vaccines, are well tolerated, with the exception of the pneumococcal polysaccharide vaccine, which might induce severe necrotic reactions.[25]

ZNF341-LOF

Homozygous mutations in the *ZNF341* gene were reported in 19 patients from 10 families as a new type of HIES.[26,27] Most of the patients are middle east origin and clinically similar to STAT3-DN HIES patients, suffering from eczema, mucocutaneous candidiasis, and elevated serum IgE levels. The patients, however, showed stronger inflammatory responses and fewer non-immunological manifestations compared to STAT3-DN HIES. *ZNF341* is a previously unexplored putative transcription factor containing 12C2H2 zinc finger (ZF) domains (Fig. 3). The mutations in ZNF341 are homozygous nonsense or frameshift mutations that induce truncation of the ZNF341 protein, but interestingly, nonsense mediated mRNA decay does not operate in this gene and truncated ZNF341 protein can be expressed at least some of the patients. ZNF341 proteins do not interact with wild-type ZNF341 even after stimulation, and two of the mutant proteins (Q195X and R302X) are retained in the cytoplasm, suggesting these mutants are complete LOF. Chromatin immunoprecipitation-sequencing (ChIP-seq) analysis with the anti-ZNF341 mAb identified that strongest ZNF341-binding site was located in the STAT3 promoter region and strong ZNF341 binding was also observed in the STAT1 promoter and ZNF341 intron 1. There are two isoforms in ZNF341 protein, both isoforms induced expression from the STAT1 and STAT3 promoters by reporter assays. Three of the five mutants induced no luciferase activity, confirming that the Q195X, R302X and K355fs mutant alleles were complete LOF. By contrast, the Y542X mutant, which can bind to the canonical motif on Electrophoresis Mobility Shift Assay (EMSA) and in pulldown assay. The mutant yielded intermediate levels of luciferase activity, suggesting that it is partial LOF, at least when overexpressed.

The patients had decreased Th17 cells, and lower central memory CD4+ and CD8+ T cells, higher proportions of naive CD4+ T cells, but had normal proportions of Treg cells, γδ T cells, and invariant NKT cells. The lymphocyte subset of ZNF341-LOF closely resembles that of STAT3-DN HIES. However, by closely looking at the cellular phenotype of the ZNF341 deficiency, the pathogenesis of this HIES might be more complex than originally conceived. Immortalized cell lines, including EBV-LCL, SV40 transformed fibroblasts, and Herpesvirus saimiri (HVS) immortalized T cell lines, from the patients displayed no major STAT3-DN phenotype. Furthermore, ZNF341 deficient monocytes are not functionally impaired in STAT3 signaling, although the expression levels of STAT3 is lower compared to wild-type ZNF341. Interestingly, STAT3 activity is impaired in ZNF341-deficient B cells and STAT3 autoinduction is impaired in ZNF341-deficient naïve CD4+ T cells,

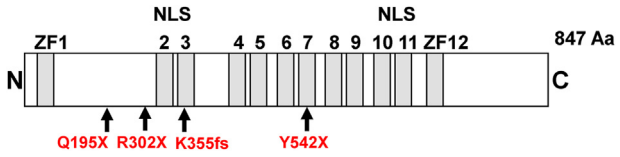

Fig. 3. Structure and mutations of ZNF341. Structure and mutations of ZNF341 is shown. Each shaded box indicates zinc finger (ZF) domain. Nuclear localization signal (NLS) is located in ZF2-ZF3 and ZF10-ZF11. LOF mutations in the ZNF341 are shown in red.

therefore Th17 cell development is impaired in ZNF341-deficient naive CD4 T cells.

It is hypothesized that ZNF341 is a positive regulator of STAT3 expression and homozygous nonsense mutations in ZNF341 lead to insufficient STAT3 expression, which is likely to cause HIES phenotypes. Because no STAT3-DN HIES caused by haploinsufficiency has been reported in the human STAT3 loci, it is conceived that in order to develop HIES manifestations, STAT3 activity needs to be lower than 50%. The authors showed that ZNF341 deficiency leads to a 50% decrease in expression levels of STAT3 and a >60% decrease in phosphorylation levels of STAT3 upon stimulation with STAT3-activating cytokines in T cells. Clearly, more work is needed to understand the exact role of ZNF341 in the pathogenesis of ZNF341-LOF HIES, since there is no clear demonstration of introduction of wild-type ZNF341 rescue STAT3 expression and signaling, and there is a possibility that STAT3-independent function of ZNF341 might also contribute to the phenotype.

IL6ST-partial LOF

IL-6 is considered to be one of the most powerful pro-inflammatory cytokines. Blockade of IL-6 by the neutralizing antibody, tocilizumab, is effective for the treatment for autoimmune disorders including rheumatoid arthritis. The blockade is also effective for the cytokine storm due to COVID-19 infection and chimeric antigen receptor (CAR) T-cell therapy.[28]

IL6ST encodes GP130 protein, a signaling subunit of IL-6 family cytokines. IL-6 family cytokines have pleiotropic functions in the regulation of the acute phase reaction, B-cell stimulation, the regulation of the balance between regulatory and effector T cells. The proximal cytoplasmic region of GP130 contains two boxes that constitutively bind to Janus kinase (JAK) family tyrosine kinases (Fig. 1). Upon IL-6 binding, JAKs phosphorylate tyrosine residues in the cytoplasmic domain, Y767, Y814, Y905, Y915, leading to the recruitment and activation of STAT1, STAT3, and, STAT5. In mice, complete GP130 deficiency is embryonic lethal[29] and in human complete LOF of IL6ST results in lethal Stüve-Wiedemann syndrome, characterized by skeletal dysplasia, neonatal lung dysfunction, congenital thrombocytopenia, atopic dermatitis, renal abnormalities, and defective acute-phase response.[30]

Two patients, South Asian and Turkish descent,[31] with homozygous missense mutations in IL6ST, N404Y and P498L, were reported (Fig. 4).[32] Signaling defects are partial by evaluating the reconstituted IL-6 family cytokine receptors in GP130 deficient HEK 293 cells. Signaling is more severely impaired in IL-6, IL-11, IL-27, and OSM but mildly impaired in LIF signaling. Patient-derived fibroblasts showed a substantially reduced STAT3 response to IL-6/IL-11 stimulation. The defect was rescued by the expression of wild-type GP130. The patients present with recurrent lung infections, eczema, eosinophilia, high serum IgE levels, impaired acute-phase responses, craniosynostosis, scoliosis, and deciduous tooth retention. These findings suggest that IL6ST is the major upstream cytokine receptor in the pathogenesis of STAT3-DN HIES.

IL6ST-DN

Dominant negative heterozygous mutations in *IL6ST* were identified in 12 patients from eight unrelated families (Fig. 4).[33] These patients have very similar clinical phenotype with STAT3-DN HIES including pneumatocele. Non-immunological features such as scoliosis, osteoporosis, retention of primary teeth were also present in the IL6ST-DN HIES. Interestingly, however, unlike the patients with STAT3-DN, IL6ST-partial LOF, or complete IL11RA deficiency, patients with IL6ST-DN do not present craniosynostosis, presumably due to residual activity in IL-11 signaling.[34]

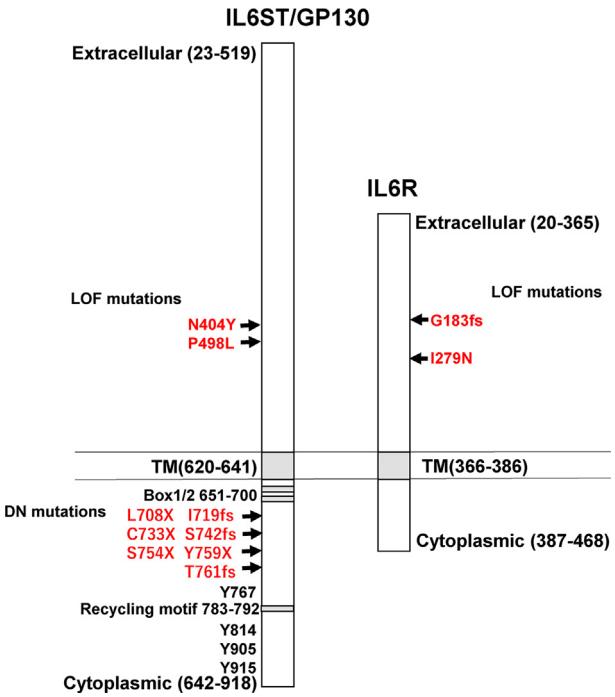

Fig. 4. Structure and mutations of IL6ST/GP130 and IL6R. The IL-6 receptor complex is composed of two different subunits, IL-6 binding subunit, IL-6R, and signal transducing subunit IL6ST/GP130. Both IL6ST/GP130 and IL6R are a single-pass transmembrane protein. LOF mutations in the IL6ST/GP130 are located in the extracellular domain, and DN mutations are located in the cytoplasmic region between JAK binding Box1/Box2 and STAT3 binding tyrosine residue 767. LOF mutations in the IL6R are located in the extracellular region.

All 10 patients had a heterozygous stop codon or frameshift mutation in *IL6ST*. The segregation patterns of the mutants were consistent with an autosomal dominant inheritance with full penetrance like STAT3-DN HIES. The mutations, (c.2121del; p.L708X), (c.2155dup; p. I719Nfs), (c.2277T > G; p.Y759X), and c.2224dup; p.742Ffs) had occurred de novo. All the IL6ST variants clustered in the intracellular region between Box1/Box2 (651–700 Aa) and tyrosine 767 (Fig. 4). Box1 proline motif interact with 4.1 protein, ezrin, radixin and moesin (FERM) domain and Box2 hydrophobic motif interacts with SH2 domain of JAK family kinases. All the mutated alleles encode receptors that could stably reach to the cell surface, due to the truncation of the recycling motif (783–792 Aa). The accumulation of the mutations in the patients suggests this character is required to be a dominant negative GP130 receptor. Again, STAT3 can transmit a signal in many non-GP130 associated receptors, but the similar phenotype between STAT3-DN and IL6ST-DN HIES strongly suggest that signaling defects of IL6ST dependent cytokines are the major players in the pathogenesis of STAT3-DN HIES. Patients with IL6ST-DN lack the characteristic features of Stüve-Wiedemann syndrome,[30] reflecting the presence of residual LIF signaling.

IL6R-LOF

Bi-allelic mutations in IL6R, which encodes a ligand binding subunit, was reported in two unrelated patients, one English and the other Pakistani origin, with atopic dermatitis, elevated IgE, reduced inflammatory responses, and recurrent skin and lung infections (Fig. 4).[35] The patients suffered from recurrent upper and lower respiratory tract infections, *S. aureus* recurrent skin abscesses, CRP was barely above the detection limit during acute

infection. No viral or fungal infections were reported. Serum IgG, IgA, and IgM levels were mildly reduced and IgE levels was elevated in both patients, but in one patient the increase was very modest for HIES; 787 kU/liter (normal range 0–100 kU/liter).

One mutation in the patients was a homozygous frameshift, G183Efs, and the other was a homozygous missense, I279N, causing normal protein expression, but impaired function. Neither was found in the genome Aggregation Database (gnomAD). Patient T cells showed impaired IL6-mediated phosphorylation of STAT3 and STAT1, which was restored by the introduction of wild-type IL6R. The patients had an increased proportion of Forkhead box P3 (FOXP3) + regulatory T cells, with increased expression of FOXP3 protein.

Based on these findings, it is hypothesized that the disruption of cellular responses to IL-6 alone can underlie most of the features of the original HIES.[36] Although this is a fascinating hypothesis due to its simplicity, but negative data against this hypothesis is that patients having neutralizing autoantibodies against IL-6 present with the similar symptoms as IL-6R LOF with respect to reduced inflammatory response but not with atopic manifestations. More studies are need, especially to identify a molecular mechanism how IL-6 and/or other signaling molecules regulate atopic manifestations in STAT3-DN HIES and related disorders.

TYK2-LOF

TYK2 is a member of the Janus kinase family (JAK1, JAK2, JAK3, and TYK2) that plays a crucial role in the signaling of subset of cytokine receptors including. IFN-α/β, IL-10, IL-12, and IL-23. Binding of the ligand to these cytokine receptor induces conformational changes and activation of the JAKs kinases via phosphorylation. The JAKs phosphorylate the intracellular part of the receptor which create a docking site for the STATs. STATs are subsequently phosphorylated and translocated to the nucleus to activate the transcription of the target genes.

TYK2-LOF is a rare molecular origin of PID, which was described in 10 patients from eight unrelated families.[37–40] The first case is a Japanese boy, living in Tokyo metropolitan area with westernized life style, suffering from mycobacterial and skin viral infections associated with hyper IgE phenotype.[37] Later, Dr. Casanova's group identified five families with TYK2 deficiency. The patients live in Turkey, Morocco, Iran and Argentina. The patients presented with mycobacterial and viral disease without hyper IgE phenotype.[37] In addition, another TYK2-LOF patient with features of hyper IgE phenotype was reported in 2016.[39] Common features of all the patients are intracellular bacterial infections including Mycobacterium and Salmonella and various viral infections including herpes simplex virus infection and molluscum contagiosum. Only two patients, however, present hyper-IgE phenotype. In these two patients, the mutations are C70HfsX21 and P216RfsX14, it is unlikely that the phenotypic difference is caused by the genotype–phenotype relationship (Fig. 5). Environmental factors might be associated with this phenotypic difference. Because TYK2-LOF patients have defects in Th1 cell differentiation due to the impaired IL-12 signaling, Th2 biased differentiation might be more easily obtained under certain circumstances. Genetic modifier genes are also a possibility, because of the difference in the IL-6 signaling between the two TYK2-LOF patients with atopic manifestations, but so far we were not successful to pin point a genetic modifier gene.

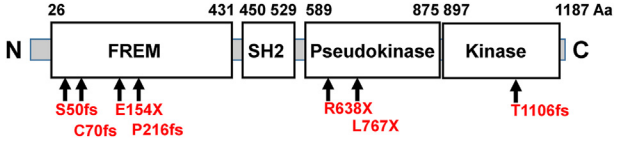

Fig. 5. Structure and mutations of TYK2. TYK2 is a non-receptor tyrosine kinase, consisting of FERM, SH2, pseudokinase, and kinase domain. The locations of homozygous LOF mutations are shown in red.

SPINK5-LOF

Comel-Netherton syndrome is an AR PID characterized by ichthyosiform erythroderma, trichorrhexis invaginata (bamboo hair), and atopic manifestations. In 1949, Comel reported this disorder is characterized by erythroderma associated with itchymosis.[41] In 1958, Netherton reported that this disorder is associated with characteristic bamboo hair.[42] The molecular cause of this disorder is LOF mutation of Serine protease inhibitor, Kazal type 5 (SPINK5), mainly expressed in skin and mucosa.[43] The identification of this disorder revealed that the serine protein inhibitor plays a critical role in the pathogenesis of PID and formation of normal hair shape.

Due to SPINK5-LOF mutations, serine protease activity increases in the stratum corneum, resulting in increased exfoliation and epidermal barrier dysfunction and immune disorders. Immune abnormalities were originally considered to be secondary to the excessive invasion of allergens due to abnormal epidermal barrier function. But more recently, intrinsic immune abnormalities in SPINK5 deficiency was reported.[44] Immediately after birth, ichthyosis begins on the face and spreads throughout the body. Bamboo hair presents with invaginated hair fissures, twisted hairs, or nodular hair splits. In severe cases, SPINK5-LOF is life-threatening, and even in mild cases, it presents with systemic features including failure to thrive., aminoaciduria, susceptibility to infection, defect in thermoregulation, and dehydration.

Atopic manifestations include food allergies, cedar pollinosis, bronchial asthma, and atopic dermatitis. Laboratory examination shows an increase in total IgE and an increase in various allergen-specific IgE, and eosinophilia. Markedly high trypsin-like enzyme activity in the stratum corneum, attenuation of SPINK5 protein expression by immunostaining in the epidermis. Mouse models lacking the Spink5 also have the similar clinical features as humans, such as abnormal epidermal detachment and abnormal hair shape.[45]

TGFBR1/2-GOF

TGF-β plays an important role in normal development and homeostasis. TGFBR1 and 2 are serine/threonine and tyrosine kinases. Canonical TGF-β signaling ignites when TGFB1/2/3 binds to TGFBR2, which recruits and phosphorylates TGFBR1. Then, activated TGFBR1 phosphorylates mothers against decapentaplegic homolog 2 (SMAD2) and SMAD3, which further recruit SMAD4 and translocate to the nucleus where it regulates the transcription of TGF-β target genes.[46] Loeys-Dietz syndrome (LDS), caused by the GOF mutations of TGFBR1/2, is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.[47] Most of the mutations are heterozygous missense mutations, located in cytoplasmic protein kinase region of the receptors (Fig. 6). The patients have craniofacial involvement consisting of cleft palate, craniosynostosis, and hypertelorism. Most of these non-immunological manifestations overlap with those of STAT3-DN HIES.

Atopic diseases of LDS include asthma, food allergy, atopic dermatitis, allergic rhinitis, and eosinophilic gastrointestinal disease, therefore, atopic manifestations are not limited to the skin. In immune organs, TGFBR1/2-GOF HIES patients show excessive nuclear accumulation of phosphorylated Smad2 in the thymus compared to age-matched unaffected individuals. Additionally,

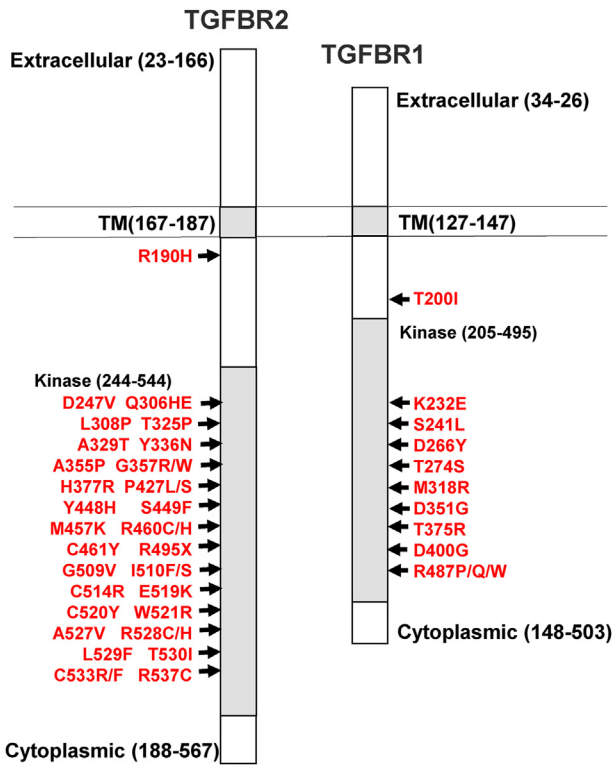

Fig. 6. Structure and mutations of TGRBR1 and TGFBR2. TGRBR1 and TGFBR2 are single-pass transmembrane protein, having protein kinase domain in the cytoplasmic region. The locations of heterozygous missense GOF mutations are shown in red.

CD4+ lymphocytes in the peripheral blood of the patients demonstrated increased expression of pSmad2/3 after stimulation with TGFβ1 when compared to unaffected individuals. These data are consistent with the idea that the causative variants function as GOF. TGFBR1/2-GOF patients exhibited elevated serum IgE levels, eosinophil number, and Th2 cytokines in the blood. Interestingly, Th2 cytokine-producing CD4+ T cells accumulate in cultures of naïve CD4+ T cells from TGFBR1/2-GOF patients after stimulation with TGF-β, suggesting that TGFBR1/2-GOF mutations support Th2 skewing in a CD4+ T cell intrinsic manner. Future studies are necessary to elucidate the molecular mechanism of TGFBR1/2-GOF mutations can induce Th2 biased iTreg differentiation in the patients.

CARD11-DN

Caspase recruitment domain-containing protein 11 (CARD11 also known as CARMA1) is a component of the trimer complex of CARD11-B-cell lymphoma/leukemia 10 (BCL10)-mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) (CBM complex), which is involved in NF-kB and mammalian target of rapamycin (mTOR) activation via T cell receptor (TCR) and B cell receptor (BCR) signaling. GOF mutations of the *CARD11* gene reported to cause a lymphoproliferative disease known as BENTA (B cell expansion with NF-kB and T cell anergy),[48–50] and bi-allelic loss of function mutations causes a Severe combined immunodeficiency (SCID)-like phenotype.[51,52] In 2017,[53] DN mutations in the *CARD11* gene were identified in patients with severe atopic dermatitis and other allergic conditions with or without infections.[54] More recently, the evaluation of larger cohort revealed that a broader phenotypic variations was associated with CARD11-DN, including cutaneous viral infections, respiratory tract infections, neutropenia, hypogammaglobulinemia, and lymphoma.[55] Laboratory investigation shows elevated serum IgE levels, eosinophilia, and low memory B lymphocytes. Serum IgG is variable, with some patients having hypogammaglobulinemia. Because most of the patients present with poor mitogen-stimulated T cell proliferation,[55] in the future, this disorder may be classified into CID category.

Most of the mutations of CARD11-DN are located in the N-terminal CARD domain and coiled coil (CC) domain (Fig. 7). Missense mutations in the N-terminal CARD domain are likely to disrupt interactions with BCL10, resulting in the defect in nuclear factor-kappa B (NF-κB) signaling. The coiled coil domain is also a hotspot for the mutations, the mutations in which is likely to disrupt

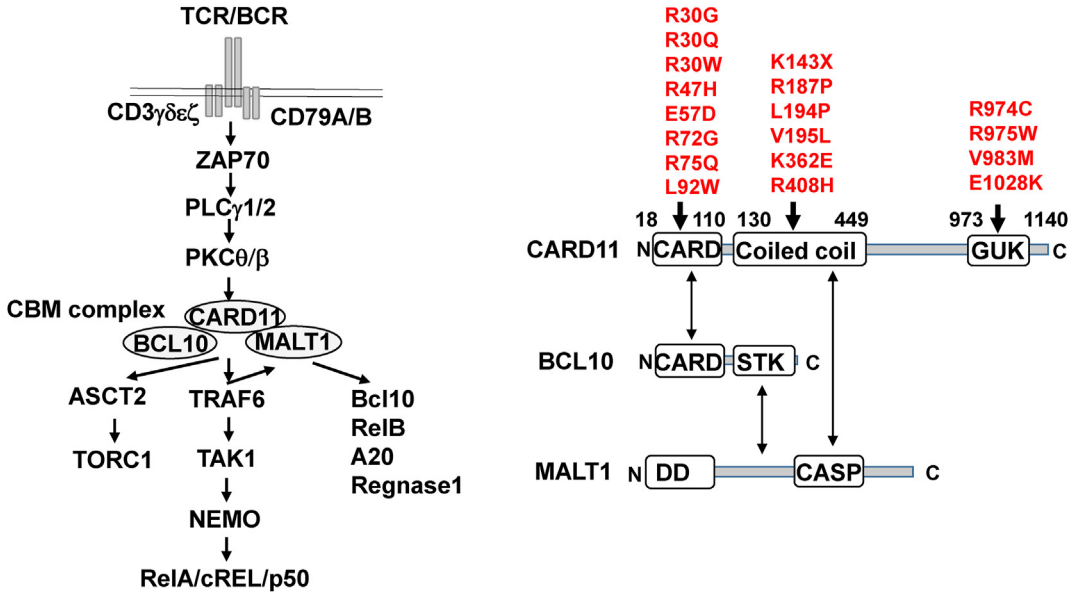

Fig. 7. Signal transduction pathway and structure and mutations of CARD11. CBM complex is located in the downstream signal transduction pathway of TCR and BCR, which transmit a signal to mTOR and NF-kB pathway. N-terminal CARD domain of CARD11 and BCL10, coiled-coil domain of CARD11 and CASP domain of MALT1 interact each other to form a CBM complex. Most of the disease-causing mutations are missense DN mutations, shown in red, are located in the CARD, coiled-coil, and GUK domain.

interactions with MALT1. Unlike CARD/CC-associated GOF mutations found in patients with BENTA, these mutations did not drive constitutive NF-κB activation in the absence of antigen receptor stimulation.

Atopic disease was the prominent feature in most patients with CARD11-DN (89%), most frequently presenting with atopic dermatitis (73%) but also including asthma (55%), food allergies (32%), and eosinophilic esophagitis (7%). However, atopy was mild or absent in at least 10% of the patients, with no discernible differences in CARD11 signaling function. Furthermore, unrelated patients with the same mutation and even family members harboring identical mutations demonstrated differences in the variety and severity of manifestations. These observation suggests that environmental factors or genetic modifiers might be associated with the development of atopic disorders in CARD11-DN HIES. Insufficient humoral responses, such as low IgM levels, appear to be a common in impaired CARD11 signaling with or without increased IgE levels. A number of families presented with more severe humoral defects resembling common variable immunodeficiency (CVID), which may be contributed by intrinsic defects in B-cell and extrinsic defects in T cells.

Cutaneous viral infections, including molluscum contagiosum and herpes simplex virus 1 infections, were also common to the CARD11-DN HIES patients. Impaired CD8+ T-cell immunosurveillance could be a causal factor. Interestingly, patients with BENTA carrying CARD11-GOF mutations often present with molluscum contagiosum and Epstein-Bar virus infections. Both CARD11-GOF and CARD-DN mutations resulted in similar skin viral infections.

Other PIDs with high serum IgE levels

Several other PIDs mainly from the CID category are characterized by high serum IgE levels and susceptibility to infections. The PIDs, including Wiskott–Aldrich syndrome, DOCK8 deficiency, PGM3 deficiency, and Omenn Syndrome, are all characterized by decreases in T-cell numbers and an impairment in T-cell proliferation. Causative genes of Omenn syndrome include Recombination-activating gene *(RAG)1, RAG2, IL2RG, IL7R, DNA ligase 4* (*LIG4), DNA cross-link repair 1C (DCLRE1C), RNA component of mitochondrial RNA processing endoribonuclease (RMRP), adenosine deaminase (ADA), protein kinase, DNA-activated, catalytic (PRKDC).* The high serum IgE levels may result from weak TCR signaling insufficient to induce Treg cells, and/or an imbalance in the Th1/Th2 differentiation. Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by the LOF mutations in the *FOXP3* gene, is also one of the PID with high serum IgE levels. This indicates that the lack of regulatory T cells alone is sufficient to induce high serum IgE levels in the patient. It is necessary to exclude these disorders/genes to diagnose HIES.

Concluding remarks

Major progress has been made in our understanding of monogenic diseases that cause hyper IgE phenotype associated with susceptibility to infection. The definition of HIES can be divided at least into three categories: (1) the definition that include only patients who present with clinical symptoms identical to the original STAT3-DN HIES, (2) the definition that includes all the patients with atopic dermatitis, high serum IgE levels, and susceptibility to infections, and (3) the definition that exclude the CID patients with defects in T cell proliferation, from patients with the definition (2). In this article, the definition 3 was adopted because the molecular pathogenesis of HIES is more relevant to the mechanism of common atopic disorders by applying this definition. Regardless of which definition is adopted, elucidation of the etiology and pathophysiology of HIES is helpful for elucidation of the human immune system, mechanism of atopic diseases, and the development of new therapeutic approaches.

At present, distinguishing HIES patients from common atopic disorders, especially early in life, is not an easy task. Consultation with the PID specialists is recommended, however, even for PID specialists, it is difficult to distinguish the HIES from common atopic disorders. In this setting, a detailed family history and clinical course associated with specific laboratory tests for HIES is essential. From a clinical standpoint, early exclusion of CID is especially important, because the number of CID patients with high serum IgE levels is relatively large and earlier and curative treatment might be crucial for the prognosis of the patients. Eventually, HIES can be distinguished from common atopic disorders by observing the clinical course, usually the development and recurrence of unusual infectious episodes or the association of non-immunological manifestations. If there is enough evidence to indicate that the patients are different from common atopic diseases, genetic testing panels for the causative genes of HIES is the method of definitive diagnosis.

There are challenges in elucidating the pathogenesis and pathophysiology of HIES. Regarding IL-6R-LOF HIES, the discussion was based on the clinical and laboratory findings of only two patients. At present, it is technically difficult to completely rule out the possibility that modifier genes may affect the phenotype of these HIES patients. Especially, if the number of the patients is limited and there are some discrepancies in the phenotype of the patients, such as severe and mild atopy. Strong regional bias of the HIES patients is also a concern for the interpretation of pathogenesis of HIES, because it is well known that environmental factors are deeply involved in the pathogenesis of atopic disorders. Although PID research has witnessed many examples of the same genetic abnormality has different phenotypes between humans and mice, but it is still necessary to make good use of mouse models for the understanding of PID pathogenesis. More new genetic causes of HIES are likely to be identified in the near future. Many new patients with HIES are likely to be identified by worldwide application of recently developed genetic technologies. These advances are certain to help HIES research to elucidate the understanding of human immunology and the development of treatments for atopic disorders.

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Conflict of interest

The author has no conflict of interest to declare.

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