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Primary immunodeficiency diseases associated with increased susceptibility to viral infections and malignancies

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Activity Objectives

1. To identify cutaneous viral infections associated with specific primary immunodeficiency diseases.
2. To identify how molecular defects associated with specific primary immunodeficiency diseases predispose affected subjects to an increased risk of virus-induced malignancy.

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Primary immunodeficiencies (PIDs) are commonly characterized by an increased susceptibility to specific infections and, in certain instances, a higher than usual incidence of malignancies. Although improved diagnosis and early treatment of PIDs have reduced early morbidity and mortality from infection, the development of cancer remains a significant cause of premature death. The emergence of cancer in patients with PIDs often results from impairments in the immune response that lead to weakened surveillance against oncogenic viruses, premalignant or malignant cells, or both. Here we review the clinical and biologic features of several PIDs associated with enhanced susceptibility to viral infections and cancer, including X-linked lymphoproliferative disease; IL-2–inducible T-cell kinase deficiency; epidermodysplasia verruciformis; warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; autosomal recessive hyper-IgE syndrome; X-linked agammaglobulinemia; and common variable immunodeficiency. It is of importance that we gain in-depth insights into the fundamental molecular nature of these unique PIDs to better understand the pathogenesis of virus-associated malignancies and to develop innovative therapeutic strategies. (J Allergy Clin Immunol 2011;127:1329-41.)

Key words: *Immunodeficiency, viral infection, malignancies, X-linked lymphoproliferative syndrome*

Primary immunodeficiencies (PIDs) comprise a rare group of genetic disorders associated with an enhanced susceptibility to specific infections and, in certain cases, an increased incidence of malignancy.[1] The susceptibility to develop tumors depends on several factors, including a defective DNA damage response (DDR) and a dysregulated immune response. The DDR pathway is responsible for sensing and repairing damaged DNA[2] and thus comprises the most powerful tumor surveillance mechanism.[3] Given the importance of specific DNA-altering mechanisms

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Terms in boldface and italics are defined in the glossary on page 1330.

during T- and B-lymphocyte development, it is not surprising that PIDs associated with DDR defects are characterized by compromised immune responses, as well as enhanced formation of lymphoid malignancies.[4] Alternatively, immune dysregulation leads to reduced clearance of viruses, such as ***EBV***, hepatitis B virus, hepatitis C virus, human papilloma virus (HPV), human T-cell lymphotropic virus, and Kaposi sarcoma–associated virus, which contribute to cellular immortalization and transformation and collectively account for 10% to 15% of cancers worldwide.[5] Inability to eliminate viral pathogens also creates a hostile inflammatory environment that promotes cell survival and proliferation.[6] As a result, there is an increased risk that rapidly dividing cells will sustain ***oncogenic mutations***.

The emergence of malignancies in a heterogeneous group of patients with PIDs associated with cellular and/or humoral immune dysfunction (including X-linked lymphoproliferative disease [XLP]; IL-2–inducible T-cell kinase [ITK] deficiency; epidermodysplasia verruciformis [EV]; warts, hypogammaglobulinemia, infections, and myelokathexis [WHIM] syndrome; autosomal recessive hyper-IgE syndrome [AR-HIES]; X-linked agammaglobulinemia [XLA]; and common variable immunodeficiency [CVID]) results from the interplay between the underlying genetic defect or defects, immune dysregulation, and increased susceptibility to specific viruses. Through the study of these rare diseases, we will gain critical insights into the mechanisms controlling host antiviral and antitumor immunity, which will facilitate the development of new treatments for patients with these and related disorders of the immune system.

XLP

XLP, also known as Duncan disease in recognition of a well-studied kindred,[7] is a rare immunodeficiency characterized by the clinical triad of fulminant infectious mononucleosis (FIM), dysgammaglobulinemia, and lymphoma (see Table E1 in this article's Online Repository at www.jacionline.org).[8,9] Affected patients commonly present with FIM, an inappropriate immune response to EBV infection that is characterized by the uncontrolled expansion of EBV-infected B cells, as well as reactive $CD8^+$ T cells and macrophages, often with evidence of ***hemophagocytic lymphohistiocytosis*** (HLH).[8,10] Abnormal humoral immune responses, ranging from increased IgA or IgM levels, selective IgG or IgG subclass deficiencies, or both[11] to hypogammaglobulinemia, and lymphoproliferative disorders, typically of B-cell origin, are the 2 other common manifestations of XLP.[8,9] Affected persons can also rarely present with aplastic anemia, lymphoid vasculitis, pulmonary lymphoid granulomatosis, and autoimmune features.[8]

On a molecular basis, XLP is caused by mutations in the Src homology 2 domain–containing gene 1A *(SH2D1A)*,[12-14] which encodes the signaling lymphocytic activation molecule (SLAM)–associated protein (SAP). A second XLP-like disorder

GLOSSARY

ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID): A key enzyme involved in antibody class-switching and affinity maturation. Mutations in *AID* are associated with autosomal recessive hyper-IgM syndrome.

$CD45RA^+$ T CELLS: Naive T cells.

EBV: EBV, also known as human herpes virus 4, has a double-stranded DNA genome. EBV plays a role in infectious mononucleosis, XLP, oral hairy leukoplakia, hemophagocytic lymphohistiocytosis, and certain malignant diseases. EBV binds to CD21, also known as the C3d receptor or CR2.

ETOPOSIDE: A chemotherapeutic agent used to treat a variety of cancers. It is in the category of topoisomerase inhibitors and works by lysing cells entering mitosis.

FRAMESHIFT MUTATION: A mutation involving the insertion or deletion of a number of nucleotides not divisible by 3, causing incorrect reading of triplet codons.

GENODERMATOSIS: A congenital disease of the skin with a genetic cause.

GENOME-WIDE LINKAGE STUDIES: Studies investigating DNA markers from affected and unaffected patients to examine whether the markers cosegregate with phenotypes of interest.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A proliferative disorder that is the result of uncontrolled hemophagocytosis and uncontrolled activation of inflammatory cytokines similar to the macrophage activation syndrome. Tissue lesions are characterized by infiltration of the involved organ with activated phagocytic macrophages and lymphocytes. Diagnostic criteria include having 5 of the following characteristics: fever; splenomegaly; cytopenia in at least 2 cell lines; triglyceride levels of 265 mg/dL or greater, fibrinogen levels of 150 mg/dL or less, or both; serum ferritin levels of 500 μg/L or greater plus soluble CD25 levels of 2400 U/mL or greater; low or absent NK cell activity; hemophagocytosis in the bone marrow, spleen, or lymph node; and no evidence of malignancy.

IMMUNOLOGIC SYNAPSE: The region of physical contact between the T cell and the antigen-presenting cell, also known as the supramolecular activation cluster (SMAC). T-cell specific signaling molecules are rapidly mobilized to the center of the synapse, including the TCR, CD3, and ζ chains; CD4 or CD8; and receptors for costimulators, signaling, and adapter proteins.

LAMELLIPODIA: Motile cytoplasmic extensions characteristic of some migrating cells.

MISSENSE MUTATION: A genetic mutation that can lead to the exchange of 1 amino acid for a different amino acid.

NATURAL KILLER T (NKT) CELLS: A small population of T cells that also express markers found on NK cells. All NKT cells recognize lipids bound to CD1, an MHC-like molecule. They are capable of rapidly secreting cytokines after stimulation.

NON-HODGKIN B-CELL LYMPHOMA: Broad categories of lymphoma are Hodgkin and non-Hodgkin lymphoma. The hallmark of Hodgkin disease is the presence of the Reed-Sternberg cell.

NONSENSE MUTATION: Genetic information that does not code for any amino acid and usually causes termination of the molecular chain in protein synthesis.

ONCOGENIC MUTATIONS: Gain-of-function mutations in alleles resulting in promotion of tumorigenesis.

PLECKSTRIN HOMOLOGY DOMAIN: Phospholipid-binding domains located on many different signaling molecules, such as BTK.

SUBARACHNOID: The space between the arachnoid (a thin membrane) and the pia mater through which the cerebrospinal fluid circulates.

WESTERN BLOTTING: An assay that allows for the identification of specific proteins in complex mixtures by means of charge- or size-based separation or a combination of both.

XIAP GENE: X-linked inhibitor of apoptosis gene

The Editors wish to acknowledge Daniel A. Searing, MD, for preparing this glossary.

Abbreviations used

AR-HIES: Autosomal recessive hyper-IgE syndrome
CVID: Common variable immunodeficiency
DDR: DNA damage response
DOCK8: Dedicator of cytokinesis 8
EV: Epidermodysplasia verruciformis
FIM: Fulminant infectious mononucleosis
GPCR: G protein–coupled receptor
HIES: Hyper-IgE syndrome
HL: Hodgkin lymphoma
HLH: Hemophagocytic lymphohistiocytosis
HPV: Human papilloma virus
HSCT: Hematopoietic stem cell transplantation
iNKT: Invariant natural killer T
ITK: IL-2–inducible T-cell kinase
IVIG: Intravenous immunoglobulin
NK: Natural killer
PID: Primary immunodeficiency
PLC-γ: Phospholipase C-γ
SAP: SLAM-associated protein
SDF-1: Stromal cell–derived factor 1
SH2D1A: Src homology 2 domain–containing gene 1A
SLAM: Signaling lymphocytic activation molecule
STAT3: Signal transducer and activator of transcription 3
TYK2: Tyrosine kinase 2
WHIM: Warts, hypogammaglobulinemia, infections, and myelokathexis
XLA: X-linked agammaglobulinemia
XLP: X-linked lymphoproliferative disease

caused by mutations in the X-linked inhibitor of apoptosis gene (***XIAP gene)*** was recently described; however, this latter condition is predominantly associated with recurrent HLH,[15,16] and thus far no cases of lymphoma have been reported.[15-17] Therefore this condition will not be discussed further here. Most affected patients harbor inactivating *SH2D1A* alterations, including ***missense mutations***, ***nonsense mutations***, and deletion mutations.[18] Mutations affecting regulatory regions of the gene might exist in the remaining patients in whom no coding region or intronic abnormalities are identified. Although DNA sequencing remains the gold standard for the molecular diagnosis of XLP, ***Western blotting***[19] and flow cytometric analysis[20,21] to detect the deficiency of SAP protein expression are of great value in facilitating a more timely diagnosis and initiation of treatment for this condition.

SH2D1A encodes the 128-amino-acid Src homology 2 domain–containing protein SAP, which interacts with a conserved tyrosine-based motif within the cytoplasmic domain of the SLAM family of immunomodulatory receptors, including SLAM (CD150, *SLAMF1*), LY9 (CD229, *SLAMF3*), 2B4 (CD244, *SLAMF4*), CD84 (*SLAMF5*), NTB-A (*SLAMF6*), and perhaps CRACC (CD319, CS1, *SLAMF7*).[22] In human subjects SAP is expressed predominantly in thymocytes, T cells, natural killer (NK) cells, ***natural killer T*** (NKT) cells, and a minor population of B cells.[8,20,23,24] Given that SAP binds to and propagates signals initiated by the SLAM family receptors, the phenotypes of disease are likely the result of altered SLAM receptor–associated immunomodulatory functions within T, NK, NKT, and possibly B cells (Fig 1).

There is accumulating evidence pointing to the important roles for SAP and specific SLAM receptors in the control of primary EBV infection. Particularly crucial is the receptor 2B4 in NK cell– and $CD8^+$ T cell–mediated cytotoxicity against EBV-infected B cells.[25,26] CD48, the natural ligand for 2B4, is upregulated on EBV-infected B cells,[27] thus directing NK and $CD8^+$ T-cell cytotoxic activity toward these targets. Accordingly, 2B4-associated defects in NK and $CD8^+$ T-cell function are likely central to the enhanced susceptibility to EBV infection in SAP-deficient patients (Fig 1).[28,29] The SLAM receptor NTB-A might also facilitate clearance of EBV-infected B cells. Interestingly, engagement of this receptor on SAP-sufficient effectors promotes cytolysis, whereas engagement on cells from patients with XLP inhibits target cell killing.[30,31] Thus the absence of SAP impairs both 2B4 and NTB-A function, which likely contributes to a defective anti-EBV immune response. More recently, a proapoptotic function has been attributed to SAP during T-cell receptor (TCR) restimulation, a process that also depends on NTB-A.[32] Impaired cell death of SAP-deficient T lymphocytes might promote the expansion of activated $CD8^+$ T cells that occurs in patients with FIM. Patients with XLP also lack iNKT cells, a lineage of innate-like T lymphocytes with regulatory properties, and it has been speculated that the marked reduction in these cells impairs host immunity to EBV (Fig 1).[24,33,34] Nonetheless, the exact role of iNKT cells in mediating antiviral responses, particularly to EBV, remains to be elucidated.

SAP-deficient patients with XLP are at increased risk of lymphomas and other lymphoproliferative diseases, which are typically high-grade ***non-Hodgkin B-cell lymphomas***.[9,35] It is possible that altered 2B4 signaling and subsequent defects in NK and $CD8^+$ T-cell cytotoxicity could facilitate the survival and persistence of EBV-transformed B cells (Fig 1). Interestingly, not all B-cell lymphomas in patients with XLP express the EBV genome, and there is no evidence of prior EBV exposure in a proportion of patients with this manifestation.[18,36,37] Thus disruption of lymphocyte function and signaling might extend beyond EBV infection, and the genetic defect *per se* might predispose to lymphomagenesis. Similar to its proapoptotic role in T cells, SAP functions under certain conditions to promote the death of B cells.[38] The loss of this property could hinder the elimination of DNA-damaged premalignant B cells independent of their infection by EBV. Furthermore, given the potential importance of iNKT cells in antitumor immune surveillance,[39,40] their absence might also contribute to the enhanced development of lymphomas in SAP-deficient patients with XLP (Fig 1).

Symptomatic, preventive, and curative therapies are the cornerstones of XLP management. Patients with HLH generally respond to early initiation of therapy, consisting of ***etoposide***, glucocorticoids, and cyclosporine A and often accompanied by rituximab (anti-CD20 antibodies) and intravenous immunoglobulin (IVIG) to control acute EBV infection.[41,42] Patients with lymphoma can be successfully treated with standard chemotherapy appropriate to the tumor diagnosis; however, they must be monitored closely for the development of infection caused by associated defects in humoral and cellular immune responses.[8] Hematopoietic stem cell transplantation (HSCT), the only curative therapy for XLP, should be strongly considered for patients with HLH who are stabilized with chemoimmunotherapy,[43-45] as well as asymptomatic patients who have unaffected HLA-matched siblings. Patients with a suspected or confirmed diagnosis of XLP might benefit from rituximab in combination with IVIG to prevent primary EBV infection before HSCT.[8]

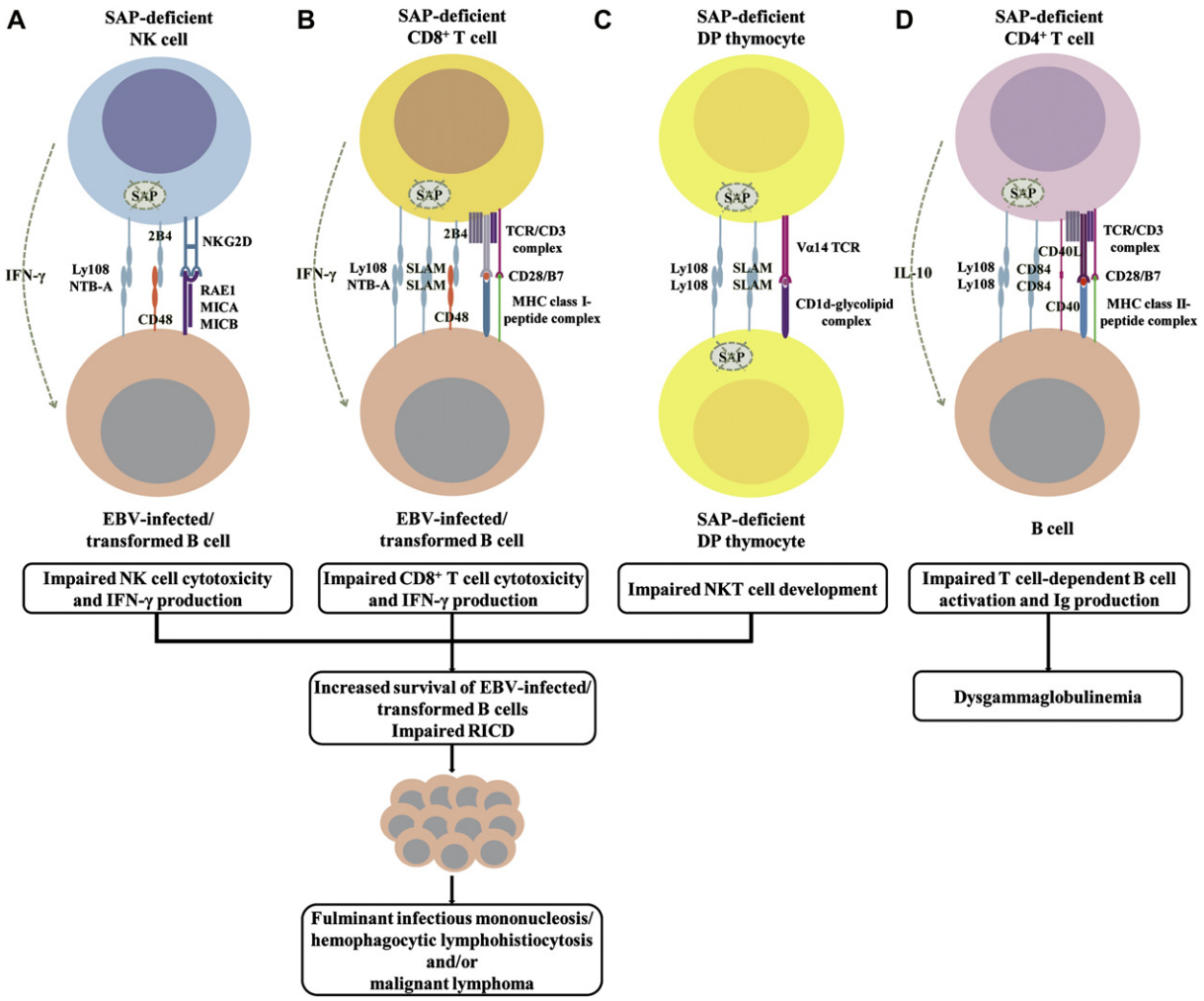

FIG 1. SAP deficiency is associated with defective cellular and humoral immune responses in patients with XLP. **A-C**, SAP deficiency profoundly affects NK (Fig 1, *A*) and $CD8^+$ T-cell (Fig 1, *B*) cytotoxicity and cytokine production and NKT cell development (Fig 1, *C*). Consequently, increased survival of EBV-infected B cells, together with impaired restimulation-induced cell death *(RICD)* of T cells, contributes to the development of FIM, malignant lymphoma, or both. **D**, SAP deficiency reduces T cell–dependent B-cell activation and immunoglobulin production.

ITK DEFICIENCY

ITK deficiency is a novel PID characterized by severe EBV-associated immune dysregulation that clinically resembles XLP (see Table E1). It was originally identified in 2 female siblings from a consanguineous Turkish family.[46] Both ITK-deficient patients had uncontrolled EBV infection and exhibited clinical and laboratory features consistent with HLH. EBV-induced B-cell proliferation progressed to Hodgkin lymphoma (HL) in both affected patients. More recently, 3 cases from a family of Arab origin, who presented with EBV-positive HL, were subsequently found to harbor a homozygous nonsense mutation in the *ITK* gene.[47] All 3 patients responded favorably to initial chemotherapy; however, the clinical phenotype varied considerably among the affected members. One patient had relapsed HL and HLH, which, despite reinitiation of therapy, proved to be fatal. Conversely, complete remission with no evidence of EBV infection, with and without HSCT, was observed in the other 2 patients. Lastly, 7 additional ITK-deficient patients were identified in a broader screen of patients with autoimmune lymphoproliferative syndrome or suspicion of congenital forms of HLH.[48,49] Among these newer cases, 4 also received diagnoses of HL.[48] Together the results of these studies suggest that sequence analysis of the *ITK* gene should be considered in all patients with EBV-associated lymphoproliferative diseases, particularly HLH and HL.[47,48]

DNA sequencing of affected patients has revealed missense or nonsense germline *ITK* mutations that reduce or eliminate ITK expression. ITK is a cytoplasmic nonreceptor tyrosine kinase that is expressed in thymocytes and mature T cells, as well as NK cells, iNKT cells, and mast cells.[50,51] Its ***Pleckstrin homology domain*** preferentially binds to phosphatidylinositol (3,4,5)-triphosphate, leading to the recruitment of ITK to the plasma membrane.[50] In T cells ITK is activated in response to antigen receptor engagement and is required for full TCR-induced phospholipase C-γ (PLC-γ) activation and Ca^{2+} mobilization (Fig 2). Indeed, PLC-γ activation is reduced rather than eliminated in $Itk^{-/-}$ T cells,[52,53] thus emphasizing a modulatory rather than an indispensible role for this kinase in the TCR signaling cascade.

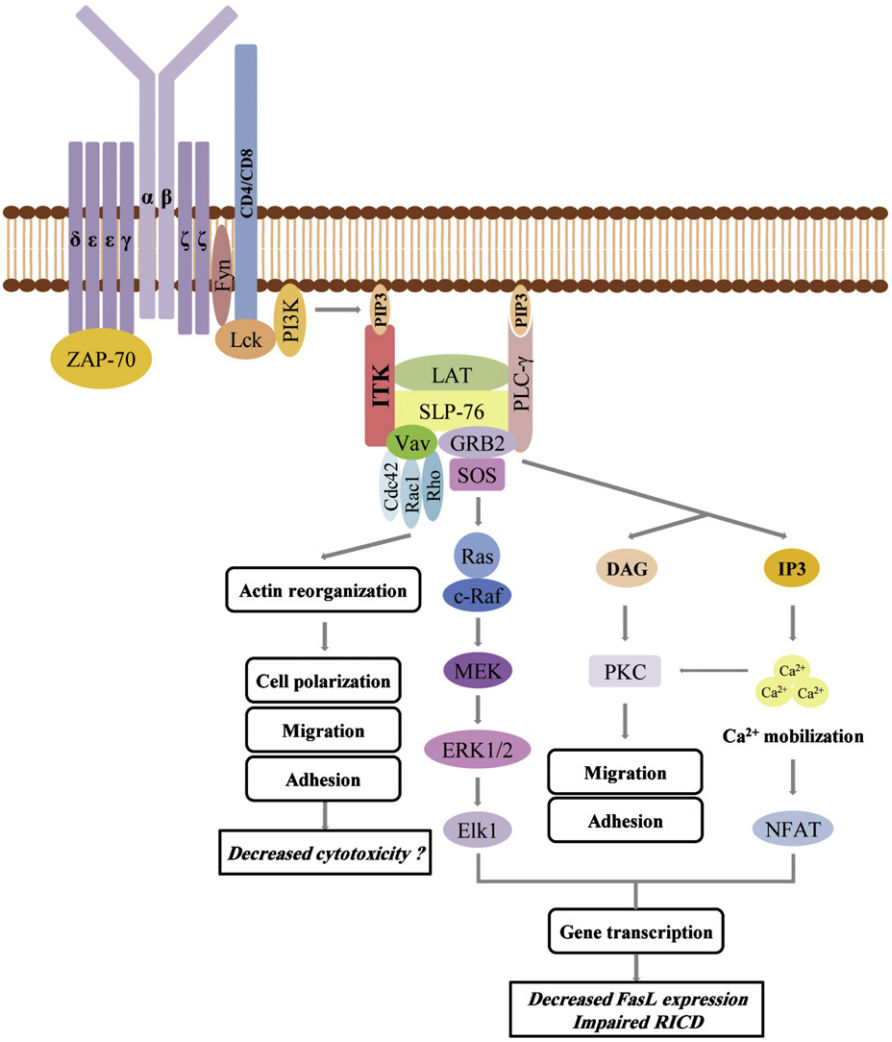

FIG 2. Contribution of the TEC family kinase ITK to TCR-mediated signaling pathways. ITK is required for full TCR-induced PLC-γ activation and Ca^{2+} mobilization, as well as Vav1 localization, signifying its role in TCR-induced signaling complex formation and stability. ITK deficiency alters actin cytoskeletal rearrangement, which probably results in reduced cellular cytotoxicity, as well as gene transcription (eg, decreased Fas ligand expression), which contribute to impaired activation-induced cell death. *DAG*, Diacylglycerol; *ERK*, extracellular signal-regulated kinase; *IP3*, inositol trisphosphate; *LAT*, linker for activation of T cells; *MEK*, mitogen-activated protein kinase kinase; *NFAT*, nuclear factor of activated T cells; *RICD*, restimulation-induced cell death; *SOS*, son of sevenless; *ZAP-70*, zeta-chain-associated protein kinase 70.

The strength of the TCR signal plays a critical role in T-cell development and lineage determination.[54,55] Consistent with this notion, the positive and negative selection of $CD4^+$ and $CD8^+$ T cells are defective in the absence of ITK in mice.[53,56] In addition, ITK plays an important role in the regulation of conventional versus innate-type $CD8^+$ T-cell development.[54,57] As opposed to conventional $CD8^+$ T cells, innate-type T cells display immediate effector functions on stimulation and are characterized by expression of activation markers, such as CD44, CD122, and NK1.1. In ITK-deficient mice, the majority of $CD8^+$ T cells have an innate-type phenotype.[58,59] Similarly, ITK-deficient patients have dramatically reduced numbers of naive ***CD45RA$^+$ T cells***.[46-48] Despite their activated phenotype, $Itk^{-/-}$ $CD8^+$ T cells fail to mount an effective primary or memory immune response to a variety of viral infections.[54,60,61] The defective antiviral immune response has been attributed to impaired cytotoxic $CD8^+$ T-cell activity, reduced $CD8^+$ T-cell proliferation, and diminished IFN-γ and TNF-α production.[60,61] Although not yet formally tested, similar defects might underlie the increased susceptibility of ITK-deficient patients to EBV infection.

ITK is also crucial for iNKT cell development in mice, as well as efficient iNKT cell cytokine production and survival in the periphery.[62] A characteristic reduction of iNKT cells has been demonstrated in ITK-deficient patients,[46-48] which is consistent with the experimental data from mutant mice. Hence, as with XLP, the severely reduced number of iNKT cells might also contribute to the increased susceptibility of ITK-deficient patients to primary EBV infection.[46-48]

The increased development of HL in ITK-deficient patients might reflect their perturbation of innate and adaptive antitumor immune responses, including lack of iNKT cells, which play an indispensable role in antitumor immune surveillance. It is also

possible that abnormal induction of Fas ligand on TCR stimulation, which results in reduced activation-induced cell death of stimulated *Itk*$^{-/-}$ T cells,[63] might contribute to tumorigenesis. Because ITK regulates distinct NK cell–activating receptors and subsequently NK cell–mediated cytotoxicity,[64] NK cell–mediated clearance of premalignant or malignant cells might be impaired in the absence of ITK protein.

Given the limited number of patients reported, the efficacy of various treatments has not yet been evaluated systematically. Rituximab, antiviral agents, and steroids can result in a marked reduction in EBV load and temporary improvement of symptoms; however, the disease follows a progressive course in many cases.[46,47] EBV-associated HL has been treated successfully with chemotherapy.[46-48] Additionally, successful HSCT has been performed in 2 patients.[46-48]

EV

EV is a rare ***genodermatosis*** that is characterized by increased susceptibility to cutaneous infection with specific HPV genotypes.[65,66] EV begins during infancy or childhood and is manifested by disseminated highly polymorphic lesions, including pityriasis versicolor–like macules and flat wart-like papules. The cutaneous lesions carry a considerable risk of malignant transformation to squamous cell carcinoma *in situ* or invasive squamous cell carcinoma and occur mainly on sun-exposed areas (see Table E1).[65-67]

EV is thought to be an autosomal recessive disease[68]; however, both X-linked recessive[69] and autosomal dominant[70] modes of inheritance have been reported. ***Genome-wide linkage studies*** have identified 2 susceptibility loci,[71] including EV1 and EV2 on chromosomal regions 17q25 and 2p21-2p24, respectively. EV1 contains the *EVER1* and *EVER2* genes,[72] in which 10 truncating or loss-of-function mutations have thus far been reported.[65] Homozygous mutations in *EVER1* or *EVER2* have been identified in approximately 75% of patients given a diagnosis of EV,[65] leaving a considerable proportion of patients with an unexplained genetic cause.

EVER1 and *EVER2* belong to an evolutionarily conserved transmembrane channel–like gene family,[73] which constitutes a novel group of modifiers of channels and ion transporters. The *EVER* genes are predicted to encode transmembrane proteins located in the endoplasmic reticulum of human keratinocytes.[72] The EVER proteins interact with ZnT-1,[74] a zinc transporter that regulates cellular zinc homeostasis. In transfected human keratinocyte cell lines, EVER and ZnT-1 negatively regulate the activity of the metal transcription factor 1 and the cytokine-stimulated transcription factors c-Jun and Elk-1.[75] Because activator protein 1 is a key transcription factor in the HPV lifecycle, it is proposed that a loss of function of either *EVER* gene would disrupt zinc homeostasis and consequently enhance the expression of viral genes, particularly the pro-oncogenic *E6* and *E7* genes, and contribute to HPV-mediated carcinogenesis.[74]

The EVER proteins are expressed in T and B lymphocytes, NK cells, endothelial cells, bone marrow myeloid cells, and dendritic cells,[76] thus pointing to their potential role in immunity against HPV. Indeed, impaired nonspecific cell-mediated immunity, including decreased total T-lymphocyte and T_H lymphocyte counts, reduced T-cell responsiveness to mitogens, and cutaneous anergy to common skin antigens,[77] and defective cell-mediated immunity toward EV-specific HPV (EV-HPV) types or infected keratinocytes[78,79] have been demonstrated, which could compromise viral clearance and lead to malignant transformation.[65,74]

Despite research on the causative role of HPV infection in cervical and anogenital cancers, the role of HPV in cutaneous oncogenesis has yet to be elucidated.[66,80] In favor of a protumorigenic role, the E6 oncoprotein of EV-HPV types inhibits UV-induced apoptosis through proteolytic degradation of the proapoptotic protein Bcl-2 (B-cell lymphoma 2) homologous antagonist killer.[81] Failure to repair UV-induced thymine dimers has also been demonstrated in cells expressing the E6 protein of HPV-5.[82] Moreover, the E6 protein of HPV-8 directly binds the XRCC1 protein required for DNA single-strand break repair,[83] thus compromising genetic stability. On the contrary, what is not in favor of the causality hypothesis is the dramatic decrease in the positivity of HPV DNA in malignant skin lesions devoid of the upper dermis,[84] which might represent a mere contamination from the surrounding skin. However, EV-HPV types could be involved in the early stages of cutaneous oncogenesis but not in the maintenance of the malignant state.[85]

Clinical vigilance and stringent sun protection are mandated for early diagnosis and surgical treatment of malignant or premalignant lesions. However, in the case of multiple cutaneous malignancies or persistent widespread nonmalignant lesions, surgical intervention is less desirable. Several nonsurgical modalities, including topical 5-fluorouracil,[86] 5% imiquimod,[87] tacalcitol,[88] systemic retinoids combined with IFN-α,[89] cimetidine,[90] and topical 5-aminolevulinic acid photodynamic therapy,[91] have been used, with inconsistent results. Hence their long-term efficacy merits further evaluation in larger randomized trials.

WHIM SYNDROME

WHIM syndrome is a rare immunodeficiency syndrome characterized by warts, hypogammaglobulinemia, infection, and myelokathexis (ie, retention of mature neutrophils in the bone marrow).[92-94] It typically manifests as recurrent bacterial infections from infancy or early childhood, most commonly gastrointestinal, pulmonary, and cutaneous infections, which, despite marked immunologic abnormalities, often follow a relatively mild clinical course (see Table E1).[93,94] The only common laboratory feature is neutropenia, which, in the face of bone marrow hypercellularity, indicates a defect in the release rather than the production of mature neutrophils.[93,94] Other abnormalities include B-cell lymphopenia, specifically of memory $CD27^+$ B cells[95]; T-cell lymphopenia with normal $CD4^+/CD8^+$ ratios and preserved proliferative responses to mitogens[95,96]; and hypogammaglobulinemia.[92,97]

WHIM syndrome is inherited in an autosomal dominant fashion and is caused primarily by heterozygous gain-of-function mutations in the gene encoding the chemokine receptor CXCR4.[98] CXCR4 is a member of the G protein–coupled receptor (GPCR) superfamily, which selectively binds the CXC chemokine stromal cell–derived factor 1 (SDF-1),[99] also known as CXCL12 (Fig 3). The identified *CXCR4* mutations, including 1 ***frameshift mutation*** and 3 nonsense mutations, result in the introduction of premature stop codons, thereby eliminating 10 to 19 amino acid residues of the cytoplasmic carboxyl-terminal domain of the receptor.[94,100] In the absence of the putative cytoplasmic phosphorylation sites, ligand-induced GPCR desensitization and endocytic internalization and degradation, which function

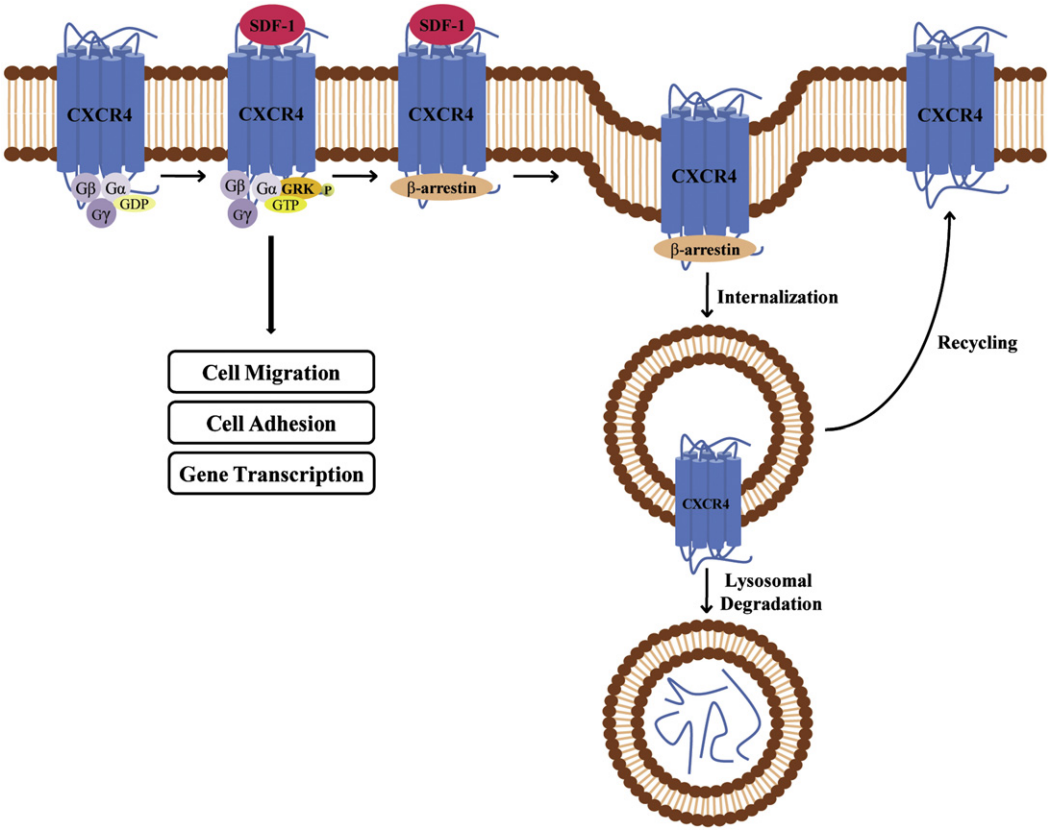

FIG 3. Regulation of CXCR4 signaling. SDF-1 binding to CXCR4 initiates multiple intracellular signal transduction pathways and gene expression. Concomitant induction of GRK-mediated phosphorylation of the CXCR4 cytoplasmic tail results in β-arrestin–mediated receptor desensitization and endocytic internalization. In patients with WHIM syndrome, mutations in the cytoplasmic tail of CXCR4 disrupt receptor downregulation, resulting in prolonged receptor activation and enhanced chemotactic responsiveness to SDF-1.

as physiological negative feedback mechanisms, are impaired.[100] Identification of 2 unrelated patients with aberrant CXCR4-mediated signaling who lack detectable mutations of the *CXCR4* gene[101] might indicate genetic heterogeneity of the disease. Interestingly, GPCR kinase 3 overexpression in cells from patients with WHIM syndrome restores SDF-1–mediated CXCR4 downregulation,[102] implicating it as a potential genetic candidate in patients who lack *CXCR4* mutations. Hence CXCR4 functional hyperactivity is believed to be the common biochemical feature in all the affected patients.

Patients with WHIM syndrome are prone to HPV infection, as demonstrated by numerous warts, most frequently on the hands, feet, and trunk, as well as condylomata acuminata of the anogenital tract, which cause severe papillomatosis and increased risk of dysplastic and neoplastic changes.[92-94] Although HPV infection is thought to be a unique viral susceptibility in patients with WHIM syndrome, EBV-associated lymphoproliferative disorders,[103,104] as well as herpes zoster[105] and severe recurrent oral[105] and genital[101] herpes simplex virus infections, have been reported. Collectively, these data reveal that patients exhibit a more generalized susceptibility to viruses of the herpes family. Given the importance of the SDF-1/CXCR4 axis in leukocyte trafficking,[92] it remains possible that defective cutaneous immunity might contribute to disease pathogenesis. Consistent with this notion, SDF-1 and CXCR4 are expressed in normal Langerhans cells and keratinocytes,[106,107] and increased levels of SDF-1 are observed in HPV-infected dermis.[101] This latter observation suggests that CXCR4 upregulation is a host susceptibility factor in facilitating HPV infection.[93,94] More recently, numeric and functional defects of blood dendritic cells have been demonstrated in patients with WHIM syndrome,[108] which might further contribute to the enhanced susceptibility to specific viral infections.

Aggressive measures are warranted to reduce the frequency of recurrent bacterial infections. Treatment with granulocyte colony-stimulating factor or GM-CSF, IVIG, and prophylactic antibiotics have proved beneficial.[94,109-111] Nonetheless, some patients experience recurrent infections despite therapy, which, in addition to the management difficulties of resistant warts, provides the rationale for performing allogeneic HSCT. Indeed, one case of successful allogeneic HSCT has been reported in a girl with WHIM syndrome.[112] Aggressive surveillance for dysplasia and cancer with surgical excision of any malignant or premalignant lesions is highly recommended.[94]

Recently, the safety and immunogenicity of Gardasil (Merck, Whitehouse Station, NJ), a prophylactic HPV vaccine, has been demonstrated in a 12-year-old female patient with WHIM syndrome.[113] Gardasil induced HPV-specific neutralizing antibodies, as well as a cellular immune response.[113] Because patients with WHIM syndrome exhibit defects in the development and maintenance of memory B cells,[95] it is possible that the effectiveness or duration of protection might be compromised. Thus patients

might require periodic booster injections to mount enduring protective effects. Cervarix (GlaxoSmithKline, Research Triangle Park, NC), the second HPV vaccine approved by the US Food and Drug Administration, is currently used for prophylactic immunization against high-grade cervical intraepithelial neoplasia and cervical cancer associated with oncogenic HPV types 16 and 18. However, to our knowledge, its efficacy has not been specifically assessed in patients with WHIM syndrome.

AR-HIES

Hyper-IgE syndrome (HIES) is a rare PID characterized by recurrent bacterial infections from infancy or early childhood predominantly involving the skin and lungs; chronic eczema, generally beginning during the neonatal period; and extremely high serum IgE levels and eosinophilia.[114] HIES shows diverse modes of inheritance, including sporadic and familial cases consistent with autosomal dominant and recessive forms.[115,116] Autosomal dominant HIES results from dominant negative mutations in the signal transducer and activator of transcription 3 *(STAT3)* gene[117] and is characterized by connective tissue, skeletal, and dental abnormalities.[114] Although patients are at higher risk of lymphoma,[118-121] tumor formation has been attributed to defective immune surveillance and chronic B-cell stimulation, with oncogenic viruses playing little or no contributing role.

AR-HIES is distinguished by recurrent sinopulmonary infections; extensive, frequently coexisting, cutaneous viral infections mainly caused by herpes simplex virus, HPV, molluscum contagiosum virus, and varicella zoster virus; and development of malignancies during late childhood or early adulthood, including squamous cell carcinoma, cutaneous T-cell lymphoma/leukemia, and Burkitt lymphoma, as well as signs of neurologic involvement mainly caused by central nervous system vasculitis (cerebral infarction and ***subarachnoid*** hemorrhage), infection (sepsis, cryptococcal meningitis, otitis, and JC virus–associated progressive multifocal leukoencephalopathy), or both in a proportion of cases (see Table E1).[116,122,123] In addition, atopic dermatitis and other allergic manifestations, including asthma and multiple food or environmental allergies, have been reported.[122,123]

With respect to the molecular basis of AR-HIES, biallelic deletions or point mutations in dedicator of cytokinesis 8 (*DOCK8*)[122,123] and a homozygous loss-of-function mutation in tyrosine kinase 2 *(TYK2)*[124] have thus far been identified. TYK2 deficiency has been reported in 1 patient,[124] making it an uncommon cause of AR-HIES. Given the fact that malignancy has not been reported in the latter case, TYK2 deficiency will not be discussed further in this review.

DOCK8 DEFICIENCY

Most cases of AR-HIES are caused by mutations in the gene encoding the DOCK8 protein,[122,123] which maps to the chromosomal locus 9p24.3. Mutations are comprised of large homozygous or compound heterozygous deletions, single or multiple exon deletions, and point mutations causing premature termination, frameshift, and disruption of splice sites.[123] These mutations are predicted to impair DOCK8 protein expression or function, as has been demonstrated by the absence of DOCK8 immunoreactive bands on Western blotting.[123]

DOCK8 mRNA expression has been detected in the human placenta, lung, kidney, and pancreas and, to a lesser extent, in the brain, heart, and skeletal muscle.[125] Monocytes, B cells, and T cells from healthy blood donors also contain *DOCK8* mRNA.[122] DOCK8 belongs to the DOCK180 superfamily of proteins, which represent novel guanine nucleotide exchange factors for Rho family GTPases.[125] DOCK180-related guanine nucleotide exchange factors function downstream of multiple cell-surface receptors to induce actin cytoskeletal rearrangement, ***lamellipodia*** formation, cell migration, integrin-mediated adhesion, phagocytosis, cell fusion, cell polarization, and synapse formation (Fig 4).[126] Although the phenotypes of autosomal dominant HIES and AR-HIES are similar, it is not yet understood whether dominant negative mutations in *STAT3* influence intracellular signaling in a manner similar to loss-of-function mutations in *DOCK8*. Because STAT3 functions as a transcription factor downstream of multiple growth factor and cytokine receptors, some of which are also likely to rely on DOCK8 for optimal function, it is certainly possible that defects in these 2 distinct genes might result in overlapping clinical and immunologic manifestations.

The available data on the immunologic profile of patients with AR-HIES are not entirely consistent. In a cohort of 27 patients, of whom 21 were identified with biallelic deletions or point mutations involving *DOCK8*, the number of $CD4^+$ T cells was selectively decreased, whereas the $CD8^+$ T-cell and NK cell populations were less affected.[123] On the contrary, in a separate report of 11 patients, numbers of both the $CD4^+$ and $CD8^+$ T-cell subsets, as well as NK and B cells, were more uniformly decreased.[122] Furthermore, although a more comprehensive proliferation defect involving both the $CD4^+$ and $CD8^+$ T-cell subsets was reported in the former study,[123] the defective proliferative response was limited to the $CD8^+$ T-cell subset in the latter.[122] Interestingly, patients demonstrate impaired T_H17 differentiation caused by a failure in the maintenance of memory T_H17 cells.[127] Although these results suggest a role for DOCK8 in the T_H17 differentiation pathway, it remains possible that the T_H17 defect reflects a more widespread derangement of T-cell activation and differentiation.[123] Thus the immunologic phenotype observed in DOCK8-deficient patients might be due to the critical role of this molecule in the regulation of actin dynamics and formation of the ***immunologic synapse***,[123,128] which are requisite for T-cell activation, proliferation, and acquisition of effector functions (Fig 4).

It is currently not known why cancer develops in patients with AR-HIES. It is possible that the increased susceptibility to squamous cell carcinoma in the setting of chronic cutaneous viral infections, cutaneous T-cell lymphoma/leukemia, and Burkitt lymphoma,[122,123] as well as microcystic adnexal carcinoma and leiomyoma,[129] can be attributed to the pivotal role of $CD8^+$ T cells in tumor immune surveillance. Furthermore, homozygous deletion and reduced expression of DOCK8 protein have been described in lung, gastric, and breast cancer cell lines[130] and in patients with hepatocellular carcinoma.[131] In addition, loss of chromosome 9p, including the *DOCK8* locus, is associated with glioma progression.[132] These latter data suggest that DOCK8 itself might have direct tumor suppressor activity.

Cutaneous viral infections are difficult to manage in DOCK8-deficient patients, with conventional antiviral medications being only partially effective in containing cutaneous viral outbreaks. IVIG therapy might benefit those with impaired humoral responses to reduce the frequency of recurrent bacterial infections; however, this treatment does not control viral infections.[133]

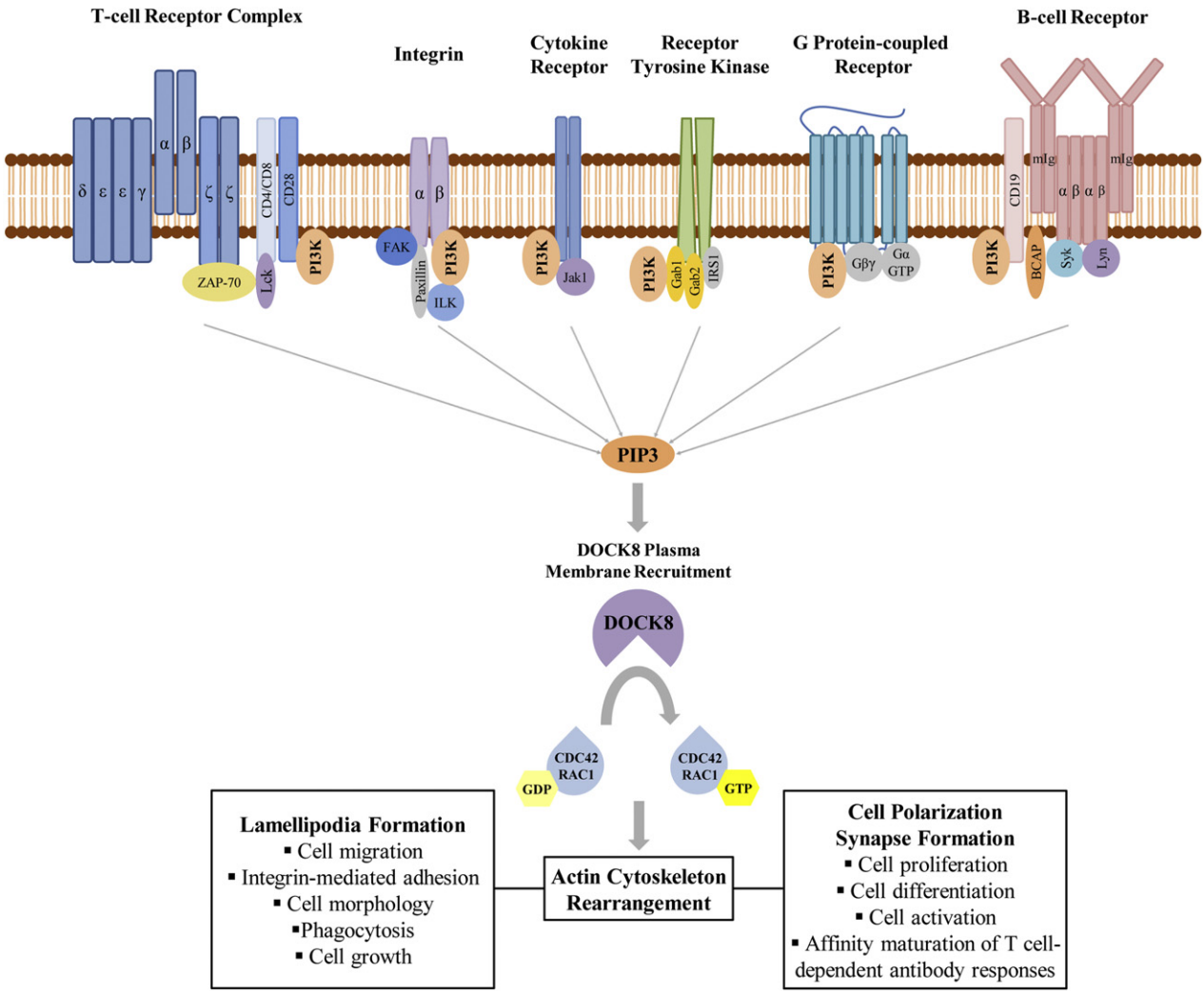

FIG 4. DOCK8-mediated cytoskeletal rearrangement. Phosphatidylinositol (3,4,5)-triphosphate *(PIP3)* is produced downstream of multiple cell-surface receptors and assists in DOCK8 plasma membrane recruitment. Subsequently, DOCK8 binds to and activates the RhoGTPases CDC42 and RAC1, exchanging bound guanosine diphosphate *(GDP)* for free guanosine triphosphate *(GTP)*, a key step in the regulation of actin cytoskeletal rearrangement, lamellipodia formation, and cell polarization, all of which are crucial for lymphocyte activation, proliferation, and effector function. *PI3K*, Phosphoinositide 3-kinase; *RAC1*, Ras-related C3 botulinum toxin substrate 1; *ZAP-70*, zeta-chain-associated protein kinase 70.

The difficulty to manage cutaneous viral complications, which carry a substantial risk of malignant degeneration, forms the basis for implementation of allogeneic HSCT.[134] Because DOCK8 can act as a tumor-suppressor molecule in nonhematopoietic tissues, long-term follow-up studies of allogeneic HSCT are required to assess its role as a curative therapeutic strategy.[133]

HUMORAL IMMUNE DEFICIENCIES

Humoral immune deficiencies are the most common PIDs and range in severity from reduction in all immunoglobulin isotypes with profoundly decreased or absent B cells to very specific antibody deficiency in association with normal immunoglobulin concentrations and B-cell numbers.[1] These disorders are commonly characterized by chronic and recurrent bacterial infections, primarily of the respiratory and gastrointestinal tracts; chronic inflammation; autoimmunity; and, in certain instances, malignancy (see Table E1).[1] Certain humoral immunodeficiencies are also associated with specific viral infections, including XLA,[135,136] CVID,[136] and hyper-IgM syndrome caused by ***activation-induced cytidine deaminase*** deficiency.[137]

Patients with XLA are uniquely susceptible to enteroviruses, namely echovirus, coxsackievirus, and poliovirus, which frequently cause chronic enteroviral meningoencephalitis.[135,136] The same clinical feature has also been reported in patients with autosomal recessive agammaglobulinemia caused by μ heavy chain deficiency[138] and less commonly in patients with CVID[135,136] or thymoma and hypogammaglobulinemia (Good syndrome).[135] There is also a slight increase in the prevalence of malignant tumors in patients with XLA, particularly lymphoid malignancies[139] and colorectal cancer[140]; however, the relationship between Bruton tyrosine kinase deficiency and the development of malignant tumors, if any, remains unknown.

CVID constitutes the most prevalent yet complex group of humoral PIDs[1] and is characterized by hypogammaglobulinemia, impaired functional antibody responses, and increased susceptibility to bacterial infections and malignancy,[141] particularly lymphoma and gastric cancer.[142] Mutations in the TNF receptor superfamily member 13B (*TNFRSF13B* or *TACI*)[143,144] and 13C (*TNFRSF13C* or *BAFF-R*),[145] *CD19*,[146] and inducible costimulator gene *(ICOS)*[147] have thus far been identified. Impaired humoral and cellular immune responses, including derangements in numeric and functional characteristics of B, T, NK, and dendritic cells,[1] along with chronic inflammatory autoimmune diseases, recurrent bacterial infections, and persistent antigenic stimulation, mainly from chronic *Helicobacter pylori*,[148] human herpes virus 8,[149] and cytomegalovirus[150] infections, are speculated to favor carcinogenesis.[151]

Regular IVIG replacement therapy combined with prophylactic antibiotics constitute the mainstay of therapy until more definitive therapy (eg, HSCT) can be performed.[1] There is clinical evidence that high-dose immunoglobulin therapy administered by means of the intravenous or intraventricular routes might prevent fatal enteroviral meningoencephalitis, as well as eradicate or possibly slow the development of cerebral disease.[152,153] However, failures of such strategies have also been reported.[153,154] Despite the fact that the casual relation between viral infections and malignancy in certain humoral immunodeficiencies is less well understood, the efficacy of IVIG therapy on decreasing the incidence of malignant tumors merits further investigation.

CONCLUSION

Substantial advances have been made in our understanding of the pathogenesis of specific cellular and humoral PIDs. Recent insights into the molecular mechanisms of infection and tumor formation in each of these conditions have allowed for genetic screening and counseling in addition to early diagnosis and treatment, which might lead to improved outcomes for affected subjects. Despite the fact that genetic testing might provide a precise diagnosis, there are several practical caveats to be considered. For instance, there are patients whose clinical immune defects appear compatible with a certain diagnosis, yet no causative gene mutations can be identified. In contrast, in certain cases the clinical and immunologic heterogeneity observed in patients with identical genotypes warrants a high degree of suspicion to make the diagnosis of a certain condition within affected kindreds. Nonetheless, a better understanding of the natural history and the molecular and cellular pathogenesis of these and related PIDs will provide insights into the prediction of disease phenotype and the development of targeted therapeutic interventions.

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TABLE E1. Characteristics of PIDs associated with increased susceptibility to viral infections and malignancies

Disease	Gene	Locus	Inheritance	Clinical features	Laboratory features	Treatment
XLP	*SH2D1A*	Xq25-q26	XL	FIM Lymphoma Hypogammaglobulinemia Vasculitis (lungs, CNS)	Anemia, thrombocytopenia, pancytopenia, hemophagocytosis, increased liver enzyme levels, disturbed coagulation studies, hyperferritinemia, increased levels of soluble IL-2R, increased EBV DNA load Hypogammaglobulinemia, impaired specific antibody responses, lack of iNKT cells, increased activated $CD8^+$ T-cell numbers, decreased memory B-cell numbers, impaired NK and $CD8^+$ T-cell cytotoxicity	Rituximab, antiviral agents, steroids, and IVIG for the treatment of acute EBV infection/FIM Protocol-based therapy for the treatment of HLH Standard chemotherapy protocols for the treatment of lymphoma Allogeneic HSCT IVIG for hypogammaglobulinemia
ITK deficiency	*ITK*	5q31-q32	AR	FIM BK polyomavirus infection *Pneumocystis jiroveci* pneumonia HL	Anemia, thrombocytopenia, pancytopenia, increased CRP and ESR levels, increased liver enzyme levels, increased EBV DNA load Hypogammaglobulinemia, decreased naive $CD45RA^+$ T cell numbers, increased $CD45RO^+$ T-cell numbers, reduced iNKT cell numbers	Rituximab, antiviral agents, and steroids for the treatment of FIM Standard chemotherapy protocols for the treatment of lymphoma Allogeneic HSCT
EV	*EVER1* *EVER2*	17q25	AR	Cutaneous HPV infection Squamous cell carcinoma	Positivity for specific HPV subtypes in affected tissues T-cell lymphopenia, decreased antigen- and mitogen-induced T-cell responses	Surgical and nonsurgical modalities, including topical 5-fluorouracil, imiquimod, and tacalcitol; systemic retinoids combined with IFN-α; cimetidine; and topical 5-aminolevulinic acid photodynamic therapy
WHIM syndrome	*CXCR4*	2q21	AD	Recurrent bacterial infections Mucocutaneous HPV infection Squamous cell carcinoma	Myelokathexis, peripheral neutropenia, B-cell lymphopenia with marked reduction of $CD27^+$ memory cell numbers, T-cell lymphopenia, hypogammaglobulinemia	G-CSF or GM-CSF, IVIG, and prophylactic antibiotics for the treatment of recurrent bacterial infections Surgical excision of any malignant or premalignant lesions Allogeneic HSCT Prophylactic administration of HPV vaccine
AR-HIES	*DOCK8*	9p24.3	AR	Recurrent bacterial infections Septicemia Mucocutaneous candidiasis Extensive cutaneous viral infections Atopic dermatitis Asthma Allergies Neurologic involvement Squamous cell carcinoma Cutaneous T-cell lymphoma/leukemia Burkitt lymphoma	Autoimmune hemolytic anemia, high serum IgE levels, eosinophilia, lymphopenia, impaired $CD8^+$ T-cell activation and proliferation, impaired T_H17 differentiation, antibody abnormalities (low IgM, high or normal IgG, high, normal, or low IgA)	Antiviral medications, including valacyclovir, acyclovir, topical imiquimod, cidofovir, and IFN-α IVIG Medical treatments for eczema Standard clinical practice for the treatment of neoplasia Allogeneic HSCT

(Continued)

TABLE E1. *(Continued)*

Disease	Gene	Locus	Inheritance	Clinical features	Laboratory features	Treatment
XLA	*BTK*	Xq21.3	XL	Recurrent bacterial infections Septicemia Chronic enteroviral meningoencephalitis Hepatitis C infection Neurologic involvement Arthritis Lymphoid malignancies Colorectal cancer	Modest to profound hypogammaglobulinemia of all isotypes, decreased numbers or absence of B lymphocytes	High-dose gamma globulin, administered either intravenously or subcutaneously, plus long-term antibiotics for the treatment of recurrent bacterial infections High-dose gamma globulin, administered either intravenously or intraventricularly, for the prevention and treatment of chronic enteroviral infections Standard clinical practice for the treatment of neoplasia Allogeneic HSCT
CVID	*TNFRSF13B* *TNFRSF13C* *CD19* *ICOS*	17p11.2 22q13.1-q13.3 16p11.2 2q33	AD, AR AR AR AR	Recurrent bacterial infections Chronic enteroviral meningoencephalitis Varicella zoster/herpes simplex infection Hepatitis C infection Lymphadenopathy Splenomegaly Chronic pulmonary and gastrointestinal complications Multisystem granulomatous disease Autoimmune disorders Lymphoma Gastric cancer	Autoimmune hemolytic anemia, autoimmune thrombocytopenia, normal numbers of B cells to mild B-cell lymphopenia with marked reduction in $CD27^+$ memory cell numbers, hypogammaglobulinemia of ≥2 isotypes (low IgG and IgA and variable IgM levels), impaired functional antibody responses, impaired T-cell proliferative responses, decreased numbers of $CD4^+$ T cells and normal to increased numbers of $CD8^+$ T cells (reversed CD4/CD8 ratio), imbalanced T_H cell differentiation, increased suppressor T-cell activity, diminished expression of CD40 ligand	High-dose gamma globulin, administered either intravenously or subcutaneously plus long-term antibiotics for the treatment of recurrent bacterial infections Corticosteroids and mAbs for the treatment of autoimmune and granulomatous diseases Standard clinical practice for the treatment of neoplasia

AD, Autosomal dominant; *AR*, autosomal recessive; *CNS*, central nervous system; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *G-CSF*, granulocyte colony-stimulating factor; *ICOS*, inducible costimulator gene; *IL-2R*, IL-2 receptor; *XL*, X-linked.