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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

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