Clinical reviews in allergy and immunology

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The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects

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Activity Objectives:

1. To recognize the various clinical manifestations of conditions with both immunodeficiency and autoimmunity.
2. To understand the underlying biological defects that contribute to the development of immunodeficiency and autoimmunity.
3. To recall common monogenetic defects underlying primary immunodeficiency, immune dysregulation, and systemic autoimmune disease.

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Autoimmune and immunodeficiency diseases are outcomes of a dysfunctional immune system and represent 2 sides of the same coin. Multiple single-gene defects have been identified, resulting in rare diseases with features of both autoimmunity and immunodeficiency. On the other hand, more common autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, show a polygenic inheritance pattern. Not surprisingly, the genes implicated in single-gene disorders have also been shown to be linked to polygenic disorders. In this review article, we discuss the contribution of various immune system genes to common polygenic autoimmune disorders, as well as the pathophysiologic pathways and clinical features of monogenic defects that result in autoimmune disease. We also explore the hypotheses underlying the development of autoimmune disease and the overlap between immunodeficiency and autoimmunity. (J Allergy Clin Immunol 2016;137:3-17.)

Key words: *Autoimmunity, primary immunodeficiency diseases, B cells, T cells*

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In medical school, we all learned that there is more than one pathway to the development of liver cirrhosis: viral infections, alcohol abuse, and inborn genetic conditions, among others. The outcome of liver cirrhosis is just a common end point of various etiopathologies. Likewise, there are many etiopathologies that

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Abbreviations used

AID: Activation-induced cytidine deaminase
AIHA: Autoimmune hemolytic anemia
AIRE: Autoimmune regulator
ALPS: Autoimmune lymphoproliferative disease
ANA: Anti-nuclear autoantibody
APC: Antigen-presenting cell
APECED: Autoimmunity–polyendocrinopathy–candidiasis–ectodermal dysplasia
BAFF: B-cell activating factor
BCR: B-cell receptor
COP: Coatomer protein
CRP: C-reactive protein
CTLA4: Cytotoxic T-lymphocyte antigen 4
CVID: Common variable immunodeficiency
DOCK8: Dedicator of cytokinesis 8
ER: Endoplasmic reticulum
FoxP3: Forkhead box P3
GOF: Gain-of-function
HSCT: Hematopoietic stem cell transplantation
IC: Immune complex
ICOS: Inducible T-cell costimulator
IRF: Interferon regulatory factor
ITGAM: Integrin alpha M
ITP: Idiopathic thrombopenic purpura
LRBA: LPS-responsive vesicle trafficking, beach and anchor containing protein
NK: Natural killer
PFS: Periodic fever syndrome
PID: Primary immunodeficiency disease
PI3K: Phosphoinositide 3-kinase
PKCδ: Protein kinase Cδ
PLCγ2: Phospholipase Cγ2
PTPN22: Protein tyrosine phosphatase, nonreceptor type 22
RA: Rheumatoid arthritis
RAG: Recombination-activating gene
RF: Rheumatoid factor
SAMHD1: SAM and HD domain 1 hydrolase
SCID: Severe combined immunodeficiency
SLE: Systemic lupus erythematosus
STAT: Signal transducer and activator of transcription
TACI: Transmembrane activator and CAML interactor
TCR: T-cell receptor
TLR: Toll-like receptor
TNFSF4: TNF ligand superfamily 4 (OX40L)
TPP2: Tripeptidyl peptidase II
Treg: Regulatory T
TREX1: Three prime repair exonuclease 1

can result in the development of fibrotic lung disease, vasculitis, or hypogammaglobulinemia.

Autoimmunity is one of the etiopathologies that can cause harm to the integrity of the body's organs by aggressively attacking self-tissue, be it organs or components of the blood. Here we define autoimmunity as the breakdown of immune tolerance to self-antigens. Currently, there are several hypotheses as to why autoimmune conditions develop in human subjects. For the purpose of clarity, we have picked some polygenic traits and monogenic defects exemplifying the affected pathways; however, this list is by no means complete.

POLYGENIC LESSONS FROM SYSTEMIC AUTOIMMUNE DISEASES

Genetic analysis of primary immunodeficiency diseases (PIDs) and systemic rheumatic diseases are paradigmatic fields of modern immunogenetic research. Although nearly 300 monogenic traits have now been observed to be associated with various forms of PIDs and autoinflammatory periodic fever syndromes (PFSs),[1] polygenic inheritance patterns are likely to account for more common systemic autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Not unexpectedly, some of the genetic variants and mutations associated with PIDs have also been identified in systemic autoimmune diseases and *vice versa*.[1-10]

In the largest genome-wide association study meta-analysis of European and Asian subjects (29,880 patients with RA [88.7% anti-citrullinated protein antibody positive] and 73,758 control subjects), 377 candidate genes were identified in 100 non-MHC RA risk loci.[11] Using an *in silico* bioinformatics pipeline, the authors systematically prioritized the most likely biological candidate genes for RA risk and came up with 98 genes with a risk score of greater than 2. Interestingly, there was a considerable overlap with PID genes (n = 15). Among other notable genes were hematological cancer somatic mutation genes (n = 17), genes associated with knockout mouse phenotypes (n = 86), and genes prioritized by molecular pathways analysis (n = 35) and protein-protein interactions (n = 63). Among PID genes, the highest proportion with RA overlap occurred in the categories of immune dysregulation (caspase 8 *[CASP8]*, caspase 10 *[CASP10]*, autoimmune regulator *[AIRE]*, and IL-2 receptor α *[IL2RA]*), followed by combined immunodeficiency (protein tyrosine phosphatase receptor *[PTPR]*, recombination-activating gene 1 *[RAG1]*, *RAG2*, and *CD40*), well-defined syndromes (ataxia telangiectasia mutated *[ATM]* and *TYK2*), primary antibody deficiencies (*CD40* and uracil-DNA glycosylase *[UNG]*), and phagocyte defects (IFN-γ receptor 2 *[IFNGR2]* and interferon regulatory factor 8 *[IRF8]*), whereas no RA risk gene was observed in the innate immunity category of the International Union of Immunological Societies classification of PIDs.[1]

To date, no single-gene defect has been identified to account for cases of adult RA. However, single-gene defects have been identified in patients with autoinflammatory diseases that affect the joints, such as the various PFSs, which include familial Mediterranean fever, TNF-α receptor–associated periodic syndrome, hyper-IgD syndrome, pediatric cryopyrin-associated fever syndromes, and deficiency of the IL-1 receptor antagonist.[1,12]

Strong genetic and environmental components have been identified in the pathogenesis of SLE: among monozygotic and dizygotic twins, the reported concordance rates range between 25% and 40% and 2% and 5%, respectively.[13] The strongest risk association for SLE has been shown to map to several loci within the MHC region,[14,15] and deficiencies of the early complement components C1q, C2, and C4 have long been known to be strongly associated with SLE.[16-24] Moreover, genome-wide association studies have identified more than 50 robust loci associated with SLE susceptibility, and follow-up studies helped to identify causative genetic variants and their biological relevance to a polygenic development of SLE.[25] Non-MHC risk alleles for