Inborn Errors in Immunity: Unique Natural Models to Dissect Oral Immunity

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Abstract

In recent years, the study of genetic defects arising from inborn errors in immunity has resulted in the discovery of new genes involved in the function of the immune system and in the elucidation of the roles of known genes whose importance was previously unappreciated. With the recent explosion in the field of genomics and the increasing number of genetic defects identified, the study of naturally occurring mutations has become a powerful tool for gaining mechanistic insight into the functions of the human immune system. In this concise perspective, we discuss emerging evidence that inborn errors in immunity constitute real-life models that are indispensable both for the in-depth understanding of human biology and for obtaining critical insights into common diseases, such as those affecting oral health. In the field of oral mucosal immunity, through the study of patients with select gene disruptions, the interleukin-17 (IL-17) pathway has emerged as a critical element in oral immune surveillance and susceptibility to inflammatory disease, with disruptions in the IL-17 axis now strongly linked to mucosal fungal susceptibility, whereas overactivation of the same pathways is linked to inflammatory periodontitis.

Keywords: monogenic immune defects, periodontitis susceptibility, oral candidiasis susceptibility, human oral immunity, IL-17, Th17

Primary Immunodeficiency Disorders and Their Role in Uncovering Basic Mechanisms of Human Immunity

Inborn errors in immunity underlie the development of primary immunodeficiency diseases (PIDs), a heterogeneous group of genetic disorders that follow a Mendelian pattern of inheritance and impair the development and/or function of one or more effector molecules that mediate immunity (Casanova and Abel 2007). To date, most described PIDs are monogenic, rare, and recessive traits, although autosomal dominant PIDs have also been reported. Over 150 Mendelian conditions associated with ~130 gene defects and an impaired immune response have been described thus far in humans (Fischer 2007). Various PIDs affect different aspects of the innate and adaptive immune system, ranging from immune surveillance and regulation to tumor surveillance (Fischer 2007). Importantly, several PIDs have recently uncovered the critical contribution of specific genetic and immune signaling pathways in the context of oral health (Table).

In this concise perspective, we discuss emerging evidence that PIDs constitute real-life models that are indispensable both for the in-depth understanding of human biology and pathophysiological mechanisms and for obtaining critical insights into common diseases, such as those affecting oral health.

In recent years, the genetic dissection of PIDs has resulted in the discovery of new genes involved in the function of the immune system and in the elucidation of the roles of known

genes whose importance was previously unappreciated. With the recent explosion in the field of genomics and the increasing number of genetic defects identified, the study of naturally occurring mutations has become a powerful tool for gaining mechanistic insight into the functions of the mammalian immune system (Milner and Holland 2013). The examination of patients with rare PIDs has evolved from a process of clinical observation to a detailed study of immune mechanisms in humans. Detailed clinical phenotyping of patients with genetic disorders is increasingly combined with parallel mechanistic studies using patients' cells and corresponding animal models of gene-deficient mice or transgenic mice expressing mutated genes. In this regard, in instances where genetically engineered mice appropriately phenocopy the human condition, they become a powerful tool to perform relevant mechanistic or interventional studies that cannot be typically addressed in humans. Moreover, mouse models may also be used to test a

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Table. Inborn Errors in Immunity Associated with Susceptibility to Oral Mucosal Disease.

Clinical Phenotype	Affected Immune Cell Type	Specific Mutation (Syndrome)	Reference
Chronic mucocutaneous candidiasis (CMC)	Th17 cells	Hypomorphic <i>STAT3</i> mutations (autosomal dominant hyper IgE syndrome [AD-HIES])	Freeman and Holland (2009)
		Gain-of-function <i>STAT1</i> mutations	Liu et al. (2011)
		<i>IL-17RA</i> mutations	Puel et al. (2011)
		<i>IL-17F</i> mutations	
		<i>ACT1</i> mutations	Boisson et al. (2013)
		<i>AIRE</i> mutations (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome)	Meloni et al. (2012)
		<i>DOCK8</i> mutations (autosomal recessive hyper IgE syndrome [AR-HIES])	Zhang et al. (2009)
		<i>CARD9</i> deficiency	Glocker et al. (2009a)
		<i>IRF8</i> mutations	Hambleton et al. (2011)
		<i>STK4</i> mutations	Abdollahpour et al. (2012)
Mucocutaneous (including oral) viral susceptibility	T cells/NKT cells/NK cells (often additional cell types involved)	Severe combined immunodeficiency (SCID)	
		SCID	Buckley (2004)
		<i>WAS/WASP</i> mutations (Wiskott-Aldrich syndrome)	Binder et al. (2006)
		<i>DOCK8</i> mutations (AR-HIES)	Zhang et al. (2009)
		<i>IKBKG/NEMO</i> mutations (ectodermal dysplasia)	Doffinger et al. (2001)
		<i>CORO1A</i> mutations: herpes simplex virus type 1 (HSV-1) and human papillomavirus (HPV)	Stray-Pedersen et al. (2014)
		MHCII deficiency: HPV	Guirat-Dhouib et al. (2012)
		<i>CXCR4</i> mutations: HPV	Cipriani et al. (2010)
		<i>ELANE</i> mutations (cyclic neutropenia and severe congenital neutropenia)	Ye et al. (2011)
		<i>WAS</i> mutations (X-linked neutropenia)	Hart and Atkinson (2007)
Aggressive periodontitis	Neutrophils	<i>COH1</i> mutations (Cohen syndrome)	Alaluusua et al. (1997)
		<i>LYST</i> mutations (Chediak-Higashi syndrome)	Delcourt-Debruyne et al. (2000)
		<i>ITGB2</i> mutations (leukocyte adhesion deficiency type I [LAD-I])	Moutsopoulos et al. (2014)
		<i>CTSC</i> mutations (Papillon-Lefèvre)	Van Dyke et al. (1984)

specific hypothesis related to a shared aspect of the disease between humans and the model (Hajishengallis et al. 2015). Knowledge gained from these complementary analyses can further highlight the roles of specific genes, their products, and the pathways they affect (Casanova et al. 2014).

PIDs first and foremost serve to uncover the role of genes and their products in the human setting after they have been subjected to evolutionary selection. PIDs also have a significant biological impact on the definition of host gene function *in natura* (Casanova and Abel 2007), in the setting of a natural ecosystem, under the constant exposure to naturally encountered antigens, pathogens, and environmental stimuli. Hence, relevant studies in humans with genetic defects are particularly important considering that often genetically engineered mice with corresponding mutations do not always share the spectrum of vulnerabilities encountered in the human natural setting. A classic example is that of mutations in MyD88, a key downstream adapter for most Toll-like receptors (TLRs) and interleukin (IL)-1 receptors (IL-1Rs). While mice with relevant mutations are vulnerable to almost all pathogens examined to date, humans bearing MyD88 mutations are resistant to most common bacteria, fungi, and viruses and demonstrate susceptibility only to a narrow spectrum of pyogenic bacterial infections (von Bernuth et al. 2008).

To date, the phenotypic characterization and mechanistic study of PIDs has had its greatest impact in the field of infectious disease, where it has played a central role in the unmasking of pathways involved in microbial surveillance by the human innate and adaptive immune systems. Indeed, PIDs provide an *in vivo* assessment of the roles of specific immune factors and pathways during an infectious challenge (Fischer 2007). These observations are of apparent value in identifying critical elements of protective immunity in individuals who do not carry the corresponding mutations. Interestingly, PIDs are linked to a spectrum of susceptibilities to various classes of microorganisms. The consequences of a given mutation can vary from a very strong predisposition to a broad spectrum of microorganisms, ranging from strict pathogens to opportunistic agents, to a predisposition to a narrow spectrum of select “signature” microbial species. For example, broad infectious susceptibility is observed in patients with various forms of severe combined immunodeficiency (SCID), while interferon (IFN)- γ receptor mutations confer specific susceptibility to intracellular pathogens such as nontuberculous mycobacteria and endemic dimorphic fungi. These observations have led us to appreciate the abundant redundancy in host defense, with nonredundant human genes ranging from “public” genes required for global protective immunity to “private” genes

conferring specific immunity to a particular microbial insult (Casanova and Abel 2007). Besides mutations that result in heightened susceptibility to infection, the discovery of other mutations that confer mendelian resistance to infection has also been very informative, as in the case of *Plasmodium vivax*, human immunodeficiency virus 1 (HIV-1), and norovirus in individuals with mutations in *DARC*, *CCR5*, and *FUT2*, respectively (Casanova and Abel 2005; Fischer 2007).

PIDs have also been very informative in defining key checkpoints that control immunity to self and regulate aberrant immune responses. Based on described hyperinflammatory syndromes in humans, genes that have been linked to immune regulation include the following: autoimmune regulator (*AIRE*) gene, involved in central immune tolerance via the deletion of self-reactive T cells in the thymus; the *IL2R*, *FOXP3*, and *CTLA-4* genes, involved in regulatory T-cell development; the *FAS* gene, linked to the autoimmune lymphoproliferative syndrome (ALPS); and *IL10R* genes, linked to colitis (Notarangelo 2010; Kuehn et al. 2014). It is also now increasingly recognized that a large number of PIDs, which are not specifically related to immunoregulatory genes, present with manifestations of chronic and/or aberrant inflammation. In this regard, it is thought that the disruption of a particular immune defense pathway required by the host to control infections or eradicate microbial pathogens and their antigens may result in an uncontrolled, often exaggerated chronic inflammatory response (Arkwright et al. 2002). A classic example is seen in patients with chronic granulomatous disease (CGD), a phagocyte defect rendering neutrophils incapable of eradicating catalase-positive bacteria and fungi; these patients develop reactive inflammatory granulomatous lesions and colitis (Arkwright et al. 2002; Marciano et al. 2004).

From Rare Genetic Defects to the Understanding of Common Multigenic Diseases

The study of rare monogenic diseases not only is directly relevant to the diagnosis and treatment of patients with these specific disorders but can also offer insights into more common conditions with similar phenotypes arising, however, from multiple genetic and environmental factors. Such common conditions include infections, allergic disorders such as eczema, inflammatory and autoimmune diseases, and cancer.

It is important to keep in mind that, while rarity is generally considered a hallmark of PIDs, accumulating evidence suggests that human genetic factors play a particularly important role in susceptibility to infectious and inflammatory diseases of polygenic etiology (i.e., where multiple affected genes cumulatively contribute to the overall disease risk). Accordingly, human genetic variations that predispose to infection could be thought of as common errors in immunity (Casanova and Abel 2005).

Indeed, much of what we know about the molecular background of common diseases is in fact based on what we have learned from rare familial forms of these traits (Peltonen et al.

2006). Specifically, the mutations identified in rare monogenic diseases have often revealed critical genes and pathways involved in the molecular pathogenesis of common health problems. For instance, a central role for IL-10 signaling has been implicated in both monogenic and common forms of inflammatory bowel disease. Specifically, loss-of-function mutations in the *IL10* receptor genes *IL10RA* and *IL10RB* (Glocker et al. 2009b) have been identified in monogenic severe forms of inflammatory bowel disease, while single-nucleotide polymorphisms of *IL-10RA* and *B* have been associated with ulcerative colitis and Crohn disease (Moran et al. 2013). The successes in the identification of genes affecting both monogenic diseases and rare familial forms of common diseases have opened new avenues for studying common disease via dissecting new pathways or molecules previously unsuspected to be associated with a given trait (Peltonen et al. 2006).

Finally, an understanding of the pathogenesis of PIDs in an effort to treat their often severe manifestations has paved the way for immunological interventions, with proof of principle demonstrated for new treatments, such as immunoglobulin G replacement, bone marrow transplantation, and gene therapy, in patients with PIDs (Casanova and Abel 2007). With the identification of specific immune factors affected in human PIDs, these conditions become the ideal setting for proof-of-principle studies evaluating the use of targeted immune-based therapeutic and/or preventive strategies.

PIDs Presenting with Oral Manifestations: A Significant Clinical Need and an Opportunity to Better Our Understanding of Oral Immunity and Susceptibility to Common Oral Diseases

The constant characterization of new PIDs and the development of an ever-expanding armamentarium of technologies aiding in the functional phenotyping of genetic defects provides a great opportunity to further our understanding of oral immunity in health and disease. Years of clinical observations in cohorts of patients with known PIDs have already offered insights into the roles of particular cells and constituents of the immune system in promoting susceptibility to oral infectious and inflammatory conditions (Hart and Atkinson 2007; Atkinson et al. 2015). In fact, various PIDs present with severe oral manifestations, which have provided us with a general understanding of key elements involved in microbial surveillance and periodontal stability in the oral cavity (Table). Nevertheless, with new genetic defects constantly being identified, there is opportunity to implicate additional critical components of the immune system in oral immunological surveillance and regulation or, alternatively, reveal redundancy in immune mechanisms. Moreover, given the increasing ability to study mucosal immunity at the tissue level and perform functional studies with patients' cells and relevant animal models that phenocopy the human susceptibility traits, there is

Figure. Regulation of the interleukin (IL)–17 axis is essential for oral immunity and homeostasis. **(Left)** Defects in the IL-17 pathway are linked to oral candidiasis. Defective generation of Th17 cells in patients with *STAT3* mutations, gain-of-function *STAT1* mutations, or impaired IL-17/IL-22 signaling (caused by IL-17 receptor or ligand mutations or neutralizing autoantibodies against IL-17/IL-22) are all linked to susceptibility to mucocutaneous (including oral) candidiasis. **(Right)** IL-17 overproduction is linked to aggressive periodontitis. Tissue neutrophils normally regulate IL-23 production by antigen presenting cells (e.g., macrophages) and expansion of Th17 cells. In contrast, leukocyte adhesion deficiency type I (LAD-I), which causes defective neutrophil transmigration, (1) leads to dysregulation of the IL-23/Th17 axis (2) and hence overproduction of the inflammatory and bone-resorptive cytokine IL-17 (3). Inflammatory tissue breakdown products serve as nutrients for the local microbiome, thereby contributing to dysbiosis (4). Microbial by-products (including lipopolysaccharide) persistently stimulate the disinhibited IL-23/17 axis (5), further amplifying the destructive response.

potential to enhance our mechanistic understanding and identify therapeutic targets in PIDs with known genetic disturbances.

Recently, through the study of patients with select gene disruptions, IL-17 signaling has emerged as a critical element in oral immune surveillance and susceptibility to inflammatory disease. Disruptions in the IL-17 axis are now strongly linked to mucosal fungal susceptibility, whereas overactivation of the same pathways is linked to inflammatory periodontitis (Figure).

Much of our understanding of mucocutaneous (including oral) fungal susceptibility has come through the study of PIDs. Indeed, it is increasingly appreciated that the Th17 subset of helper T cells is essential in mediating antifungal immunity at barrier sites, through their production of IL-17/IL-22 and downstream IL-17/IL-22-dependent antimicrobial peptides with potent antifungal activity (Gaffen et al. 2014; Lionakis et al. 2014). The critical contribution of IL-17 signaling in host defense against chronic mucocutaneous candidiasis (CMC) in humans has been directly shown in patients with mutations in *IL-17RA*,

IL-17F, and the adaptor molecule *ACT1* (Puel et al. 2011; Lionakis et al. 2014). The identification of other PIDs associated with impaired differentiation of Th17 cells (*STAT3* deficiency, *DOCK8* mutations, and gain-of-function *STAT1* mutations) or neutralizing autoantibodies against IL-17 and IL-22 (*AIRE* mutations in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome who develop universal and specific susceptibility to CMC) has further reinforced the importance of IL-17 signaling in host defense against CMC (Figure, Table). Importantly, the introduction of IL-17–targeting modalities for the treatment of inflammatory conditions has recapitulated the lessons learnt from the IL-17–related PIDs, as these patients are at higher risk for development of mucosal *Candida* infections (Langley et al. 2014).

The study of patients with PIDs linked to periodontitis susceptibility has also given us insights into mechanisms necessary for periodontal immunity and homeostasis in humans (Moutsopoulos et al. 2014; Betts et al. 2015). While it had been

recognized for decades that patients with severe neutrophil defects have early-onset aggressive periodontitis, the disease was attributed to impaired neutrophil surveillance of the bacterial infection in the periodontium. Recent studies in patients with leukocyte adhesion deficiency (LAD) type I (LAD-I), a rare disease caused by mutations in the CD18 subunit of β_2 integrins that lead to defective neutrophil recruitment to tissues, have implicated tissue neutrophils in important regulatory homeostatic roles in the periodontium (Moutsopoulos et al. 2014). Indeed, clinical and laboratory studies using tissues and mucosal immune cells from LAD patients in combination with mechanistic studies in mouse models of LAD have shown that defective neutrophil transmigration leads to dysregulated overproduction of IL-17, a molecule also overproduced in common forms of chronic periodontitis, albeit via a different mechanism (Allam et al. 2011; Moutsopoulos et al. 2012). In LAD-I periodontitis, IL-17 was shown to drive oral pathology since inhibition of the IL-17 pathway in mice mimicking the LAD phenotype both abrogated inflammatory periodontal bone loss and diminished the microbial burden. These data suggest that impaired neutrophil recruitment leads to dysregulated IL-17-driven inflammation that fuels microbial overgrowth, thereby supporting an IL-17-targeted therapy for this currently untreatable condition (Moutsopoulos et al. 2014). Detailed characterization of this patient population has also allowed us to define how the setting of an exacerbated IL-17 inflammatory response may shape the local microbiome, which, in turn, can further exacerbate the inflammatory destruction (Moutsopoulos et al. 2015).

It is possible that an IL-17-driven mechanism may also underlie periodontitis susceptibility associated with other genetic conditions characterized by poor or no accumulation of neutrophils in extravascular sites (Hajishengallis and Hajishengallis 2014). The concept that genetic defects affecting neutrophil function predispose to periodontitis through immunoregulatory defects rather than through inefficient control of the periodontal bacteria is supported by additional evidence. It has been recently recognized in Papillon-Lefèvre syndrome that although neutrophils bear defects affecting proteases, they maintain their capacity to kill pathogens (Sorensen et al. 2014). In fact, severe periodontitis in patients with Papillon-Lefèvre could be attributed, at least in part, to a dysregulated inflammatory response. Indeed, in these patients, cathepsin C (dipeptidyl peptidase-I) deficiency results in failure to activate neutrophil-derived serine proteases, potentially impairing proteolytic degradation of proinflammatory chemokines and cytokines (Ryu et al. 2005), a mechanism important for periodontal tissue homeostasis.

In summary, a lot has been learned via the characterization of genetic and immunological defects that lead to PIDs, and much more is to be discovered. Importantly, the study of patients with genetic defects that lead to impaired or excessive production of key elements in mucosal immunity, such as IL-17 (Figure, Table), sheds ample light on both the protective and detrimental roles of immune pathways regulating oral mucosal homeostasis and hence on the cellular and molecular mechanisms of susceptibility to common oral diseases.

Author Contributions

N.M. Moutsopoulos, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript; M.S. Lionakis, contributed to conception and data acquisition, critically revised the manuscript; G. Hajishengallis, contributed to design and data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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