INSIGHTS

IL2RB maintains immune harmony
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How the IL-2 receptor β-chain specifically shapes immunity has remained enigmatic. In this issue of JEM, Zhang et al. (https://doi.org/10.1084/jem.20182304) and Fernandez et al. (https://doi.org/10.1084/jem.20182015) independently report the first observations of autosomal recessive mutations in IL2RB, revealing a requirement for IL2RB in immunity and peripheral immune tolerance.

Human primary immunodeficiencies have provided key insights into immune function that often also raise new, unexpected questions. In a landmark paper published in 1993, Warren Leonard and colleagues identified mutations in IL2RG, encoding the IL-2 receptor γ-subunit, as a cause of X-linked severe combined immunodeficiency (X-SCID) associated with defective T and natural killer (NK) cell development (Noguchi et al., 1993). Biochemical studies had previously determined that the IL-2 receptor consists of a heterotrimeric receptor complex comprised of a low-affinity α-chain (CD25), a β-chain (IL2Rβ/CD122), and the γ-chain (CD132). While providing a molecular explanation for X-SCID (popularly known as “bubble boy” syndrome), the association of IL2RG mutations with X-SCID was initially puzzling to immunologists, as IL-2 is not required for the development of T cells in the thymus. We now know that the IL-2 receptor γ-chain is shared between multiple cytokine receptors, including those for IL-4, IL-7, IL-9, IL-15, and IL-21 (Rochman et al., 2009). Consequently, SCID is also associated with autosomal recessive mutations in IL7RA, which encodes a polypeptide forming the IL-7 receptor together with the common γ-chain, thereby explaining the defective T cell development observed in X-SCID. However, important questions still remain with respect to the role of the shared IL-2 and IL-15 receptor in human immunity. This receptor is expressed on T cells and NK cells and is comprised of the common γ-chain and IL-2Rβ. One missing piece to this puzzle is the immunological phenotypes and clinical characteristics of individuals with mutations in IL2RB, who have hitherto not been described.

In the current issue of JEM, Zhang et al. and Fernandez et al. describe a total of five kindreds with autosomal recessive mutations in IL2RB—seven affected live-born children with immunodeficiency and autoimmune disease, and three perinatally affected fatalities. Clinical hallmarks of the disease included enteropathy, skin abnormalities, autoimmune hemolytic anemia, and hypergammaglobulinemia, in addition to susceptibility to respiratory and herpes-virus infections. As such, human IL2RB deficiency shares several features of immune dysregulation with IL2rb knock-out mice, including autoimmune hemolytic anemia, hypergammaglobulinemia, elevated autoantibodies, lymphadenopathy, and splenomegaly (Suzuki et al., 1995). In contrast to IL2rb knock-out mice, however, human patients also displayed enteropathy and skin abnormalities. The severe, early-onset autoimmune manifestations of human IL2RB deficiency bear resemblance to the immunodysregulation, polyendocrinopathy and enteropathy X-linked (IPEX) syndrome caused by mutations in FOXP3 (Ziegler, 2006). However, a distinctive feature of patients with IL2RB mutations is their susceptibility to herpesviruses, especially CMV and EBV. The combination of early-onset autoimmunity and severe CMV infections has also been reported in three patients with different IL2RA mutations (Sharfe et al., 1997; Caudy et al., 2007; Goudy et al., 2013). Notably, an additional patient lacking IL2RB transcripts and IL2Rβ expression was previously described by Gaspar and colleagues (Gilmour et al., 2001). This infant presented with severe viral and fungal infections; however, no autoimmune manifestations were reported. Nonetheless, overall, autosomal recessive mutations in IL2RA and IL2RB are characterized by severe autoimmunity and susceptibility to viral infections.

In their studies, the teams of Lenardo and Hsieh characterized patients with several different IL2RB mutations. Fernandez et al. (2019) identified a nine nucleotide in-frame IL2RB deletion resulting in the loss of three amino acids (p.Pro222_Gln225del) that disrupts the extracellular, highly conserved WSXWS motif. This motif is common to type I cytokine receptors and serves to stabilize interactions between the subunits and conduce ligand-binding conformational changes for receptor activation. As assessed by flow cytometry on patient lymphocytes, the IL2RB p.Pro222_Gln225del mutation drastically reduced IL-2Rβ surface expression. Despite this, cells still retained some capacity to respond to IL-2 or IL-15, exhibiting induction of low levels of STAT5 phosphorylation upon...
An illustrative representation of genetic deficiencies comparable to the IL2RB deficiencies reported by Zhang et al. (2019) and Fernandez et al. (2019). Genes are clustered by afflication with presentation of autoimmune disease (left, blue) or defective viral immunity (right, orange), with increasing severity depicted by proximity to the center. IPEX syndrome, a hallmark autoimmune disorder, occurring through a lack of regulatory T cells. In this issue, it is reported that patients with IL2RB mutations presented with an IPEX-like syndrome and viral susceptibility. Similarly, patients with deficiencies in IL2RA, DOCK8, CTLA4, and ITCH have been described with IPEX-like disease. IL-2Rγ forms a signaling complex with the common γ-chain, and deficiencies in IL2RG cause X-SCID, which imparts extreme susceptibility to viral infection. SCID is also associated with deficiencies in JAK3 (which transmits signals from the γ-chain) as well as IL7RA mutations. Finally, STAT5 transduces signals downstream of IL-2Rγ (among other receptors), with deficiencies in STAT5B involving autoimmune presentation and some increased susceptibility to viral infection. Human deficiencies in STAT5A have yet to be identified.

Il2rb deficiency differentially affects NK cell functions. The activating NKG2C receptor has been associated with protective NK cell responses to CMV, driving expansions of NKG2C+ NK cells that display a so-called adaptive phenotype. A large population of NKG2C+ NK cells was observed in one of the patients with the IL2RB p.Leu77Pro mutation, but these NK cells lacked other hallmarks of adaptive NK cells, but the relative contribution of differentiated CD8+ T cells and NK cells to control of these viruses in the patients is difficult to determine.

The severe clinical manifestations of IL2RB deficiency raise important questions with respect to the pathophysiological basis of the disease. The infant-onset autoimmune manifestations are shared with IPEX syndrome, in which an absence of regulatory T cells breaks peripheral immune tolerance through uncontrolled autoreactive T cells. Fittingly, the frequency of CD4+CD25+FoxP3+ regulatory T cells was clearly diminished in the two IL2RB-deficient patients examined. Relative to Il2rb-deficient mice, autoimmune manifestations in IL2RB-deficient patients appear more severe. These differences could in part be explained by the use of syngeneic animal models housed in pathogen-free environments, but could also represent distinctions between human and mouse fetal immune development (Mold and McCune, 2012). In humans, CD4+CD25+FoxP3+ regulatory T cells constitute a large fraction of T cells during the second trimester of fetal development where they can control responses to maternal alloantigens (Mold et al., 2008). Thus, mutations in IFN-γ production through IL-2 or IL-15 stimulation, while responding normally to IL-12 and IL-18. These findings suggest IL2RB deficiency differentially affects NK cell functions.

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discern as these lymphocytes share several molecular pathways promoting differentiation (Tesi et al., 2016). Furthermore, other immune cells mediating antiviral immunity, including γδ T cells and mature dendritic cells, express IL-2Rβ. Although not examined in the papers published in this issue, these cell types may also be affected by the IL2RB mutations, potentially influencing the course of CMV disease in these patients.

Importantly, two IL2RB-deficient patients were successfully treated with allogeneic hematopoietic stem cell transplantation. Zhang et al. (2019) also discuss the potential use of engineered IL-2 proteins as a means of stimulating lymphocytes in patients with hypomorphic IL2RB mutations, but the efficacy of such therapeutic approaches remains to be tested. Using this strategy may also present challenges given the patients already expressed elevated serum IL-2 and IL-15.

In summary, mutations in IL2RB, FOXP3, and IL2RA share clinical features of severe immune dysregulation, reflecting an important role of regulatory T cells in maintaining immune tolerance. Contrasting FOXP3 deficiency, however, mutations in IL2RB and IL2RA predispose to severe herpesvirus disease, highlighting the requirement for intact signaling through the IL-2/IL-15 receptor for effective immunity to complex viral infections. An outstanding question is the relative contributions of IL-2 versus IL-15 to immune tolerance and antiviral immunity. With time, the study of new primary immunodeficiency patients promise to provide answers to this and other intriguing questions.