A loss of naïveté

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Monogenic disorders leading to primary immunodeficiency have fascinated scientists and clinicians alike by their capacity to reveal the complexities of intracellular signaling pathways. Two articles in this issue of Blood by Abdollahpour et al and Nehme et al illustrate this point vividly, describing for the first time the clinical and immunologic phenotype associated with genetic mutations in STK4, manifested largely by a loss of T-cell naïveté.1,2

STK4 encodes the Mammalian Ste20-like Kinase (MST) 1, a protein that is ubiquitously expressed in mammalian cells. The functions of homologous kinases Hippo in Drosophila and Ste20 Kinase in Yeast have been well described, largely as regulators of proliferation, apoptosis, morphology, and cell shape, but the function of the Ste20 mammalian kinases in the immune system and other organs is less well explored.

Mammalian MST1 was first conceptualized as an enhancer of apoptosis in neuronal cells, in the setting of oxidative stress. MST1 activation was shown to phosphorylate and retain nuclear localization of Foxo1, a transcriptional activator of pro-death genes.3 Subsequently, MST1 was identified as a regulator of leukocyte adhesion in mammals. Knockdown of MST1 cDNA in T cells prevented the activation of LFA1-induced T-cell adhesion after T-cell receptor (TCR) or chemokine stimulation of lymphocytes.4

Studies in MST1-deficient mice confirmed the dual role of MST1 in both LFA1-mediated adhesion and apoptosis.5-7 MST1-deficient mice exhibit decreased numbers of lymphocytes in the blood, lymph nodes, and spleen, resulting from both reduced homing to the lymph tissues and, paradoxically, from reduced survival of naive T cells. Induction of oxidative stress by whole body γ irradiation led to a further reduction of CD4 T cells in the peripheral blood of MST1-deficient mice, suggesting MST1 modulates stress-induced lymphocyte apoptosis.

Two manuscripts in this issue describe a phenotype of recurrent infections (bacterial and viral), EBV-driven lymphoproliferative disease, dermatitis, subclinical cardiac anomalies, autoimmune cytopenias, and significant lymphopenia in 7 children (from 3 unrelated families) diagnosed with biallelic MST1 mutations. The clinical phenotype is characteristic of a growing group of primary immunodeficiencies marked by chronic viral infections, autoimmunity, and malignancy.8 The immunologic phenotype is distinct: instead of hypogammaglobulinemia and absent serologic titers typically seen in severe combined immune-deficiency and other combined immunodeficiencies, MST1-deficient patients demonstrated hypogammaglobulinemia and a humoral response to viral infection (HSV, EBV) and vaccines. However, the B-cell phenotype was not entirely normal. In the report from...
Abdollahpour et al, B-cell numbers were significantly reduced, especially memory B cells. Further studies are needed to dissect if the B-cell phenotype is simply related to defective T-cell function or an intrinsic B-cell defect.

Humoral responses depend on a T-cell–dependent, germinal center reaction. Thus, with evidence of serologic titers and hypergammaglobulinemia, one would expect intact T-cell proliferation in response to TCR stimulation. Paradoxically, peripheral blood T cells from MST1-deficient patients displayed markedly impaired thymidine uptake in response to mitogens (phytohaemagglutinin) and anti-CD3 antibody. The mechanism proposed for this apparent contradiction is intriguing—T cells from affected individuals were remarkably sensitive to mitogen and/or anti-CD3–induced death. Instead of proliferating, the cells underwent apoptosis. The circulating T cells were also phenotypically abnormal, with decreased CD4/8 ratios, restricted T cell–receptor repertoire, and a severe reduction of circulating naive (CD45RA+) cells. The CD45RA+ T cells were phenotypically abnormal, with decreased IL-7 receptor α and CD62L and up-regulated Fas on the cell surface, more typical for an antigen-experienced cell.

A loss of naive CD4 T cells is seen in many primary immunodeficiencies, such as DiGeorge Syndrome, common variable immunodeficiency, ITK deficiency, and XLP. However, T cells generally exhibit intact function. The findings of viral infections and viral-associated malignancy in patients suggest a potential mechanism whereby cytotoxic lymphocyte function; how-ever, neither CTL nor NK function was reported. Because cytotoxic lymphocytes rely on LFA1 activation to form a functional immune synapse, it may be useful to test for cytotoxic dysfunction in MST1 deficiency (NK or CTL).

The discovery of a novel, primary immunodeficiency because of homozygous mutations in MST1 confirms that MST1 is a critical regulator of T-cell function. According to a simplified model (see figure) in naive T cells, MST1 likely potentiates TCR– and/or chemokine-activated LFA1 activation. In addition, MST1 preserves the life of naive T cells by an unknown mechanism, theoretically involving Foxo1 activation, IL-7R maintenance, and lymph node trafficking. Future studies are needed to dissect the downstream targets of MST1 in T cells.

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REFERENCES

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