Immune dysregulation in patients with PTEN hamartoma tumor syndrome: Analysis of FOXP3 regulatory T cells

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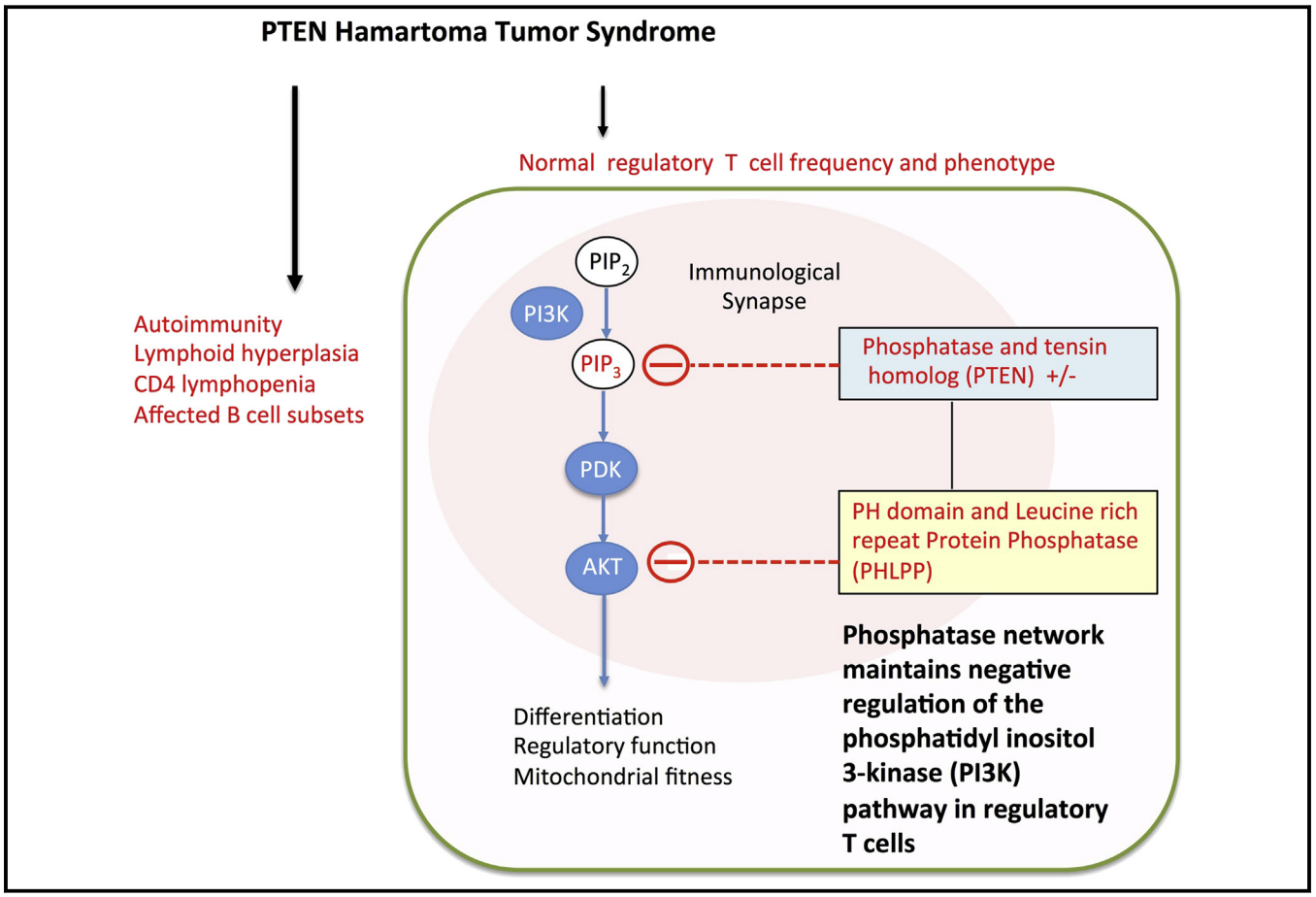
GRAPHICAL ABSTRACT



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Background: Patients with heterozygous germline mutations in phosphatase and tensin homolog deleted on chromosome 10 *(PTEN)* experience autoimmunity and lymphoid hyperplasia.
Objectives: Because regulation of the phosphoinositide 3-kinase (PI3K) pathway is critical for maintaining regulatory T (Treg) cell functions, we investigate Treg cells in patients with heterozygous germline PTEN mutations (PTEN hamartoma tumor syndrome [PHTS]).
Methods: Patients with PHTS were assessed for immunologic conditions, lymphocyte subsets, forkhead box P3 (FOXP3)$^+$ Treg cell levels, and phenotype. To determine the functional importance of phosphatases that control the PI3K pathway, we assessed Treg cell induction *in vitro*, mitochondrial depolarization, and recruitment of PTEN to the immunologic synapse.
Results: Autoimmunity and peripheral lymphoid hyperplasia were found in 43% of 79 patients with PHTS. Immune dysregulation in patients with PHTS included lymphopenia, CD4$^+$ T-cell reduction, and changes in T- and B-cell subsets. Although total CD4$^+$FOXP3$^+$ Treg cell numbers are reduced, frequencies are maintained in the blood and intestine. Despite pathogenic PTEN mutations, the FOXP3$^+$ T cells are phenotypically normal. We show that the phosphatase PH domain leucine-rich repeat protein phosphatase (PHLPP) downstream of PTEN is highly expressed in normal human Treg cells and provides complementary phosphatase activity. PHLPP is indispensable for the differentiation of induced Treg cells *in vitro* and Treg cell mitochondrial fitness. PTEN and PHLPP form a phosphatase network that is polarized at the immunologic synapse.
Conclusion: Heterozygous loss of function of PTEN in human subjects has a significant effect on T- and B-cell immunity. Assembly of the PTEN-PHLPP phosphatase network allows coordinated phosphatase activities at the site of T-cell receptor activation, which is important for limiting PI3K hyperactivation in Treg cells despite PTEN haploinsufficiency. (J Allergy Clin Immunol 2017;139:607-20.)

Key words: *Regulatory T cells, phosphatases, phosphoinositide 3-kinase, PTEN, PH domain leucine-rich repeat protein phosphatase, PHTS, immunologic synapse, autoimmunity*

Generation of the second messenger phosphatidylinositol-3,4,5-trisphosphate by phosphoinositide 3-kinase (PI3K) constitutes a critical checkpoint for immune activation.[1] This pathway is controlled by phosphatases, such as PTEN, a dual-specific protein and lipid phosphatase. *Pten* deletion in immune cell subsets in mice caused defects in T cells,[2,3] CD4$^+$Foxp3$^+$ regulatory T (Treg) cells[4-6] and B cells.[7] Heterozygous *Pten* deletion caused autoimmunity, intestinal lymphoid hyperplasia, thymus hyperplasia, and thymoma and T-cell lymphoma formation.[8,9]

Heterozygous PTEN mutations are found in a group of hereditary disorders known as *PTEN* hamartoma tumor syndrome (PHTS).[10] Patients with PHTS can present with autoimmunity, lymphoid hyperplasia, colitis and lymphopenia, as well as defects in B cell responses[11,12] and low immunoglobulin levels.[11,13]

The PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway is pivotal for Treg cell development and

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