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Therapeutic targeting of notch receptor-ligand signaling ameliorates immune-mediated bone marrow failure

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For the majority of patients it affects, severe aplastic anemia (AA) is an autoimmune bone marrow failure disease caused by aberrant immune destruction of blood progenitor cells. Although its Th1-mediated pathology is well-described, the molecular mechanisms that drive disease progression remain ill-defined. The Notch signaling pathway can influence Th1 differentiation in the presence of polarizing cytokines. This action requires enzymatic processing of its receptors and ligands by γ-secretase. Using a mouse model of aplastic anemia, we demonstrate that Notch signaling contributes to immune-mediated bone marrow failure and that disease severity can be modulated using γ-secretase inhibitors (GSI). During active disease, the expression levels both of intracellular Notch1^{IC} and its Th1-reinforcing ligand, Delta-like-1, were increased on bone marrow-infiltrating T cells and antigen presenting cells, respectively. Notably, Notch1^{IC} was significantly elevated in peripheral T cells from patients with AA, while treatment with GSI in vitro lowered its expression and reduced other Th1-associated molecules to control levels. These data indicate that Notch signaling was responsive to GSI during active disease. Importantly, conditionally deleting notch1 or administering GSI in vivo attenuated disease and rescued mice from lethal bone marrow failure. These results identify Notch signaling as a primary driver of the pathogenesis of the autoimmune bone marrow failure syndrome, aplastic anemia, and as a novel target for therapeutic intervention.

Biography

Lisa M. Minter received her PhD and post-doctoral training at the University of Massachusetts/Amherst, and is now an Assistant Professor in the Dept. of Veterinary & Animal Sciences at UMass/Amherst. She has publications in Nature Immunology, Nature Reviews Immunology, EMBO, Blood, Journal of Immunology, Frontiers in Biology and Current Opinions in Microbiology. She has served as an ad hoc reviewer for Blood, Cellular and Molecular Immunology, Future Medicine and the American Journal of Pathology. Her research interests focus on Notch signaling in peripheral T cells and its contribution to autoimmunity.

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