Effector T cells utilize NF-kappaB-regulated CXCR4 expression to traffic to the bone marrow during immune-mediated bone marrow failure

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Aplastic Anemia is a bone marrow failure disease, mediated by aberrant T helper type-1 (Th1) immune responses, that destroys blood stem and progenitor cells in the bone marrow, and results in loss of circulating platelets, white and red blood cells. Notch and NF-kappaB proteins play a critical role during T cell activation and differentiation, and their signaling pathways are closely inter-related. In mice, Notch and NF-kappaB regulate the expression of signature Th1 molecules, including T-bet and IFN-gamma. The chemokine receptor CXCR4, which can facilitate the migration of cells to the bone marrow, is also regulated by NF-kappaB in several cancer models. Given the documented role of NF-kappaB in promoting Th1-mediated immune responses, together with the potential for modulating this response using NF-kappaB inhibitors, we asked whether NF-kappaB signaling contributed to disease pathology in a mouse model of aplastic anemia. Here, we show that inhibiting NF-kappaB, genetically or pharmacologically, in vivo, attenuates disease in a mouse model of aplastic anemia. Blocking NF-kappaB signaling increased bone marrow cellularity, white and red blood cells and decreased the percentage of bone marrow-infiltrating T cells, as well as the expression of intracellular Notch1 within these cells. Compared to controls, bone marrow-infiltrating T cells from treated mice show decreased expression of CXCR4, suggesting inhibiting NF-kappaB prevented CXCR4-mediated migration to the bone marrow. Our findings suggest that NF-kappaB signaling may contribute to pathogenesis in aplastic anemia through its regulation of CXCR4 and blocking CXCR4 expression may represent a novel therapeutic strategy in the treatment of aplastic anemia.

Biography

Lisa M. Minter received her Ph.D. 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 several high-impact journals. 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 the pathology of autoimmune bone marrow failure.

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