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

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Abstract

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 IFNgamma. 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 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 several high-impact journals including *Nature Immunology, Nature Reviews Immunology, Journal of Experimental Medicine, EMBO,* and *Blood.* 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.