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MDS/MPN: A complex disease of the hematopoietic stem cell compartment and its environment

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CREB binding protein (CREBBP) interacts with transcription factors and the basal transcription machinery and can acetylate histones or other proteins. Aberrant expression of CREBBP greatly affects hematopoiesis, as demonstrated in some patients with leukemia or myelodysplastic syndrome (MDS) and in mice heterozygous for Crebbp. The latter develop an MDS/myeloproliferative neoplasm (MDS/MPN), characterized by dysfunctional hematopoietic stem cells (HSCs), excessive myelopoiesis, myelodysplasia and progression to leukemia. In order to elucidate the cellular origin of MDS/MPN, we transplanted Crebbp+/- Lin-Sca-1+cKit++ (LSK) cells, a population highly enriched for HSCs, and immature myeloid progenitors (common myeloid progenitors [CMPs]) and granulocyte/macrophage progenitors [GMPs]) into wild-type recipients. Transplantation of LSK cells resulted in classic MDS development with leukemic progression. Interestingly, transplantation of Crebbp+/- CMPs or GMPs into wild-type recipients also resulted in excessive myelopoiesis and in some cases even MDS and myeloid leukemia, however, the disease was of wild-type origin. This suggests that paracrine effects play an important role in the development of MDS/MPN in Crebbp+/- mice. Moreover, transplantation studies in which wild-type cells were injected into Crebbp+/- mice revealed that Crebbp+/- stroma lacks the ability to properly maintain HSCs and immature progenitors; instead it stimulates myeloid differentiation. Although the exact molecular mechanisms remain to be elucidated, we found that known hematopoietic modulators such as matrix metallopeptidase-9 and kit ligand were decreased in Crebbp+/- mice and that cadherin-5 and endothelial cell adhesion molecule-1 were increased on Crebbp+/- bone marrow endothelial cells. Together, these findings suggest a multi-cellular origin of MDS/MPN in the Crebbp+/- mouse model.

Biography

Vivienne I. Rebel is an assistant professor at the Greehey Children's Cancer Research Institute of the UT Health Science Center in San Antonio, TX (USA). Her research is focused on identifying gene regulatory networks governing cell-intrinsic and cell-extrinsic control of normal and leukemic hematopoietic stem cells using mouse models. Rebel received her M.D. from the Free University of Amsterdam (The Netherlands). She did her Ph.D. at the Terry Fox laboratory in Vancouver, BC (Canada) in collaboration with the Free University of Amsterdam and her post-doctoral training at the Dana-Farber Cancer Institute, Harvard Medical School in Boston, MA (USA).

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