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Growth factor independent 1 (Gfi1) as a new target for the therapy of Lymphoid leukemia and lymphoma

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Lymphoma and leukemia have an incidence of approximately 8% in North America and Europe. However, a large proportion of patients cannot be cured despite intensive therapy and new therapeutic approaches are warranted. We found that the transcriptional repressor protein Growth factor independent-1 (Gfi1) is critical for the initiation and progression of lymphoid leukemia and lymphoma and that inhibition or ablation of Gfi1 significantly delayed or completely prevented the initiation of T-cell lymphoma. This was observed using several independent experimental models in which we provoked a T-cell tumor by injecting mice with a carcinogen (N-ethyl-N-nitrosourea (ENU)) or infecting them with a non acute transforming retrovirus (MoMuLV) or where we overexpressed a truncated Notch transgene (NotchΔCT) mimicking Notch mutations of human T-ALL cases. Most striking was that the ablation of Gfi1 in these tumor models led to the cure of mice without use of additional chemotherapy. In addition, we also observed that inhibition of Gfi1 could stop the expansion of leukemic cells from T-ALL patients grafted into immune-deficient mice. Biochemical analyses indicated that Gfi1 exerts its function by restricting the activity of the tumor suppressor p53 by limiting its methylation at K372 and thus its ability to activate pro-apoptotic targets genes such as *Bax, Noxa (Pmaip1)* and *Puma (Bbc3)*. Since malignant transformation can induce stress and a DNA damage response, tumors with non-mutated p53 such as many lymphoid leukemias or lymphomas have to select for Gfi1 expression to counteract p53 induced cell death. In this situation, the inhibition or removal of Gfi1 leads to accelerated p53 mediated cell death and to tumor regression. We conclude that lymphoid leukemia are dependent upon Gfi1 and that Gfi1 may be suitable as a new therapeutic target to treat lymphoid malignancies, in particular by complementing the classical radio- and chemotherapy, which induce a DNA damage response in tumor cells.

Biography

Tarik Möröy obtained a Ph.D. in Biochemistry from the Ludwig-Maximilians Universität München in Germany. He is the IRCM's President and Scientific Director, Full IRCM Research Professor and Director of the Hematopoiesis and Cancer research unit. He is also Full research professor in the Department of Microbiology and Immunology (accreditation in biochemistry) at the Université de Montréal, and Adjunct Professor in the Department of Medicine (Division of Experimental Medicine) and the Department of Biochemistry at McGill University. He holds the Canada Research Chair in Hematopoiesis and Immune Cell Differentiation.

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