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The Src and c-Kit kinase inhibitor dasatinib enhances p53-mediated targeting of human Acute myeloid leukemia stem cell by chemotherapeutic agents

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The SRC Family Kinases (SFKs) and the receptor tyrosine kinase c-Kit, are activated in human acute myeloid leukemia (AML) cells. We show here that the SFKs LYN, HCK or FGR are overexpressed and activated in AML progenitor cells. Treatment with the SFK and c-KIT inhibitor dasatinib selectively inhibits human AML stem/progenitor cell growth in vitro. Importantly, dasatinib markedly increases the elimination of AML stem cells capable of engrafting immunodeficient mice by chemotherapeutic agents. In vivo dasatinib treatment enhances chemotherapy induced targeting of primary murine AML stem cells capable of regenerating leukemia in secondary recipients. Our studies suggest that enhanced targeting of AML cells by the combination of dasatinib with daunorubicin (DNR) may be related to inhibition of AKT mediated HDM2 phosphorylation, resulting in enhanced p53 activity in AML cells. Combined treatment using dasatinib and chemotherapy provides a novel approach to increase p53 activity and enhance targeting of AML stem cells.

Biography

Cedric Dos Santos received his Bachelors and Masters degrees from University Paul Sabatier, Toulouse III, France, and completed his Ph.D. from the same university in December 2008. He has a long time interest in studying deregulated signaling pathways and has published several high impact publications in 2008 in *Blood*, like "A critical role of Lyn in Acute Myeloid *Leukemia*" and in 2009 in *Leukemia*. He joined Ravi Bhatia laboratory, City of Hope, Duarte, CA, as a post-doctoral fellow in February 2009. In one of his work, he discovered a new original and efficient therapeutic avenue for the treatment of AML, and this study is published in the journal *Blood* last month. In August 2013, he accepted a faculty position at the University of Pennsylvania in the group of Martin Carroll and Gwenn Danet-Desnoyers.

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