Abstract

This proposal will study the role of the transcription factor *Prdm16* in the maintenance of leukemic stem cells (LSCs), specifically in acute myelogeous leukemia (AML). LSCs have the ability to self-renew, but unlike normal blood progenitors, they incompletely differentiate and instead develop into immature blast cells. The mechanisms behind this are unclear. Failure to eliminate LSCs during chemotherapy is likely a primary cause of relapse, and removal of these cells may be necessary and sufficient to treat leukemia. *Prdm16* is a transcription factor that plays an important role in the maintenance of hematopoietic stem cells (HSCs). It contains an N-terminal PR methyltransferase domain, whose presence or absence defines two distinct isotypes -- *f-Prdm16*, the full-length form of the protein, and *s-Prdm16*, which lacks the PR domain. Evidence suggests that *s-Prdm16*, or similarly, a deletion of the PR domain, may play a role in the development of leukemia. The goal of this proposal is to determine the role *Prdm16* in LSC maintenance. Preliminary data has shown that *Prdm16* deletion affects the development of leukemia in an *MLL-AF9* model of AML in leukemia derived specifically from HSCs. *MLL-AF9* leukemias derived from granulocyte-macrophage progenitors (GMPs) have been shown to have different properties than HSC-derived leukemias, with GMP-derived leukemias being less aggressive and having longer disease latency. Because *Prdm16* is highly expressed in HSCs and is not detectable in GMPs, this research proposal will compare the role of *Prdm16* in HSC- and GMP-derived leukemias, with the hypothesis that *Prdm16* will affect leukemogenicity in HSC, but not GMP-derived AML. This proposal will also use conditional mouse deletion models to determine the stage at which *Prdm16* is required for leukemogenesis in this model. Studies from HSCs suggest that *Prdm16* will not be required for the homing or engraftment of cells, but rather initiation and propagation of LSCs, which would also more in line with a role for *Prdm16* in LSC maintenance. Finally, this proposal will contrast the role of *f-Prdm16* and *s-Prdm16* in *MLL-AF9* leukemia. These isoforms will be expressed individually in $Prdm16^{+/+}$ and $Prdm16^{-/-}$ leukemic cells and their effect on leukemogenesis will be determined. It is predicted that *s-Prdm16* will restore leukemogenicity of $Prdm16^{-/-}$ cells and enhance the leukemogenicity of $Prdm16^{+/+}$ cells, whereas *f-Prdm16* will not, and may even have the opposite effect. This proposal possesses clinical relevance, as the subsets of leukemia associated with *Prdm16* have poor to intermediate outcomes in a clinical setting. Furthermore, additional members of the PR family of proteins have been shown to be associated with leukemia, so a more complete understanding of the role of *Prdm16* in leukemia may yield further insights into a general mechanism of leukemogenesis established by these proteins.