The subtype-specific features of *EVI1* and *PRDM16* in acute myeloid leukemia

We read with interest the response "The closely related rare and severe acute myeloid leukemias carrying *EVI1* or *PRDM16* mutations share singular biological features" by Eveillard *et al.*[1] to our recent publication.[2] *EVI1* and *PRDM16* belong to the Prdm family, which is characterized by an N-terminal PR domain with multiple zinc fingers. Prdm family members control gene expression through modification of the chromatin state. It has been shown that *EVI1* and *PRDM16* have similar functions in normal and malignant hematopoiesis.[3,4] They both cause acute myeloid leukemia (AML), and loss of either leads to severe defects of hematopoietic stem cell (HSC) activity. Here, we would like to clarify similarities and differences of *EVI1* and *PRDM16* as poor prognosis biomarkers in AML.

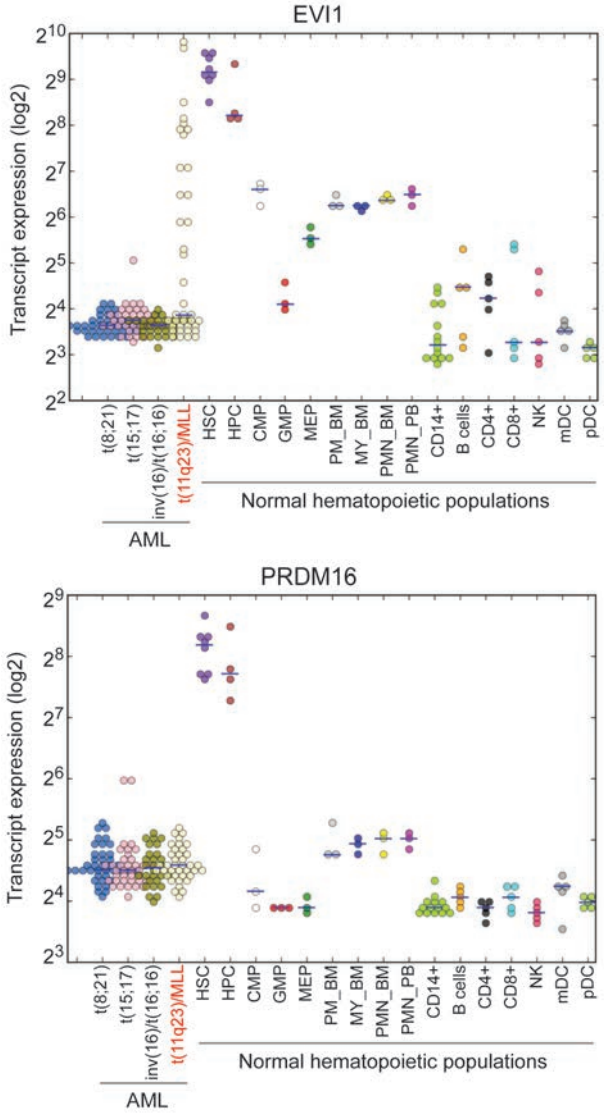

Figure 1. Expression of *EVI1* and *PRDM16* in different subtypes of AML cells and hematopoietic cell populations derived from the HemaExplorer website (*http://servers.binf.ku.dk/hemaexplorer/*). Both *EVI1* and *PRDM16* are highly expressed in hematopoietic stem cells. *EVI1*, but not *PRDM16*, is up-regulated in some *MLL*-rearranged leukemia. HSC_BM: hematopoietic stem cells from bone marrow; early HPC_BM: hematopoietic progenitor cells from bone marrow; CMP: common myeloid progenitor cell; GMP: granulocyte monocyte progenitors; MEP: megakaryocyte-erythroid progenitor cell; PM_BM: promyelocyte from bone marrow; MY_BM: myelocyte from bone marrow; PMN_BM: polymorphonuclear cells from bone marrow; PMN_PB: polymorphonuclear cells from peripheral blood; mDC: myeloid dendritic cells; pDC: plasmacytoid dendritic cells.

Eveillard *et al.* provide evidence that *EVI1*- and *PRDM16*-rearranged AML share many features including micromegakaryocytes, multilineage dysplasia, and low myeloperoxidase (MPO)-expressing blasts. Given the critical role of Evi1 and Prdm16 to maintain HSCs,[5,6] the low expression of MPO probably indicates the undifferentiated stem cell-like properties of these types of leukemia. Eveillard *et al.* also showed that rearrangements of these genes are associated with inferior survival, and are frequently found in patients with secondary AML. These findings, together with those in previous reports,[3,4] suggest that both *EVI1* and *PRDM16* are activated by chromosomal rearrangements, confer a poor prognosis presumably by promoting stem cell program in leukemia cells, and are involved in the development of secondary AML. It should be noted, however, that another study found only *EVI1*-rearrangement is associated with monosomy 7, while *PRDM16*-rearrangement had no preferential association with other cytogenetic abnormalities.[7] Therefore, there may be some mechanistic differences between *EVI1*- and *PRDM16*-induced leukemogenesis. In addition, whether high expressions of *EVI1* and *PRDM16* are independent prognostic factors even in secondary AML remains to be elucidated.

High expressions of *EVI1* and *PRDM16* are also found in a subgroup of AML patients without translocations of these gene loci. We and others have previously shown that *EVI1* is a poor prognostic factor in *MLL*-rearranged AML.[2] *PRDM16* was also shown to be a transcriptional target of *MLL*,[8] but interestingly, *PRDM16* is not up-regulated in *MLL*-rearranged AML according to the HemaExplorer[9] website (*http://servers.binf.ku.dk/hemaexplorer/*) (Figure 1). Furthermore, a very recent report showed the mutually exclusive expression of *EVI1* and *PRDM16* in AMLs without obvious translocation.[10] High *EVI1* expression was mainly detected in *MLL*-rearranged AML and megakaryocytic-lineage AML, while high *PRDM16* expression was detected in myelocytic-lineage AML and myelomonocytic-lineage AML without *MLL*-rearrangements. Thus, it appears that *PRDM16* is up-regulated through different mechanisms from those for *EVI1* in AML patients. Further investigation is necessary to understand how these Prdm factors are activated in specific types of AML, and to elucidate their subtype-specific roles in AML development.

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