

Aplidin-treatment prevents development of myelofibrosis in Gata1^{low} mouse model

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Aplidin is a cyclic depsipeptide originally derived from the marine tunicate *Aplidium albicans* and currently obtained by chemical synthesis. This drug inhibits cancer growth through direct and indirect mechanisms. It has been reported to directly induce apoptosis and growth arrest of those tumor cells expressing low p27(Kip1) levels. In addition, Aplidin, by inhibiting secretion and/or response to VEGF, reduces endothelial cell proliferation in several in vitro and in vivo models of angiogenesis. The primary myelofibrosis (PMF) is associated with alterations of stem/progenitor cell trafficking which results in extramedullary hematopoiesis. The abnormal trafficking is caused by defective interactions between the stem/progenitor cells and their niches in the marrow. The stem/progenitor cells fail to express CXCR4, the receptor that recognizes the chemokine SDF-1 responsible for interaction with the vascular niche. In addition, in PMF, the marrow vascular niches are increased in numbers and abnormally coated with pericytes. Gata1^{low} mice develop myelofibrosis with age and are considered an animal model for PMF. The Gata1^{low} mice include reduced expression of CXCR4 on the stem/progenitor cells, increased numbers of pericyte-coated vessel in the marrow and extramedullary hematopoiesis in the liver. To assess the effects of Aplidin-treatment in myelofibrosis, Gata1^{low} mice received Aplidin or saline and were sacrificed for analyses of disease development. Similar results were observed after each cycle and those obtained after the 4th cycle are summarized here. Gata1^{low} stem/progenitor cells were found to express low levels of p27(Kip1), the proposed biomarker for Aplidin-sensitivity and responded to treatment by increasing their levels of p27(Kip1) (by 10-fold) and Gata1 (2-fold) expression. Aplidin-treated Gata1^{low} progenitor cells acquired the ability to form Gata1^{pos} megakaryocytes in vivo and hematopoietic colonies in vitro. Accordingly, Aplidin-treatment increased by 3-fold blood platelet counts significantly and prevented fibrosis and bone growth normalizing the femur cellularity. Although stem/progenitor cells from Aplidin-treated Gata1^{low} mice did not express CXCR4 and were found in high numbers in the liver, they did not develop hematopoiesis in this organ. In conclusion, Aplidin-treatment, by restoring Gata1 expression in the stem/progenitor cells and reducing the numbers of vascular niches in the marrow, restored the functional interactions between Gata1^{low} progenitor cells and their marrow niches, preventing development of myelofibrosis, including extramedullary hematopoiesis in liver.

Key words

GATA-1, Bone Marrow, Myelofibrosis, Stem Cell, Aplidin