Divergent roles of histone deacetylases in human adult eythropoiesis

[130] Divergent Roles of Histone Deacetylases In Human Adult Eythropoiesis. Session Type: Oral Session

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Histone deacetylases (HDACs) plays a regulatory role in the expression and activity of transcription factors. Several studies suggested that HDACs influence the proliferation and differentiation of hematopoietic progenitors. Here, we studied the role of HDACs in human adult erythropoiesis, using a HDAC inhibitor FK228 [depsipeptide]. We first examined the effect of FK228 on the growth of erythroid progenitors by incubating G-CSF-mobilized peripheral blood $CD34^+$ cells (500 cells/well) in semisolid serum-free cultures containing IL-3, SCF, or IL-3+SCF in the presence or absence of FK228. Addition of FK228 (0.5 ng/ml) to the cultures with IL-3 and SCF+IL-3 resulted in 32-fold and 12-fold increases, respectively, in the number of erythroid colonies that consist of $CD36^+$ glycophorin A $(GPA)^{low/negative}$ cells, compared with the cultures without FK228. FK228 also increased the number of cells comprising erythroid colonies in the cultures with IL-3 and SCF+IL-3. No colony growth was detected with SCF and SCF+FK228. We next examined the effect of FK228 on BFU-E colony formation by incubating $CD34^+$ cells with EPO or SCF+EPO in the presence or absence of FK228. While BFU-E colony formation was observed with SCF+EPO but not with EPO alone, addition of FK228 to the cultures containing SCF+EPO almost completely inhibited BFU-E colony formation. To further elucidate the effect of FK228 on BFU-E progenitors that grow in an EPO-dependent fashion, $CD34^+$ cells were cultured for 7 days with SCF, Flt3L, TPO, and IL-3, and $CD36^+$ cells were purified. Although BFU-E colony formation was induced by incubation of the $CD36^+$ cells with EPO, it was strongly repressed by the presence of FK228. Suspension cultures of $CD36^+$ cells revealed that viable cell numbers in the cultures with EPO+FK228 rapidly declined from 2 days of cultures, in contrast to an increase in the number of erythroid cells in the cultures with EPO. Annexin V/propidium iodide assay showed that, upon exposure to FK228, a remarkably higher fraction of the $CD36^+$ erythroid progenitors expressed an annexin V^+PI^- phenotype, indicative of an apoptotic cell death, compared with the control cultures ($71 \pm 8\%$ vs $4 \pm 1\%$). On the other hand, even though FK228 blocked the BFU-E colony formation from $CD34^+$ cells in the presence of SCF+EPO, FK228 did not significantly increase the population of cells that undergo an apoptotic cell death in $CD34^+$ cells. These findings suggest that HDACs, while playing an essential role in SCF/EPO- and EPO-dependent erythropoiesis, negatively regulate the action of IL-3 and IL-3+SCF on the growth of early erythroid progenitors. Our results indicate that HDACs have diverse functions in human adult erythropoiesis.

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