Atypical Modulation of Heme-oxygenase by Heme during Erythropoiesis

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Various pathologic conditions are characterized by the release of large amounts of heme from erythrocytes. Recent reports showed that heme is a signaling molecule. Heme reduces its synthesis inhibiting the 5-aminolevulinate synthase-1 and stimulates its breakdown inducing heme-oxygenase (HO). HO-2 is believed to be constitutive, whereas HO-1 is induced by numerous stimuli including heme. We investigated the effects of heme on myeloid differentiation. K562 cells have been used as a common precursor for erythroblasts and megakaryocytes since it can be bidirectionally differentiated by heme or phorbol ester, respectively. Its protein expression profile was investigated using both Western blot and flow cytometric analysis. Surprisingly, Western Blotting analysis showed that in K562, heme was unable to induce HO-1. Unexpectedly, under similar conditions HO-2 expression was inhibited by heme. These results were corroborated by real-time PCR showing that during heme exposure HO-1 mRNA levels remained unaltered while HO-2 mRNA was reduced. We also determined the expression of specific markers of erythroid differentiation, such as CD36, CD71, CD105 e CD235a during the treatment with heme. We evaluated the heme-oxygenase expression during normal erythropoiesis in samples of human bone marrow and verified a similar unusual regulation of heme metabolism observed with K562. An intense heme synthesis is the hallmark of hemoglobin production during erythropoiesis. This unexpected heme-oxygenase inhibition by heme prevent a futile cycle involving simultaneous breakdown and synthesis of heme.

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