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Editorial

ERYTHROPOIETIN CONSUMPTION BY ERYTHROID PROGENITOR AND PRECURSOR CELLS – AN OLD DILEMMA

Hormone erythropoietin (Epo) is hematopoietic growth factor produced primarily in the kidney and also to a small extent in the liver. The physiological role of this hormone is to adjust the red cell mass to the actual oxygen demand (1). This obligatory factor for erythoid cells interacts with erythroid progenitor cells in the bone marrow stimulating them into a cell cycle, supporting their survival and permitting their terminal differentation. Epo exerts its effect on erythroid progenitors after binding to specific receptors that are expressed on respective target cells. The stimulation of the Epo production depends on the relationship between oxygen need and oxygen supply (2), oxygen regulated feedback being the major control mechanism of Epo production. However other factors may play a role too.

In the early days of Epo studies, in 1959, Stohlman (3) have suggested that the size of erythron might influence the clearance of Epo through the consumption of the hormone by erythropoietin target cells. However, recent animal studies provided no evidence that such an effect is quantitatively significant (4). Still, some of our and other authors' data are in consensus with the Stohlman's suggestion (3).

In 1979 we have indirectly determined serum Epo levels in 25 aplastic anemia patients by measuring Fe^{59} incorporation into red blood cells polycythemic mice (5). When the Epo levels were compared to the serum Epo levels in patients with anemia due to iron deficiency it was observed that patients with aplastic anemia have higher levels of Epo at any given hemoglobin concentration than do patients with hyperactive erythroid marrows. The data were quoted in an Editorial by Nathan and Sytkowsky (6) as demonstrating the inverse correlation of Epo levels with marrow activity. The finding that patients with aplastic anemia have high Epo levels was confirmed by Jelkmann and Wiedemann (7) but not confirmed by others (8). Similar results to what we have found by mouse bioassay were obtained by Schrezenmeier et al (9) in 1994 by means an ELISA serum Epo concentration measurement in a much larger group of aplastic anemia patients. Significant negative correlation of log Epo on hematocrit was found both in aplastic anemia and iron deficiency or hemolytic anemia patients. However, for the same degree of anemia log Epo levels were significantly higher than in patients with two other anemias. Authors have suggested the possibility that the high serum Epo levels in aplastic anemia patients might be due to a diminished number of Epo receptor bearing erythropoietic progenitor cells. In conclusion they have stated that results argue against the model of simple feedback regulation via hypoxic anemia.

In 1992 we have published the paper dealing with serum Epo levels in hemodialysed patients with anemia due to renal failure after administration of recombinant human Epo (rHuEpo) (10). In this and the next work of ours Epo was measured using the radioimmunoassay procedure by Dr Gisela Clemons at Lawrence Berkeley Laboratories. Monitoring serum Epo concentrations after the first i.v. rHuEpo injection and following another regular injection after two months of rHuEpo therapy, at the time expansion of the cell pool of erythroid progenitors and precursors was found in the bone marrow, demonstrated that Epo elimination half life was reduced from 7.48h to 4.68h. Futhermore, number of CFU–E derived colonies from the bone marrow of rHuEpo treated patients correlated significantly with Epo elimination half life after one bolus i.v. injection of rHuEpo. In that paper we suggested that the expansion of erythroid progenitors and precursor cells bearing Epo receptors and faster Epo elimination after two months of Epo therapy in the patients studied is in line with Epo catabolism by utilization as first proposed by Stohlman.

In consensus with our findings are the data of

Kendall et al (11) showing that in patients with megaloblastic anemia Epo levels fall immediately after initiation of therapy, preceding the rise in the reticulocyte count. An immediate reduction in serum Epo has been noted following therapy of patients with iron deficiency anemia too. Kendall has suggested that the explanation of these observations is that proliferating pool of erythroid progenitor cells consumes available Epo.

In the same line are our results obtained by following Epo levels and erythroid progenitors in rats exposed to chronic hypoxia. High Epo levels after 24 hours of hypoxia were declining but were higher than in controls after one week of hypoxia. A pronounced fall of Epo concentration was found after two weeks of hypoxia.

The frequency of erythroid progenitors in the bone marrow and spleen increased during the hypoxic treatment. As the most pronounced increase in CFU–E number was found after two weeks of hypoxia, at the time of the greatest decrease of Epo levels, it is possible that the levels of Epo could be to some extent the consequence of an increased consumption of Epo by enlarged CFU–E population (12).

Oxygen regulated feedback is the major control mechanism of Epo production, but potential role of erythroid progenitor cell consumption in the regulation Epo should not be neglected.

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