Chapter 13

Lessons to better understanding of hypoxia sensing

Acquired and congenital mutations resulting in polycythemia

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Abstract: Adaptation of the organism to hypoxia has profound effect on multiple tissues including regulation of erythropoiesis, vasculogenesis, a proper regulation of embryogenesis as well as other functions. The elucidation of those congenital or acquired mutations giving rise to disease states affecting physiological systems devoted to oxygen homeostasis provides not only a practical diagnostic and potential therapeutic target, but also allows to identify the essential, non-redundant physiological pathways that may be hitherto unknown. The erythropoietin gene was the first gene expression found to be upregulated by hypoxia; the mechanism of this regulation lead to our current understanding of hypoxia sensing. Thus it is appropriate that the disorders resulting from augmented erythropoiesis are subject of this review.

Key words: erythropoiesis; erythropoietin; erythropoietin receptor; mutations in polycythemia; hypoxia-inducible factor 1; Chuvash polycythemia

INTRODUCTION: The Regulation Of Erythropoiesis And Its Relevance To Polycythemic Disorders

Polycythemia is literally translated as “many cells in the blood”. Only erythrocytosis (an alternative term for these disorders) produces polycythemia since leukocytes and platelets are present in blood in far smaller proportions. Polycythemia may be due to increased proliferation or decreased apoptosis of erythroid progenitors, or to delayed erythroid differentiation with an increased number of progenitor cell divisions.
Prolonged red cell survival, another theoretical cause of polycythemia, has not yet been described and with intact regulatory mechanisms polycythemia would be unlikely to occur. Primary polycythemia results from abnormalities expressed in hematopoietic progenitors. In contrast, circulating factors cause secondary polycythemia (69). Both primary and secondary polycythemia can be acquired or congenital (69).

Erythropoiesis is the physiological process of the production and renewal of the red blood cell mass. This process is influenced by a number of hormones, receptors and transcription factors (reviewed in Refs. 23, 47, 60). The principal hormone that regulates erythropoiesis is erythropoietin (EPO). In adults, the kidney is the main source of EPO. After erythroid commitment, erythroid progenitors express their own EPO (88). In vitro studies have shown that variable levels of EPO are required at various stages of erythroid maturation (47). Instead of EPO, multipotent myeloid progenitors and primitive erythroid progenitors, i.e. early burst-forming units-erythroid (BFU-E), require stem cell factor (SCF), interleukin 3 (IL-3), granulocyte/macrophage-colony stimulating factor (GM-CSF) and/or thrombopoietin (TPO) for growth (47).

**EPO, O₂-sensing, and hypoxia-inducible factor**

Regulation of oxygen homeostasis is critical to survival. In response to anemia or hypoxia compensatory mechanisms occur. Under normal conditions, EPO production is mediated either by reduced red blood cell mass (anemia) or decreased O₂ saturation of red cell hemoglobin, i.e. hypoxemia (reviewed in Ref. 47). Hypoxic stimulation results in increased production of hypoxia-inducible factor (HIF-1), which is the major factor for transcriptional activation of the EPO gene (80). HIF-1 is also found in cells that do not express EPO, thus HIF-1 is part of a widespread O₂-sensing mechanism providing transcriptional regulation of genes for vascular endothelial growth factor (VEGF), glycolytic enzymes and other genes (78, 79, 101). The identity of the O₂ sensor and the mechanism by which it regulates HIF-1 are unknown at the present time. Overall, HIF-1 is a physiological regulator of genes that promote cell survival under ischemia and are expressed in response to decreased cellular O₂ tension (8). HIF-1 regulates vasculogenesis, is required for proper embryonic development, elevates glucose uptake by cells, augments production of glycolytic enzymes and also plays an important role in cancerogenesis (9, 33, 72). Thus, polycythemia may be only one of many phenotypic manifestations of a congenital or acquired augmentation of the HIF-1 pathway (77).

HIF-1 is composed of two subunits, HIF-1α and HIF-1β [aryl hydrocarbon nuclear translocator (ARTN)] that form a heterodimer (97); only HIF-1α is regulated by hypoxia. HIF-1α mRNA and protein levels are