

Historical Background

In 1836, Richard Bright first commented on the pallor of patients with poor kidney function. In 1918, Professor Paul Carnot (1869 – 1957), Paris, France, suggested a hormonal link to renal anemia and postulated a substance “hemopoietin” which stimulated red cell production. Other scientists researched further [1, 2, 3]. In 1948, two Finnish scientists renamed the hormonal substance “erythropoietin” (EPO) [4]. In 1950, Reisman showed that the hypoxic rat caused erythropoiesis in its parabiotic, non-hypoxic partner [5]. In 1953, Erslev demonstrated a hormone in anemic animals which stimulated erythropoiesis when injected into non-anemic recipients [6]. Research between 1950 until 1970 revealed the kidneys as the main production site [7]. In 1988, Koury and Lacombe detected significant EPO-levels in the peritubular interstitium by cDNA-analysis [8, 9]. The highest concentrations were found in the proximal convoluted tubule and in the cortical ascending loop of Henle. In 1989, epoetin alfa was first licensed and, in the same year, the EPO-receptor (EPO-R) was described [10].

Definition of Anemia

The WHO defines anemia in general as hemoglobin < 13 g/dl in males and < 12 g/dl in females [11]. Similarly, KDOQI defines anemia as Hb < 13.5 g/dl in adult males and < 12.0 g/dl in adult females.

The European Best Practice Guidelines for patients with renal disease has defined anemia as hemoglobin < 13.5 g/dl in males younger than 70 years, < 12.0 g/dl in males > 70 years and < 11.5 g/dl in females of any age [12]. Typical renal anemia is normocytic and normochromic. Depending on the underlying renal disease, iron availability and co-morbidities, the degree of anemia shows interindividual variability, but, however, correlates with the degree of renal insufficiency and is caused primarily by a relative deficiency of EPO (erythropoiesis-stimulating peptide hormone).

Physiology of Erythropoiesis

The kidneys sense an oxygen deficit and respond by increasing EPO production. The degree of anemia is approximately proportional to the level of renal dysfunction as measured by blood urea nitrogen (BUN), serum creatinine or creatinine clearance (Ccr). Although EPO is also produced in non-renal tissues (e.g. liver), the amounts are insufficient to compensate for loss of normal renal parenchyma. Hematocrit rarely falls below 20% solely due to uremia. Reticulocytes are diminished relative to the degree of anemia.

Under normal conditions, a plasma EPO level of 4–25 mU/ml will maintain a baseline rate of erythrocyte synthesis and, therefore, also adequate oxygen delivery to the kidneys. In severe anemia, the plasma level of EPO may increase by a factor of 100 in an attempt to restore the erythrocyte mass and, thus, oxygen supply to normal [13].

Oxygen tissue levels are determined by oxygen dependent, hypoxia-inducible transcription factors (HIF) comprising HIF-1 β and HIF-1 α heterodimer subunits. Under normal oxygenated conditions, HIF-1 β and HIF-1 α are degraded rapidly via the ubiquitin proteasome system. The HIF subunits are regulated by prolylhydroxylase domain-containing enzymes (PHDs). Because of their dependence on O₂ as a direct substrate, PHDs have been designated ‘oxygen sensors’ linking cellular O₂ concen-

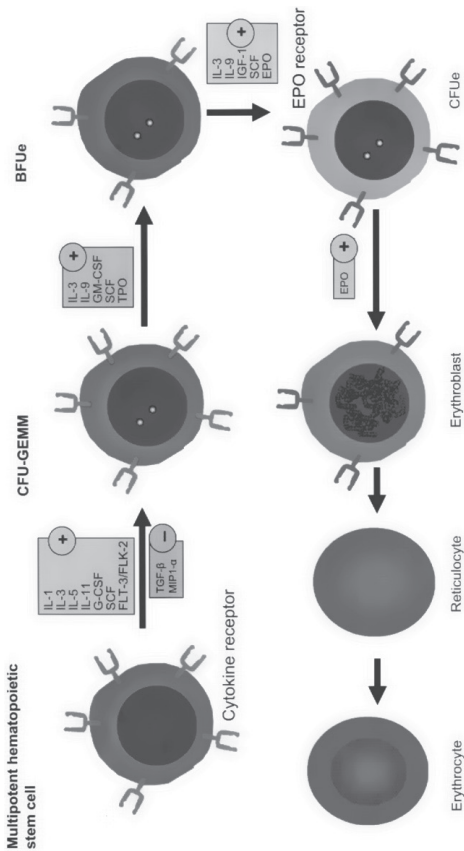


Figure 1. Erythropoiesis. BFUe: burst-forming unit-erythroid; CFUe: colony-forming unit-erythroid; EPO: erythropoietin; FLK: fetal liver tyrosine kinase; FLT: fetal liver tyrosine kinase; G-CSF: granulocyte-colony stimulating factor; GEMM: granulocyte, erythrocyte, monocyte, megakaryocyte; GM-CSF: granulocyte macrophage CSF; IL: interleukin; MIP: macrophage inflammatory protein; SCF: stem cell factor; TGF: transforming growth factor; TPO: thrombopoietin [26].

tration to HIF molecular responses. Furthermore, HIF3a has been identified which may be a negative regulator of hypoxia-inducible gene expression [14]. Under hypoxic conditions, HIF-1 β dimerizes with HIF-1 α , thus, escaping degradation. The HIF-1 heterodimer binds to hypoxia response elements recruiting coactivator (Co-act) molecules and resulting in increased transcription initiation complex (TIC) formation and mRNA synthesis and, finally, in the production of proteins that mediate physiological responses to hypoxia including apoptosis, e.g. erythropoietin, vascular endothelial growth factor (VEGF) and glucose transporter-1 (GLUT1). Non-hypoxic cells do not demonstrate significant levels of HIF-1 α and 2 α -protein, whereas, hypoxic cells can excrete de novo HIF-1 α -protein within 30 minutes [15].

The red cell lineage is modulated by several cytokines: granulocyte-colony-stimulating factor (G-CSF), interleukins (IL-3, IL-4, IL-9, IL-11), stem cell factor (SCF), granulocyte-macrophage-colony-stimulating factor (GM-CSF), insulin-like growth factor (IGF-1) and EPO. Pro-inflammatory cytokines such as interleukin-1 and -6 and tumor-necrosis factor- α inhibit proliferation and maturation of erythrocyte progenitors in the bone marrow. However, insufficient EPO-production is the main cause of renal anemia. EPO targets mainly the mature burst-forming units-erythroid (BFUe) and the colony-forming units-erythroid (CFUe) by suppressing apoptosis and, thus, enhancing proliferation and maturation of