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Review Article

Molecular mechanism and systemic response of erythropoietin:A Review

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Abstract

This paper reviews the molecular mechanism and systemic response of erythropoietin (Epo).Erythropoietin(Epo) is a glycoprotein hormone that causes the production of red blood cell.This helps to increase the level of haemoglobin and packed cell volume.It is produced mainly in the interstitial fibroblast of the renal cortex.It has additional nonhaematopoietic effects.Erythropoietin enhancer is activated by hypoxia-inducible transcription factors (HIFs) which is composed of an O_2-labile α-subunit and a constitutive subunit.Erythropoietin synthesis follows a negative feedback mechanism and is regulated by hypoxia.There is an inverse relationship between erythropoietin (Epo) level and haematocrit (Hct) or haemaoglobin (Hb) concentration.The level of erythropoietin varies greatly between individuals and there is no serious sex or age differences.This diurnal fluctuation with a nadir occuring in the morning.Therefore,the kidneys shoud be kept in good health conditions always to maintain the daily requirement of erythropoietin level to prevent anaemia and apoptosis of the red blood cells.

Keywords: Erythropoietin,Molecular Mechanism , Systemic Response Of Erythropoietin,Regulation Of Erythropoietin Synthesis

Introduction

The hormone erythropoietin (Epo) maintains red blood cell mass by promoting the survival,proliferation and differentiation of erythrocytic progenitors (Jelkman,2011).Erythropoietin is essential for erythropoiesis.Erythropoietin is a 30.4Kda glycoprotein produced by the kidney,and is mostly well-known for its physiological function in regulating red blood cell production in the bone marrow (Moore and Bellomo,2011).Erythropoietin has additional protective effects,which may be useful in the prevention or treatemnt of acute kidney injury.These protective mechanisms are multifactorial in nature and include inhibition of apoptotic cell death,stimulation of cellular regeneration,inhibition of deleterious pathways, and promotion of recovery (Moore and Belloman,2011).Erythropoietin originates mainly from fibroblasts in the renal cortex.

Physiology of erythropoietin

Erythropoietin is primarily expressed by hepatocytes during the fetal state.After birth,peritubular fibroblasts in the renal cortex become the main production site.Erythropoietin synthesis is controlled at the transcriptional level.Erythropoietin mRNA is also detectable in brain,liver,spleen,lung and testis,but these organs are not able to substitute for renal erythropoietin in chronic kidney disease (CKD).Brain-derived erythropoietin acts locally as a neuroprotective factor (Noguchi et al.,2007).Erythropoietin is an acidic

glycoprotein of about 30.4 Kda and comprises of 165 amino acids and four glycans.Circulating erythropoietin exhibits several glycosylation isoforms that differ in electrical charge and bilogical activity.Erythropoietin amounts are usually expressed in international units (IU),with one iu exerting the same erythropoiesis stimulating activity in rodents as 5µmol cobaltous chloride (Jelkman,2007).Systemic erythropoietin is an anti-apoptotic agent for erythrocytic progenitors,predominantly the colony-forming units-erythroids (CFU-Es).In response to erythropoietin the CFU-Es proliferate and differentiate to generate cohorts of proerythroblasts and normoblasts.The human haematopoietic Epo-receptor(Epo-R) is a 484 amino acid glycoprotein of about 60 Kda, which belongs to the cytokine class1 receptor family and forms homodimers.On the binding of erythropoietin to the Epo-R dimer,cytoplasmic Janus Kinases 2(JAK2) catalyse the phosphorylation of tyrosine residues of the Epo-R and of various intracellular proteins(Jelkman,2011).

A role has been proposed for erythropoietin as a cytoprotective agent for several non-haematopoietic tissues,including the brain,the haert,blood vessels and the kidneys (Brines and Cerami,2006).Some researchers believe that the effects of erythropoietin on non-erytrhocytic cells are mediated by a heterodimeric receptor consisting of one Epo-R molecule in complex with a dimer of the common cytokine β receptor (β CR).The Epo-R/ βCR concept is mainly based on the observation that erythropoietically inactive erythropoietin derivatives and analogues provide tissue protection in animal models (Leist et al.,2004).

Molecular mechanism of erythropoietin synthesis by hypoxia

The mechanisms of the renal and hepatic erythropoietin expression differ.Renal cells respond in all-or- nothing fashion to hypoxia (Koury et al.,1989),whereas hepatoma cells respond in a graded way.The hypoxia-response elements (HREs) in control of the erythropoietin gene are located upstream in the kidney but downstream in the liver as opined by Kochling et al.,1998).The erythropoietin promoter is suppressed by GATA-2 in normoxia (Tsuchiya et al.,1997).GATA-2 levels decrease in hypoxia (Imagawa et al.,2003).Erythropoietin enhancer is activated by hypoxia-inducible transcription factors(HIFs).These are composed of an O_2-labile α-subunit(120KDA;Isoforms 1 α,2 α or 3 α) and a constitutive β-subunit (90-95Kda)(Warnecke et al.,2004;Haase,2010).HIF-2 α is activated by the stress-responsive deacetylase sirtuin 1 (Dioum et al.,2009).Interestingly,hepatocyte-derived HIF-2 is also involved in the regulation of iron metabolism genes,supporting a role for HIF-2 in the coordination of erythropoietin synthesis with iron homeostasis (Kapitsinou et al.,2010).HIFs cooperate with hepatocyte nuclear factor 4 (HNF-4) and the transcriptional co-activators P300 and cAMP response elemnt-binding protein (CREB)-binding protein (CBP)(Bunn et al.,1998).

The C-terminus of the HIF- α subunits comprises O_2-dependent degradation domains(O-DDD) that are proply hydroxylated in the presence of O_2(Epstein et al.,2001;Ivan et al.,2001;Yu et al.,2001;Jacakkola et al.,2001;Bruick and McKnight,2001).The reaction is catalysed by specific Fe^{2+}-containing propyl-4-hydroxylase (PHD-1,-2,and -3),which transfer one O-atom to the proline and the other to 2-oxoglutarate yielding CO_2 and succinate (Bruegge et al.,2007).The propyl hydoxylated HIF- α combines with Von Hippel-Lindau tumour suppressor protein (VHL)/E3 ligase and promptly undergoes proteosomal degradation (Huang et al.,1998;Maxwell et al.,1999).As PHD-2 and PHD-3 are themselves HIF-target genes,their expression increases and HIF- α levels decline during lon-term hypoxic periods (del Peso et al.,2003;Marxsen et al., 2004;Aprelikova et al.,2004;Stiehl et al.,2006).The transcriptional activity of the HIFs is suppressed by HIF- α asparingyl hydroxylation,which prevents the binding of the transcriptional co-activator CBP/P300.The reaction is catalysed by the factor inhibiting HIF-1(Maho et al.,2001;McNeill et al.,2002),another Fe^{2+} is required for HIF- α degradation may provide an expalnation for the incraesed plasma Epo level in patients traeted with the iron chelator deferoxamine (Kling et al., 1996).Cobalt is thought to enhance Epo expression by replacing the essential Fe^{2+} in the HIF-αdioxygenases,which results in HIF- α stabilisation.2-oxoglutarate competitors likewise inhibit the hydoxylation of HIF- α.

Systemic erythropoietin response

The major roles of erythropoietin emoglobin are to keep red blood cell mass and haemoglobin constant day by day,and to hasten red blood cell recovery after

haemorrhage.The basal plasma concentration of Epo ranges from 6 to 32 iu/l.The levels vary graetly between individuals,with the result that significant sex or age –specific differences cannot be detected.Of note is the diurnal fluctuation,with a nadir in the morning.The response is dynamic,with initially very high Epo values that drop towards the normal ones before haemoglobin normalises.The mechanism of rapid decrease may in part be caused by lowered HIF-α levels during long-term hypoxia (Stiehl et al.,2006).Epo level is not only dependent on the rate of Epo production,but also on its removal.In vitro studies have demontrated that Epo is internalised and degraded by its target cells(Gross and Lodish,2006).Anaemic patients with bone marrow hypoxia exhibit extremely high plasma Epo level(10,000 iu/l or more) compared with subjects suffering from haemolytic anaemia.

Because Epo production depends on the tissue PO_2 declines or when the O_2 affinity of the blood increases.On ascent to altitude,Epo levels reach peak values after 1-2 days and then fall to a new plateau at about twice that present at sea level 9Abbrecht and Littell,1972).

Role of angiotensin II

The signal to produce more erythrocytes following haemorrhage is apparently linked to the signals to retain salt and water by means of the renin-angiotensin sysytem (Dunn et al.,2007).Angiotensin ii(Ang ii) is thought to stimulate erythropoiesis by two means.First,Ang ii increases Epo production.Second,Ang ii is a growth factor for the myeloid erythrocytic progenitors(Dunn et al.,2007;Vlahakos et al.,2010).The infusion of Ang ii has been shown to riase the plasma Epo level to 17 iu/l in healthy men (Glossman et al.,2001).

A feedback regulation of red cell mass and blood volume by means of Epo and Ang ii seems to exist.Treatment of healthy men with recombinant human Epo (rhEpo) produces an incraese in red cell mass.However,the incraese in haematocrit (HctI is accompanied by a decraese in plasma volume,which is probably due to a down-regulation of the renin-angiotensin-aldesterone system and results in a constancy of the blood volume.Thus,Epo treatment in healthy humans raises haemoglobin by two mechanisms:an incraese in red cell mass,and a decrease in plasma volume (Lundby et al.,2007).

Conclusion

Erythropoietin (Epo) is a glycoprotein hormone that regulates erythropoiesis and other nonhaematopoietic functions.It is mainly produced in the intersitial fibroblasts of renal cortex in adults and in the liver cells in the foetus.It performs its functions by binding to erythropoietin receptor (Epo-R) which induces the expression of hypoxia-inducible factor (HIF) which regulates the synthesis of erythrocytes.Erythropoietin can be used in the traetment of anaemia and will reduce the rate of blood transfusion among patients.The kidneys should be properly cared to ensure the continual sustenance of the tissues where the erythropoietin for the up keep of the human system.

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