Published in final edited form as:
Prog Neurobiol. 2008 June ; 85(2): 194–213.

ERYTHROPOIETIN: ELUCIDATING NEW CELLULAR TARGETS THAT BROADEN THERAPEUTIC STRATEGIES

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Abstract

Given that erythropoietin (EPO) is no longer believed to have exclusive biological activity in the hematopoietic system, EPO is now considered to have applicability in a variety of nervous system disorders that can overlap with vascular disease, metabolic impairments, and immune system function. As a result, EPO may offer efficacy for a broad number of disorders that involve Alzheimer's disease, cardiac insufficiency, stroke, trauma, and diabetic complications. During a number of clinical conditions, EPO is robust and can prevent metabolic compromise, neuronal and vascular degeneration, and inflammatory cell activation. Yet, use of EPO is not without its considerations especially in light of frequent concerns that may compromise clinical care. Recent work has elucidated a number of novel cellular pathways governed by EPO that can open new avenues to avert deleterious effects of this agent and offer previously unrecognized perspectives for therapeutic strategies. Obtaining greater insight into the role of EPO in the nervous system and elucidating its unique cellular pathways may provide greater cellular viability not only in the nervous system but also throughout the body.

Keywords

Alzheimer's disease; Akt; angiogenesis; apoptosis; cancer; cardiac; caspases; diabetes; endothelial; erythropoietin; forkhead; GSK-3β; inflammation; microglia; mitochondria; neurodegeneration; NF-κB; renal; STATs; Wnt

1. Introduction

1.1 Historical Perspective of Hormones

"These chemical messengers, however, or hormones, as we might call them, have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream and the continually recurring physiological needs of the organism must determine their repeated production and circulation throughout the body" (Starling, 1905). As part of his second Croonian lecture to the Royal College of Surgeons in 1905 entitled "The chemical

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control of the functions of the body," Ernest Starling unexpectedly to the audience introduces the term "hormones" that was initially derived from the Greek term "excite" or "arouse." He used this term to describe chemicals that can be set into action in the blood stream to elicit activity in different organs of the body (Maiese, 2007). How Starling selected the term "hormone" has many historical versions and the reasons that prompted him to present the term during this particular lecture may never be known, but the most accurate accounts appear to describe his conversations with William Hardy and the Greek poet scholar W. T. Vesey. These meetings sometimes focused upon the Greek verb "ormao" for "arouse" or "excite" (Henderson, 2005; Tata, 2005).

Although prior to this point the use of the term "hormone" in the scientific literature was considered to be minimal at best, early work during the mid-nineteenth century, such as by Claude Bernard, depicted processes responsible for internal secretion of chemicals as described with the release of glucose from glycogen in the liver (Bernard, 1855). During this period, other pioneers such as Arnold Adolphe Berthold spoke of the interaction and communication between the different organs in the body. As these concepts became more accepted, physicians later in the nineteenth century reported the use of extracts of animal thyroid, pancreas, and even adrenal glands to treat patients suspected of suffering from the loss of circulating chemicals.

By the early twentieth century, Starling and William Bayliss demonstrated that the duodenum, when stimulated with acid through local application, could lead to pancreatic secretion (Bayliss and Starling, 1901). They furthered these results by illustrating that duodenal extracts injected into the blood stream in animals also resulted in pancreatic secretion (Bayliss and Starling, 1902). From these studies, Starling and Bayliss suggested that the agent released from the duodenum should be termed "secretin." The Nobel Laureate Pavlov was initially impressed with these results that had suggested the presence of several mechanisms in the control of the digestive system, but later stood firm to promote his personal concepts that pancreatic secretion and the organs of the gut were controlled principally by innervation of the nervous system during his acceptance of the Nobel Peace Prize for his work in 1904 (Pavlov, 1904).

In spite of the political undercurrents, subsequent investigations in endocrinology and the study of hormones have fostered the development of numerous fields that involve vascular biology, neuroscience, physiology, genetics, metabolomics, development, cancer, and molecular medicine. Clinically, the advances from these fields that rely upon the understanding of the chemistry of hormones have resulted in remarkable strides for treatment protocols that involve the care and management of diabetes, the replenishment of hormone deficiencies, the success of fertility treatments that utilize *in vitro* fertilization, and the treatment of disorders associated with anemia.

1.2 The Discovery of Erythropoietin (EPO)

The initial studies by pioneers such as Starling, Bernard, Berthold, and Bayliss have led us to remarkable advances in clinical medicine and exposed us to the novel and protean effects that agents functioning as hormones can impart upon the body. Our progressive knowledge of the cellular and molecular processes that involve these agents have alerted us to the intimate relationship that exists between the intricate cellular systems and organs of the body that may be "aroused" or "excited" by a single agent. These discoveries bring us to the novel discussion of the hormone, growth factor, and cytokine termed erythropoietin (EPO).

First presented as "hemopoietine," EPO became known as a factor that could stimulate new red blood cell development through the pioneering work of Carnot and Deflandre in 1906 (Carnot and DeFlandre, 1906; Fisher, 2003). These investigators demonstrated that plasma removed from rabbits following a bleeding stimulus that was later injected into control

untreated rabbits would lead to the development of immature red blood cells. A number of other investigations followed these studies, which showed similar findings demonstrating that plasma from bled animals would yield a significant reticulocytosis (Erslev, 1974; Gibelli, 1911; Sandor, 1932). More elegant experiments subsequently demonstrated that a rise in hemoglobin levels with reticulocytosis occurred in parabiotic rats when only one partner was exposed to hypoxia, illustrating that depressed oxygen tensions could stimulate EPO production (Reissmann, 1950). Later, human EPO protein was purified, which paved the way for the cloning of the EPO gene and the development of recombinant EPO for clinical use (Jacobs et al., 1985; Lin et al., 1985).

2. Structural and Molecular Determinants of EPO Activity

EPO is a 30.4 kDa glycoprotein with approximately half of its molecular weight derived from carbohydrates that can vary among species (Maiese et al., 2005c). EPO contains four glycosylated chains including three *N*-linked and one *O*-linked acidic oligosaccharide side chains. *N*-linked glycosylation sites occur at the positions 24, 38, and 83 of aspartyl residues, while the *O*-linked glycosylation site is at Serine^{126}. Three *N*-glycan chains of human EPO consist of the tetra-antennary structure with or without N-acetyllactosamine repeating units (Tsuda et al., 1988). The *O*-linked sugar chain is composed of Gal-GalNAc and sialic acids (Sasaki et al., 1987). The production and secretion of the mature EPO also relies upon the integrity of the *N*- and *O*-linked chains. The EPO gene is located on chromosome 7, exists as a single copy in a 5.4 kb region of the genomic DNA, and encodes a polypeptide chain containing 193 amino acids (Jacobs et al., 1985). During the production and secretion of EPO, a 166 amino acid peptide is initially generated following the cleavage of a 27 amino acid hydrophobic secretory leader at the amino-terminal (Imai et al., 1990). In addition, a carboxy-terminal arginine in position 166 is removed both in the mature human and recombinant human EPO (rhEPO) resulting in a circulatory mature protein of 165 amino acids (Chong et al., 2002a).

The glycosylated chains are important for the biological activity of EPO and can protect EPO from oxygen radical degradation. EPO is stabilized by the carbohydrate chains (Toyoda et al., 2000) and the oligosaccharides in EPO may protect the protein from oxygen radical activity (Uchida et al., 1997). The N-glycosylated chains are believed to contribute to the thermal stability of EPO (Tsuda et al., 1988). In addition, the *N*- and *O*-linked chains may be necessary for the production and secretion of the mature EPO (Krantz, 1991). Replacement of asparagines 38 and 83 by glutamate or serine 126 by glycine can decrease the production and secretion of EPO (Dube et al., 1988). The presence of the carbohydrates also are important in the control of the metabolism of EPO, since EPO molecules with high sialic acid content can be easily cleared by the body through specific binding in the liver (Tsuda et al., 1990).

In addition, the biological activity of EPO also relies upon two disulfide bonds formed between cysteines at positions 7 and 160 and at positions 29 and 33 (Li et al., 2004a). The requirement of these disulfide bridges has been demonstrated by the evidence that reduction of these bonds results in the loss of the biologic activity of EPO. Alkylation of the sulfhydryl groups results in irreversible loss of the biological activity of EPO. Re-oxidization of EPO after reduction by guanidine restores eighty-five percent of the biological activity of EPO (Wang et al., 1985). Cysteine 33 replacement with proline also reduces the biological function of EPO.

3. Expression and Signal Transduction for EPO and its Receptor

3.1 Cellular Expression of EPO

EPO can be detected in the breath of healthy individuals (Schumann et al., 2006), suggesting its ubiquitous presence in the body (Maiese et al., 2007a; Maiese et al., 2007c). In addition, it

has been suggested that EPO may provide developmental cognitive support in humans with the recent observations that elevated EPO concentrations during infant maturation have been correlated with increased Mental Development Index scores (Bierer et al., 2006). The primary organs of EPO production and secretion are the kidney, liver, brain, and uterus. EPO production and secretion occurs foremost in the kidney (Fliser and Haller, 2007). The kidney peritubular interstitial cells are responsible for the production and secretion of EPO (Fisher, 2003). With the use of cDNA probes derived from the EPO gene, peritubular endothelial cells (ECs), tubular epithelial cells, and nephron segments in the kidney also have been demonstrated to be vital cells for the production and secretion of EPO (Lacombe et al., 1991; Mujais et al., 1999). During periods of acute renal failure, EPO may provide assistance for the protection of nephrons (Sharples et al., 2005; Sharples and Yaqoob, 2006).

Secondary sites of EPO production and secretion occur in the liver and the uterus (Chong et al., 2002a). Hepatocytes, hepatoma cells, and Kupffer cells of the liver can produce EPO (Fisher, 2003) and, in turn, EPO may provide a protective environment for these cells (Schmeding et al., 2007). In regards to the uterine production of EPO, it is believed that the occurrence of neonatal anemia that can take place in the early weeks after birth may partly result from the loss of EPO production and secretion by placenta (Davis et al., 2003).

EPO is approved by the Food and Drug Administration for the treatment of anemia, but a body of recent work has revealed that EPO is not only required for erythropoiesis, but also functions in other organs and tissues, such as the brain, heart, and vascular system (Chong et al., 2002b; 2003b; Chong and Maiese, 2007a; Mikati et al., 2007; Moon et al., 2006; Um et al., 2007). It is the discovery of EPO and its receptor in the nervous and vascular systems that has resulted in a heightened level of interest and enthusiasm for the potential clinical applications of EPO, such as in Alzheimer's disease, cardiac insufficiency (Assaraf et al., 2007; Palazzuoli et al., 2006), and cardiac transplantation (Gleissner et al., 2006; Mocini et al., 2007). In the nervous system, the major sites of EPO production and secretion are in the hippocampus, internal capsule, cortex, midbrain, cerebral ECs, and astrocytes(Digicaylioglu et al., 2004; Genc et al., 2004; Maiese et al., 2004; 2005c). Further work has revealed several other organs as secretory tissues for EPO that include peripheral ECs (Anagnostou et al., 1994), myoblasts (Ogilvie et al., 2000), insulin-producing cells (Fenjves et al., 2003), and cardiac tissue (Fliser and Haller, 2007; Maiese et al., 2005c).

3.2 Signal Transduction of EPO and the EPO receptor

After the EPO gene was cloned (Jacobs et al., 1985; Lin et al., 1985), work was initiated to identify a receptor for EPO. The EPO receptor (EPOR) was found to be expressed in both normal and transformed erythroid cells (D'Andrea and Zon, 1990). The EPOR is part of the type 1 super-family of cytokine receptors and is activated via homodimerization (Bazan, 1990; Watowich et al., 1994). This receptor family shares a common domain structure consisting of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain. The extracellular domain is necessary for the initial binding of EPO and the intracellular domain is responsible for the transduction of intracellular signaling (Mulcahy, 2001).

EPO regulates bone marrow erythroid cell proliferation, differentiation, and survival through its binding to an erythroid progenitor cell surface EPOR. The EPOR also is expressed in numerous non-erythroid blood lines, which include neurons, microglia, astrocytes, and in cerebral ECs (Anagnostou et al., 1994; Fliser and Haller, 2007; Genc et al., 2004; Maiese et al., 2004; 2005c) as well as on myelin sheaths of radicular nerves in human peripheral nerves (Hassan et al., 2004), suggesting both a developmental and potential protective role for EPO in the central and peripheral nervous systems. The EPOR also is expressed in primary cerebral

ECs (Chong et al., 2003a; c) as well as in human umbilical veins, bovine adrenal capillaries, and rat brain capillaries (Anagnostou et al., 1994; Yamaji et al., 1996).

During the development of an organism, production of EPO and the expression of its receptor are altered. Elevated expression of the EPOR occurs in early embryonic neuronal tissues at levels similar to that observed in the adult spleen and bone marrow (Liu et al., 1994). Yet, the level of endogenous EPOR expression is significantly reduced following the maturation of the brain (Liu et al., 1997). During gestation, EPO production is increased, but later becomes suppressed following birth to be regulated by the tissue oxygen supply (Chong et al., 2002c). A deficiency in tissue oxygen results in the production of EPO and an increase in the expression of the EPOR not only in peripheral organs (Fliser and Haller, 2007; Li et al., 2004a; Maiese et al., 2004; 2005c) but also in the brain (Li et al., 2007a), which may be responsible for hypoxic tolerance in some species (Ravid et al., 2007). EPO secretion in the brain appears to be more sustained than in peripheral organs such as the kidney (Chikuma et al., 2000), suggesting that EPO production may originate in the brain and possibly cross the blood-brain barrier to reach the blood and peripheral organs (Li et al., 2004a). Work performed *in vivo* with subjects exposed to hypoxia also demonstrates an increase in expression of EPO and EPOR mRNA following reduced oxygenation (Marti et al., 1996). Furthermore, both primary neurons (Chikuma et al., 2000; Liu et al., 2006) and neuronal cell lines (Stolze et al., 2002) have been found to retain the capacity to express EPO in an oxygen-dependent manner.

Although EPO is recognized as a critical modulator of erythropoiesis, a low concentration of red blood cells alone does not directly stimulate EPO production, but requires the presence of a diminished oxygen tension. Once a hypoxic stimulus is received, EPO is subsequently released into the peripheral blood circulation, and upon arrival in the bone marrow, EPO binds to its receptor that is highly expressed on the surface of erythroid progenitor cells and leads to erythropoiesis (Broudy et al., 1991). This results in an elevation in the number of mature erythrocytes and the improvement of oxygen supply. EPO also functions to stimulate colony-forming erythroid cells to induce these cells to proliferate, mature into erythrocytes, and possibly assist with reticulocyte release to the blood (Sathyanarayana et al., 2007).

Hypoxia-dependent expression of EPO and EPOR are controlled by hypoxia-inducible factor 1 (HIF-1) in both vascular and neuronal systems. HIF-1 is essential for the production and secretion of EPO in response to hypoxia (Ikeda, 2005). At the transcriptional level, the hypoxia-dependent gene transcription of EPO and EPOR directly results from the activation of the HIF-1 pathway under hypoxic conditions. Gene transcription of EPO is mediated by the transcription enhancer located in the 3′-flanking region of the EPO gene that specifically binds to HIF-1 (Wang and Semenza, 1995).

HIF-1 is a basic helix-loop-helix heterodimeric transcription factor containing two subunits, HIF-1α and HIF-1β. HIF-1β is a constitutively expressed 91-94 kDa subunit that was characterized previously as aryl hydrocarbon receptor nuclear translocator (ARNT) (Hoffman et al., 1991). HIF-1α is a 120 kDa oxygen-labile subunit that is degraded through the ubiquitin-proteasome pathway under normoxic conditions (Huang et al., 1998). During hypoxia or conditions such as iron chelation that can mimic hypoxia, degradation of HIF-1α is impaired by blocking its association with von Hippel-Lindau protein that targets HIF-1α for proteasome destruction (Maxwell et al., 1999). HIF-1α subsequently translocates to the nucleus and heterodimerizes with HIF-1β to form a stable HIF-1 complex. The HIF complex then binds to the conserved sequence (5′RCGTG3′) near the 5′ end of the hypoxia-responsive enhancer of the EPO gene to up-regulate EPO gene transcription (Bunn et al., 1998). Increased DNA binding activity of HIF-1 occurs in rat cortical neurons during oxidative stress, suggesting that HIF-1 may function as oxygen sensor regulating adaptive gene transcription and resulting in the production and secretion of the EPO protein during hypoxia in the nervous system (Maiese

et al., 2004; 2005c). It is important to note that each of the HIF family members HIF-1α, HIF-1β, and HIF-3α plays important roles in regulating the expression of EPO and the EPOR to foster protection against hypoxic cell injury (Heidbreder et al., 2003).

Hypoxia is not the only factor responsible for the expression of EPO and the EPOR. The production and secretion of EPO in female reproductive organs is estrogen-dependent. During the cyclic development of the uterine endometrium, 17β-estradiol can lead to a rapid and transient increase in EPO mRNA in the uterus (Yasuda et al., 1998), oviducts, and ovaries (Masuda et al., 2000). Hypoxic induced EPO mRNA expression in uterine tissue occurs only in the presence of 17β-estradiol. EPO mRNA expression by hypoxia in the uterus is less pronounced than the EPO expression that occurs in the kidney and the brain (Chikuma et al., 2000). Interestingly, a variety of cellular disturbances may lead to either increased or decreased EPO expression through the control of HIF, such as hypoglycemia, cadmium exposure, raised intracellular calcium, or intense neuronal depolarizations generated by mitochondrial reactive oxygen species (Chong et al., 2002c; Genc et al., 2004; Obara et al., 2003). Anemic stress, insulin release, and several cytokines, including insulin-like growth factor, tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) (Nagai et al., 2001), also can lead to increased expression of EPO and the EPOR (Maiese et al., 2004; 2005c).

4. The Impact of EPO Upon Cellular Metabolism, Survival, and Proliferation

4.1 EPO and Cellular Metabolism

In both clinical and basic experimental studies, EPO has been intimately associated with the modulation of cellular metabolism. When one considers cellular dysfunction in relation to cellular metabolism, diabetes mellitus (DM) comes to mind since it represents a significant health concern in the clinical population (Maiese et al., 2007a). DM occurs in at least 16 million individuals in the United States and more than 165 million individuals worldwide (Quinn, 2001). Furthermore, by the year 2030, it is predicted that more than 360 million individuals will be afflicted with DM and its debilitating conditions (Wild et al., 2004). Type 2 DM represents at least 80 percent of all diabetics and is dramatically increasing in incidence as a result of changes in human behavior and increased body mass index (Laakso, 2001). Type 1 insulin-dependent diabetes mellitus accounts for only 5–10 percent of all diabetics (Maiese et al., 2007c), but is increasing in adolescent minority groups (Dabelea et al., 2007). Yet, the incidence of undiagnosed diabetes, impaired glucose tolerance, and fluctuations in serum glucose in the young raises further concerns (Jacobson et al., 2007). Individuals with impaired glucose tolerance have greater than two times the risk for the development of diabetic complications than individuals with normal glucose tolerance (Harris and Eastman, 2000). Healthcare costs for diabetic complications are a significant driver for government resource consumption with costs of $214.8 million for outpatient expenditures and $1.45 billion for inpatient expenditures (Maciejewski and Maynard, 2004). If one examines cognitive impairments resulting from diabetes in the general population that can mimic Alzheimer's disease (Chong et al., 2005f), annual costs equal $100 billion (Maiese and Chong, 2004; McCormick et al., 2001; Mendiondo et al., 2001).

Both type 1 and type 2 DM represent important health concerns whether they begin early or later in life (Maiese et al., 2007a), since each can result in long-term complications throughout the body (Daneman, 2006). In regards to the vascular and nervous systems, patients with DM can develop severe neurological and vascular disease (Donahoe et al., 2007) that can lead to an increased risk for cognitive decline especially from vascular disease (Chong et al., 2005e; Li et al., 2006a; Schnaider Beeri et al., 2004). Disease of the nervous system can become the most debilitating complication for DM and affect sensitive cognitive regions of the brain, such as the hippocampus, which modulates memory function, resulting in significant functional impairment and dementia (Awad et al., 2004; Gerozissis, 2003). DM also has been found to

increase the risk for vascular dementia in elderly subjects (Schnaider Beeri et al., 2004; Xu et al., 2004). DM also may affect the course of Alzheimer's disease. Although some studies have found that diabetic patients may have less neuritic plaques and neurofibrillary tangles than non-diabetic patients (Beeri et al., 2005), contrasting work suggests a modest adjusted relative risk of Alzheimer's disease in patients with diabetes as compared with those without diabetes to be 1.3 (Luchsinger et al., 2001).

Closely tied to the development of insulin resistance and the complications of DM in the nervous and vascular systems is the presence of cellular oxidative stress and the release of reactive oxygen species (Maiese et al., 2007c). In patients with DM, elevated levels of ceruloplasmin are suggestive of increased reactive oxygen species (Memisogullari and Bakan, 2004), and acute glucose fluctuations may promote oxidative stress (Monnier et al., 2006). Hyperglycemia can lead to increased production of reactive oxygen species in endothelial cells, liver and pancreatic β-cells (Ceriello et al., 1996; Ihara et al., 1999; Ling et al., 2003; Yano et al., 2004). Prolonged duration of hyperglycemia is not necessary to lead to oxidative stress injury, since even short periods of hyperglycemia generate reactive oxygen species, such as in vascular cells (Yano et al., 2004). Recent clinical correlates support these experimental studies to show that acute glucose swings in addition to chronic hyperglycemia can trigger oxidative stress mechanisms during type 2 DM, illustrating the importance for therapeutic interventions during acute and sustained hyperglycemic episodes (Monnier et al., 2006).

The preservation of cellular energy reserves is dependent upon the maintenance of mitochondrial integrity during DM (Newsholme et al., 2007). For example, free fatty acids, which can lead to reactive oxygen species, have been shown to also contribute to mitochondrial DNA damage and impaired pancreatic β-cell function (Rachek et al., 2006). In patients with type 2 DM, skeletal muscle mitochondria have been described to be smaller than those in control subjects (Kelley et al., 2002). Furthermore, a decrease in the levels of mitochondrial proteins and mitochondrial DNA in adipocytes has been correlated with the development of type 2 DM (Choo et al., 2006). Insulin resistance in the elderly also has been associated with elevation in fat accumulation and reduction in mitochondrial oxidative and phosphorylation activity (Petersen et al., 2003). In addition, an association exists with insulin resistance and the impairment of intramyocellular fatty acid metabolism in young insulin-resistance offspring of parents with type 2 DM (Petersen et al., 2004).

Given that administration of antioxidants during elevated glucose concentrations can block free radical production and prevent the production of advanced glycation endproducts (AGEs) known to produce reactive oxygen species during DM (Giardino et al., 1996), EPO may offer an attractive alternative therapy to maintain proper cellular metabolism and mitochondrial membrane potential during DM (Table 1). In clinical studies with DM, plasma EPO is often low in diabetic patients with anemia (Mojiminiyi et al., 2006) or without anemia (Symeonidis et al., 2006). Furthermore, the failure of these individuals to produce EPO in response to a declining hemoglobin level suggests an impaired EPO response in diabetic patients (Thomas et al., 2005). Yet, increased EPO secretion during diabetic pregnancies may represent the body's attempt at endogenous protection against the complications of DM (Teramo et al., 2004). Similar to the potential protective role of insulin (Duarte et al., 2006), EPO administration has been shown both in diabetics as well as non-diabetics with severe, resistant congestive heart failure to decrease fatigue, increase left ventricular ejection fraction, and significantly decrease the number of hospitalization days (Silverberg et al., 2006). *In vitro* studies with vascular cells exposed to elevated glucose also have elucidated a strong cytoprotective effect of EPO. Administration of EPO can significantly improve EC survival in a 1.0 ng/ml range (Chong et al., 2007c). EPO administration in patients also can significantly increase plasma levels of EPO well above this range of 1.0 ng/ml that has been associated with potential EPO cellular protection in patients with cardiac or renal disease (Mason-Garcia et

al., 1990; Namiuchi et al., 2005), suggesting that the effects of EPO observed during *in vitro* studies may parallel the cellular processes altered by EPO in patients with DM (Bierer et al., 2006). Furthermore, EPO can block apoptotic DNA degradation in ECs during elevated glucose similar to other models of oxidative stress in cardiac and vascular cell models (Avasarala and Konduru, 2005; Chong et al., 2002b; 2003a; Chong and Maiese, 2007a; Moon et al., 2006).

Cytoprotection by EPO also is related to the maintenance of mitochondrial membrane potential ($\Delta\Psi_m$). Loss of $\Delta\Psi_m$ through the opening of the mitochondrial permeability transition pore represents a significant determinant for cell injury and the subsequent induction of apoptosis (Leuner et al., 2007; Maiese and Chong, 2004). EPO has the capacity to prevent the depolarization of the mitochondrial membrane that also affects the release of cytochrome c (Chong et al., 2002b; Chong et al., 2003e; Miki et al., 2006).

4.2 EPO and Neurodegeneration

As a robust cytoprotectant, EPO can enhance the survival of cells during several types of injury models in the nervous system (Lykissas et al., 2007; Maiese et al., 2004; 2005c). In cells that involve the brain or the retina, EPO can prevent injury from hypoxic ischemia (Chong et al., 2002b; 2003b; Liu et al., 2006; Meloni et al., 2006; Wei et al., 2006; Yu et al., 2005), excitotoxicity (Montero et al., 2007; Yamasaki et al., 2005), infection (Kaiser et al., 2006), free radical exposure (Chong et al., 2003a; Chong et al., 2003e; Yamasaki et al., 2005), staurosporine (Pregi et al., 2006), and dopaminergic cell injury (Demers et al., 2005; McLeod et al., 2006; Signore et al., 2006). In addition, administration of EPO also represents a viable option for the prevention of retinal cell injury during glutamate toxicity (Zhong et al., 2007) and glaucoma (Tsai et al., 2007). Systemic application of EPO also can improve functional outcome and reduce cell loss during spinal cord injury (King et al., 2007; Okutan et al., 2007), traumatic cerebral edema (Verdonck et al., 2007), cortical trauma (Cherian et al., 2007), and epileptic activity (Mikati et al., 2007; Nadam et al., 2007).

Interestingly, EPO may provide hope for individuals that suffer from cognitive disability, such as memory loss or psychiatric illness (Chong et al., 2005c; f; Ehrenreich et al., 2007; Pacary et al., 2006). In animal studies, EPO has been shown to reduce cognitive loss during mechanical injury to the hippocampus (Mala et al., 2005). As a result, Alzheimer's disease has become a prime consideration for the applications of EPO. Alzheimer's disease leads to a progressive deterioration of cognitive function with memory loss and injury to hippocampal neurons. The generation of extracellular plaques of amyloid-β peptide aggregates composed of a 39–42 amino acid peptide (Aβ) is considered to be one of the pathological mechanisms that may promote the development of Alzheimer's disease (Chong et al., 2005f). Accumulation of Aβ can lead to apoptotic injury with chromatin condensation, DNA fragmentation, and cellular membrane PS exposure (Chong et al., 2005c; f). Aβ also can release reactive oxygen species and lead to toxicity in neurons. In addition, Aβ can not only precipitate a significant inflammatory response with microglial activation and the secretion of TNF-α (Bornemann et al., 2001), but also Aβ can elicit the neuronal expression of inducible nitric oxide synthase, peroxinitrite production, and neuronal apoptosis during an acute inflammatory response (Chong et al., 2005e; Combs et al., 2001). Furthermore, Aβ may lead to the induction of caspase mediated pathways (Nakagawa et al., 2000; Troy et al., 2001) that work in concert with oxidative stress (Tamagno et al., 2003). As a result, therapeutic strategies that address the toxicity of Aβ as a result of oxidative stress may foster novel developments for the treatment of Alzheimer's disease. EPO appears to be both necessary and sufficient to protect neurons from Aβ toxicity. For example, application of a blocking antibody of EPO, which can bind to EPO and block its biological activities in cells (Koshimura et al., 1999), can otherwise negate the protective effects of EPO to increase neuronal hippocampal cell survival and prevent apoptotic injury during Aβ exposure (Chong et al., 2005d).

In direct relation to the potential protective cognitive effects of EPO, enhanced survival by EPO also extends to afford protection of the neurovascular unit during cerebral vascular disease (Demers et al., 2005; Dzietko et al., 2004; Maiese et al., 2004; Wei et al., 2006). In addition, EPO can protect sensitive hippocampal neurons from both focal and global ischemic brain injury (Keogh et al., 2007; Wei et al., 2006; Yu et al., 2005; Zhang et al., 2006). Systemic administration of EPO also represents a viable option for several other disorders. EPO administration for retinal cell injury can protect retinal ganglion cells from apoptosis (Grimm et al., 2002), EPO can improve functional outcome and reduce lipid peroxidation during spinal cord injury (Kaptanoglu et al., 2004), and EPO can maintain autoregulation of cerebral blood flow, reverse basilar artery vasoconstriction, and enhance neuronal survival and functional recovery following subarachnoid hemorrhage (Olsen, 2003).

4.3 EPO and Inflammatory Cell Activation

Of equal importance to the functional preservation of cells is the role of EPO during cellular inflammation. In particular, one can consider the role of microglia in the brain that can lead to the phagocytic removal of both neurons and vascular cells (Chong et al., 2005a; Chong et al., 2004a; Kang et al., 2003b). During inflammation, microglial cells require the activation of intracellular cytoprotective pathways (Chong et al., 2007b; Li et al., 2006b) to proliferate and remove injured cells (Li et al., 2005; Mallat et al., 2005). Subsequently, microglia can form a barrier for the removal of foreign microorganisms from the central nervous system and promote tissue repair during neuronal and vascular cell injury (Chong et al., 2007b; Dringen, 2005). Yet, microglia also may lead to cellular damage through the generation of reactive oxygen species (Maiese and Chong, 2004; Sankarapandi et al., 1998) and through the production of cytokines (Benzing et al., 1999; Mehlhorn et al., 2000). Furthermore, microglial activation has been correlated with several neurodegenerative disorders, such as Alzheimer's disease with the co-localization of microglia and amyloid plaque development (Sheng et al., 1997).

Given the impact that inflammatory cells, such as microglia, may have upon the progression or resolution of degenerative insults throughout the body, it becomes essential to consider agents that can control inflammatory pathways. To this end, cytoprotective agents that are known to modulate inflammatory cell function may offer attractive therapeutic considerations. EPO appears to fill such a need in regards to its role during periods of cellular inflammation. EPO can reduce cytokine gene expression in endothelial cells exposed to tumor necrosis factor (Avasarala and Konduru, 2005), prevent ulcer progression in cases of scleroderma (Ferri et al., 2007), and block primary microglial activation and proliferation during oxidative stress (Chong et al., 2003b; Chong et al., 2005d) (Figure 1). Furthermore, EPO can block microglial cell activation and proliferation to prevent phagocytosis of injured cells through pathways that involve cellular membrane PS exposure, protein kinase B (Chong et al., 2004a), and the regulation of caspases (Chong et al., 2003a; b; Wu et al., 2007a). EPO can directly inhibit several pro-inflammatory cytokines, such as IL-6, TNF-α, and monocyte chemoattractant protein 1 (Li et al., 2004a; Maiese et al., 2005c), as well as reduce leukocyte inflammation (Contaldo et al., 2007). In addition, EPO may foster the preservation of microglial cells for neuronal and vascular restructuring by preventing apoptotic injury in microglia (Li et al., 2006b; Vairano et al., 2002). In regard to the capacity of EPO to maintain microglial cellular integrity, EPO retains its capacity to prevent early apoptotic injury with membrane PS externalization as well as later stages of apoptotic injury involving DNA fragmentation in microglia (Li et al., 2006b) similar to other cell systems of neurovascular origin (Chong et al., 2002b; 2003b; Chong et al., 2005d; Parsa et al., 2003; Sharples et al., 2004).

4.4 EPO and Cardiovascular-Renal Protection

Clinical studies have suggested an important role for EPO in the cardiovascular system (Maiese et al., 2004; 2005c) and in the renal system (Sharples and Yaqoob, 2006) that ultimately can

affect the function and integrity of the nervous system. For example, in patients with anemia EPO administration can increase left ventricular ejection fraction and stroke volume (Goldberg et al., 1992). This work has been followed by randomized control studies with EPO administration in patients with congestive heart failure or diabetes combined with congestive heart failure that demonstrate improved cardiac output and a decrease in medical resource utilization (Silverberg et al., 2003). More recent studies have shown that patients with acute myocardial infarction have increased plasma EPO levels within seven days of the cardiac insult, suggesting a possible protective response from the body (Ferrario et al., 2007). In addition, EPO administration in patients with anemia and congestive heart failure can improve exercise tolerance, renal function, and left ventricular systolic function (Palazzuoli et al., 2006; Palazzuoli et al., 2007).

Randomized control studies with EPO administration in patients with congestive heart failure or diabetes combined with congestive heart failure also demonstrate an improved cardiac output and a decrease in medical resource utilization (Maiese et al., 2005c; Silverberg et al., 2006). Tightly integrated with cardiac performance, pulmonary function also is believed to be enhanced during EPO administration, especially in the setting of ischemic reperfusion injury of the lung (Wu et al., 2006). Serum levels of EPO also may function as a biomarker for cardiovascular injury (Fu and Van Eyk, 2006). Work from experimental studies illustrates that EPO plays a critical role in the vascular and renal systems with the maintenance of erythrocyte (Foller et al., 2007) and podocyte (Eto et al., 2007) integrity, regulates the survival of ECs (Chong et al., 2002b; 2003a), and may act as a powerful endogenous protectant during cardiac injury (Asaumi et al., 2007).

It is important to note that as a large molecule, EPO may maintain the establishment of EC communication and function, which could become crucial in a number of scenarios, such as repair of the blood-brain barrier during injury (Martinez-Estrada et al., 2003). In addition, by assuring EC integrity, EPO prevents ischemic cardiac demise by reducing myocardial injury and cardiomyocyte apoptosis (Burger et al., 2006), lessening myocardial ischemia (Bullard et al., 2005), modulating cardiac remodeling (Miki et al., 2006; Toma et al., 2007), reducing ventricular dysfunction (Parsa et al., 2004; Parsa et al., 2003), and improving cardiac function (Gao et al., 2007; Westenbrink et al., 2007). Overall, EPO can protect against myocardial cell apoptosis and decrease infarct size, resulting in improved left ventricular contractility. In isolated rat heart preparations following ischemia/reperfusion experiments, beneficial effects of treatment with EPO have been shown to significantly improve post-ischemic recovery of left ventricular pressure (Moon et al., 2003; van der Meer et al., 2004a). EPO treatment also can prevent myocardial cell apoptosis and decrease infarct size, resulting in enhanced cardiac function and recovery (Parsa et al., 2004). At the onset of coronary artery occlusion, EPO administered also can significantly inhibit apoptosis in the central region of myocardial ischemia (Tramontano et al., 2003). Even in acute scenarios following coronary artery ligation, EPO leads to a decrease in apoptotic cells by fifty percent in the myocardium and significantly improves cardiac function (Moon et al., 2003; Parsa et al., 2003).

Some of the results from experimental studies with EPO have correlated well with a number of positive clinical observations for EPO in cardiac patients. Clinical studies in patients with anemia or on chronic hemodialysis have indicated that administration of EPO can increase left ventricular ejection fraction, stroke volume, and cardiac output, suggesting improved cardiac function secondary to the correction of anemia (Maiese et al., 2004; 2005c; Silverberg et al., 2006). Other clinical randomized control studies in patients with mild anemia and severe or resistant congestive heart failure have demonstrated that EPO in combination with intravenous iron can lead to increased left ventricular ejection fraction and a reduction in hospitalization days by almost eighty percent (Silverberg et al., 2001). In addition to the correction of anemia, EPO can promote microvascular growth in the heart, suggesting that functional cardiac

recovery with EPO may ensue also from the generation of new blood vessels (Westenbrink et al., 2007).

4.5 EPO and Angiogenesis

In the vascular system, EPO not only offers direct preservation of EC integrity (Chong et al., 2002a; b; 2003a), but also promotes new capillary formation from pre-existing vessels into an avascular area, a process known as angiogenesis (Chong et al., 2002a). Angiogenesis is present during embryogenesis, during menstruation, and during pathological processes that involve wound healing, chronic inflammation, and tumor growth (Risau, 1997). EPO has both a mitogenic and chemotactic effect that can lead to matrix metalloproteinase-2 production, cell proliferation, and vessel formation in EC lines (Maiese et al., 2004; 2005c). In cultured human and bovine ECs, EPO stimulates EC proliferation and fosters the migration of ECs (Anagnostou et al., 1990). In neonatal mesenteric microvascular ECs, EPO also leads to vasculogenesis (Ashley et al., 2002). In clinical studies, EPO serum levels are significantly associated with the number and function of circulating endothelial progenitor cells and EPO can stimulate postnatal neovascularization by increasing endothelial progenitor cell mobilization from the bone marrow (Heeschen et al., 2003). Angiogenesis also has been observed in endothelial samples derived from human adult myocardial tissue following treatment with EPO (Jaquet et al., 2002). In addition, the uterine endometrium and the ovaries are dependent upon EPO for the induction of angiogenesis to compensate for lost vessels during the estrus cycle. EPO has been shown to be necessary to foster blood vessel formation in the endometrium in ovariectomized mice and to be required for the formation of a capillary network for the development of follicles and the corpora lutea (Yasuda et al., 1998).

Angiogenesis by EPO offers an additional level of cytoprotection in various cell systems. For example, in models of cerebral ischemia, EPO promotes factors for angiogenesis such as Tie-2 and Angiopoietin-2 that may assist with the restoration of cerebral blood flow to pre-ischemic levels (Li et al., 2007a). EPO controlled angiogenesis also may play a significant role during renal inflammation and prevention of allograft rejection (Reinders et al., 2006). In addition, EPO may promote the viability of transplanted marrow stromal cells and enhance capillary density during experimental cardiac ischemia (Zhang et al., 2007a). On the converse side, it also is vital to consider paradigms that require inhibition of angiogenesis. Although EPO induced angiogenesis may impart beneficial effects to ischemic cells of the nervous and cardiovascular systems for nutrient and oxygen supply, other scenarios that involve ocular neovascularization may seek to block or limit angiogenesis by EPO to prevent disease progression (Zhang and Ma, 2007).

5. EPO and the Modulation of Critical Cellular Pathways

5.1 EPO and Cellular Oxidative Stress

EPO regulates several signal transduction pathways during cellular oxidative stress that can involve protein kinase B, signal transducer and activator of transcription pathways, forkhead transcription factors, caspases, and nuclear factor κB. Strongly associated to these pathways of EPO that control cell longevity are the injury mechanisms associated with apoptosis. Oxidative stress occurs as a result of the development of reactive oxygen species that consist of oxygen free radicals and other chemical entities.

Oxygen consumption in organisms, or at least the rate of oxygen consumption in organisms, has intrigued a host of investigators and may have had some of its original origins with the work of Pearl. Pearl proposed that increased exposure to oxygen through an increased metabolic rate could lead to a shortened life span (Pearl, 1928). Subsequent work by multiple investigators has furthered this hypothesis by demonstrating that increased metabolic rates

could be detrimental to animals in an elevated oxygen environment (Muller et al., 2007). When one moves to more current work, oxygen free radicals and mitochondrial DNA mutations have become associated with oxidative stress injury, aging mechanisms, and accumulated toxicity for an organism (Yui and Matsuura, 2006).

In clinical terms, oxygen free radicals can be generated in elevated quantities during the reduction of oxygen and subsequently lead to cell injury and apoptosis. Reactive oxygen species can involve superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite (Chong et al., 2005e). Most species are produced at low levels during normal physiological conditions and are scavenged by endogenous antioxidant systems that include superoxide dismutase (SOD), glutathione peroxidase, catalase, and small molecule substances such as vitamins C and E. Other closely linked pathways to oxidative stress may be tempered by different vitamins, such as vitamin D_3 (Regulska et al., 2007) and the amide form of niacin or vitamin B_3, nicotinamide (Chlopicki et al., 2007; Chong et al., 2002d; Feng et al., 2006; Hara et al., 2007; Ieraci and Herrera, 2006; Lin et al., 2000; Maiese and Chong, 2003).

Oxidative stress represents a significant mechanism for the destruction of cells that can involve apoptotic cell injury and neuronal or vascular degeneration (Chong et al., 2006a; De Felice et al., 2007; Lin and Maiese, 2001). In fact, it has recently been shown that genes involved in the apoptotic process are replicated early during processes that involve cell replication and transcription, suggesting a much broader role for these genes than originally anticipated (Cohen et al., 2007). Apoptotic induced oxidative stress in conjunction with processes of mitochondrial dysfunction can contribute to a variety of disease states such as diabetes, ischemia, general cognitive loss, Alzheimer's disease, and trauma (Chong et al., 2005e; f; Harris et al., 2007; Leuner et al., 2007; Okouchi et al., 2007). Oxidative stress can lead to apoptosis in a variety of cell types that involve neurons, ECs, cardiomyocytes, and smooth muscle cells through multiple cellular pathways (Chong et al., 2004a; Chong et al., 2007b; Harris et al., 2007; Kang et al., 2003b; Karunakaran et al., 2007; Verdaguer et al., 2007).

Membrane phosphatidylserine (PS) externalization is an early event during cell apoptosis (Maiese et al., 2000; Mari et al., 2004) and can become a signal for the phagocytosis of cells (Chong et al., 2005a; Li et al., 2006b; Lin and Maiese, 2001). As an example, externalization of membrane PS residues occurs in neurons during anoxia (Maiese, 2001; Maiese and Boccone, 1995; Vincent and Maiese, 1999a), nitric oxide exposure (Chong et al., 2003f; Maiese et al., 1997), and during the administration of agents that induce the production of reactive oxygen species, such as 6-hydroxydopamine (Salinas et al., 2003). Membrane PS externalization on platelets also has been associated with clot formation in the vascular cell system (Leytin et al., 2006).

The translocation of membrane PS residues from the inner cellular membrane to the outer surface is a necessary component under most conditions for the removal of apoptotic cells (Maiese et al., 2003; Maiese and Vincent, 2000a; b). The loss of membrane phospholipid asymmetry leads to the externalization of membrane PS residues and assists microglia to target cells for phagocytosis (Chong et al., 2003d; Kang et al., 2003a; b; Maiese and Chong, 2003; Mallat et al., 2005). This process occurs with the expression of the phosphatidylserine receptor (PSR) on microglia during oxidative stress (Li et al., 2006a; c), since blockade of PSR function in microglia prevents the activation of microglia (Chong et al., 2003b; Kang et al., 2003a).

In contrast to the early externalization of membrane PS residues, the cleavage of genomic DNA into fragments (Maiese et al., 1999; Maiese and Vincent, 2000a; b) is considered to be a later event during apoptotic injury (Dombroski et al., 2000; Jessel et al., 2002; Kang et al., 2003b; Maiese and Vincent, 2000b). Endonucleases lead to DNA degradation and have been

differentiated based on their ionic sensitivities to zinc (Torriglia et al., 1997), magnesium (Sun and Cohen, 1994), and calcium (Maiese et al., 1999), an important regulator that can independently impair cell survival. In the nervous system, three separate endonuclease activities are present. These include a constitutive acidic cation-independent endonuclease, a constitutive calcium/magnesium-dependent endonuclease, and an inducible magnesium dependent endonuclease (Chong et al., 2005f; Vincent and Maiese, 1999b; Vincent et al., 1999a).

Oxidative stress also can impair mitochondrial function. Mitochondrial membrane transition pore permeability is increased (Chong et al., 2003a; Di Lisa et al., 2001; Kang et al., 2003b; Lin et al., 2000) and leads to a significant loss of mitochondrial NAD^+ stores and subsequent apoptotic cell injury (Chong et al., 2005g; Maiese and Chong, 2003). In addition, mitochondria are a significant source of superoxide radicals that are associated with oxidative stress (Chong et al., 2005e; Maiese and Chong, 2004). Blockade of the electron transfer chain at the flavin mononucleotide group of complex I or at the ubiquinone site of complex III results in the active generation of free radicals, which can impair mitochondrial electron transport and enhance free radical production (Chong and Maiese, 2007b; Li et al., 2006a). Furthermore, mutations in the mitochondrial genome have been associated with the potential development of a host of disorders, such as hypertension, hypercholesterolemia, and hypomagnesemia (Li et al., 2004b; Wilson et al., 2004). Reactive oxygen species also may lead to the induction of acidosis-induced cellular toxicity and subsequent mitochondrial failure (Chong et al., 2005f). Disorders, such as hypoxia (Roberts and Chih, 1997), diabetes (Cardella, 2005; Kratzsch et al., 2006), and excessive free radical production (Ito et al., 1997; Vincent et al., 1999a; b) can result in the disturbance of intracellular pH. In the consideration of oxidative stress-induced pathways, EPO offers a unique opportunity to prevent the exposure of membrane PS residues, inhibit the committed stages of genomic DNA destruction, and block cell injury.

5.2 EPO and Jak2, STATS, ERKs, Caspases

Cellular signal transduction with EPO requires the activation of the EPOR which specifically binds to and activates Janus-tyrosine kinase 2 (Jak2) through phosphorylation. Jak2 is a member of a family of Janus-type protein-tyrosine kinases including Jak1, Jak2, Jak3, and Tyk2, which are characterized by a kinase domain in the carboxyl portion, a kinase-like domain, and a large amino-terminal domain (Wilks et al., 1991). The amino-terminal domain of Jak2 is responsible for the binding of Jak2 with the β-subunit of the EPOR at a region proximal to the membrane that contains the Box 1 sequence (Zhao et al., 1995). EPO can prevent apoptotic injury through its reliance on Jak2 phosphorylation (Kawakami et al., 2001; Sharples et al., 2004), since loss of Jak2 activity reduces protection by EPO (Digicaylioglu et al., 2004; Lipton, 2007) (Figure 2).

The signal transducer and activator of transcription (STAT) proteins are direct substrates of Janus kinases. Seven mammalian STAT genes encoding proteins exist and are considered to be latent DNA binding factors that can be activated by tyrosine phosphorylation (Reich, 2007). Activation of Janus kinases results in tyrosine phosphorylation and dimerization of STATs. Once activated, STATs translocate to the nucleus and bind to specific DNA sequences in the promoter regions of responsive genes to lead to gene transcription. Associated with these transcription pathways are the mitogen-activated protein kinases, which include the extracellular signal-related kinases (ERKs), the c-Jun-amino terminal kinases, and p38 MAP kinase, which can oversee erythroid proliferation and differentiation (Nagata et al., 1998). Yet, in regard to cytoprotection, EPO has been shown to not only activate STAT 3 (Asaumi et al., 2007; Chong and Maiese, 2007a; Parsa et al., 2003), STAT 5 (Chong and Maiese, 2007a; Menon et al., 2006b; Moon et al., 2006; Um and Lodish, 2006; Wei et al., 2006), and ERK 1/2 (Bullard et al., 2005; Menon et al., 2006a), but also to employ these pathways for cell

development and cell protection (Figure 2). For example, EPO significantly activates STAT3, STAT5, and ERK 1/2 in primary cerebral vascular cells, suggesting that EPO may require these cellular pathways to confer EC cytoprotection during oxidative stress (Chong and Maiese, 2007a) (Table 2). In addition, activation of STAT5 also can modulate EPO proliferation as well as protection against cellular apoptosis (Damen et al., 1995). In erythroleukemic cell lines, EPO-dependent cell survival is accompanied by sustained STAT5 DNA-binding activity. Stable expression of the truncated STAT5a has been shown to enhance STAT5-DNA binding activity and reduce the induction of apoptosis (Bittorf et al., 2000). In contrast, induction of apoptosis can be observed in cells that lack STAT5 (STAT5a$^{-/-}$/5b$^{-/}$) function (Socolovsky et al., 2001). For example, STAT5a$^{-/-}$5b$^{-/-}$fetal liver erythroid progenitors show higher levels of apoptosis and are less responsive to the presence of EPO (Socolovsky et al., 1999).

Downstream from Janus kinases, STATS, and the ERKs are the apoptotic pathways of the caspase family. Caspases are a family of cysteine proteases that are synthesized as inactive zymogens, which are proteolytically cleaved into subunits at the onset of apoptosis (Li et al., 2006a; Maiese et al., 2005a; Okouchi et al., 2007). Caspases are composed of three domains including an N-terminal prodomain, a large subunit, and a small subunit (Earnshaw et al., 1999). As a result of their activation sequence, caspases are classified as either initiator caspases (also known as apical caspases) or effector caspases (Shi, 2004). An initiator caspase cleaves and subsequently activates an effector caspase. The apoptotic-associated caspases include initiator caspases, such as caspase 2, 8, 9, and 10, that activate downstream effector caspases, resulting in an amplification of cascade activity. The initiator caspases consist of long N-terminal prodomains that contain caspase recruitment domains (CARDs) in caspase 2 and caspase 9 or death effector domains (DEDs) in caspase 8 and caspase 10 (Hofmann et al., 1997). The effector caspases consist of caspase 3, 6, and 7, which function to directly cleave crucial cellular protein substrates to result in cell destruction.

The caspases 1 and 3 have each been linked to the independent apoptotic pathways of genomic DNA cleavage and cellular membrane PS exposure (Chong et al., 2003a; Chong et al., 2003e; Takahashi et al., 1999). These caspases, in addition to caspase 8 and 9, are also tied to the direct activation and proliferation of microglia (Chong et al., 2003b; Kang et al., 2003a; b). Caspase 1 is believed to be principally responsible for the externalization of membrane PS residues in several cell systems that can subsequently activate microglial phagocytosis (Maiese and Vincent, 2000b; Vanags et al., 1996). Furthermore, caspase 9 is activated through a process that involves the cytochrome c -apoptotic protease-activating factor-1 (Apaf-1) complex (Chong et al., 2004b; Li et al., 1997). In addition, caspase 8 serves as an upstream initiator of executioner caspases, such as caspase 3, and also leads to the mitochondrial release of cytochrome c (Engels et al., 2000; Stegh et al., 2002). Following caspase 8 and caspase 9 activation, caspase 3 directly leads to genomic DNA degradation.

Modulation of caspase activity by EPO may offer several avenues for protection against cell injury (Table 2). The ability of EPO to prevent specific caspase 1- and caspase 3-like activities appears to play a significant role in its cellular protection (Chong et al., 2002b;2003b;Chong et al., 2003e;Digicaylioglu et al., 2004;Li et al., 2007a;Okutan et al., 2007;Wu et al., 2007a). In regards to caspase 1, EPO prevents PS externalization primarily through the inhibition of caspase 1-like activity and, to a lesser degree, through other caspases such as 3, 8, and 9 (Chong et al., 2002b;2003a;b;Chong et al., 2003e) (Figure 2). EPO also can block genomic DNA degradation through the inhibition of cytochrome c and the subsequent inhibition of caspase 3-like activity (Chong et al., 2003b). Regulation of caspase 3-like activity by EPO has recently been linked to a unique regulatory mechanism that blocks the proteolytic degradation of phosphorylated forkhead transcription factors by caspase 3. Given that specific pro-apoptotic transcription factors, such as FoxO3a which is a member of the mammalian FoxO proteins assigned to the O class of the forkhead transcription superfamily, have been shown to be a

substrate for caspase 3-like proteases at the consensus sequence DELD^{304}A (Charvet et al., 2003), current work demonstrates that blockade of caspase 3-like activity prevents the destruction of the inactive phosphorylated FoxO3a during oxidative stress to increase cell survival (Chong and Maiese, 2007a). In relation to caspase 8 and caspase 9, EPO can also target these pathways (Chong et al., 2003a;b;Chong et al., 2003e;Sharples et al., 2004;Signore et al., 2006). EPO prevents cellular apoptosis through parallel pathways that prevent the induction of Apaf-1 and caspase 9 as well as by preserving mitochondrial membrane potential in conjunction with enhanced Bcl-x_L expression (Chong et al., 2003a).

5.3 EPO and Akt, Forkhead Transcription Factors

The ability of EPO to enhance cell survival during injury also directly relies upon the phosphatidylinositol 3-kinase (PI 3-K) pathway through protein kinase B (Akt). Phosphorylation of Akt in conjunction with EPO administration leads to its activation and protects against genomic DNA degradation and membrane PS exposure (Chong et al., 2003a; b; Chong et al., 2003e). Up-regulation of Akt activity during multiple injury paradigms, such as vascular and cardiomyocyte ischemia (Miki et al., 2006; Parsa et al., 2003), free radical exposure (Chong et al., 2003b; Matsuzaki et al., 1999), matrix detachment (Rytomaa et al., 2000), neuronal axotomy (Namikawa et al., 2000), N-methyl-D-aspartate toxicity (Dzietko et al., 2004), hypoxia (Chong et al., 2002b; Zhang et al., 2007b),β-amyloid toxicity (Chong et al., 2005d; Martin et al., 2001), DNA damage (Chong et al., 2002b; 2004a; Henry et al., 2001; Kang et al., 2003a), metabotropic receptor signaling (Chong et al., 2005a; Chong et al., 2006b; Maiese et al., 2005a), cell metabolic pathways (Chong et al., 2005g; Maiese and Chong, 2003), and oxidative stress (Chong et al., 2004a; Kang et al., 2003a; b), increases cell survival. Akt also can directly control microglial activation through the prevention of Bcl-x_L degradation (Chong et al., 2004a) and the inhibition of caspase 1-, 3-, and 9-like activities (Chong et al., 2005a; Kang et al., 2003a; b).

In addition, modulation of Akt activity can critically affect cell survival during hyperglycemia and the outcome of diabetic complications. Furthermore, endoplasmic reticulum stress inducers can lead to dephosphorylation and inactivation of Akt with subsequent cell death (Hyoda et al., 2006). On the converse side, overexpression of Akt, such as in endothelial cells, can protect cells from injury during elevated glucose concentrations (Varma et al., 2005). Therefore, Akt may be an essential component for EPO protection especially during disease processes such as diabetes, since inhibition of Akt activity blocks cellular protection and anti-inflammatory mechanisms by EPO (Chong et al., 2003a; b; Chong et al., 2003e). EPO has been shown to employ the PI 3-K/Akt pathway in a variety of experimental models of injury (Bahlmann et al., 2004; Chong et al., 2002b; 2003b; Chong et al., 2003e; Chong and Maiese, 2007a; Li et al., 2006b; Miki et al., 2006; Parsa et al., 2003; Sharples et al., 2004; Um et al., 2007; Um and Lodish, 2006; Wu et al., 2007b) (Figure 2). These can involve transcription factor regulation (Chong and Maiese, 2007a), maintenance of $\Delta\Psi_m$, prevention of cytochrome c release (Chong et al., 2003a; b; Chong et al., 2003e), and blockade of caspase activity (Chong et al., 2002b; 2003a; b) (Table 2).

Interestingly, a number of novel pathways that may mediate the ability of EPO to prevent cellular apoptosis are linked to Akt. For example, Akt is a central regulatory element for the mammalian forkhead transcription factor family that oversees processes that can involve cell metabolism, hormone modulation, and apoptosis (Cuesta et al., 2007; Maiese et al., 2007a; Maiese et al., 2007b). The mammalian forkhead transcription factor family functions as transcription factors by preferentially binding to the core consensus DNA sequence 5′-TTGTTTAG-3′, the forkhead response element (Chong et al., 2005e; Chong et al., 2004c; Wijchers et al., 2006). The first member of this family was the *Drosophila melanogaster* gene *Fork head*. Since this time, greater than 100 forkhead genes and 19 human subgroups are known

to exist that extend from FOXA to FOXS (Maiese et al., 2007b; Wijchers et al., 2006). The forkhead box (FOX) family of genes is characterized by a conserved forkhead domain commonly noted as a “forkhead box” or a “winged helix” as a result of the butterfly-like appearance on X-ray crystallography (Clark et al., 1993) and nuclear magnetic resonance (Jin et al., 1998). All Fox proteins contain the 100-amino acid winged helix domain, but it should be noted that not all winged helix domains are Fox proteins (Larson et al., 2007).

Of the mammalian forkhead transcription factors assigned to the O class, FoxO3a has emerged as a versatile target for a number of disorders. Akt can phosphorylate FoxO3a and inhibit its activity to sequester FoxO3a in the cytoplasm by association with 14-3-3 proteins (Brunet et al., 2002; Chong and Maiese, 2007a; Dong et al., 2007; Kino et al., 2005; Munoz-Fontela et al., 2007). In the absence of inhibitory Akt1 phosphorylation, FoxO3a can translocate to the nucleus, and controls a variety of functions that involve cell cycle progression, cell longevity, and apoptosis (Lehtinen et al., 2006; Li et al., 2006a; Maiese et al., 2007a). As a result, control of FoxO3a is considered to be a viable therapeutic target for agents such as metabotropic glutamate receptors (Chong et al., 2006b), neurotrophins (Zheng et al., 2002), and NAD^+ precursors (Chong et al., 2004c; Li et al., 2006a; b) to increase cell survival (Figure 2). In addition, FoxO3a interfaces with several pathways that regulate cellular lifespan (Lehtinen et al., 2006) and function to control neoplastic growth (Li et al., 2007b). In a similar manner, EPO controls the phosphorylation and degradation of FoxO3a to retain it in the cytoplasm through binding to 14-3-3 protein and foster vascular cell protection during oxidative stress (Chong and Maiese, 2007a) (Table 2).

5.4 EPO and Wnt, GSK-3β, NF-κB

Wnt proteins, derived from the *Drosophila Wingless* (*Wg*) and the mouse *Int-1* genes, have been shown to play a role in both cell development and cell demise with recent recognition that the Wnt pathway also is dependent upon Akt signaling (Chong et al., 2007a; Chong et al., 2007c; Li et al., 2006c; Speese and Budnik, 2007). Wnt proteins are secreted cysteine-rich glycosylated proteins that play a role in a variety of cellular functions that involve embryonic cell proliferation, differentiation, survival, and death (Li et al., 2006c; Patapoutian and Reichardt, 2000; Wodarz and Nusse, 1998). In general, all Wnt signaling pathways are initiated by interaction of Wnt proteins with Frizzled receptors and the binding of the Wnt protein to the Frizzled transmembrane receptor in the presence of the co-receptor LRP-5/6 (Mao et al., 2001). Once Wnt protein binds to the Frizzled transmembrane receptor and the co-receptor LRP-5/6, this is followed by recruitment of dishevelled, a cytoplasmic multifunctional phosphoprotein (Li et al., 2005; Patapoutian and Reichardt, 2000; Salinas, 1999).

Of interest, Wnt signaling can prevent cell injury through a variety of mechanisms. Wnt prevents apoptosis through β-catenin/Tcf transcription mediated pathways (Chen et al., 2001) and also can protect cells against c-myc induced apoptosis through cyclooxygenase-2 and Wnt induced secreted protein (You et al., 2002). Wnt signaling also can inhibit apoptosis during oxidative stress (Chong and Maiese, 2004) and β-amyloid toxicity that may require modulation of glycogen synthase kinase-3 β (GSK-3β) and β-catenin (Chong et al., 2007a).

Current experimental work suggests that abnormalities in the Wnt signaling pathways, such as with transcription factor 7-like 2 gene, may impart increased risk for type 2 diabetes in some populations (Grant et al., 2006; Lehman et al., 2007; Scott et al., 2006) as well as have increased association with obesity (Guo et al., 2006). Yet, intact Wnt family members may offer glucose tolerance and increased insulin sensitivity (Wright et al., 2007) as well as protect glomerular mesangial cells from elevated glucose induced apoptosis (Lin et al., 2006). These observations suggest a potential protective cellular mechanism for EPO through Wnt signaling to improve clinical cardiac function in diabetic patients (Silverberg et al., 2006) and decrease complications in women with diabetic pregnancies (Teramo et al., 2004) (Figure 2). New *in*

vitro studies demonstrate that the Wnt1 protein is necessary and sufficient to impart cellular protection during elevated glucose exposure (Chong et al., 2007c) (Table 2). Administration of exogenous Wnt1 protein can significantly prevent apoptotic EC injury during elevated glucose exposure. Interestingly, EPO maintains the expression of Wnt1 during elevated glucose exposure and prevents loss of Wnt1 expression that would occur in the absence of EPO during elevated glucose. More importantly, blockade of Wnt1 with a Wnt1Ab can neutralize the protective capacity of EPO, illustrating that Wnt1 is a critical component in the cytoprotection of EPO during elevated glucose exposure (Chong et al., 2007c).

In the Wnt pathway, dishevelled is phosphorylated by casein kinase Iε to form a complex with Frat1 and inhibit GSK-3β activity. Inhibition of GSK-3β activity can increase cell survival during oxidative stress and, as a result, GSK-3β is considered to be a therapeutic target for some neurodegenerative disorders (Balaraman et al., 2006; Chong et al., 2005e; Nurmi et al., 2006; Qin et al., 2006). GSK-3β also may influence inflammatory cell survival (Chong et al., 2007b) and activation (Tanuma et al., 2006). In regard to metabolic disease, inactivation of GSK-3β by small molecule inhibitors or RNA interference prevents toxicity from high concentrations of glucose and increases rat beta cell replication, suggesting a possible target of GSK-3β for pancreatic beta cell regeneration (Mussmann et al., 2007). Clinical applications for GSK-3β are attractive (Rowe et al., 2007), especially in concert with EPO. For example, both the potential benefits of EPO to improve cardiovascular function in diabetic patients (Silverberg et al., 2006; Silverberg et al., 2001) and the positive effects of exercise to improve glycemic control during DM (Maiorana et al., 2002) appear to rely upon the inhibition of GSK-3β activity. EPO blocks GSK-3β activity (Chong et al., 2007c; Li et al., 2006b; Wu et al., 2007a) and combined with exercise may offer synergistic benefits, since physical exercise also has been shown to phosphorylate and inhibit GSK-3β activity (Howlett et al., 2006).

Expression and cytoprotection of EPO also is dependent, in part, upon Akt and the activation of nuclear factor-κB (NF-κB). NF-κB proteins are composed of several homo- and heterodimer proteins that can bind to common DNA elements. It is the phosphorylation of IκB proteins by the IκB kinase (IKK) and their subsequent degradation that lead to the release of NF-κB for its translocation to the nucleus to initiate gene transcription (Hayden and Ghosh, 2004). Dependent upon Akt controlled pathways, the transactivation domain of the p65 subunit of NF-κB is activated by IKK and the IKKα catalytic subunit to lead to the induction of protective anti-apoptotic pathways (Chong et al., 2005b). Increased expression of NF-κB during injury models can occur in inflammatory microglial cells (Chong et al., 2005d; 2007b; Guo and Bhat, 2006) and in neurons (Sanz et al., 2002). NF-κB does represent a critical pathway that is responsible for the activation of inhibitors of apoptotic proteins (IAPs), the maintenance of Bcl-x_L expression, (Chen et al., 2000; Chong et al., 2005f), and protection against cell injury during oxidative stress (Chong et al., 2005d). NF-κB also is strongly associated with the cytoprotection of trophic factors that includes EPO (Chong et al., 2005d; Nakata et al., 2004; Sae-Ung et al., 2005). NF-κB also plays a key role in the expression of EPO during HIF-1 induction. Akt can significantly increase NF-κB and HIF-1 activation resulting in the enhancement of EPO expression. Although NF-κB has not consistently been found to be beneficial in all cell systems (Esposito et al., 2006; Jacobsen et al., 2006) and may sometimes not be cytoprotective (Nurmi et al., 2006; Xu et al., 2005), EPO subsequently uses NF-κB to prevent apoptosis through the enhanced expression and translocation of NF-κB to the nucleus to elicit anti-apoptotic gene activation (Bittorf et al., 2001; Chong et al., 2005d; Li et al., 2006b; Spandou et al., 2006).

6. Future Perspectives and Considerations for EPO

Since EPO has been identified as a candidate treatment for a number of disease entities that involve disorders of cardiac, nervous, and vascular systems, it may not be surprising to learn

that marketing expenditures for EPO by manufacturers continues to rise at a fast pace that has been reported to equal 31% of the total marketing budget geared to consumer advertising (Donohue et al., 2007). Furthermore, United States annual sale revenues for EPO have recently been reported to approach 9 billion dollars (Donohue et al., 2007). At present, there are at least 100 trials with the National Institutes of Health website (clinicaltrials.gov) that are either recruiting or in preparation to examine the clinical effects of EPO in patients with a variety of disorders that include anemia, cancer, cardiac ischemia, or spinal cord trauma. Although some cardiac injury experimental models do not consistently demonstrate a benefit with EPO (Olea et al., 2006), initial studies in patients with anemia or on chronic hemodialysis have suggested a direct cardiac benefit from EPO administration (Goldberg et al., 1992; Silverberg et al., 2001) (Table 1). Subsequent work has demonstrated that EPO administration can improve exercise tolerance either during cardiac or renal insufficiency in patients with anemia and congestive heart failure (Mancini et al., 2003; Palazzuoli et al., 2006) and that this may be tied to improved pulmonary function (Wu et al., 2006). Of significant interest is a recent randomized, concealed, multicenter trail of 1460 patients who received 40,000 U of epoetin alfa up to a 3 week maximum following intensive care unit admission and demonstrated a reduced mortality in patients with trauma (Corwin et al., 2007).

Unfortunately, agents such as EPO may not be tolerated by all individuals, especially those with co-morbid conditions such as congestive heart failure, hypertension, and neoplasms. Some studies suggest that elevated plasma levels of EPO independent of hemoglobin concentration can be associated with increased severity of disease in individuals with congestive heart failure (van der Meer et al., 2004b) and that EPO may contribute to vascular stenosis with intima hyperplasia (Reddy et al., 2007) (Table 1). Adverse effects during treatment with EPO are not uncommon, such as an increased incidence of thrombotic vascular effects (Corwin et al., 2007) or the use of EPO in cancer patients receiving chemotherapy that has been associated with nonfatal myocardial infarction, pyrexia, vomiting, shortness of breath, paresthesias, and upper respiratory tract infection (Henry et al., 2004). In addition, the use of EPO in patients with hypertension must proceed with caution, since both acute and long-term administration of EPO can significantly elevate mean arterial pressure (Kanbay et al., 2007).

The potential progression of cancer has been another significant concern raised with EPO administration (Kokhaei et al., 2007; Maiese et al., 2005b). Not only have both EPO and its receptor been demonstrated in tumor specimens, but under some conditions EPO expression has been suggested to block tumor cell apoptosis through Akt (Hardee et al., 2006), enhance tumor progression, increase metastatic disease, (Lai and Grandis, 2006), and negate the effects of radiotherapy by assisting with tumor angiogenesis (Ceelen et al., 2007) (Table 1). In studies of patients with head and neck cancer, EPO decreased disease progression-free survival and overall survival (Henke et al., 2003). Similar results were reported in trials with metastatic breast cancer (Leyland-Jones et al., 2005) and the expression of the EPOR in tumors appeared to suggest a worse prognosis (Henke et al., 2006). It should be noted though that the potential risk of EPO administration to either initiate tumor growth or lead to tumor progression is not entirely understood. In regards to the possible tumor promoting ability of EPO (Rades et al., 2007), a number of competing factors must be considered that include the possible benefits of EPO administration in patients with cancer that involve the synergistic effects of EPO with chemotherapeutic modalities (Ning et al., 2005; Sigounas et al., 2004), potential protection against chemotherapy tissue injury (Joyeux-Faure, 2007), and the treatment of cancer-related anemia. The deployment of further large scale prospective trials that can more clearly examine the attributes and contraindications for EPO, especially in patients with neoplastic disease, is required.

However, in addition to the concerns outlined in patients with cancer, other important considerations for EPO exist. Irrespective of the problems associated with EPO abuse and gene

doping (Baoutina et al., 2007; Diamanti-Kandarakis et al., 2005; Segura et al., 2007), EPO has been correlated with the alteration of red cell membrane properties leading to a cognitive decrement in rodent animal models (Li et al., 2004a; Maiese et al., 2004; 2005c). In addition, development of potentially detrimental side-effects during EPO therapy, such as for cerebral ischemia with increased metabolic rate and blood viscosity (Frietsch et al., 2007), could severely limit or halt the use of EPO for neurovascular diseases. As a result, alternate strategies have been suggested. New investigations are studying the role of targeted bioavailability for EPO such as in bone marrow stromal cells genetically engineered to secrete EPO (Eliopoulos et al., 2006) and controlled release of EPO from encapsulated cells (Orive et al., 2005; Ponce et al., 2006). The passage of EPO entry into the central nervous system continues to attract significant interest (Doolittle et al., 2007) as well as does the use of novel intranasal routes for EPO administration (Yu et al., 2005). Other avenues of study are directed to the development of derivations of EPO to reduce erythropoietic activity and the potential associated vascular complications (Montero et al., 2007). Yet, these lines of investigation are not without limitations, since chemical derivatives of EPO can become absent of clinical efficacy (Maiese et al., 2004; 2005c) as well as possibly lose the ability to promote sustainable cytoprotective effects, such as neurogenesis (Gonzalez et al., 2007) and angiogenesis (Li et al., 2007a; Reinders et al., 2006; Slevin et al., 2006; Zhang and Ma, 2007).

Use of EPO is now considered a promising strategy not only for erythropoiesis but also for cellular maintenance, survival, and the modulation of inflammatory pathways. New work conducted through basic research as well as through clinical trials should continue to broaden the therapeutic applications for EPO. However, precise focus upon the intricate cellular pathways governed by EPO is required to elucidate the benefits and risks of this agent. With this approach in place, EPO or the pathways that determine its biological effects should be warranted for the treatment of patients with a variety of disorders that can involve neurodegeneration, cardiac insufficiency, diabetes, and cancer.

Acknowledgements

This research was supported by the following grants (KM): American Diabetes Association, American Heart Association (National), Bugher Foundation Award, Janssen Neuroscience Award, LEARN Foundation Award, MI Life Sciences Challenge Award, Nelson Foundation Award, NIH NIEHS (P30 ES06639), and NIH NINDS/NIA.

Abbreviations

Aβ
: β-amyloid

AGES
: advanced glycation endproducts

Akt
: protein kinase B

Apaf-1
: apoptotic protease-activating factor

ARNT
: aryl hydrocarbon receptor nuclear translocator

CARD
: caspase recruitment domain

DED
: death effector domain

DM
diabetes mellitus

EC
endothelial cell

EPO
erythropoietin

EPOR
erythropoietin receptor

ERK
extracellular signal-related kinase

FOX
Forkhead box

GSK-3β
glycogen synthase kinaseβ

IAP
inhibitor of apoptosis protein

IKK
IκB kinase

IL-1β
interleukin-β

IL-6
interleukin-6

Jak
Janus-tyrosine kinase

$\Delta\Psi_m$
mitochondrial membrane potential

NF-κB
nuclear factor-κB

NO
nitric oxide

PI 3-K
phosphatidylinositol 3-kinase

PS
phosphatidylserine

PSR
phosphatidylserine receptor

STAT
signal transducer and activator of transcription

SOD
superoxide dismutase

TNF-α

tumor necrosis factor-α

Wg

Drosophila Wingless

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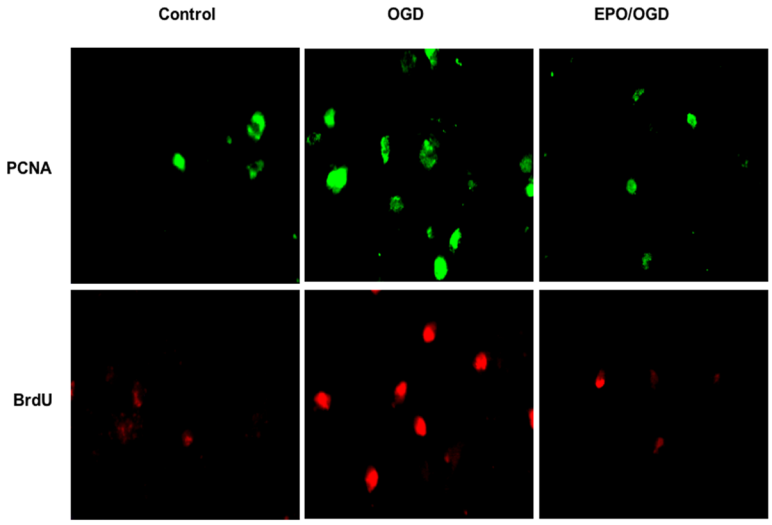

Figure 1. Erythropoietin (EPO) prevents the activation and proliferation of microglia during oxygen-glucose deprivation (OGD)

EPO (10ng/ml) was applied to microglial cultures (EOC-2) 1 hour prior to a 6 hour period of OGD. Proliferating cell nuclear antigen (PCNA) that can assess activation of microglia and bromodeoxyuridine (BrdU) that can follow microglia proliferation were performed with anti-mouse antibody against PCNA (1:100) or BrdU (1:100) and visualized through fluorescence conjugated anti-mouse IgG (1:50) for PCNA and Texas Red conjugated anti-mouse IgG for BrdU. BrdU (10 μM) and fluorodexyuridine (1 μM) were applied 1 hour prior to the time of fixation. Untreated control microglia have minimal PCNA and BrdU expression. Expression of PCNA and BrdU in microglia significantly increases during OGD exposure. In contrast, PCNA expression and BrdU expression is significantly less in microglia treated with EPO (10 ng/ml), illustrating the ability of EPO to prevent the activation and proliferation of inflammatory microglia during oxidative stress.

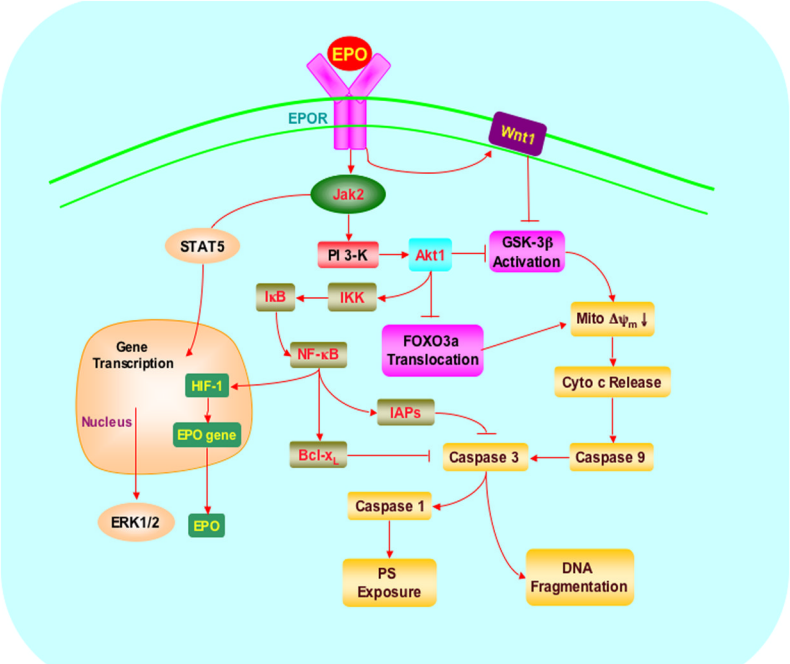

Figure 2. Erythropoietin (EPO) prevents apoptotic injury through a series of interconnected cellular pathways

With HIF-1 activation, EPO and the EPO receptor (EPOR) can increase cell survival, promote progenitor cell development, and control inflammatory cell activation through pathways that involve the Janus-tyrosine kinase 2 (Jak2) protein, protein kinase B (Akt), and signal transducer and activator of transcription (STAT) proteins. Interconnected pathways involve Wnt1, IκB kinase (IKK), IκB, inhibitors of apoptotic protein (IAPs), extracellular signal-related kinases (ERKs), the forkhead family member FOXO3a, glycogen synthase kinase-3β(GSK-3β), nuclear factor-κB (NF-κB), mitochondrial membrane potential ($\Delta\psi_m$), cytochrome c, (Cyto-c), and caspases. Ultimately these pathways converge upon early apoptotic injury with phosphatidylserine (PS) exposure and later apoptotic DNA degradation.

Table 1

Therapeutic Potential and Adverse Aspects of Erythropoietin (EPO)

Therapeutic Potential/ Clinical Trials	Outcomes	Selected References
Anemia	Left ventricular ejection improved, stroke volume increased	Goldberg et al., 1992, Silverberg et al., 2001
Cancer Treatment Synergy	Improve efficacy of chemotherapy	Ning et al., 2005; Sigounas et al., 2004
Congestive Heart Failure	Cardiac output improved, medical resource utilization decreased	Silverberg et al., 2003; 2006
Chronic Cardiac Insufficiency	Excise tolerance increased, left ventricular function improved, renal function improved decreased	Mancini et al., 2003; Palazzuoli et al., 2006; 2007
Diabetes	Improved cardiac function, protection of vascular cells	Silverberg et al., 2003; Chong et al., 2007c
Pulmonary Distress	Improved pulmonary function	Wu et al., 2006
Renal Transplantation	Prevention of allograft rejection	Reinders et al., 2006
Trauma	Mortality decreased	Corwin et al., 2007
Section II Adverse effects/ Conditions		
Breast Cancer	Apoptosis of cancer cells inhibited	Hardee et al., 2006
Cancer with Chemotherapy	Myocardial infarction, pyrexia, vomiting, paresthesias, upper respiratory infection increased	Henry et al., 2004
Congestive Heart Failure, Hypertension	Associated with disease severity, mean arterial pressure increased	van der Meer et al., 2004b; Kanbay et al., 2007
Head and Neck Cancer	Survival decreased	Henke et al., 2003; Henke et al., 2006
Metastatic Disease	Further disease progression	Leyland-Jones et al., 2005; Lai and Grandis, 2006
Radiotherapy	Decreased efficacy	Ceelen et al., 2007
Trauma	Incidence of thrombosis increased	Corwin et al., 2007
Vascular Thrombosis	Potential vascular stenosis, thrombosis	Corwin et al., 2007; Reddy et al., 2007

Table 2

Novel Cellular Pathways Modulated by Erythropoietin (EPO)

Cellular Pathways	Selected References
EPO and Jak2, STATs, ERKs, Caspases	
Janus-Tyrosine Kinase 2 (Jak2)	Kawakami et al., 2001; Digicaylioglu et al., 2004; Sharples et al., 2004
The Signal Transducer and Activator of Transcription (STAT)	
STAT3	Parsa et al., 2003; Asaumi et al., 2007; Chong and Maiese, 2007a
STAT5	Damen et al., 1995; Bittorf et al., 2000; Menon et al 2006b; Moon et al., 2006; Um and Lodish, 2006; Wei et al., 2006; Chong and Maiese, 2007a
The Extracellular Signal-Related Kinases (ERKs)	Bullard et al., 2005; Menon et al., 2006a; Chong and Maiese, 2007a
Mitochondrial Permeability and Caspases	Chong et al., 2002b; 2003a; 2003b; 2003e, Sharples et al., 2004; Li et al., 2007a; Okutan et al., 2007; Wu et al., 2007a
EPO and Akt, Forkhead Transcription Factors	
Akt	Chong et al., 2002b; 2003a; 2003b; 2003e; Parsa et al., 2003; Bahlmann et al., 2004; Sharples et al., 2004, Li et al., 2006b; Miki et al., 2006; Um and Lodish, et al., 2006; Um et al., 2007; Chong and Maiese, 2007a; Wu et al., 2007b
FOXO3a	Chong and Maiese, 2007a
EPO and Wnt, GSK-3β, *NF-κB*	
Wnt	Chong et al., 2007c
Glycogen Synthase Kinase (GSK)-3β	Li et al., 2006b; Chong et al., 2007c; Wu et al., 2007a
Nuclear Factor (NF)-κB	Bittorf et al., 2001; Chong et al., 2005d; Li et al., 2006b; Spandou et al., 2006