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OXIDATIVE STRESS: BIOMARKERS AND NOVEL THERAPEUTIC PATHWAYS

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Abstract

Oxidative stress significantly impacts multiple cellular pathways that can lead to the initiation and progression of varied disorders throughout the body. It therefore becomes imperative to elucidate the components and function of novel therapeutic strategies against oxidative stress to further clinical diagnosis and care. In particular, both the growth factor and cytokine erythropoietin (EPO) and members of the mammalian forkhead transcription factors of the O class (FoxOs) may offer the greatest promise for new treatment regimens since these agents and the cellular pathways they oversee cover a range of critical functions that directly influence progenitor cell development, cell survival and degeneration, metabolism, immune function, and cancer cell invasion. Furthermore, both EPO and FoxOs function not only as therapeutic targets, but also as biomarkers of disease onset and progression, since their cellular pathways are closely linked and overlap with several unique signal transduction pathways. However, biological outcome with EPO and FoxOs may sometimes be both unexpected and undesirable that can raise caution for these agents and warrant further investigations. Here we present the exciting as well as complicated role EPO and FoxOs possess to uncover the benefits as well as the risks of these agents for cell biology and clinical care in processes that range from stem cell development to uncontrolled cellular proliferation.

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Keywords

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1. Introduction

1.1 Oxidative stress

Release of reactive oxygen species that consist of oxygen free radicals and other chemical entities can result in the development of oxidative stress in the body. Oxygen free radicals can be generated in elevated quantities during the reduction of oxygen and lead to cell injury. Reactive oxygen species (ROS) can involve superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite (Chong et al., 2005e; Maiese, 2008b; Maiese et al., 2008a). 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).

Initial investigations into oxidative stress may have begun with studies that examined the rate of oxygen consumption in organisms. Work by Pearl proposed that increased exposure to oxygen through a high metabolic rate could lead to a shortened life span (Pearl, 1928). Additional work by other investigators has demonstrated that increased metabolic rates could be detrimental to animals in an elevated oxygen environment (Muller et al., 2007). Current studies show that oxygen free radicals and mitochondrial DNA mutations have become associated with cellular injury, aging mechanisms, and accumulated toxicity for an organism (Yui and Matsuura, 2006) that must be considered for the rational design of future therapies (Bolognesi et al., 2009).

Oxidative stress leads to the destruction of multiple cell types through apoptotic pathways (Chong et al., 2006a; De Felice et al., 2007; Lin and Maiese, 2001). However, it also 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 (He et al., 2009; Maiese et al., 2008g; Plecita-Hlavata et al., 2008) can contribute to a variety of disease states such as diabetes, ischemia, cognitive loss, Alzheimer's disease, pain sensation, and trauma (Chong et al., 2005e, f; Chuang and Lin, 2009; Harris et al., 2007; Leuner et al., 2007; Lin et al., 2009; Okouchi et al., 2007). Oxidative stress can lead to apoptosis in neurons, endothelial cells (ECs), cardiomyocytes, and smooth muscle cells that involve separate as well as overlapping 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).

Apoptosis is a dynamic process that consists of both the early exposure of membrane phosphatidylserine (PS) residues and the late destruction of genomic DNA (Chong et al., 2005c; Maiese et al., 2008f). Externalization of membrane PS residues 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). The loss of membrane phospholipid asymmetry leads to the exposure of membrane PS residues on the

cell surface 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). It has been shown that blockade of PSR function in microglia prevents the activation of microglia (Chong et al., 2003b; Kang et al., 2003a). Externalization of membrane PS residues occurs in neurons, vascular cells, and inflammatory microglia during reduced oxygen exposure (Lin et al., 2001; Lin and Maiese, 2001; Maiese, 2001; Maiese et al., 1999; Vincent and Maiese, 1999a), β-amyloid (Aβ) exposure (Chong et al., 2007a; Shang et al., 2009a), nitric oxide exposure (Chong et al., 2003e, f; Maiese and Boccone, 1995; Maiese et al., 1993; 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 system (Leytin et al., 2006).

The cleavage of genomic DNA into fragments (Maiese et al., 1999; Maiese and Vincent, 2000a, b) usually occurs after membrane PS exposure (Chong et al., 2004b) and 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). Several enzymes responsible for DNA degradation include the acidic, cation independent endonuclease (DNase II), cyclophilins, and the 97 kDa magnesium - dependent endonuclease (Chong et al., 2005e; Chong and Maiese, 2007b). Three separate endonuclease activities also have been found in neurons that include a constitutive acidic cation-independent endonuclease, a constitutive calcium/magnesium-dependent endonuclease, and an inducible magnesium dependent endonuclease (Vincent and Maiese, 1999b; Vincent et al., 1999a).

During oxidative stress, mitochondrial membrane transition pore permeability also is increased (Chong et al., 2003a; Di Lisa et al., 2001; Kang et al., 2003b; Lin et al., 2000), a significant loss of mitochondrial NAD^+ stores occurs, and further generation of superoxide radicals leads to cell injury (Chong et al., 2005g; Maiese and Chong, 2003). 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). ROS also may lead to cellular acidosis 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.

1.2 Biomarkers

For biological systems, a “biomarker” can consist of any entity that occurs in the body and that can be measured to predict the diagnosis, onset, or progression of a disease process. A biomarker does not have to be confined to a single entity. As a result, the definition of a biomarker is intentionally broad and application of biomarkers can be used for the determination of specific genes, proteins, products of cellular and biological processes as well as the response of cells or tissues to therapeutic strategies (Maiese, 2009; Maiese et al., 2009g).

Interestingly, some biomarkers can offer the additional benefit to function as a surrogate marker to be able to be used to predict clinical outcome in some cases. For example, biomarkers such as estrogen levels may predict the onset of postmenopausal breast cancer and a poor clinical

outcome. In other scenarios, biomarkers may suggest the body's attempt to initiate reparative processes. Novel pathways that involve the cytokine and growth factor erythropoietin (EPO) may indicate that the increased presence of this agent during periods of oxidative stress may lead to cellular mechanisms to protect against ROS (Maiese et al., 2008b; Maiese et al., 2008d; Maiese et al., 2005c). Furthermore, the activation of transcription factors during tumor invasion that control cell cycle regulation such as of the forkhead family of the "O" class may suggest the initiation of cell pathways that are attempting to restrict neoplastic growth (Maiese et al., 2008c; Maiese et al., 2009e, f). However, reliance on any single biomarker may be imperfect and lead to initially unpredicted outcomes such as uncontrolled hypertension or cancer with EPO (Maiese et al., 2008b; Maiese et al., 2008d; Maiese et al., 2005b) or the onset of detrimental apoptotic programs with forkhead transcription factors (Maiese et al., 2008f). A number of other pathways that occur in combination with a particular biomarker during oxidative stress also may also influence outcome (Maiese et al., 2009c). In the case of breast cancer, studies suggests that the release of androgens, cytokines, or even changes in body mass and exercise can influence outcome as well as alter the predictability of a specific biomarker (Bloomer and Fisher-Wellman, 2009; Fisher-Wellman et al., 2009). For these reasons, it becomes imperative to elucidate the components and function of the novel pathways for EPO and forkhead transcription factors during oxidative stress to understand their role not only as biomarkers, but also as therapeutic strategies to offer new insight for clinical care for a number of disease entities.

2. The growth factor and cytokine erythropoietin (EPO)

2.1 Historical perspective for EPO

EPO was initially known as "hemopoietine" that could stimulate new red blood cell development. Carnot and Deflandre in 1906 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 (Carnot and DeFlandre, 1906; Fisher, 2003; Maiese et al., 2008b; Maiese et al., 2008d). A number of other investigators followed these studies and found similar results demonstrating that plasma from bled animals would yield a significant reticulocytosis (Erslev, 1974; Gibelli, 1911; Sandor, 1932). More elegant experiments eventually 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 that led 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).

2.2 Structure and chemical properties for EPO

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. 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. 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 (Maiese et al., 2004,2005c). Once a mature protein, EPO becomes a 30.4 kDa glycoprotein with approximately half of its molecular weight derived from carbohydrates that can vary among species (Maiese et al., 2008d;Maiese et al., 2005c). EPO contains four glycosylated chains including three *N*-linked and one *O*-linked acidic oligosaccharide side chains. 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). The oligosaccharides in EPO also 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). 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 (Maiese et al., 2009g;Maiese et al., 2004).

2.3 Expression and regulation of EPO and the EPO receptor

The principal 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 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 the kidneys and nephrons (Chang et al., 2009; Sharples et al., 2005; Sharples and Yaqoob, 2006). Other 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 and, in turn, EPO may protect these cells from injury and assist with regeneration (Schmeding et al., 2008; 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). In addition, increased levels of EPO in the fetal plasma and amniotic fluid during gestation may function as a biomarker of intrauertine hypoxia (Teramo and Widness, 2009).

Although EPO is approved by the Food and Drug Administration for the treatment of anemia, recent studies have demonstrated 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). EPO production is believed to occur throughout the body (Arcasoy, 2008;Maiese et al., 2008a;Maiese et al., 2005c) and can be detected in the breath of healthy individuals (Schumann et al., 2006). In addition, it has been suggested that EPO may provide developmental cognitive support. In experimental animal models, EPO may reduce apoptotic pathways during periods of hyperoxia in the developing brain (Kaindl et al., 2008;Yis et al., 2008). Furthermore, clinical disorders may have periods of hyperoxia followed by cerebral hypoperfusion and hypoxia that can lead to cerebral injury with associated oxidative stress (He et al., 2008). In these circumstances, EPO also may be protective since it can promote neurite outgrowth (Berkingali et al., 2008) and also may regulate hemoglobin levels that have recently been associated with cognitive decline (Shah et al., 2009). In other work, elevated EPO concentrations during infant maturation have been correlated with increased Mental Development Index scores (Bierer et al., 2006) and EPO may prevent toxic effects of agents used to control cognitive function such as haloperidol (Pillai et al., 2008).

However, new knowledge that EPO and its receptor are present in the nervous and vascular systems has generated great 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, primary 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., 2004a; Maiese et al., 2008b; Maiese et al., 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., 2008d; Maiese et al., 2009g).

EPO controls erythroid cell proliferation, differentiation, and survival through its binding to a target cell surface receptor the EPO receptor (EPOR) (Sanchez et al., 2009). The EPOR also is expressed in numerous non-erythroid blood lines that include neurons, microglia, astrocytes, and in cerebral ECs (Anagnostou et al., 1994; Fliser and Haller, 2007; Maiese et al., 2008b; Maiese et al., 2009g) 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. During gestation, EPO production is increased, but later becomes suppressed following birth to be regulated by the tissue oxygen supply (Chong et al., 2002c). 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).

Despite the fact that EPO is a critical modulator of erythropoiesis, the presence of a diminished oxygen tension is required rather than a low concentration of red blood cells (Maiese et al., 2009b; Maiese et al., 2008a; Maiese et al., 2008b; Maiese et al., 2008d). In most tissues including the brain, hypoxia-dependent expression of EPO and EPOR are controlled by hypoxia-inducible factor 1 (HIF-1). HIF-1 is essential for the production and secretion of EPO in response to hypoxia. 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 (Maiese et al., 2008b; Maiese et al., 2009g; Maiese et al., 2005c). Yet, hypoxia is not the only condition that can alter 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., 2004b; Obara et al., 2003). Anemic stress, insulin release, and several cytokines, including insulin-like growth factor, tumor necrosis factor-α (TNF-α) (Li et al., 2009), 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., 2008b; Maiese et al., 2008d) and may provide a feed-back loop that is regulated by EPO such as TNF-α (Pregi et al., 2009).

3. Forkhead transcription factors of the “O” class

3.1 Background and structure for FoxOs

Mammalian forkhead transcription factors of the O class (FoxOs) to either block or activate target gene expression (Maiese et al., 2009f). These proteins must bind to DNA through the forkhead domain that relies upon fourteen protein-DNA contacts. The forkhead domain in Fox proteins consists of three α-helices, three β-sheets, and two loops that are referred to as the wings (Clark et al., 1993), but not all winged helix domains are considered to be Fox proteins (Larson et al., 2007). The forkhead domain is described as a “winged helix” as a result of a butterfly-like appearance on X-ray crystallography (Clark et al., 1993) or nuclear magnetic resonance imaging (Jin et al., 1998). High sequence homology is present in the α-helices and β-sheets with variations described in either absent β-sheets and loops or additional α-helices.

Although both the first and second loops make contact with DNA, it is the second loop that can influence the stability of DNA binding. In addition, post-translational modification of FoxO proteins, such as phosphorylation or acetylation that block FoxO activity, alter the binding of the C-terminal basic region to DNA to prevent transcriptional activity (Tsai et al., 2007b). Yet, other mechanisms may influence DNA binding of forkhead proteins, such as variations in the N-terminal region of the DNA recognition helix, changes in electrostatic distribution, and the ability of forkhead proteins to be shuttled to the cell nucleus (Maiese et al., 2008c; Wijchers et al., 2006).

In regards to the forkhead family, at least 100 forkhead genes and 19 human subgroups that range from *FOXA* to *FOXS* are now known to exist since the initial discovery of the fly *Drosophila melanogaster gene forkhead* (Weigel et al., 1989). The original nomenclature for these proteins, such as forkhead in rhabdomyosarcoma (*FKHR*), the Drosophila gene fork head (*fkh*), and Forkhead RElated ACtivator (FREAC)-1 and -2, has been replaced (Maiese et al., 2009a). The current nomenclature for human Fox proteins places all letters in uppercase, otherwise only the initial letter is listed as uppercase for the mouse, and for all other chordates the initial and subclass letters are in uppercase (Kaestner et al., 2000). FoxOs were first reported in fusion genes in human soft-tissue tumors and leukemias. FOXO1, termed forkhead in rhabdomyosarcoma (FKHR), and FOXO3a, also known as FKHRL1 (forkhead in rhabdomyosarcoma like protein 1), and their genes were identified through chromosomal translocations in alveolar rhabdomyosarcoma tumors (Maiese et al., 2007b). The acute leukemia fusion gene located in chromosome X (*AFX*), also known as the *FOXO4* gene, was demonstrated as a gene that fused to MLL transcription factor as a result of the *t(X; 11)* chromosomal translocation in acute lymphoblastic leukemia (Parry et al., 1994). A fusion between FOXO2 and MLL also occurs in some cases of acute myeloid leukemia that may be identical to FOXO3a (Hillion et al., 1997).

3.2 Expression and regulation of FoxO proteins

FoxO proteins (FoxO1, FoxO3, FoxO4, and FoxO6) are present throughout the body and are expressed in tissues of the reproductive system of males and females, skeletal muscle, the cardiovascular system, lung, liver, pancreas, spleen, thymus, and the nervous system (Castrillon et al., 2003; Furuyama et al., 2000; Furuyama et al., 2002; Hoekman et al., 2006; Lappas et al., 2009; Maiese et al., 2009a; Maiese et al., 2008c; Modur et al., 2002). Interestingly, FoxO proteins are not equally expressed in all tissues, suggesting that individual FoxO proteins may have specificity in regards to cellular function (Maiese et al., 2009a). For example, FoxO6 expression is found in several regions of the brain that play a significant role in cognitive function and emotion, such as the hippocampus, the amygdala, and the nucleus accumbens (Hoekman et al., 2006). In contrast, FoxO1 may be more suited for the control of motor function and memory formation, since the expression of this protein is primarily in the striatum and sub-regions of the hippocampus (Hoekman et al., 2006). In addition, FoxO3 is more diffusely represented in the hippocampus, cortex, and cerebellum, suggesting a complementary role for this FoxO protein to control cognitive and motor function. FoxO expression can be variable in other tissues (Maiese et al., 2009a; Maiese et al., 2009h). Although studies in mice have shown that the mRNA distribution of Foxo1, Foxo3a, and Foxo4 is similar in the embryo and adult (Furuyama et al., 2000), Foxo1 expression was highest in adipose tissue, Foxo3a expression was greatest in the liver, and Foxo4 expression was strongest in muscle (Furuyama et al., 2000). Subsequent work in mice has described Foxo1 expression in all tissues with high levels in the ovaries (Biggs et al., 2001). Foxo3a also is expressed in all tissues and Foxo4 expression was considered to be more tissue specific in skeletal muscle (Biggs et al., 2001).

Post-translational control of FoxO proteins employs pathways associated with ubiquitylation and acetylation (Matsuzaki et al., 2003; Plas and Thompson, 2003). IκB kinase (IKK) can

phosphorylate and block the activity of FoxO proteins, such as FoxO3a (Maiese et al., 2007b, 2008c). This leads to the proteolysis of FoxO3a via the Ub-dependent proteasome pathway (Jagani et al., 2008; Maiese et al., 2007b, 2008c; Maiese et al., 2008e; van der Horst and Burgering, 2007). FoxO proteins also are acetylated by histone acetyltransferases that include p300, the CREB-binding protein (CBP), and the CBP-associated factor. In addition, FoxO proteins are deacetylated by histone deacetylases. These include Sirt1, a NAD^+-dependent deacetylase and the mammalian ortholog of the silent information regulator 2 (Sir2) protein (Maiese et al., 2008c), that can control multiple processes such as cell injury, lifespan, and metabolism (Taylor et al., 2008; Zschoernig and Mahlknecht, 2008). Acetylation of FoxO proteins provides another avenue for the control of these proteins. Once acetylated such as by CBP, FoxO proteins may translocate to the cell nucleus but have diminished activity since acetylation of lysine residues on FoxO proteins has been shown to limit the ability of FoxO proteins to bind to DNA (Matsuzaki et al., 2005). Acetylation also can increase phosphorylation of FoxO proteins by the serine-threonine kinase protein kinase B (Akt) (Matsuzaki et al., 2005).

In addition to acetylation, and ubiquitylation, post-translational modulation of FoxO proteins also involves pathways associated with phosphorylation (Jagani et al., 2008; Maiese et al., 2007b, 2008c; Maiese et al., 2008e; van der Horst and Burgering, 2007). Protein phosphorylation is a critical pathway in the scheme for protein regulation (Song et al., 2009). Akt is a primary mediator of phosphorylation of FoxO1, FoxO3a, and FoxO4 that can block activity of these proteins (Chong et al., 2005b; Maiese et al., 2007b). Akt phosphorylation of FoxO proteins not only retains these transcription factors in the cytoplasm, but also leads to ubiquitination and degradation through the 26S proteasome (Jagani et al., 2008; Plas and Thompson, 2003). The serum- and glucocorticoid-inducible protein kinase (Sgk), a member of a family of kinases termed AGC (protein kinase A/protein kinase G/protein kinase C) kinases which includes Akt, also can phosphorylate and retain FoxO3a in the cytoplasm (Leong et al., 2003). Knowledge that Sgk and Akt can phosphorylate FoxO3a at different sites suggests other avenues to more effectively prevent apoptotic cell injury that may be mediated by FoxO3a activity. Yet, phosphorylation of FoxO proteins does not always lead to negative regulation. The protein kinase mammalian sterile 20-like kinase-1 also can phosphorylate FoxO proteins directly and lead to their activation (Lehtinen et al., 2006). The ability of sterile 20-like kinase-1 to activate FoxO proteins may be linked to c-Jun N-terminal kinase (JNK), since sterile 20-like kinase-1 can increase JNK activation (Song and Lee, 2008).

Interestingly, activation of Akt in pathways that involve EPO or FoxOs is usually cytoprotective, but may mediate other processes. For example, Akt either alone or through EPO can lead to cell proliferation (Gayer et al., 2009), blood-brain barrier permeability (An et al., 2008), or cell protection during inflammation (Slaets et al., 2008; Williams et al., 2009), neurodegeneration (Rodriguez-Blanco et al., 2008), hyperglycemia (Anitha et al., 2006), hypoxia (Chong et al., 2002b), Aβ toxicity (Burgos-Ramos et al., 2009a; Burgos-Ramos et al., 2008, 2009b; Chong et al., 2005d, 2007a), excitotoxicity (Campos-Esparza et al., 2009), cardiomyopathy (Kim et al., 2008), cellular aging (Tajes et al., 2009), and oxidative stress (Chong et al., 2004a; Kang et al., 2003a, b). In addition, Akt can prevent cellular apoptosis through the phosphorylation of FoxO proteins (Maiese et al., 2008a). Post-translational phosphorylation of FoxO proteins, such as during EPO administration, will maintain FoxO transcription factors in the cytoplasm by association with 14-3-3 proteins and prevent the transcription of pro-apoptotic target genes (Chong and Maiese, 2007a). An exception to these observations involving the subcellular trafficking of FoxO proteins involves FoxO6. This FoxO protein usually resides in the nucleus of cells and is phosphorylated by Akt in the nucleus. FoxO6 does not contain a conserved C-terminal Akt motif which limits nuclear shuttling of this protein, but FoxO6 transcriptional activity can be blocked by growth factors independent of shuttling to the cytosol through a FoxO6 N-terminal Akt site (van der Heide et al., 2005).

Modulation of Akt activity also controls apoptotic pathways of caspases that may offer an alternative mechanism to regulate FoxO proteins (Maiese et al., 2009e). Caspases are a family of cysteine proteases that are synthesized as inactive zymogens that are proteolytically cleaved into subunits at the onset of apoptosis (Li et al., 2006a; Maiese et al., 2005a; Salvesen and Riedl, 2008). The caspases 1 and 3 have been linked to the apoptotic pathways of genomic DNA cleavage, cellular membrane PS exposure, and activation of inflammatory cells (Chong et al., 2003a, b, 2004b). Caspase pathways may be tied to the forkhead transcription factor FoxO3a since increased activity of FoxO3a can result in cytochrome c release and caspase-induced apoptotic death (Chong et al., 2006b; Chong et al., 2004c; Chong and Maiese, 2007a; Obexer et al., 2007). Pathways that can inhibit caspase 3 appear to offer a unique regulatory mechanism. For example, studies suggests that cell death pathways that rely upon FoxO3a also appear to involve caspase 3 activation (Shang et al., 2009a, b) (Figure 1). FoxO3a activity promotes caspase-induced apoptotic death (Chong et al., 2006b; Chong et al., 2004c; Chong and Maiese, 2007a; Obexer et al., 2007), but inhibition of caspase 3 also can maintain the phosphorylated “inactive” state of FoxO3a to prevent cell injury (Chong et al., 2006b; Chong et al., 2004c; Chong and Maiese, 2007a). Other work has shown that caspase 3 activity and cleavage is promoted during transfection of a triple mutant FoxO3a expression in which three phosphorylation sites have been altered to prevent inactivation of FoxO3a (Gomez-Gutierrez et al., 2006). Furthermore, FoxO3a may control early activation and subsequent apoptotic injury in microglia during Aβ exposure and oxygen glucose deprivation (OGD) through caspase 3 (Shang et al., 2009a, b) (Figure 1). Since Aβ exposure can facilitate the cellular trafficking of FoxO3a from the cytoplasm to the cell nucleus to potentially lead to “pro-apoptotic” programs by this transcription factor (Shang et al., 2009a), one program in particular that may be vital for apoptotic injury appears to involve the activation of caspase 3. Aβ exposure leads to a rapid and significant increases in caspase 3 activity with 6 hours following Aβ administration, but that this induction of caspase 3 activity by Aβ requires FoxO3a, since loss of FoxO3a through gene silencing prevents the induction of caspase 3 activity by Aβ.

4. EPO, FoxOs, and cellular metabolism

Both EPO and FoxOs play a significant role during cellular metabolism and metabolic disorders such as diabetes mellitus (DM). DM is a significant health concern for both young and older populations (Maiese et al., 2007a; Maiese et al., 2007c). Almost 18-20 million individuals in the United States and more than 165 million individuals worldwide suffer from DM. By the year 2030, it is predicted that more than 360 million individuals will be afflicted with DM and its debilitating conditions. 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 (Maiese, 2008a; Maiese et al., 2007a). Type 1 insulin-dependent DM is present in 5-10 percent of all diabetics, but is increasing in adolescent minority groups (Maiese, 2008a; Maiese et al., 2007a). Furthermore, the incidence of undiagnosed diabetes and impaired glucose tolerance in the population raises additional concerns.

Patients with DM can develop immune dysfunction (Hao et al., 2009), cognitive disorders (Hao et al., 2009; Kuhad et al., 2009), hepatic dysfunction (Wu et al., 2009b), renal disease (Guarnieri et al., 2009), hematological disease (Gossai and Lau-Cam, 2009), neurodegenerative disorders (Maiese, 2008a, b; Maiese et al., 2009b), and cardiovascular disease (Donahoe et al., 2007; Maiese, 2008a). Interestingly, the development of insulin resistance and the complications of DM can be the result of cellular oxidative stress (Maiese, 2008a; Maiese et al., 2007a). Hyperglycemia can lead to increased production of ROS in endothelial cells, liver cells, and pancreatic β-cells (Maiese, 2008a; Maiese et al., 2007a; Maiese et al., 2007c). Recent clinical correlates support these experimental studies to show that elevated levels of ceruloplasmin are suggestive of increased ROS (Maiese, 2008a; Maiese

et al., 2007a; Maiese et al., 2007c). Furthermore, acute glucose swings in addition to chronic hyperglycemia can trigger oxidative stress mechanisms, illustrating the importance for therapeutic interventions during acute and sustained hyperglycemic episodes (Maiese, 2008a; Maiese et al., 2007a).

In regards to EPO during DM, plasma EPO is often low in diabetic patients with anemia (Mojiminiyi et al., 2006) or without anemia (Symeonidis et al., 2006). The inability 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). However, 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 demonstrated that 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 during elevated glucose and similar to other models of oxidative stress can block neuronal degeneration (Chattopadhyay et al., 2009) and apoptotic DNA degradation in ECs in cardiac and vascular cell models (Avasarala and Konduru, 2005; Chong et al., 2002b, 2003a; Chong and Maiese, 2007a; Moon et al., 2006). Protection 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).

Additional work suggests that proteins derived from the *Drosophila Wingless* (*Wg*) and the mouse *Int-1* genes may be associated with the complications of DM (Maiese et al., 2008f). The Wnt proteins are secreted cysteine-rich glycosylated proteins that can control cell proliferation (Wilusz and Majka, 2008), differentiation, survival, and tumorigenesis (Li et al., 2006c; Maiese et al., 2008h). These genes are present in several cellular populations (Kikuchi et al., 2009), such as neurons, cardiomyocytes, endothelial cells, cancer cells, and pre-adipocytes (Maiese, 2008b). Abnormalities in the Wnt pathway, 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. Cell culture studies demonstrate that the Wnt1 protein is necessary and sufficient to impart cellular protection during elevated glucose exposure (Chong et al., 2007c). 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. In addition, blockade of Wnt1 with a Wnt1 antibody 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).

Metabolic signaling with FoxOs is conserved among multiple species including *Caenorhabditis elegans, Drosophila melanogaster*, and mammals. FoxO proteins are

homologous to the transcription factor DAuer Formation-16 (DAF-16) in the worm *Caenorhabditis elegans* that can determine metabolic insulin signaling and lead to lifespan extension (Lin et al., 1997; Ogg et al., 1997), suggesting a significant role for FoxO proteins in relation to mammalian cell function (Maiese et al., 2007b, 2008c). FoxO proteins can stimulate the insulin-like growth factor binding protein-1 (IGFBP1) promoter by binding to the insulin-responsive sequence (IRS) (Guo et al., 1999). Both insulin and insulin-like growth factor-1 (IGF-1) can suppress this activity through activation of Akt (Guo et al., 1999; Nakae et al., 1999).

Analysis of the genetic variance in *FOXO1a* and *FOXO3a* on metabolic profiles, age-related diseases, fertility, fecundity, and mortality in patients have observed higher HbA_{1c} levels and increased mortality risk associated with specific haplotypes of *FOXO1a* (Kim et al., 2006). These clinical observations may coincide with the demonstration in human endothelial progenitor cells that elevated glucose levels can reduce post-translational phosphorylation of FOXO1, FOXO3a, and FOXO4 and allow for the nuclear translocation of these proteins to initiate an apoptotic program in endothelial progenitor cells (Marchetti et al., 2006). In experimental models, FoxO proteins may prevent the toxic effects of high serum glucose levels. Interferon-gamma driven expression of tryptophan catabolism by cytotoxic T lymphocyte antigen 4 may activate Foxo3a to protect dendritic cells from injury in nonobese diabetic mice (Fallarino et al., 2004). Additional studies have demonstrated that adipose tissue-specific expression of Foxo1 in mice improved glucose tolerance and sensitivity to insulin during an elevated fat diet (Nakae et al., 2008). FoxO proteins also may protect against diminished mitochondrial energy levels known to occur during insulin resistance such as in the elderly populations (Maiese, 2008a; Maiese et al., 2007a; Maiese et al., 2007c). In caloric restricted mice that have decreased energy reserves, Foxo1, Foxo3a, and Foxo4 mRNA levels were noted to progressively increase over a two year course (Furuyama et al., 2002). These observations complement studies in *Drosophila* and mammalian cells that demonstrate an increase in insulin signaling to regulate cellular metabolism during the up-regulation of FoxO1 expression (Puig and Tjian, 2005).

It should be noted that the ability for FoxO proteins to maintain proper physiologic controls over cellular metabolism may be limited and occur only during specific circumstances. For example, mice with a constitutively active Foxo1 transgene have increased microsomal triglyceride transfer protein and elevated plasma triglyceride levels (Kamagate and Dong, 2008). Studies in cardiomyocytes also suggest detrimental results with enhanced FoxO activity. Increased transcriptional activity of FoxO1, such as by the Sirt1 activator resveratrol, can diminish insulin mediated glucose uptake and result in insulin resistance (Ni et al., 2007). Over-expression of Foxo1 in skeletal muscles of mice also can lead to reduced skeletal muscle mass and poor glycemic control (Kamei et al., 2004), illustrating that activation of FoxO proteins also may impair cellular energy reserves. Other studies that block the expression of Foxo1 in normal and cachectic mice (Liu et al., 2007a) or reduce FoxO3 expression (Sandri et al., 2006) show the reverse with an increase in skeletal muscle mass or resistance to muscle atrophy. These results become especially relevant in patients with cancer and cachexia, since FoxO protein expression may further muscle wasting for these individuals. With this in mind, one potential agent to consider for the maintenance of cellular metabolism in patients is nicotinamide (Li et al., 2006a; Maiese and Chong, 2003; Maiese et al., 2009d), an agent that also can inhibit FoxO protein activity (Chong et al., 2004c) and control differentiation of human embryonic stem cells (Idelson et al., 2009). In patients with DM, oral nicotinamide protects β-cell function, prevents clinical disease in islet-cell antibody-positive first-degree relatives of type-1 DM, and can reduce HbA_{1c} levels (Li et al., 2006a; Maiese and Chong, 2003; Maiese et al., 2007a). Nicotinamide, which is closely linked to cell longevity pathways (Balan et al., 2008; Chong and Maiese, 2008), may derive its protective capacity through two separate mechanisms of post-translational modification of FoxO3a. Nicotinamide not only can maintain

phosphorylation of FoxO3a and inhibit its activity, but also can preserve the integrity of the FoxO3a protein to block FoxO3a proteolysis that can yield pro-apoptotic amino-terminal fragments (Chong et al., 2004c; Maiese et al., 2009g).

5. EPO, FoxOs, cellular proliferation, and cardiovascular outcome

The observation that EPO may promote tumor proliferation (Maiese et al., 2005b; Solar et al., 2008) and the initial identification of FoxO proteins in soft-tissue tumors and leukemias, neoplasms now believed to contain cancer stem cells for tumor self-renewal (Sauvageot et al., 2007), suggests that EPO and FoxO proteins may be closely tied to stem cell proliferation and differentiation. In regards to cell development for EPO, it can promote angiogenesis (Chong et al., 2002a, b, 2003a). 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., 2008b; Maiese et al., 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). Angiogenesis by EPO offers an additional level of cytoprotection in various cell systems. For example, in models of cerebral ischemia during which EPO expression can be enhanced, 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., 2007c). 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., 2007). 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 also seek to block or limit angiogenesis by EPO to prevent disease progression (Zhang and Ma, 2007). In clinical studies, EPO serum levels also 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). Recently, EPO has been shown to increase the motility of human bone marrow multipotent stromal cells (Koh et al., 2009), suggesting that EPO may lead to increased cell viability during oxidative stress via progenitor cell recruitment (Brunner et al., 2009; Lin et al., 2008; Uitterdijk et al., 2009). Interestingly, the ability of EPO to foster eythroid progenitor cell development is dependent upon the inhibition of FoxO3a activity (Maiese et al., 2008b; Maiese et al., 2005c), but also may require regulation of specific gene expression through an EPO-FoxO3a association to promote erythropoiesis in cultured cells (Bakker et al., 2007b). In addition, a close association with EPO (Arcasoy, 2008; Cariou et al., 2008; Maiese et al., 2008b) also may be required to modulate FoxO protein activity such as during erythroid progenitor cell development (Maiese et al., 2008b; Maiese et al., 2008d), further indicating that use of EPO in patients with combined anemia and cancer may have unexpected detrimental effects (Maiese et al., 2008b; Maiese et al., 2008d; Maiese et al., 2005b).

When one considers progenitor cell proliferation for FoxO proteins, either simultaneous deletion of *Foxo1*, *Foxo3a*, and *Foxo4* or single deletion of *Foxo3a* in mice prevents the repopulation of hematopoietic stem cells and leads to apoptosis in these stem cell populations (Miyamoto et al., 2007; Tothova et al., 2007). In regards to the reproductive potential of an organism, deletion of the *FoxO3a* gene results in the depletion of oocytes and subsequent infertility (Furukawa-Hibi et al., 2002). Other work using a mouse model of FoxO3a over-expression in oocytes suggests that FoxO3a also may retard oocyte growth and follicular development and leads to anovulation and luteinization of unruptured follicles (Liu et al., 2007b). In clinical studies, a small percentage of women who suffer from premature ovarian failure have mutations in *FOXO3a* and *FOXO1a* (Watkins et al., 2006). In neuronal

populations, FoxOs also may prevent stem cell proliferation, since the proliferation of human neural progenitor cells appears to require the inhibitory phosphorylation of FOXO3a (Wu et al., 2009c).

Similar to EPO, FoxO proteins also play a significant role to modulate new vessel growth that can impact upon cardiovascular development. FoxO proteins are intimately involved in endothelial cell development and angiogenesis. For example, *Foxo3a* -/- and *Foxo4* -/- mice develop without incidence and are indistinguishable from control littermates. However, mice that are singly deficient in *Foxo1* die by embryonic day eleven and lack development of the vascular system (Hosaka et al., 2004). Additional studies illustrate that endothelial cell colonies in *Foxo1*-deficient mice fail to respond to vascular endothelial growth factor in a manner similar to wild-type endothelial cells (Furuyama et al., 2004), suggesting that FoxOs are necessary for the development of vascular cells as well as for the biological response to cellular mediators.

During cardiac development, FoxO proteins also appear to be necessary to modulate cardiomyocyte proliferation. Both FoxO1 and FoxO3 are expressed during embryonic through prenatal stages in the developing myocardium. The expression of these FoxO proteins is believed to negatively regulate cardiomyocyte growth, since overexpression of FoxO1 blocks cardiomyocyte proliferation but expression of dominant negative FoxO1 leads to enhanced cardiomyocyte growth (Evans-Anderson et al., 2008). These observations may provide clues into the roles of FoxO proteins during cardiac hypertrophy. Atrogin-1, a protein that can block cardiac hypertrophy, may rely upon the up-regulation of Foxo1 and Foxo3a to disrupt cardiac hypertrophy, since mice lacking atrogin-1 are susceptible to cardiac hypertrophy and do not yield increased expression of Foxo1 and Foxo3a (Li et al., 2007b). In regards to smooth muscle cell growth, gene transfer of FoxO3a can inhibit neointimal hyperplasia through the prevention of vascular smooth muscle growth (Abid et al., 2005). However, not all FoxO proteins may exert an inhibitory effect upon vascular smooth muscle cells. FoxO4 may inhibit smooth muscle cell differentiation through the repression of the transcriptional coactivator of smooth muscle genes myocardin (Liu et al., 2005), but other work suggests that FoxO4 also can increase matrix metalloproteinase 9 expression to promote vascular smooth muscle migration and foster neointimal hyperplasia (Li et al., 2007a).

In consideration of the ability of FoxO proteins to regulate vascular smooth muscle cell proliferation, these transcription factors may have a significant clinical role in regards to disorders that involve hypertension and cardiac failure. Vascular smooth muscle cells are vital for the regulation of vascular tone and systemic arterial blood pressure. High flow states in vessels can reduce FoxO1 activity, resulting in the potential proliferation of vascular smooth muscle cells, vascular neointimal hyperplasia, and subsequent pathological states such as hypertension (Goettsch et al., 2008). Furthermore, α1-adrenergic agonists that increase systemic blood pressure can have the reverse effect and stimulate the expression of FoxO1 and its nuclear translocation that ultimately may lead to apoptotic endothelial cell injury (Morris et al., 2005). More than moderate levels of vessel cyclic stretch that can occur during hypertension may lead to the phosphorylation and inhibition of Foxo1 and Foxo3a in smooth muscle cells to further contribute to pathological smooth muscle cell proliferation (Sedding et al., 2003). In human as well as murine models of cardiac failure, increased expression of Fox transcription factors, such as FoxO1a, also have been observed to suggest a potential association of FoxO proteins with imminent cardiac failure (Hannenhalli et al., 2006).

6. EPO, FoxOs, cell survival, and the immune system

During a number of scenarios, EPO and FoxO proteins directly govern cell survival. With EPO, it can prevent cell injury during hypoxia (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;Yoo et al., 2009), parasitic disease (Bienvenu et al., 2008;Casals-Pascual et al., 2009;Kaiser et al., 2006), endotoxin shock (Aoshiba et al., 2009;Wagner et al., 2008), free radical exposure (Chong et al., 2003a;Chong et al., 2003e;Yamasaki et al., 2005), cardiac disease (Chen et al., 2008;Mao et al., 2008), amyloid toxicity (Chong et al., 2005d;Sun et al., 2008), and pulmonary disease (Tascilar et al., 2007;Wu et al., 2009a). EPO also represents a potential option for the prevention of retinal degeneration or neovascularization (Chen et al., 2009;Wang et al., 2009;Zhong et al., 2007;Zhong et al., 2008) as well as glaucoma (Lagreze et al., 2009;Tsai et al., 2007a). 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 (Okutan et al., 2008;Verdonck et al., 2007), cortical trauma (Cherian et al., 2007), and epileptic activity (Chu et al., 2008;Mikati et al., 2007;Nadam et al., 2007).

In contrast to EPO cytoprotection, FoxO transcription factors can lead to apoptosis during oxidative stress (Maiese et al., 2008a). For example, forkhead transcription factors such as FoxO1 and FoxO3a must be present for oxidative stress to result in apoptotic cell injury (Nakamura and Sakamoto, 2007). FoxO3a in conjunction with JNK also has been shown to modulate an apoptotic ligand activating a Fas-mediated death pathway in cultured motoneurons (Barthelemy et al., 2004), to lead to apoptosis through tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) and BH3-only proteins Noxa and Bim in neuroblastoma cells (Obexer et al., 2007), and to promote pro-apoptotic activity of p53 (You et al., 2006). In addition, loss of FoxO expression during oxidative stress is protective to cells. Protein inhibition or gene knockdown of FoxO1 or FoxO3a can lead to reduction in ischemic infarct size in the brain (Won et al., 2006), mediate protection of metabotropic glutamate receptors during vascular injury (Chong et al., 2006b), enhance pancreatic β-cell or neuronal survival through NAD^+ precursors during oxidative stress (Chong et al., 2004c), and provide trophic factor protection with EPO (Chong and Maiese, 2007a) and neurotrophins (Caporali et al., 2008). Furthermore, similar to pathways tied to EPO and Wnt, the canonical Wnt pathway (Slotkin and Seidler, 2009; Slotkin et al., 2008) that involves β-catenin (Li et al., 2006c; Maiese et al., 2008h) also appears to link FoxO proteins and Wnt signaling together (Maiese et al., 2008f). For example, in relation to Alzheimer's disease, Aβ is toxic to cells (Chong et al., 2005d, 2007a; Lu et al., 2009) and is associated with the phosphorylation of FoxO1 and FoxO3a that can be blocked with ROS scavengers (Smith et al., 2005). A common denominator in the pathways linked to Aβ toxicity involves Wnt signaling (Chong et al., 2007a; Mercado-Gomez et al., 2008) and β-catenin. β-catenin may increase *FoxO* transcriptional activity and competitively limit β-catenin interaction with members of the lymphoid enhancer factor/T cell factor family (Hoogeboom et al., 2008). This may lead to cell injury, since β-catenin has been demonstrated to be necessary for protection against Aβ toxicity in neuronal cells (Chong et al., 2007a). However, not all conditions with FoxOs may lead to cell demise. Some studies suggest that the loss of FoxO1, FoxO3a, and FoxO4 protein expression may actually lead to an increase in free radical release that can be responsible for oxidative stress (Tothova et al., 2007). Furthermore, FoxO proteins may be protective during aging and exercise, since FoxO3a activity may enhance vascular smooth muscle antioxidant properties in aged animals and be beneficial to the cardiovascular system during physical exertion (Ferrara et al., 2008).

Given the significant roles EPO and FoxOs play during cell survival which is tightly linked to the immune system and allergic disorders (Gilfillan and Rivera, 2009; Maiese et al., 2009f), it may come as no surprise that these proteins are closely associated with modulation of the immune system not only in the brain but also throughout the body. For example, in the brain, microglia 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). Microglia also 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 may lead to cell injury 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).

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), reduce inflammation in murine arthritis models (Cuzzocrea et al., 2005), and block primary microglial activation and proliferation during oxidative stress (Chong et al., 2003b; Chong et al., 2005d) 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., 2007). 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., 2008b), and reduce leukocyte inflammation (Contaldo et al., 2007). EPO also 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 general, forkhead transcription factors also have an important role in maintaining immune system function. The forkhead family member FoxP3 can control the development and function of thymic-derived CD4(+)CD25(+) regulatory T cells (Treg) that impart autoimmunity. Loss of FoxP3 can result in autoimmune disorders (Cools et al., 2007). Additional studies demonstrate the expression of FoxP3 in tumor cells, such as melanoma (Ebert et al., 2008), as well as in Tregs which may significantly affect patient mortality since the increased presence of Tregs in cancer patients combined with FoxP3 expression in tumors may impair antitumor autoimmune responses and lead to high mortality (Kono et al., 2006).

In regards to FoxO proteins, these transcription factors also may influence early apoptotic membrane PS externalization. The ability to regulate early apoptotic membrane PS exposure (Chong et al., 2003b) and inflammatory cell activity (Kang et al., 2003b) can ultimately affect cell survival since activated immune cells can lead to the phagocytic removal of injured cells or tumor cells (Chong et al., 2005a; Chong and Maiese, 2007b). Recent work suggests a relationship between the regulation of immune system activity and the induction of apoptotic pathways that are dependent upon FoxO proteins. Prevention of inflammatory activation and apoptosis in the nervous system such as in systemic lupus erythematosus in animal models may require the up-regulation of different Fox proteins, such as FoxJ1 and FoxO3a, that can block NF-κB activation and interferon-gamma secretion (Sela et al., 2006). FoxO proteins also may work in concert with Fas signaling to clear activated T cells following a decrease in cytokine stimulation in patients with autoimmune lymphoproliferative syndromes (Bosque et al., 2007), suggesting that activation of specific FoxO proteins may be beneficial for autoimmune disorders but may impair treatments designed to target tumor cells through immune mediated pathways. Furthermore, in mice deficient for *Foxo3a*, lymphoproliferation, organ inflammation of the salivary glands, lung, and kidney, and increased activity of helper T cells results, supporting an important role for FoxO3a in preventing T cell hyperactivity (Lin et al., 2004). FoxO3a also appears to be necessary for neutrophil activity, since *Foxo3a* null mice are resistant to models of neutrophilic inflammation that involve immune complex-mediated inflammatory arthritis (Jonsson et al., 2005). Patients with rheumatoid arthritis and osteoarthritis show phosphorylation of FOXO3a in T lymphocytes as well as FOXO1 and FOXO4 in synovial macrophages, suggesting that loss of functional FOXO family members may lead to inflammatory cell activation in these disorders (Ludikhuize et al., 2007). *FOXO1* gene transcript levels also are down-regulated in peripheral blood mononuclear cells of patients with systemic lupus erythematosus and rheumatoid arthritis (Kuo and Lin, 2007), illustrating a potential etiology through the loss of functional FOXO proteins for these disorders and possibly providing a biomarker of disease activity. Other studies show that FOXO1 protein

controls L-selectin expression that can regulate human T lymphocyte trafficking (Fabre et al., 2008).

7. Therapeutic considerations for cancer

The potential for the initiation or progression of cancer during EPO administration supports investigations that can elucidate the downstream mechanisms of this growth factor and cytokine to avoid unwanted clinical outcomes. In particular, the close association that EPO holds with FoxO proteins suggest potential avenues to limit or block tumor cell proliferation. FoxO proteins can control tumor growth through the induction of apoptosis and the blockade of cell cycle progression. For example, FoxO3a and FoxO4 can promote cell cycle arrest in mouse myoblastic cell lines through modulation of growth-arrest and DNA-damage-response protein 45 (Maiese et al., 2008b; Maiese et al., 2008c). Treatment of chronic myelogenous leukemia cell lines with the Bcr-Abl tyrosine kinase inhibitor imatinib requires FoxO3a activation to antagonize cell proliferation and promote apoptotic cell death through increased TRAIL production (Kikuchi et al., 2007). In addition, the transcription factor E2F-1 that controls the induction of the cell cycle has been reported in cell lines to increase the endogenous expression of FoxO1 and FoxO3a to lead to cell cycle arrest (Nowak et al., 2007). In contrast, the loss of FoxO3a activity in association with c-myc, p27, and nuclear factor-κB (NF-κB) can result in cell cycle induction and malignant transformation of mouse cells in the presence of oncogene activation (Maiese et al., 2007b, 2008c). Other work suggests that FoxO proteins utilize the p53 upstream regulator p19(Arf) through myc to block cell cycle induction and lymphoma progression (Bouchard et al., 2007).

Studies with prostate cancer have shown that the tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (PTEN) is mutated in approximately eighty percent of tumors with the loss of FOXO1 and FOXO3a activity. In cell cultures, over-expression of FoxO1 and FoxO3a in prostrate tumor cell lines also leads to apoptosis, suggesting that FoxO1 and FoxO3a are necessary for limiting prostate cell tumor growth (Modur et al., 2002). Inhibition of FoxO3a activity can result in enhanced prostate tumor cell growth (Lynch et al., 2005) while agents that increase FoxO3a activity in both androgen sensitive and androgen insensitive prostate cell lines prevent prostate cancer cell progression (Li et al., 2007d). Therapeutic strategies that rely upon the over-expression of a non-phosphorylatable form of FoxO3a that cannot be inactivated can also sensitize prostate cancer cells to androgen-withdrawal-induced apoptosis (Cornforth et al., 2008). However, in prostate cell lines FoxO3a can be a positive regulator of androgen receptor expression and therefore may play a complex role in prostate cancer cell proliferation and growth inhibition (Yang et al., 2005). Other factors that control FoxO protein function also may play a role during prostate tumor progression. In prostate cancer cells, cyclin-dependent kinase 1 (CDK1) can become over-expressed and subsequently phosphorylate FOXO1 to block its transcriptional activity and contribute to prostate tumorigenesis (Liu et al., 2008). In a similar manner, it has been shown that astrocyte-elevated gene-1 (AEG-1) can be upregulated in clinical prostate cancer (Kikuno et al., 2007), possibly lead to activation of Akt that suppresses FOXO3a (Trotman et al., 2006) and apoptosis in prostate tumor cells.

Initial investigations of FOXO3a in clinical breast cancer suggested that activation of FOXO3a was associated with lymph nodal metastasis and a poor prognosis (Jin et al., 2004). In contrast to these observations, other work has shown that FOXO3a was inactivated by IKK and that inactivation of FOXO3a was associated with a poor prognosis in breast cancer (Hu et al., 2004), suggesting that FOXO3a sub-cellular localization and pathways that enhance its activity could be used not only as a biomarker assay, but also as therapeutic targets. Other work in breast cancer cells demonstrate the tumor repressive ability of FoxOs by illustrating that increased activity of FoxO3a in association with JNK in breast cancer cell lines (Sunters et al.,

2006) or in association with cyclin-dependent kinase inhibitor p27 in isolated human breast cancer cells can prevent breast cancer growth (Eddy et al., 2007). In addition, FoxO proteins may be able to modulate estrogen function and indirectly block breast cancer growth. Over-expression of FoxO3a in breast cancer cell lines can decrease the expression of estrogen receptor regulated genes and inhibits 17beta-estradiol (E2)-dependent breast cancer growth (Zou et al., 2008).

FoxO proteins also may represent a viable option to control tumor progression in other tissues. FoxO proteins can function as redundant repressors of tumor growth. For example, somatic deletion in mice of *Foxo1*, *Foxo3a*, and *Foxo4* results in the growth of thymic lymphomas and hemangiomas (Paik et al., 2007). Other work illustrates that FoxO3a activation in colon carcinoma cell lines prevents tumor proliferation through Myc target genes that involve the Mad/Mxd family of transcriptional repressors (Delpuech et al., 2007). In addition, the loss of FoxO3a activity may participate in oncogenic transformation in B-chronic lymphocytic leukemia (Ticchioni et al., 2007) and in the progression of chronic myelogenous leukemia cell lines (Kikuchi et al., 2007). Furthermore, studies suggest that some proteins, such as the Kaposi's sarcoma-associated herpes virus latent protein LANA2, may specifically block the transcriptional activity of FoxO3a to lead to tumor growth (Munoz-Fontela et al., 2007). In cell models of endometrial cancer, pre-sensitization of cells to block Akt activation and foster transcription activity of FoxO1 enhances the effect of chemotherapy to limit tumor growth (Hoekstra et al., 2008).

8. Conclusions and perspectives

As biomarkers for disease onset and progression as well as candidates for the treatment of numerous disorders, EPO and FoxO transcription factors generate excitement for the potential to yield new strategies for the treatment of neurovascular injury, immune mediated diseases, and cancer related disorders. In reference to EPO, United States annual sale revenues for EPO have recently been reported to approach 9 billion dollars (Donohue et al., 2007) and over 100 trials with the National Institutes of Health website (clinicaltrials.gov) presently exist that are either recruiting or in preparation to examine the role of EPO in patients with a variety of disorders that include anemia, cancer, cardiac ischemia, or spinal cord trauma. Although some cardiac injury studies do not always demonstrate a benefit with EPO (Mocini et al., 2008; Olea et al., 2006), early 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). In addition, 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 may be dependent upon improved pulmonary function (Wu et al., 2006). Furthermore, a randomized, concealed, multicenter trial of 1460 patients who received 40,000 U of epoetin alfa up to a 3 week maximum following intensive care unit admission for trauma demonstrated a reduced mortality (Corwin et al., 2007).

Yet, EPO is not well tolerated 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., 2004) and that EPO may contribute to vascular stenosis with intima hyperplasia (Reddy et al., 2007). 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, both acute and long-term administration of EPO can significantly elevate mean arterial pressure that may place patients with hypertension at risk (Kanbay et al., 2007).

Cancer progression has been another significant concern raised with EPO administration (Kokhaei et al., 2007; Maiese et al., 2005b). EPO and its receptor can be found in tumor specimens, may block tumor cell apoptosis through Akt (Hardee et al., 2006), enhance metastatic disease, (Lai and Grandis, 2006), and complicate radiotherapy by assisting with tumor angiogenesis (Ceelen et al., 2007). The potential for EPO to lead to neoplastic growth is not well defined or understood at this time (Rades et al., 2008). A number of competing factors must be considered and weighed that include the possible benefits of EPO administration in patients with cancer, the synergistic effects of EPO with chemotherapeutic modalities (Ning et al., 2005; Sigounas et al., 2004), the potential protection against chemotherapy tissue injury (Joyeux-Faure, 2007), and the treatment of cancer-related anemia.

Additional considerations for EPO also exist (Dharmarajan and Widjaja, 2009). In addition to 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., 2008b; Maiese et al., 2005c). 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 also severely limit the use of EPO for neurovascular diseases. As a result, alternate strategies have been suggested. New proposals examine 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). The development of derivations of EPO to reduce erythropoietic activity and the potential associated vascular complications (Montero et al., 2007) have also been put forth as new directions for treatment. Yet, these lines of investigation are not without limitations, since chemical derivatives of EPO can become absent of clinical efficacy (Li et al., 2004a; Maiese et al., 2008b; Maiese et al., 2008d; Maiese et al., 2005c) as well as possibly loose the ability to promote sustainable cytoprotective effects, such as neurogenesis (Gonzalez et al., 2007) and angiogenesis (Li et al., 2007c; Reinders et al., 2006; Slevin et al., 2006; Zhang and Ma, 2007).

In contrast to the concerns of EPO to promote cancer, FoxO proteins offer the potential to target and prevent neoplastic progression. The ability of FoxO proteins to control cell cycle progression and promote apoptosis supports the premise that FoxOs may be an important component for new strategies directed against tumorigenesis. For example, use of triple mutant FoxO1 or FoxO3a expression in which three phosphorylation sites have been altered to prevent inactivation of this protein has been proposed to block melanoma tumors (Gomez-Gutierrez et al., 2006) and endometrial cancer (Ward et al., 2008). Other work also offers additional support for the use of FoxO proteins as biomarkers of cancer growth. Down regulation of the phosphatidylinositol 3 kinase and Akt pathways have been associated with increased transcript levels for FOXO1a and FOXO3a in clinical prostate cancer samples and may indicate the onset of pre-cancerous changes or the progression of on-going tumor growth (Hellwinkel et al., 2008). Although loss of Akt activity in prostate cancer cells can result in enhanced FoxO3a activity and subsequent apoptosis of tumor cells (Kikuno et al., 2007), it is conceivable that early stages of cancer may lead to reduced Akt activity with insufficient levels of active forkhead transcription factors to limit tumor progression. In addition, the early and persistent expression of phosphorylated FOXO1a in gastric tumors may not only indicate the onset of cancer, but also suggest an improved prognosis for patients (Kim et al., 2007).

The known mutations in FoxO proteins that exist in several disease entities may provide novel insights for the treatment of other disorders. Future analysis in larger populations of patients

with premature ovarian failure and diabetes could strengthen our understanding of the role of FoxO proteins in these disorders. In addition, targeting the activity of FoxO1, FoxO3a, or FoxO4 in cardiac and endothelial cells may prevent the onset of pathological cardiac hypertrophy and neointimal hyperplasia that may result in atherosclerosis. Recent studies also suggest that the utilization and combination of multiple biomarkers may improve risk assessment for patients suffering from cardiovascular disorders (Zethelius et al., 2008). These studies illustrate that FoxO proteins may serve as biomarkers of disease activity such as in individuals with imminent cardiac failure (Hannenhalli et al., 2006).

However, similar to studies with EPO, FoxO transcription factors may have complicated and sometimes detrimental clinical outcomes. For example, FoxO protein inhibition of cell cycle progression may not consistently lead to apoptotic cell death. Some investigations suggest that during oxidative stress, FoxO3a activation in association with Sirt1 can lead to cell cycle arrest, but not result in apoptotic cell injury (Brunet et al., 2004). Furthermore, during hypoxic stress, forkhead transcription factors, such as FOXO3a, may potentiate anti-apoptotic pathways in breast cancer cells to further tumor growth (Bakker et al., 2007a). FoxO proteins also have been linked to potential chemotherapy drug resistance with increased expression of MDR1 (P-glycoprotein) that has been associated with chemotherapy drug resistance in breast cancer cells. FoxO1 can stimulate the transcriptional activity of MDR1 that may promote increased tolerance of tumor cells (Han et al., 2008). In addition, the common pathways shared between Wnt and forkhead proteins may lead to other outcomes that alter the ability to control tumor growth (Emami and Corey, 2007; Li et al., 2006c). FoxO proteins may assist with β-catenin activation in the Wnt pathway and lead to tumor cell proliferation (Maiese et al., 2008h). In the presence of Wnt deregulation and increased β-catenin activity, tumorigenesis may ensue, such as with the proliferation of medulloblastoma tumors (Sauvageot et al., 2007). Therefore, the role of FoxO protein involvement in several disorders may not be consistently known and may be influenced by multiple parameters such as tissue characteristics, cellular metabolic state, and the age of an individual.

As combined therapeutic entities and biomarkers, EPO and FoxO proteins share a number of similarities and pathways to offer novel therapeutic strategies for a broad range of disorders. Future studies that involve both basic research as well as clinical trials are warranted for EPO and FoxO proteins. Yet, critical to this process is the clear focus upon the intricate cellular pathways governed by EPO and FoxOs to uncover the benefits and risks of these agents for processes that range from stem cell biology to mechanisms of cell demise and uncontrolled cell proliferation.

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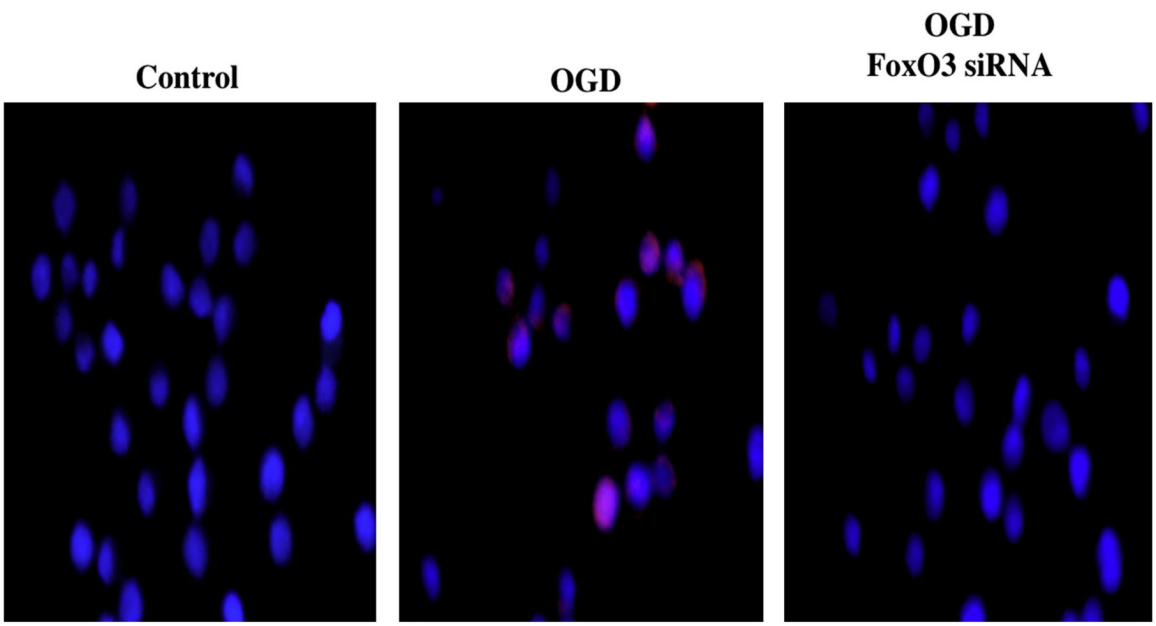

Figure 1. FoxO3a can control the activity of caspase 3

Inflammatory microglial cells were exposed to oxidative stress through oxygen-glucose deprivation (OGD) and caspase 3 activation was determined six hours after OGD exposure through immunocytochemistry with antibodies against cleaved active caspase 3 (17 kDa). Representative images show no caspase 3 activity staining (blue) in control (untreated cells), but active caspase 3 staining (red) in cells following OGD. In contrast, gene silencing of FoxO3a during transfection with FoxO3a siRNA yields significantly reduced caspase 3 activity with demonstration of minimal red staining.