

Diabetes Mellitus: Regulatory Component of Erythropoietin Motor Signaling and Cytoprotection

Campagna Sara*

Department of Translational Medicine and LTTA Centre, University of Ferrara, Ferrara, Italy

Abstract

New treatment strategies with erythropoietin (EPO) offer exciting opportunities to prevent the onset and progression of neurodegenerative disorders that currently lack effective therapy and can progress to devastating disability in patients. EPO and its receptor are present in multiple systems of the body and can impact disease progression in the nervous, vascular, and immune systems that ultimately affect disorders such as Alzheimer's disease, Parkinson's disease, retinal injury, stroke, and demyelinating disease. EPO relies upon wingless signaling with Wnt1 and an intimate relationship with the pathways of phosphoinositide 3-kinase, protein kinase B, and mammalian target of rapamycin. Modulation of these pathways by EPO can govern the apoptotic cascade to control β -catenin, glycogen synthase kinase-3 β , mitochondrial permeability, cytochrome c release, and caspase activation. Yet, EPO and each of these downstream pathways require precise biological modulation to avert complications associated with the vascular system, tumorigenesis, and progression of nervous system disorders. Further understanding of the intimate and complex relationship of EPO and the signaling pathways of Wnt, PI 3-K, Akt, and mTOR are critical for the effective clinical translation of these cell pathways into robust treatments for neurodegenerative disorders.

Keywords: Alzheimer's disease; PI 3-K; Parkinson's disease; Wnt; Amyotrophic lateral sclerosis; Apoptosis; Cancer; Erythropoietin; mTOR; Oxidative stress

Introduction

The concept of biological agents functioning as hormones may have had its early origins with Ernest Starling when he introduced the term to the Royal College of Surgeons in 1905. Starling was discussing the potential existence of agents in the blood that could stimulate organs in the body and chose the term "hormone" that was derived from the Greek term meaning to excite or arouse. During this period, Carnot and Deflandre were investigating the agent "hemopoietine". They removed plasma following a bleeding stimulus in rabbits and demonstrated that injecting this plasma into untreated animals would promote the development of immature red blood cells. Other work confirmed the findings of Carnot and Deflandre to show that plasma obtained by bleeding animals acted as a stimulus to produce new red blood cells in untreated animals [1]. As "hemopoietine" became known as erythropoietin (EPO), studies later demonstrated that loss of oxygen tension in one parabiotic rat would lead to reticulocytosis in the normoxic partner. With the subsequent purification of human EPO, the EPO gene was cloned and approval was obtained for the clinical use of recombinant EPO.

Oxidative Stress, Cellular Survival and Programmed Cell Death

Oxidative stress can significantly negatively impact cellular survival and longevity and lead to programmed cell death. The generations of reactive oxygen species (ROS) that result in oxidative stress include nitrogen based free radical species such as nitric oxide and peroxynitrite as well as superoxide free radicals, hydrogen peroxide, and singlet oxygen. ROS can result in DNA damage, mitochondrial and other organelle injury, protein misfolding, and neuronal synaptic dysfunction. Protective pathways serve to alleviate damage from ROS and involve vitamins B, C, D, and K, coenzyme Q10, glutathione peroxidase, and superoxide dismutase. Oxidative stress can lead to the induction of programmed cell death through apoptosis and autophagy [2]. Apoptosis has an early phase with the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry and a later phase that leads to

genomic DNA degradation. Blockade of the early phase with membrane PS externalization is vital for cellular survival since membrane PS externalization can direct inflammatory cells to engulf and remove injured cells that may be functional and available for repair. The later phase of cell death with apoptosis leads to the destruction of cellular DNA. Autophagy is another pathway of programmed cell death that permits cells to recycle cytoplasmic components while removing dysfunctional organelles for tissue remodeling. Of the three categories for autophagy, microautophagy employs the invagination of lysosomal membranes for the sequestration and digestion of cytoplasmic components. In chaperone-mediated autophagy, cytosolic chaperones transport cytoplasmic components across lysosomal membranes. The most prevalent category of autophagy is macroautophagy that consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. These autophagosomes then combine with lysosomes for degradation and are subsequently recycled for future cellular processes [3].

Diabetes Mellitus and clinical implications

Early diagnosis and proper care of individuals with DM also may be crucial for extending human longevity by modulating epigenetic changes in age-related genes involved with DM and other degenerative disorder. The presence of impaired glucose tolerance in the young raises additional concerns for the future development of DM in these individuals. Obesity is another risk factor for the development of DM. Obesity results in cellular oxidative stress and

*Corresponding author: Campagna Sara, Department of Translational Medicine and LTTA Centre, University of Ferrara, Ferrara, Italy, E-mail: saracampagna@edu.com

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insulin resistance, altered trophic factor release [4], lipid-induced impairment of pancreatic β -cells, and dysfunctional protein tyrosine phosphatase signaling. In insulin dependent DM, defective insulin secretion can result from impaired β -cell function, oxidative stress, the absence of inhibitory feedback through plasma glucagon levels, chronic exposure to free fatty acids, lipotoxicity, and hyperglycemia. Type 2 DM is the most prevalent subtype for this disorder occurring in ninety percent of individuals that are usually over the age of 40. A progressive deterioration of glucose tolerance occurs with early β -cell compensation that is followed by a decrease in pancreatic β -cell mass with insulin resistance and impaired insulin secretion. In contrast to Type 2 DM, Type 1 DM is an autoimmune disorder with the presence of alleles of the human leukocyte antigen (HLA) class II genes within the major histocompatibility complex (MHC). Type 1 DM occurs in approximately 5–10% of patients with DM. Activation of T-cell clones that are capable of recognizing and destroying pancreatic β -cells to result in insulin deficiency may not always lead to programmed cell death but rather relies upon the necrotic death of β -cells. Destruction of pancreatic β -cells with inflammatory infiltration of the islets of Langerhans results in the loss of insulin production and regulation [5]. Almost all patients with Type 1 DM have increased titers of autoantibodies (Type 1A DM). However, approximately 10% of Type 1 DM individuals do not have serum autoantibodies and are considered to have maturity-onset diabetes of the young (MODY) that can be a result of β -cell dysfunction with autosomal-dominant inheritance. Type 1 and Type 2 DM may have common links since approximately 10% of individuals with Type 2 DM may have elevated serum autoantibodies similar to Type 1 DM and insulin resistance also may be a component of Type 1 DM in some patients.

Diabetes Mellitus, Oxidative Stress, and Programmed Cell Death

Progressive disease in the body that occurs during DM is mediated to a significant extent through the release of ROS and oxidative stress. Patients with Type 2 DM have serum markers of oxidative stress with ischemia modified albumin. Acute rises in serum glucose as well as chronic elevations can result in the release of ROS during DM. In addition, some studies suggest that treatment with antioxidants may limit the prevention of cardiovascular disease during DM. In cell culture models of DM, elevated glucose levels result in oxidative stress and cell injury in cardiomyocytes, endothelial cells, and neurons [6]. Oxidative stress also results in elevated glutathione levels and increased lipid peroxidation in murine animal models of Type 2 DM. Advanced glycation end products (AGEs), entities that foster complications in DM, lead to the release of ROS and caspase activation. At the cellular level, uncoupling proteins (UCPs), a family of carrier proteins found in the inner membrane of mitochondria and consist of the mammalian members UCP1, UCP2, UCP3, UCP4, and UCP5, can significantly influence cell survival in DM. UCPs uncouple oxygen consumption through the respiratory chain from ATP synthesis. Subsequently, this leads to oxidative stress as UCPs disperse a proton electrochemical potential gradient across the mitochondrial inner membrane resulting in the activation of substrate oxidation and dissipation of oxidation energy as heat instead of ATP. Uncoupling of respiration by UCPs modulates ATP synthesis, fatty acid release, and glucose oxidation. Overexpression of UCP in skeletal muscle of mice enhances responsiveness to insulin, improves glucose transport in skeletal muscle, and increases resistance to obesity. In addition, skeletal muscle respiratory uncoupling can improve insulin sensitivity in obesity. In regards to UCP3, it can stimulate insulin uptake, can facilitate fatty acid oxidation, and can limit ROS production. However, it should be

recognized that not all UCPs are beneficial. Overexpression of UCP2 in isolated pancreatic islets leads to decreased ATP levels and reduced glucose-stimulated insulin secretion. Loss of UCP2 improves insulin secretion and decreases hyperglycemia in leptindeficient mice [7].

Mechanistic Target of Rapamycin

The mechanistic target of rapamycin (mTOR), also termed the mammalian target of rapamycin and FK506-binding protein 12-rapamycin complex-associated protein 1, is a principal pathway in DM that can significantly affect apoptosis and autophagy. mTOR is a 289-kDa serine/threonine protein kinase. It is encoded by a single gene FRAP1 and is a component of the protein complexes mTOR Complex 1 and mTOR Complex 2. mTORC1 consists of Raptor, the proline rich Akt substrate 40 kDa, Deptor, and mammalian lethal with Sec13 protein 8. mTORC2 consists of Rictor, Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein, and the protein observed with Rictor-1 [8]. mTOR is a vital component of cytokine and growth factor signaling such as erythropoietin. EPO uses mTOR for cytoprotection. Through mTOR, EPO protects vascular cells, prevents cell injury during β -amyloid exposure, modulates bone homeostasis, promotes retinal progenitor cell survival during oxidant stress and blocks retinal degeneration in models of polycystic kidney disease, promotes the neuronal phenotype of adult neuronal precursor cells, improves cognitive function in sepsis associated encephalopathy, and limits cell injury during oxygen-glucose deprivation [9]. In regards to cellular metabolism, EPO promotes wound healing during DM, maintains cellular mitochondrial function and energy metabolism, reduces the detrimental effects of obesity in animal models, limits high glucose-induced oxidative stress in renal tubular cells, and protects endothelial cells during experimental models of DM [10].

Conclusions

Oxidative stress is a significant mediator of multisystem disease in the body during DM. Clinical studies and experimental models point to cell injury that involves both apoptosis and autophagy during DM as a result of oxidative stress and the release of ROS. Given that DM is predicted to become the seventh leading cause of death by the year 2030, the need for new therapeutic opportunities to treat DM and its complications becomes increasingly acute. One exciting strategy for consideration is mTOR. mTOR activation oversees stem cell development, fosters pancreatic β -cell proliferation, limits insulin resistance, and can prevent pathways that may lead to atherosclerosis. Protective cytokines and growth factors such as EPO rely upon mTOR for vascular cell protection, neuronal cell survival, and bone homeostasis. Furthermore, EPO can lead to wound healing during DM, maintains cellular mitochondrial function and energy metabolism, and reduces the detrimental effects of obesity in animal models. Yet, inhibitory pathways of mTOR that involve AMPK also have a critical role during DM. AMPK activity can reduce insulin resistance and lessen oxidative stress through activation of autophagy. In addition, metformin, an agent that controls hyperglycemia in DM, activates AMPK and inhibits mTOR activity to promote autophagy and cytoprotection. Metformin reduces cardiomyopathy in experimental models of DM, prevents endothelial cell senescence, and prevents neuronal apoptotic cell death. Interestingly, SIRT1 also relies upon AMPK for the regulation of insulin sensitivity and to induce autophagy that is necessary for endothelial cell protection during exposure to oxidized low density lipoproteins that can lead to atherosclerosis. Yet, AMPK activity is not consistently beneficial and can lead to $A\beta$ stress, $A\beta$ toxicity, cardiac tissue hypertrophy, and neuroinflammation. In some experimental

models of Type 2 DM, AMPK activation can lead to apoptosis in pancreatic islet cells. SIRT1 importantly modulates stem cell survival, blocks apoptotic cell injury, controls autophagy for mitochondrial pool maintenance, and limits oxidative stress that affects cellular survival during DM. Although SIRT1 can increase cell survival and preserve insulin signaling by blocking apoptotic pathways, SIRT1 also can foster autophagy and limit mTOR activation to preserve mitochondria, promote stem cell proliferation, and prevent insulin resistance. WISP1 incorporates the pathways of mTOR and SIRT1 to control stem cell migration as well as stem cell differentiation. WISP1 may offer protection against cell loss in DM since it is one of several transcripts that are expressed during pancreatic regeneration. WISP1 can activate PI 3-K, Akt, and mTOR to protect against $A\beta$ exposure, cardiomyocyte injury, DNA damage, and oxidative stress. WISP1 also increases SIRT1 activity and maintains the integrity of SIRT1 during oxidative stress to prevent SIRT1 degradation. New insights that develop mTOR, SIRT1, and WISP1 as effective therapeutic strategies against DM offer great hope for the millions of individuals that presently suffer from this disabling disorder. Fruits of such investigations will weigh heavily upon careful analysis of the intricate and complex pathways controlled by the proliferative properties of mTOR, SIRT1, and WISP1 to achieve high clinical efficacy for patients with DM and limit adverse effects that can involve organ dysfunction, pancreatic cell loss, tumor growth, and inflammation.

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