EDITORIAL

mTOR: Driving apoptosis and autophagy for neurocardiac complications of diabetes mellitus

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Abstract

The World Health Organization estimates that diabetes mellitus (DM) will become the seventh leading cause of death during the next two decades. DM affects approximately 350 million individuals worldwide and additional millions that remain undiagnosed are estimated to suffer from the complications of DM. Although the complications of DM can be seen throughout the body, the nervous, cardiac, and vascular systems can be significantly affected and lead to disorders that include cognitive loss, stroke, atherosclerosis, cardiac failure, and endothelial stem cell impairment. At the cellular level, oxidative stress is a significant determinant of cell fate during DM and leads to endoplasmic reticulum stress, mitochondrial dysfunction, apoptosis, and autophagy. Multiple strategies are being developed to combat the complications of DM, but it is the mechanistic target of rapamycin (mTOR) that is gaining interest in drug development circles especially for protective therapies that involve cytokines and growth factors such as erythropoietin. The pathways of mTOR linked to mTOR complex 1, mTOR complex 2, AMP activated protein kinase, and the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) complex can ultimately influence neuronal, cardiac, and vascular cell survival during oxidant stress in DM through a fine interplay between apoptosis and autophagy. Further understanding of these mTOR regulated pathways should foster novel strategies for the complications of DM that impact millions of individuals with death and disability.

Key words: Apoptosis; Autophagy; Cardiac disease; Diabetes mellitus; Erythropoietin; Metformin; Oxidative stress; Neurodegeneration; Mechanistic target of rapamycin; Vascular disease

Core tip: The pathways of mechanistic target of rapamycin (mTOR) linked to mTOR complex 1, mTOR complex 2, AMP activated protein kinase, and tuberous sclerosis 1/tuberous sclerosis 2 complex can offer novel strategies for the complications of diabetes mellitus to prevent death and disability for the millions of individuals afflicted with this disorder.

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THE GROWING THREAT FROM DIABETES MELLITUS

The incidence of diabetes mellitus (DM) throughout the world is increasing at an exponential rate such that the World Health Organization predicts that DM will be the seventh leading cause of death by the year 2030[1]. In 2013, greater than a million deaths were attributable to DM that is believed to affect 347 million individuals throughout the world. In the United States, 21 million individuals are diagnosed with DM and another 8 million individuals are estimated to suffer from DM but are currently undiagnosed[2]. Reduced activity, increased body weight, and poor nutritional intake are considered significant factors that can lead to adult onset DM[3,4]. Duration of obese-years rather than body mass index can become a significant risk for developing DM[5].

DM is defined as being either non-insulin dependent (type 1) or insulin dependent (type 2)[6,7]. Type 1 DM occurs in approximately 5%-10% of DM patients and is an autoimmune disorder with the presence of alleles of the human leukocyte antigen class Ⅱ genes within the major histocompatibility complex. Destruction of pancreatic β-cells with inflammatory infiltration of the islets of Langerhans results in lost insulin production and regulation. About 90% of patients with type 1 DM have increased titers of autoantibodies (type 1A DM). The remaining 10% of type 1 DM individuals do not have serum autoantibodies and are considered to have maturity-onset diabetes of the young that can be a result of β-cell dysfunction with autosomal-dominant inheritance (type IB DM). Type 2 DM occurs in approximately 80%-90% of individuals with DM greater than the age of 40. Although approximately 10% of individuals with type 2 DM may have elevated serum autoantibodies similar to type 1 DM, type 2 DM represents a progressive deterioration of glucose tolerance with early β-cell compensation that has cell hyperplasia followed by a decrease in β-cell mass. Insulin resistance ensues as well as impairments in insulin secretion. Insulin resistance also may be a component of type 1 DM in some patients. Defective insulin secretion can result from impaired β-cell function, chronic exposure to free fatty acids and hyperglycemia, as well as the absence of inhibitory feedback through plasma glucagon levels.

CLINICAL IMPLICATIONS OF DM IN THE NERVOUS, CARDIAC, AND VASCULAR SYSTEMS

As a disease that affects all systems of the body, DM can lead to multiple clinical impairments especially in the nervous, cardiac, and vascular systems. DM results in cognitive loss not only through vascular disease and stroke[8], but also during chronic neurodegenerative disorders such as Alzheimer's disease[9,10]. Insulin resistance similar to its occurrence in DM also has been reported in patients with Alzheimer's disease, suggesting that degenerative disorders such as Alzheimer's disease could be mediated in some patient populations by impaired cellular metabolism[11]. DM also results in neuropsychiatric disorders[12,13], retinal disease[14-16], and peripheral nerve disorders[17]. In the cardiac system, DM can lead to sympathetic nerve dysfunction[18], cardiac fibrosis[19,20], ischemic reperfusion injury[21], cardiomyocyte injury[22], and cardiac hypertrophy[23]. DM also can significantly impact endothelial cells either in the brain or elsewhere in the body. Exposure to elevated glucose levels can result in endothelial cell senescence[24], dysfunctional mobilization of endothelial progenitor cells from the bone marrow[25], injury to the neuroglialvascular unit[14], loss of angiogenesis[26], and endothelial cell injury and loss[27-33].

During DM, oxidative stress is an important driver of cell injury[4,6,34-39]. In murine animal models of type 2 DM, oxidative stress can lead to elevated glutathione levels and increased lipid peroxidation[23]. "Highly-oxidized glycated" low density lipoproteins that can occur in DM lead to oxidative and endoplasmic reticulum stress in human retinal capillary pericytes. Subsequently, mitochondrial dysfunction and cell death with apoptosis and autophagy ensues[15]. Exposure of glucolipotoxicity caused by elevated plasma glucose and lipid levels to pancreatic β-cells promotes oxidative stress with cytochrome c release, caspase activation, and apoptosis[40]. Advanced glycation end products (AGEs), entities that promote complications in DM[41], lead to the release of reactive oxygen species (ROS) and caspase activation[37]. In addition, high fat diets[42] as well as free fatty acids have been shown to release ROS, lead to mitochondrial DNA damage, and impair pancreatic β-cell function[43]. In cardiomyocytes[20,22,44], neurons[8,15,30,45,46], and endothelial cells[14,25,27-29,47], exposure to elevated glucose levels foster oxidant stress mechanisms that can impair cellular function and lead to cell death. In clinical studies, patients with type 2 DM display serum markers of oxidative stress with ischemia-modified albumin[48]. Interestingly, elevations in serum glucose can increase antioxidant enzyme levels in human endothelial cells, suggesting that some cells may initiate a reparative process against oxidative stress injury[49]. Of note, chronic hyperglycemia is not necessary to lead to oxidative stress injury, since even brief periods of hyperglycemia generate ROS[50]. Clinical correlates support these experimental studies to show that both acute glucose swings as well as chronic hyperglycemia can trigger oxidative stress mechanisms during type 2 DM[51].

NOVEL STRATEGIES FOR DM WITH MECHANISTIC TARGET OF RAPAMYCIN

Numerous cellular pathways can lead to oxidative stress during DM. As a result, multiple therapeutic avenues are being pursued to develop therapy against
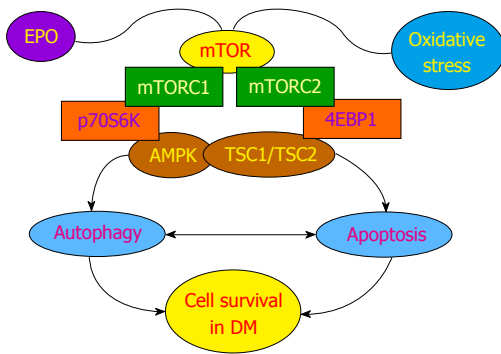
Figure 1 Cellular signaling of mechanistic target of rapamycin in diabetes mellitus. mTOR is a component of the protein complexes mTORC1 and mTORC2 with two important targets of p70S6K and 4EBP1 that promote mTOR kinase activity. mTOR signaling is controlled by AMPK that oversees the activity of TSC1/TSC2, an inhibitor of mTORC1. During periods of oxidative stress in DM, EPO uses mTOR to protect cell survival from programmed cell death injury. For example, EPO blocks cell injury in studies of diabetic retinal degeneration, maintains endothelial cell integrity during experimental models of DM, and regulates the detrimental effects of obesity in animal models. AMPK can have dual roles in cell survival. AMPK can limit oxidative stress that can lead to hypertension and reduce insulin resistance through autophagy that can have linked pathways to apoptosis. However, under other circumstances AMPK also can lead to neuroinflammation and cardiac dysfunction. Ultimately, a careful balance in the activities of autophagy and apoptosis is required through mTOR to foster cell survival during DM. mTOR: Mechanistic target of rapamycin; DM: Diabetes mellitus; AMPK: AMP activated protein kinase; EPO: Erythropoietin; p70S6K: p70 ribosomal S6 kinase; 4EBP1: 4E-binding protein 1; mTORC1: mTOR complex 1; TSC1/TSC2: Tuberous sclerosis 1/ tuberous sclerosis 2.

the complications of DM. These strategies include the recent focus upon sirtuins[24,47,52-56], protein tyrosine phosphatases[57,58], broad antioxidant therapies[3,7,17,31,34, 38,59], forkhead transcription factors[56,60-63], and growth factors[32,64-68].

In reference to growth factors, the cytokine and growth factor erythropoietin (EPO) serves as a provocative model for potential treatments for the complications of DM (Figure 1). EPO blocks cell injury in studies of diabetic retinal degeneration[14], maintains endothelial cell integrity during experimental models of DM[27,28], facilitates wound healing during DM[65], reduces high glucose-induced oxidative stress in renal tubular cells[69], maintains cellular mitochondrial function and energy metabolism[32], and regulates the detrimental effects of obesity in animal models[33]. Although EPO affects multiple cellular signal transduction pathways in the body[70,71], of particular interest are the signal transduction pathways of the mechanistic target of rapamycin (mTOR) controlled by EPO that are intimately linked to cellular metabolism and DM[72-76]. mTOR can influence neuronal, glial, and cell to cell activity[77,78]. EPO uses mTOR to protect cells against oxygen-glucose deprivation[79,80], limit cell injury during β-amyloid exposure[81], control bone homeostasis[82], improve cognitive function in models of sepsis-associated encephalopathy[83], foster retinal progenitor cell survival during oxidant stress[84], and promote the neuronal phenotype of adult neuronal precursor cells[85].

mTOR, also known as the mammalian target of rapamycin and FK506-binding protein 12-rapamycin complex-associated protein 1, is a 289-ku serine/threonine protein kinase. mTOR is encoded by a single gene *FRAP1*[86-88] and is a component of the protein complexes mTOR complex 1 (mTORC1) and mTORC2 (Figure 1). Rapamycin, an agent that inhibits mTOR activity, blocks mTORC1 by preventing the phosphorylation of mTOR. In some cases with chronic administration, rapamycin also can inhibit mTORC2. mTORC1 is composed of raptor (regulatory-associated protein of mTOR), the proline rich Akt substrate 40 ku, deptor (DEP domain-containing mTOR interacting protein), and mLST8/G L (mammalian lethal with Sec13 protein 8, termed mLST8). Two important targets of mTORC1 through mLST8 that promote mTOR kinase activity are p70 ribosomal S6 kinase and the eukaryotic initiation factor 4E-binding protein 1[89,90]. mTORC2 is composed of rictor (rapamycin-insensitive companion of mTOR), deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with rictor-1 (Protor-1)[75,91].

In addition to phosphoinositide 3-kinase and protein kinase B (Akt)[6,92], mTOR signaling also is governed by AMP activated protein kinase (AMPK)[75,91]. AMPK can control the activity of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that is an inhibitor of mTORC1. AMPK phosphorylates TSC2 as well as Raptor to block the activity of mTORC1 during energy stress[93]. AMPK also controls TSC1/2 activity through RTP801 (REDD1/ product of the *Ddit4* gene). AMPK activity can increase REDD1 expression, such as in the presence of hypoxic environments, to suppress mTORC1 activity by releasing TSC2 from its inhibitory binding to protein 14-3-3[94].

AMPK can have dual roles in cell survival (Figure 1). AMPK activation can suppress β-amyloid (Aβ) production[95], regulate tau phosphorylation[96], limit oxidative stress that can lead to hypertension[97], increase cell survival during hypoxia[98], and promote autophagy that may resolve memory impairment[99]. However, in other experimental models, AMPK activity has been suggested to influence neuroinflammation[100], lead to aberrant Aβ stress[96] and Aβ toxicity[101], result in cardiac dysfunction[102], and result in the hypertrophy of cardiac tissues[103]. In regards to cellular metabolism with AMPK[104], AMPK can reduce insulin resistance and diminish oxidative stress mediated through the programmed cell death pathway of autophagy[105], reduce myocardial ischemia in experimental models of diabetes[21], be necessary for proper metabolic function of cells[106], and block adipocyte differentiation, lipid accumulation, and obesity[107]. Loss of AMPK may lead to insulin resistance[108].

TARGETING APOPTOSIS AND AUTOPHAGY WITH mTOR FOR DM

For the development of new strategies against DM with mTOR, a careful balance in the activity of the programmed

cell death pathways of apoptosis and autophagy must be considered. Both apoptosis[4,7,17,32,38,109] and autophagy[6,74,110,111] can influence cell survival during oxidative stress[112]. In regards to cellular metabolic pathways, activation of mTOR that blocks apoptotic pathways may limit insulin resistance and vascular thrombosis in patients with metabolic syndrome[113]. Increased activity of mTOR also may prevent the development of atherosclerosis[114]. Furthermore, mTOR activation through glucagon-like peptide-1 agonists has recently been reported to protect pancreatic β-cells from cholesterol mediated apoptotic cell injury[115], promote pancreatic β-cell proliferation[116], and prevent neural apoptotic cell loss during DM through the epidermal growth factor receptor[117].

In other studies with DM, it is the induction of autophagy with requisite mTOR inhibition that is suggested to foster cellular protection. For example, metformin, an agent used to control hyperglycemia in DM, inhibits mTOR activity and promotes autophagy. Metformin can offer protection against endothelial cell senescence[24], limit androgen up-regulation during prostate cancer through mTOR inhibition[118], prevent cell loss during hypoxia through increased AMPK activity[98], and protect against neuronal cell apoptosis[119]. Metformin through pathways that activate AMPK also prevents cardiomyopathy in experimental models of DM[120], fosters cardiomyocyte cell survival[121], and reduces cortical infarction in stroke models[122].

Additional work suggests that autophagy irrespective of the contribution of mTOR may be protective during DM. Autophagy haploinsufficiency in murine animal models of obesity leads to increased insulin resistance with elevated lipids and inflammation[123], suggesting that loss of autophagy may foster the progression from obesity to DM. Autophagy also may be required to remove misfolded proteins and eliminate non-functioning mitochondria to prevent β-cell dysfunction and the onset of DM[124]. In addition, exercise in mice has been shown to initiate autophagy and regulate glucose homeostasis[125]. These results may be associated with observations that autophagy has been reported to improve insulin sensitivity during high fat diets in mice[105].

Yet, in other experimental models, autophagy may not be beneficial even though it can be less of a prominent modulator of cell survival than apoptosis in some experimental models[126]. Autophagy during high glucose exposure has been shown to impair endothelial progenitor cells, lead to mitochondrial oxidative stress, and prevent the formation of new blood vessels[127]. Increased autophagy also has been associated with significant loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification[128]. During periods of elevated glucose that occur in DM, AGEs have been shown to lead to the induction of autophagy and vascular smooth muscle proliferation that can result in atherosclerosis[129] as well as cardiomyopathy[44].

FUTURE CONSIDERATIONS

DM is a significant and growing disorder throughout the world that leads to increased disability and death through multiple complications in the nervous, cardiac, and vascular systems. Current therapies for these complications are limited. As a result, novel therapeutic strategies are required to address the cellular mechanisms of oxidant stress and cell injury that can mediate complications of DM. Given the recent discovery that cytoprotective strategies against oxidative stress, *i.e.*, EPO, employ mTOR, the mTOR signaling pathways that include AMPK and TSC1/TSC2 have become increasingly recognized as a potential targets for the treatment of the complications of DM. However, future work will need to concentrate upon the complex relationship that the programmed cell death pathways of apoptosis and autophagy hold over cellular survival and longevity to attain both efficacy and safety for mTOR targeted strategies.

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