NEURAL REGENERATION RESEARCH
March 2016, Volume 11, Issue 3
www.nrronline.org

INVITED REVIEW

Novel nervous and multi-system regenerative therapeutic strategies for diabetes mellitus with mTOR

Kenneth Maiese*

Cellular and Molecular Signaling, Newark, NJ, USA

How to cite this article: *Maiese K (2016) Novel nervous and multi-system regenerative therapeutic strategies for diabetes mellitus with mTOR. Neural Regen Res 11(3):372-385.*

Funding: *This research was supported by American Diabetes Association, American Heart Association, NIH NIEHS, NIH NIA, NIH NINDS, and NIH ARRA.*

Abstract

Throughout the globe, diabetes mellitus (DM) is increasing in incidence with limited therapies presently available to prevent or resolve the significant complications of this disorder. DM impacts multiple organs and affects all components of the central and peripheral nervous systems that can range from dementia to diabetic neuropathy. The mechanistic target of rapamycin (mTOR) is a promising agent for the development of novel regenerative strategies for the treatment of DM. mTOR and its related signaling pathways impact multiple metabolic parameters that include cellular metabolic homeostasis, insulin resistance, insulin secretion, stem cell proliferation and differentiation, pancreatic β-cell function, and programmed cell death with apoptosis and autophagy. mTOR is central element for the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) and is a critical component for a number of signaling pathways that involve phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), AMP activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), Wnt1 inducible signaling pathway protein 1 (WISP1), and growth factors. As a result, mTOR represents an exciting target to offer new clinical avenues for the treatment of DM and the complications of this disease. Future studies directed to elucidate the delicate balance mTOR holds over cellular metabolism and the impact of its broad signaling pathways should foster the translation of these targets into effective clinical regimens for DM.

Key Words: *Akt; AMP activated protein kinase (AMPK); apoptosis; Alzheimer's disease; autophagy; β-cell; cancer; cardiovascular disease; caspase; CCN family; diabetes mellitus; epidermal growth factor; erythropoietin; fibroblast growth factor; forkhead transcription factors; FoxO; FRAP1; hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2); insulin; mechanistic target of rapamycin (mTOR); mTOR Complex 1 (mT ORC1); mTOR Complex 2 (mTORC2); nicotinamide; nicotinamide adenine dinucleotide (NAD^+); non-communicable diseases; oxidative stress; phosphoinositide 3-kinase (PI 3-K); programmed cell death; silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1); sirtuin; stem cells; wingless; Wnt; Wnt1 inducible signaling pathway protein 1 (WISP1)*

Correspondence to:
Kenneth Maiese, M.D., wntin75@yahoo.com.

orcid:
0000-0002-5049-9116 (Kenneth Maiese)

doi: *10.4103/1673-5374.179032*
http:*//www.nrronline.org/*

Accepted: *2016-02-19*

Introduction

The incidence of non-communicable diseases (NCDs) is increasing throughout the world. According to the World Health Organization, greater than 60 percent of the 57 million global deaths are attributable to NCDs (World Health Organization, 2011). In low and middle-income countries, NCDs can affect almost one-third of the population under the age of 60. Conversely, slightly greater than 10 percent of the population under 60 is affected in high-income countries (World Health Organization, 2011). The rise in NCDs parallels the increase in life expectancy of the world's population. Improvements in effective treatments for multiple disorders and broader access to preventive care have most likely contributed to the increased life span of the global population. For example, the number of individuals over the age of 65 has doubled during the previous 50 years with life expectancy approaching 80 years of age. In addition, life expectancy has been marked by a 1 percent decrease in the age-adjusted death rate from the years 2000 through 2011 (Minino, 2013).

One of the most significant NCDs that affect the global population is diabetes mellitus (DM) (Haldar et al., 2015; Maiese, 2015h). DM is increasing in incidence throughout the world. It is estimated that approximately 350 million individuals currently have DM (Maiese et al., 2011, 2013a; Rutter et al., 2012; Jia et al., 2014; Xu et al., 2014a) and another 8 million individuals are believed to suffer from metabolic disorders but remain undiagnosed at present (Harris and Eastman, 2000; Maiese et al., 2007; Maiese, 2015f). Financial costs for DM are also significant. In the United States (US), almost 9,000 US dollars are required to care for each individual with DM per year. The care for patients with DM consumes 17 percent of the Gross Domestic Product in the US as reported by the Centers for Medicare and Medicaid Services (CMS) (Centers for Medicare and Medicaid Services, 2013). Approximately $176 billion is required for direct medical costs and another $69 billion in lost finances

results from reduced productivity tied to DM.

Obesity and impaired glucose tolerance further complicate the clinical presentation for DM (Maiese, 2015e; Tulsulkar et al., 2016). Impaired glucose tolerance in the young as well as the presence of obesity increases the risk of developing DM in these individuals (Maiese et al., 2011). Obesity and excess body fat can lead to alterations in protein tyrosine phosphatase signaling, insulin resistance, oxidative stress mediated cell death, cellular inflammation, mitochondrial dysfunction, impairments in growth factor function, injury to pancreatic β cells, and altered DNA methylation (Xu et al., 2014a,b; Maiese, 2015c; Mikhed et al., 2015; Snyder and Stefano, 2015; Wang et al., 2015; Xiao et al., 2015).

Early diagnosis of DM and quickly instituting available therapies for individuals with DM can offer some degree of improvement and slow the progression of DM. However, tight serum glucose control does not always lead to the resolution of complications from DM (Maiese et al., 2011; Coca et al., 2012). Use of diet control treatments may be effective to prevent hyperglycemic events, but these strategies also can potentially decrease organ mass through processes that involve autophagy (Lee et al., 2014).

DM can be classified as either non-insulin dependent (Type 1) DM or insulin dependent (Type 2) DM (Maiese et al., 2010, 2013b). Type 1 DM occurs in ten percent of patients. It is an autoimmune disorder associated with the alleles of the human leukocyte antigen class II genes within the major histocompatibility complex (Maiese et al., 2007). Insulin production and homeostasis is lost with the destruction of pancreatic β-cells with inflammatory infiltration of the islets of Langerhans. Almost 90 percent of patients with Type 1 DM have increased titers of autoantibodies (Type 1A DM), but the remaining ten percent of Type 1 DM individuals do not have these serum autoantibodies (Maiese, 2015f, h). These individuals have maturity-onset diabetes of the young (MODY) that can occur form the β-cell dysfunction with autosomal-dominant inheritance (Type IB DM). Type 2 DM is present in ninety percent of individuals and usually occurs in individuals over the age of 40. A progressive deterioration of glucose tolerance with early β-cell compensation results with Type 2 DM (Maiese et al., 2007, 2013a). Loss of insulin secretion is a result of multiple factors that involve prolonged exposure to free fatty acids and hyperglycemia, impaired β-cell function, and the absence of inhibitory feedback through plasma glucagon levels. Type 1 and Type 2 DM have functional overlap. Approximately ten percent of individuals with Type 2 DM can have elevated serum autoantibodies similar to Type 1 DM. Insulin resistance also may exist in some patients with Type 1 DM (Maiese, 2015e).

DM is a multi-system disease that can lead to progressive deterioration of the body (Esser et al., 2015; Gomez-Brouchet et al., 2015; Haldar et al., 2015; Maiese, 2015f). For example, DM can affect the nervous system and lead to peripheral nerve disorders, cognitive loss that also may be associated with Alzheimer's disease (AD) (Maiese et al., 2008a; Du et al., 2015; Kapogiannis et al., 2015; White, 2014), loss of neuronal cell longevity (White, 2014), psychiatric disorders (Hadamitzky et al., 2014; Ignacio et al., 2015), visual impairment (Fu et al., 2012; Lee et al., 2012a; Busch et al., 2014; Maiese, 2015f), and stroke (Maiese et al., 2008b; Alexandru et al., 2012; Jiang et al., 2014; Xu et al., 2014b; Maiese, 2015a; Xiao et al., 2015). In the central nervous system, insulin resistance and dementia that occur during DM has been shown to be present in patients with Alzheimer's disease (Maiese et al., 2007; Sonnen et al., 2009), demonstrating that degeneration in the nervous system may be the result of impaired cellular metabolism similar to that which occurs during DM (Kapogiannis et al., 2015). In the peripheral nervous system, DM can lead to autonomic neuropathy (Albiero et al., 2014) and peripheral nerve disease (Gomes and Negrato, 2014; Gomez-Brouchet et al., 2015). It is estimated that at least seventy percent of individuals with DM can develop some degree of diabetic peripheral neuropathy. Assessment of the course of the disease may be difficult since the disorder is chronic in nature, may be sub-clinical, and prior deficits may go undetected if improved control over glucose homeostasis is initiated. Closely tied to neuronal degeneration is the loss of the neurovascular unit. DM can lead to impairment of the neuroglialvascular unit (Busch et al., 2014), endothelial cell injury (Chong et al., 2007, 2011; Hou et al., 2010a; Schaffer et al., 2012; Liu et al., 2013b; Wang et al., 2014a; Zhang et al., 2014), loss of angiogenesis (Chen et al., 2012), endothelial cell senescence (Arunachalam et al., 2014), depletion and dysfunction of endothelial progenitor cells (Barthelmes et al., 2014; Kim et al., 2014), and cardiovascular complications (Chong and Maiese, 2012; Xu et al., 2014b; Yu et al., 2015a). DM also can have detrimental effects on the immune system, musculoskeletal function, hepatic metabolism, and renal clearance (D'Onofrio et al., 2015; Esser et al., 2015).

Given the significant impact DM has only multiple systems of the body and especially the nervous system, new therapeutic strategies that can address the onset and progression of DM in the body are desperately needed. In particular, the mechanistic target of rapamycin (mTOR) is one such avenue to consider the development of novel effective strategies to repair and potentially regenerate injured portions of the nervous system during DM. mTOR is tightly linked to DM cellular metabolism (Maiese et al., 2013c; Maiese, 2014b; Johnson et al., 2015). For example, mTOR can lead to pancreatic β- cell proliferation (Miao et al., 2013), block neuronal cell apoptosis during DM through the epidermal growth factor (EGF) receptor (Kimura et al., 2013), stimulate adipocyte differentiation to enhance glucose uptake (Jung et al., 2015), may protect against cognitive loss during DM through increased expression of acetylcholinesterase (AChE) (Liu et al., 2015), and can foster glucose homeostasis (Malla et al., 2015a).

mTOR Signaling in Metabolic Disease

mTOR, a 289-kDa serine/threonine protein kinase that is encoded by a single gene FRAP1, represents one such target for novel strategies of drug development for the treatment of DM and the complications of this disorder (Chong and Maiese, 2012; Zhou et al., 2015; Berry et al., 2016). mTOR also is recognized as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1. The target of rapamycin (TOR) was initially

described in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* (Maiese et al., 2013c). Through the use of rapamycin-resistant TOR mutants, TOR1 and TOR2 were found to encode the Tor1 and Tor2 isoforms in yeast (Heitman et al., 1991). Rapamycin is a macrolide antibiotic (Singh et al., 1979) in *Streptomyces hygroscopicus* that blocks TOR and mTOR activity (Maiese, 2015j). mTOR forms the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (**Figure 1**) (Gulhati et al., 2011; Zoncu et al., 2011; Chong et al., 2012c; Maiese, 2014d). Rapamycin can prevent mTORC1 activity by binding to immunophilin FK-506-binding protein 12 (FKBP12) that attaches to the FKBP12 -rapamycin-binding domain (FRB) at the carboxy (C) -terminal of mTOR to interfere with the FRB domain of mTORC1. The precise mechanism of how rapamycin interaction with the domain of FRB leads to inhibition of mTORC1 is unclear, but may involve allosteric changes on the catalytic domain as well as the inhibition of phosphorylation of protein kinase B (Akt) and p70 ribosomal S6 kinase (p70S6K) (Xue et al., 2009). In general, mTORC1 is more sensitive to inhibition by rapamycin than mTORC2, but chronic administration of rapamycin can inhibit mTORC2 activity as a result of the disruption of the assembly of mTORC2 (Sarbassov et al., 2006). Overall, mTOR is ubiquitous in the body and drives gene transcription, protein formation, cellular proliferation, and the metabolic function of cells.

mTORC1 consists of Raptor, the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8/G L) (**Figure 1**) (Maiese et al., 2013c). mTORC1 can bind to its constituents through the protein Ras homologue enriched in brain (Rheb) that phosphorylates the Raptor residue serine^{863} and other residues that include serine^{859}, serine^{855}, serine^{877}, serine^{696}, and threonine^{706} (Foster et al., 2010). The inability to phosphorylate serine^{863} limits mTORC1 activity, as demonstrated using a site-direct mutation of serine^{863} (Wang et al., 2009). In this system, mTOR can control Raptor activity that can be blocked by rapamycin (Wang et al., 2009). Deptor also is inhibitory. Deptor blocks mTORC1 activity by binding to the FAT (FKBP12-rapamycin-associated protein (FRAP), ataxia-telangiectasia (ATM), and the transactivation/transformation domain-associated protein) domain of mTOR. If the activity of Deptor is diminished, protein kinase B (Akt), mTORC1, and mTORC2 activity are increased (Peterson et al., 2009). PRAS40 also can inhibit mTORC1 activity. PRAS40 blocks mTORC1 activity by preventing the association of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) with Raptor (Maiese, 2014b; Malla et al., 2015b). mTORC1 becomes active once Akt phosphorylates PRAS40. This releases PRAS40 from Raptor to sequester PRAS40 in the cytoplasm with the docking protein 14-3-3 (Fonseca et al., 2007; Chong et al., 2012b; Shang et al., 2012; Wang et al., 2012a; Xiong et al., 2014). In contrast to Deptor and PRAS40, mLST8 fosters mTOR kinase activity. This involves the binding of p70S6K and 4EBP1 to Raptor (Kim et al., 2003). mLST8 also controls insulin signaling through the transcription factor FoxO3 (Guertin et al., 2006; Maiese, 2015i), is necessary for Akt and protein kinase C-α (PKCα) phosphorylation, and is required for Rictor to associate with mTOR (Guertin et al., 2006).

In relation to mTORC2 (**Figure 1**), mTORC2 consists of Rictor, mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (Chong et al., 2010; Glidden et al., 2012; James et al., 2012; Kamarudin et al., 2014; Maiese, 2014a; Tang et al., 2014). mTORC2 is involved in cytoskeleton remodeling through PKCα and cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling (Jacinto et al., 2004). mTORC2 may be necessary to maintain glucose homeostasis, since loss of this pathway can promote sever hyperglycemia (Treins et al., 2012). Impairment in mTORC2 signaling also leads to oxidative damage and insulin resistance (Wang et al., 2011a). In addition, mTORC2 signaling plays a significant role for the maintenance of pancreatic β-cell proliferation and mass (Gu et al., 2011).

mTORC2 can activate protein kinases, such as glucocorticoid induced protein kinase 1 (SGK1), a member of the protein kinase A/protein kinase G/protein kinase C (AGC) family of protein kinases. Protor-1, a Rictor-binding subunit of mTORC2, activates SGK1 (Garcia-Martinez and Alessi, 2008; Pearce et al., 2011). The kinase domain of mTOR can phosphorylate mSIN1 and prevent lysosomal degradation of this protein. Rictor (Sarbassov et al., 2005) and mSIN1 (Frias et al., 2006) also can phosphorylate Akt at serine^{473} and foster threonine^{308} phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) to enhance cell survival.

Phosphoinositide 3-kinase (PI 3-K) and Akt are critical in mTOR signaling (Neasta et al., 2014; Korpi et al., 2015; Liu et al., 2015; Moon et al., 2015; Sun et al., 2015) (**Figure 2**). The terminal domains of mTOR control the catalytic activity, binding, and phosphorylation of mTOR (Maiese et al., 2013c). In particular, the C-terminal domain of mTOR possesses a sequence homology to the catalytic domain of the PI 3-K family and contains several phosphorylation sites that regulate mTOR. Downstream from PI 3-K, Akt can block activity of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that inhibits mTORC1 (Chong et al., 2012a; Janku et al., 2012; Maiese, 2013; Morgan-Warren et al., 2013). Control of the TSC1/TSC2 complex is principally controlled though Akt and its phosphorylation of TSC2 (Maiese, 2014a). Extracellular signal-regulated kinases (ERKs), protein p90 ribosomal S6 kinase 1 (RSK1), glycogen synthase kinase -3β (GSK-3β), and AMP activated protein kinase (AMPK) also can modulate the activity TSC1/TSC2 complex. Akt can phosphorylate TSC2 at serine^{939}, serine^{981}, and threonine^{1462} to lead to the binding of TSC2 to cytoplasmic protein 14-3-3, disengagement of the TSC1/TSC2 complex, and activation of Rheb and mTORC1 (Cai et al., 2006). However under some conditions that promote cell survival, a limited activity of TSC2 and AMPK is necessary since complete knockdown of TSC2 can result in cell death (Shang et al., 2013). In contrast to the TSC1/TSC2 complex inhibiting mTORC1 activity, mTORC2 activity is increased during activation of the TSC1/TSC2 complex through the amino (N)-terminal region of TSC2 and the C-terminal region of Rictor (Huang et al., 2008).

Similar to PI 3-K and Akt, AMPK plays a significant role in the control of mTOR activity, especially in metabolic disease (**Figure 2**). AMPK can inhibit mTORC1 activity through the activation of the TSC1/TSC2 complex. TSC2 functions as a GTPase-activating protein (GAP) converting G protein Rheb (Rheb-GTP) into the inactive GDP-bound form (Rheb-GDP). Once Rheb-GTP is active, Rheb-GTP associates with Raptor to oversee the binding of 4EBP1 to mTORC1 and increase mTORC1 activity (Sato et al., 2009). AMPK phosphorylates TSC2 to increase GAP activity to change Rheb-GTP into the inactive Rheb-GDP and to block mTORC1 activity (Inoki et al., 2003). AMPK also can increase RTP801 (REDD1/ product of the *Ddit4* gene) expression, an inhibitor of mTOR signaling (Benyoucef et al., 2015), to increase TSC1/TSC2 activity and suppress mTORC1 activity by releasing TSC2 from its association with protein 14-3-3. AMPK interfaces with other cellular pathways that can affect cell survival and stem cell maintenance, such as the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) (Favero et al., 2015; Maiese, 2015a). AMPK increases nicotinamide phosphoribosyltransferase (NAMPT) activity to convert nicotinamide to nicotinamide mononucleotide (Maiese et al., 2009b; Wang et al., 2014b; Maiese, 2015k). As a result, this increases nicotinamide adenine dinucleotide (NAD^+) levels, decreases levels of the SIRT1 inhibitor nicotinamide, and promotes SIRT1 transcription (Wang et al., 2011b; Chong et al., 2012d; Maiese, 2015h). With an increased intracellular NAD+/NADH ratio, AMPK deacetylates the SIRT1 targets peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1β) and forkhead transcription factors that include FoxO1 (Maiese et al., 2009a) and FoxO3a (Canto and Auwerx, 2009). Together, SIRT1 and AMPK can function as inhibitors of mTOR (Maiese et al., 2013a).

In regards to metabolic disease, AMPK has been shown to reduce insulin resistance, since the loss of AMPK results in reduced tolerance to the development of insulin resistance (Liu et al., 2014b). AMPK activation may improve memory retention in models of AD and DM (Du et al., 2015), maintain the proper metabolic function of cells, prevent adipocyte differentiation, lipid accumulation, and obesity, and limit cardiac ischemia in animal models (Maiese, 2015k). In addition, metformin, an agent that controls hyperglycemia in DM, inhibits mTOR activity and leads to the induction of autophagy. Metformin can activate AMPK (Leclerc et al., 2013) and also block mTOR activity through pathways independent of AMPK (Kalender et al., 2010). Metformin prevents cell loss during hypoxia through increased AMPK activity (Sheng et al., 2012), confers neuroprotection (Jiang et al., 2014), reduces cardiomyopathy in experimental models of DM (Xie et al., 2011) and prevents endothelial cell senescence (Arunachalam et al., 2014). With SIRT1, AMPK inhibits mTOR activity and SIRT1 assists with mesangial cell proliferation during high glucose exposure (Zhang et al., 2012). In combination, SIRT1 and AMPK may offer cellular protection of endothelial cells through the induction of autophagy against oxidized low-density lipoproteins (Jin et al., 2014). However, under some conditions, limited AMPK activity may be better suited for cellular protection in DM. Reduced AMPK activity can promote the protection of pancreatic islet cells in mice (Guan et al., 2014), limit amyloid (Aβ) toxicity (Shang et al., 2013), and prevent inflammation in the nervous system (Russo et al., 2014).

mTOR and Programmed Cell Death

For mTOR to control the survival of cells during DM, mTOR must oversee the programmed cell death pathways of apoptosis and autophagy (**Figure 1**) (Maiese et al., 2012b). Apoptosis consists of a cascade that activates nucleases and proteases involving caspases that can affect both the early phase of apoptosis with the loss of plasma membrane phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation (Shang et al., 2010; Viola et al., 2012; Wong et al., 2012). Membrane PS externalization, a reversible process, activates inflammatory cells to engulf and remove injured cells (Shang et al., 2009; Bailey et al., 2010; Hou et al., 2010b; Wei et al., 2013). If this process is prevented, loss of functional cells expressing membrane PS residues can be averted and genomic DNA degradation does not result (Yang et al., 2013; Weinberg et al., 2014; Maiese, 2015e). The destruction of cellular DNA is not a reversible process (Kim et al., 2015; Maiese, 2015f; Xin et al., 2015; Yu et al., 2015b).

During DM, apoptosis affects multiple cell types leading to cell death in endothelial cells, renal cells, neurons, cardiomyocytes, and pancreatic β-cells. In addition, DM can incite multiple pathways of programmed cell death. "Highly-oxidized glycated" low-density lipoproteins that are formed during DM lead to oxidative stress in human retinal capillary pericytes with subsequent induction of both apoptosis and autophagy (Fu et al., 2012). Impairment of mitochondrial dysfunction that can occur during DM and oxidative stress also can affect the induction of apoptotic pathways (Perez-Gallardo et al., 2014; Maiese, 2015k; Mikhed et al., 2015; Parmar et al., 2015; Wang et al., 2015). Mitochondrial dysfunction results in the opening of the mitochondrial membrane permeability transition pore, release of cytochrome c, and caspase activation (Maiese et al., 2010; Perez-Gallardo et al., 2014; Wang et al., 2014a; Poulose and Raju, 2015). Glucolipotoxicity exposure to pancreatic β-cells results in oxidative stress and mitochondrial dysfunction with cytochrome c release, caspase activation, and apoptosis (Liu et al., 2012). In addition, loss of functional mitochondrial proteins and mitochondrial DNA in adipocytes has been associated with the development of Type 2 DM (Choo et al., 2006). Patients with Type 2 DM also have impaired skeletal muscle mitochondrial activity than those in control subjects (Petersen et al., 2004; Newsholme et al., 2012).

mTOR activation blocks apoptosis to limit insulin resistance and vascular thrombosis in patients with metabolic syndrome (**Figure 1**). Increased activity of mTOR also may prevent the development of atherosclerosis (Peng et al., 2014). mTOR activation through glucagon-like peptide-1 agonists can protect pancreatic β-cells from cholesterol mediated apoptotic cell injury (Zhou et al., 2015), prevent neural apoptotic cell loss during DM through the epidermal growth factor receptor (EGF) (Kimura et al., 2013), and foster pancreatic β-cell proliferation (Miao et al., 2013) (**Figure 2**).

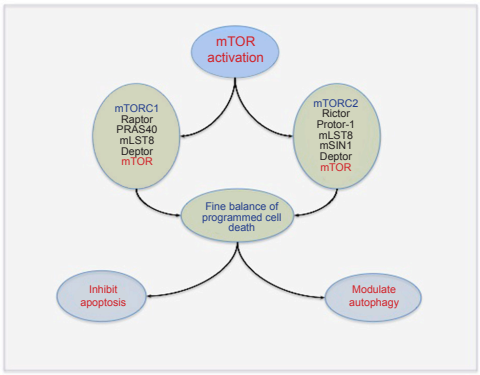

Figure 1 mTOR controls the structure and function of mTORC1 and mTORC2 to ultimately impact programmed cell death in diabetes mellitus through apoptosis and autophagy.
The mechanistic target of rapamycin (mTOR) is a critical element of both mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). mTORC1 is composed of mTOR, Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), the mammalian lethal with Sec13 protein 8 (mLST8/G L), and Deptor (DEP domain-containing mTOR interacting protein). mTORC2 consists of mTOR, Rictor (Rapamycin-Insensitive Companion of mTOR), the mammalian stress-activated protein kinase interacting protein (mSIN1), the protein observed with Rictor-1 (Protor-1), Deptor, and mLST8. Activation of mTOR can block apoptotic cell injury while inhibition of mTOR can lead to the induction of autophagy that affects insulin resistance and inflammation.

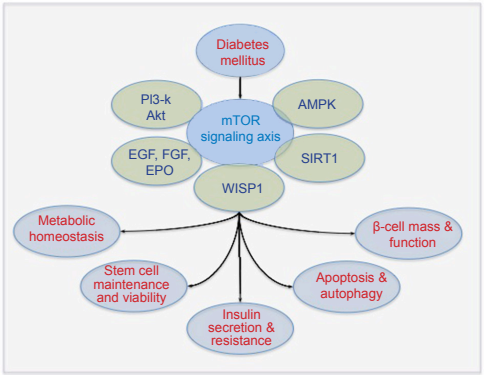

Figure 2 mTOR signaling in diabetes mellitus is intimately tied to several critical pathways that can govern cellular metabolism.
The mTOR signaling axis relies upon phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), AMP activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), Wnt1 inducible signaling pathway protein 1 (WISP1), and the growth factors epidermal growth factor (EGF), fibroblast growth factor (FGF), and erythropoietin (EPO) to regulate metabolic pathways. mTOR and its related signaling pathways can oversee metabolic homeostasis, stem cell maintenance and viability, insulin secretion and resistance, apoptosis, autophagy, and pancreatic β-cell mass and function.

During periods of reduced mTOR activity, induction of autophagy can result that can be either beneficial or detrimental during DM (**Figure 1**) (Maiese, 2015h). At least 33 autophagic related genes (*Atg*) that have been identified in yeast with TOR can affect multiple disorders including DM (Weckman et al., 2014; Maiese, 2015k). Atg1, Atg13 (also known as Apg13), and Atg17 are associated with the PI 3-K, Akt, and TOR pathways (Klionsky et al., 2016). Either the Atg1 complex in yeast or the UNC-51 like kinase 1 (ULK1) complex in mammals is necessary for the induction of autophagy (Kamada et al., 2000; Maiese et al., 2012b). The mammalian homologues of Atg1 are UNC-51 like kinase 1 (ULK1) and ULK2 (Chong et al., 2012c). Mammalian Atg13 binds to ULK1, ULK2, and FIP200 (focal adhesion kinase family interacting protein of 200 kDa) to activate ULKs, promote the phosphorylation of FIP200 by ULKs, and lead to autophagy induction (Jung et al., 2009). mTOR activity blocks the onset of autophagy by phosphorylating Atg13 and ULKs to prevent formation of the ULK-Atg13-FIP200 complex (Jung et al., 2009). In general, autophagy recycles components of the cell cytoplasm to remove non-functional organelles and initiate tissue remodeling (Maiese et al., 2012b; Francois et al., 2014; Vakifahmetoglu-Norberg et al., 2015; Nakka et al., 2016). Macroautophagy is the classification of autophagy most often responsible for the recycling of organelles and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes that combine with lysosomes for degradation and recycling (Maiese, 2014b; Frederick et al., 2015; Sasazawa et al., 2015). Other categories for autophagy include microautophagy that uses the invagination of the lysosomal membrane for the sequestration and digestion of cytoplasmic components (Maiese et al., 2012b). Another category, chaperone-mediated autophagy, uses cytosolic chaperones to transport cytoplasmic components across lysosomal membranes (Maiese, 2015i).

Loss of autophagy pathways may be detrimental during DM. Autophagy haploinsufficiency with deletion of an essential *Atg7* gene in mouse models of obesity promotes increased insulin resistance with elevated lipids and inflammation (Lim et al., 2014). These results suggest that the loss of autophagy may lead an individual's status to progress from obesity to DM. Autophagy also may be necessary for the removal of misfolded proteins and to eliminate non-functioning mitochondria to maintain β-cell function and prevent the onset of DM (Liu et al., 2012). Exercise in mice can promote the induction of autophagy and regulate glucose homeostasis (He et al., 2012). These observations are consistent with studies that report autophagy can improve insulin sensitivity during high fat diets in mice (Liu et al., 2014b). Autophagy also may control apoptotic cell pathways that would otherwise lead to cell death. Induction of autophagy may protect cardiomyocytes from apoptosis during DM (He et al., 2013). During the inhibition of mTOR, induction of autophagy can offer protection during DM. As previously noted, metformin, an agent that that is currently used to treat DM and hyperglycemia, blocks mTOR activity and leads to the induction of autophagy. Metformin inhibits mTOR activity, promotes autophagy, and protects against endothelial cell senescence (Arunachalam et al., 2014). During the induction of autophagy, metformin through AMPK activation and mTOR inhibition prevents cardiomyopathy in models of DM (Xie et al., 2011), reduces cortical infarction in stroke models (Jiang et al., 2014), and increases cardiomyocyte survival (Xie et al., 2011; He et al., 2013).

However, induction of autophagy may be harmful even during periods when it is not the primary determinant of

cell injury, such as during apoptotic cell death (Wang et al., 2012b). Heightened activity of autophagy can lead to significant loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification (Lee et al., 2014). During periods of elevated glucose that occur in DM, advanced glycation end products (AGEs), agents that can result in complications during DM, have been shown to lead to the induction of autophagy and vascular smooth muscle proliferation that can result in atherosclerosis (Hu et al., 2012) as well as cardiomyopathy (Lee et al., 2012b). During elevated glucose exposure, autophagy also can impair endothelial progenitor cells, lead to mitochondrial oxidative stress (Martino et al., 2012), and block angiogenesis (Kim et al., 2014).

mTOR and Stem Cell Proliferation

In multiple systems of the body, mTOR can influence the proliferation and differentiation of stem cells (**Figure 2**) (Maiese, 2015j). Stem cell strategies are an important component for maintaining glucose homeostasis during DM (Balestrieri et al., 2013). Loss of the C-terminal six amino acids of mTOR that results in the inhibition of kinase activity decreases embryonic stem cell proliferation (Murakami et al., 2004). Reduced trophoblast growth, faulty implantation, and inability to establish embryonic stem cells occur during the deletion of the *mTOR* gene (Gangloff et al., 2004). Loss of mTOR activity also leads to cell pluripotency, cell proliferation, and inhibition of mesoderm and endoderm activities in embryonic stem cells (Zhou et al., 2009). Once active, mTOR can foster mesenchymal stem cell senescence (Zhang et al., 2015a). Activation of mTOR also results in stem cell differentiation. For example, increased mTOR and p70S6K activity leads to embryonic stem cell differentiation (Easley et al., 2010).

In the regulation of stem cell proliferation, mTOR is closely linked with the activity of SIRT1 (Zhou et al., 2009) (**Figure 2**). As noted, SIRT1 inhibits mTOR pathways through AMPK. SIRT1 protects embryonic stem cells during oxidative stress through the induction of autophagy (Ou et al., 2014). SIRT1 blocks mTOR signaling to promote neuronal growth as well as mesangial cell proliferation during high glucose exposure (Zhang et al., 2012). SIRT1 activity is necessary for telomere elongation and genomic stability of induced pluripotent stem cells (De Bonis et al., 2014). SIRT1 can regulate autophagic flux to promote the transition of muscle stem cells from a quiescence state to an active state (Tang and Rando, 2014) and prevent the death of endothelial progenitor cells through autophagy and inhibition of mTOR (Jin et al., 2014). SIRT1 fosters endothelial progenitor cell mobilization and vascular repair during DM in mice (Albiero et al., 2014) and can preserve angiogenesis with bone marrow-derived early outgrowth cells in models of DM (Albiero et al., 2014). In endothelial progenitor cells, SIRT1 prevents cell senescence and impaired cellular differentiation (Lemarie et al., 2011). SIRT1 is required for the angiogenic properties of human mesenchymal stem cells (Chiara et al., 2014). Activation of SIRT1 for stem cell growth may be vital during DM, since patients with Type 2 DM have a down-regulation of endothelial progenitor cells associated with decreased SIRT1 protein levels (Balestrieri et al., 2013). SIRT1 also may function in combination with growth factors to foster improved cardiac performance during glucose depletion through the activation of aged mesenchymal stem cells (Choudhery et al., 2012). In addition, SIRT1 can increase the astrocytic subpopulation of cells that are necessary to support neuronal cell populations (Aranha et al., 2011). SIRT1 may offer stem cell protection through the oversight of mitochondrial pathways. Mitochondrial impairment can occur in endothelial progenitor cells during elevated glucose exposure (Kim et al., 2014). SIRT1 can maintain mitochondrial function during cell injury and block mitochondrial depolarization, cytochrome c release, Bad, and caspase activation (Hou et al., 2010b; Ou et al., 2014).

However, a fine balance in the activities of mTOR and SIRT1 may be required to achieve optimal stem cell survival, proliferation, and differentiation. A decrease in SIRT1 activity that would mirror an increase in mTOR activity is associated with neural differentiation and the maturation of embryonic cortical neurons (Liu et al., 2014a). Differentiation of human embryonic stem cells into motoneurons also occurs with decreased SIRT1 activity. Increased activity of SIRT1 through microRNA-34a also can promote the apoptotic cell death of mesenchymal stem cells (Zhang et al., 2015b).

mTOR and Metabolic Regulation

mTOR activation can positively influence cellular metabolism and insulin signaling. Activation of mTOR pathways that involve p70S6K and 4EBP1 can improve insulin secretion in pancreatic β-cells and increase resistance to β-cell streptozotocin toxicity and obesity in mice (Hamada et al., 2009). Loss of p70S6K activity leads to hypoinsulinemia, insulin insensitivity to glucose secretion, glucose intolerance, and decreased pancreatic β-cell size (Pende et al., 2000). Rapamycin administration leads to reduced β-cell function and mass, insulin resistance, decreased insulin secretion, and the onset of DM (Fraenkel et al., 2008). Although inhibition of mTOR activity with rapamycin can limit food intake and prevent fat-diet induced obesity in mice (Deblon et al., 2012), rapamycin can impair glucose uptake and increase mortality in models of Type 2 DM (Sataranatarajan et al., 2015). Rapamycin prevents insulin generated Akt activation and alters the translocation of glucose transporters to the plasma membrane in skeletal muscle (Deblon et al., 2012). Activation of mTOR can protect pancreatic β-cells against cholesterol-induced apoptosis (Zhou et al., 2015) and glucolipotoxicity (Miao et al., 2013). mTOR activation limits vascular disease with atherosclerosis (Peng et al., 2014).

Interestingly, mTOR functions through growth factors to also offer cellular protection during DM (**Figure 2**). mTOR in conjunction with PI 3-K and Akt can inhibit neuronal cell apoptosis through the epidermal growth factor (EGF) receptor during DM (Kimura et al., 2013). EGF and fibroblast growth factor (FGF) rely upon mTOR to maintain the proliferation of neural stem and progenitor cells (Sato et al., 2010). Erythropoietin (EPO) also is of interest for DM since this trophic factor relies upon mTOR signaling pathways

(Andreucci et al., 2009; Marfia et al., 2011; Sanghera et al., 2011; Shang et al., 2011; Maiese et al., 2012a; Yu et al., 2013; Maiese, 2016) (**Figure 2**). EPO uses mTOR for the differentiation of neural precursor cells to achieve a neuronal phenotype and for the protection of retinal progenitor cells from oxidative stress (Sanghera et al., 2011). During hypoxia-reoxygenation stress, EPO increases mTOR activity to protect hippocampus-derived neuronal cells (Ryou et al., 2015) and oversees mTOR signaling pathways that involve PRAS40 to increase neuronal survival during oxygen-glucose deprivation (Chong et al., 2012b). In relation to cellular metabolism (Maiese, 2015l), EPO can reduce blood glucose levels in animal models of DM and obesity (Katz et al., 2010), promote wound healing during DM (Hamed et al., 2014), and protect endothelial cells during experimental models of DM (Chong et al., 2007, 2011). EPO can limit the detrimental effects of obesity in animal models (Zhang et al., 2014), maintain cellular mitochondrial function (Chong et al., 2003; Hou et al., 2011; Shang et al., 2011; Costa et al., 2013; Parvin et al., 2014) and energy metabolism (Wang et al., 2014a), and limit oxidative stress and apoptosis in Schwann cells mediated by AGEs (Yu et al., 2015b).

In addition to mTOR, AMPK is closely associated with EPO cytoprotection. The regulation of inflammation in the nervous system by EPO is tied to AMPK (Tsai et al., 2015). EPO concentration and activity influence the protective actions of mTOR and signaling pathways associated with AMPK. EPO modulates a specific level of AMPK and mTOR activity to alleviate detrimental effects of oxidative stress (Chong et al., 2012b; Wang et al., 2014b). Yet, high concentrations of EPO can promote cellular damage and lessen the activity of mTOR (Andreucci et al., 2009).

The CCN family member Wnt1 inducible signaling pathway protein 1 (WISP1) also has a significant role in cellular metabolism that employs mTOR signaling pathways (Chong et al., 2012c; Maiese, 2014a) (**Figure 2**). The CCN family of proteins has six secreted extracellular matrix associated proteins and are defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene (Maiese, 2014c; Krupska et al., 2015). WISP1 is a matricellular protein and a downstream target of the *wingless* pathway Wnt1 that also regulates cellular metabolism (Maiese et al., 2008c). In conjunction with mTOR, WISP1 may offer important strategies for the complications of DM. WISP1 expression is affected by weight change in humans and increases during insulin resistance in glucose-tolerant individuals (Murahovschi et al., 2015). These results suggest that WISP1 may represent an important reparative process in individuals with DM. Expression of WISP1 is increased during human adipocyte differentiation (Murahovschi et al., 2015) and is reported to promote vascular regeneration during saphenous vein crush injury that may be vital during complications of DM (Price et al., 2004). WISP1 also fosters vascular smooth muscle proliferation that can assist with tissue repair during injury (Reddy et al., 2011; Liu et al., 2013a). Importantly, WISP1 can modulate cellular senescence (Du et al., 2014) to a degree that does not promote excessive cellular proliferation in aging vascular cells (Marchand et al., 2011) that could lead to atherosclerosis during DM. WISP1 also is one of several genes that are over-expressed during pancreatic regeneration, indicating that WISP1 may assist with protection of tissues necessary for metabolic homeostasis (Lim et al., 2002).

WISP1 leads to mTOR activation to block PRAS40 (Shang et al., 2012) and TSC2 (Shang et al., 2013) for cellular protection during oxidative stress. WISP1 regulates the post-translational phosphorylation of AMPK for glucose homeostasis (Chong et al., 2010; Maiese et al., 2013c; Kopp et al., 2014; Martinez de Morentin et al., 2014). The ability of WISP1 to control AMPK activity is critical to control cellular metabolism during DM (Martinez de Morentin et al., 2014). WISP1 modulates AMPK activation by differentially decreasing phosphorylation of TSC2 at serine^{1387}, a target of AMPK, and increasing phosphorylation of TSC2 at threonine^{1462}, a target of Akt (Shang et al., 2013). This enables WISP1 to provide a minimal level of TSC2 and AMPK activity to control both cell survival and cell metabolism. The level of AMPK activity can become an important factor for cellular survival. Increased AMPK activity can reduce insulin resistance and oxidative stress mediated through the activation of autophagy (Liu et al., 2014b). AMPK activation can correct metabolic parameters of cells and prevent adipocyte differentiation, lipid accumulation, and obesity (Lai et al., 2012). However, under some conditions, AMPK activation promotes apoptotic cell death in pancreatic islet cells in experimental models of Type 2 DM (Guan et al., 2014).

Similar to the importance of controlling the degree of activity for AMPK, controlled activity of mTOR also may prove to provide a vital clinical benefit. mTOR can function in a negative feedback loop and produce glucose intolerance by inhibiting the insulin receptor substrate 1 (IRS-1). In studies with high fat fed obese rats, mTOR leads to inhibitory phosphorylation of IRS-1, impaired Akt signaling, and insulin resistance (Khamzina et al., 2005). Activation of mTOR signaling with p70S6K can phosphorylate IRS-1 in the renin-angiotensin-aldosterone system during consumption of high fat diets that results in high circulating angiotensin II (ANG II) and insulin resistance (Kim et al., 2012).

SIRT1 may be a crucial counterpart to regulate the activity of mTOR during DM. Genes with the greatest statistical change following caloric restriction in mice have included those associated with sirtuin activation and mTOR inhibition (Estep et al., 2009). SIRT1 can increase lifespan in higher organisms (Balan et al., 2008; D'Onofrio et al., 2015; Ma et al., 2015; Maiese, 2015b; Poulose and Raju, 2015), modulates stem cell survival (Hua, 2015; Maiese, 2015a, d; Zhang et al., 2015b; Okada et al., 2016), and offers protection against oxidative stress (Hung et al., 2015; Maiese, 2015g,h; Yu et al., 2015a; Zhang et al., 2015c). Hepatic SIRT1 deficiency results in hepatic glucose overproduction, hyperglycemia, oxidative stress, and inhibition of the gene encoding Rictor that results in impaired mTORC2 and Akt signaling (Wang et al., 2011a), suggesting that SIRT1 is necessary to effectively control mTOR activity. During DM, SIRT1 also can function as a negative regulator of unfolded protein response signaling and inhibit mTOR to lessen hepatic steatosis, insulin resistance,

and glucose insensitivity (Li et al., 2011). In addition, SIRT1 uses AMPK for the regulation of insulin sensitivity. Endothelial cell protection from oxidized low-density lipoproteins requires SIRT1 as well as AMPK activation (Lai et al., 2012; Jin et al., 2014). SIRT1 activation with AMPK may be necessary to protect against spatial memory impairment in combined experimental models of DM and AD. Loss of SIRT1 and AMPK activities can lead to cognitive loss, oxidative stress, and neuronal cell apoptosis (Du et al., 2015).

Conclusions and Future Perspectives

Accompanied by the increase in life expectancy of the global population, NCDs are affecting a greater percentage of individuals in the world. Of particular significance for NCDs is the increasing incidence of DM that now affects at least 350 million individuals. Additional concerns exist for the millions of individuals who are currently undiagnosed and for those individuals that pose high risk for the development of DM, such as those with obesity and impaired glucose tolerance. Current therapies for the management and resolution of DM are limited and lead to significant healthcare costs for the global economy.

New therapies for DM are desperately needed. mTOR is a promising target for launching unique strategies against DM (**Table 1**). mTOR is an essential component of the protein complexes mTORC1 and mTORC2 and interfaces with PI 3-K, Akt, AMPK, and SIRT1 signaling to affect multiple metabolic parameters that include insulin resistance, insulin secretion, and pancreatic β-cell function. mTOR also plays a significant role in controlling cellular survival during DM.

mTOR offers exciting prospects for the treatment of DM and the multi-systemic complications that can arise from this disorder (**Table 1**). Yet, several considerations need to be addressed when targeting mTOR for clinical disorders involving cellular metabolism. Under a number of conditions, mTOR may not function independently but works through a PI 3-K, Akt, and mTOR axis. The degree of activity of each of these pathways should be considered that function alongside of mTOR when designing new therapies for DM. mTOR also can exert control over the downstream signaling pathways of AMPK, SIRT1, and WISP1. PI 3-K and Akt are vital in regulating the activity of mTOR and function in tandem with mTOR through growth factor signaling that includes EGF, FGF, and EPO.

As a result, targeting mTOR for clinical benefit must also take account of the dependency mTOR has with PI 3-K and Akt and subsequent downstream pathways. Studies have shown that down-regulation of mTOR and mTORC1 signaling can foster a significant feedback activation of PI 3-K, Akt, and Ras-mitogen activated protein kinase signaling that can counteract any expected clinical benefits (Maiese, 2015j). In addition, inhibition of mTOR signaling can impair glucose uptake, increase mortality in models of Type 2 DM (Sataranatarajan et al., 2015), prevent insulin generated Akt activation, and alter the translocation of glucose transporters to the plasma membrane in skeletal muscle (Deblon et al., 2012). However, increased activity of PI 3-K and Akt signaling may significantly enhance mTOR activity that sometimes limits protective pathways. During such circumstances, drug efficacy, such as with metformin, could be affected. Similarly, long-term mTOR activity may lead to vasculopathy (Sinha et al., 2008).

Levels of mTOR activity also can impact stem cell proliferation and maintenance, such that mTOR activation may be necessary for stem cell proliferation and differentiation. mTOR also functions in combination with Akt to prevent mesenchymal stem cell aging (Zhang et al., 2015a). However, in relation to SIRT1 and stem cell maintenance, a repressed level of mTOR may be more suited to stem cell survival to regulate autophagy pathways and promote stem cell proliferation and differentiation during DM.

mTOR is vital in the regulation of programmed cell death that appears to require a fine balance in the regulation of apoptotic and autophagic pathways. Activation of mTOR is protective against apoptotic cellular injury. During mTOR activation, apoptotic pathways can be averted. mTOR activation during metabolic impairment can protect pancreatic β-cells from cholesterol mediated apoptotic cell injury (Zhou et al., 2015), block the development of vascular complications, such as atherosclerosis (Peng et al., 2014), foster pancreatic β-cell proliferation, and prevent neuronal cell injury (Maiese, 2015k). PI 3-K, Akt, and mTOR can block neuronal cell apoptosis through the EGF receptor during DM (Kimura et al., 2013). EPO also relies upon PI 3-K and Akt with mTOR to protect hippocampus-derived neuronal cells (Ryou et al., 2015) and block endothelial cell injury in experimental models of DM (Chong et al., 2007, 2011). In addition, Akt is vital in maintaining the activity of mTOR through the control of the TSC1/TSC2 complex (Maiese et al., 2013c).

Yet, autophagy that occurs during mTOR inhibition can have a dual role that either protects cell survival and normalizes metabolic parameters or promotes impairment of some progenitor cells and fosters oxidative stress injury. A reduction in mTOR activity to allow for the induction of autophagy may be necessary for treatment strategies in DM. Loss of autophagy pathways can lead to increased insulin resistance with elevated lipids and inflammation (Lim et al., 2014). Autophagy also may be necessary to control apoptosis. Induction of autophagy can protect cardiomyocytes from apoptotic demise during DM (He et al., 2013). In contrast, autophagy also may promote cellular and tissue pathology during DM. Autophagy may be responsible for the loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification (Lee et al., 2014). AGEs in DM can result in the induction of autophagy and vascular smooth muscle proliferation that can result in atherosclerosis (Hu et al., 2012). Induction of autophagy also can injure endothelial progenitor cells and lead to mitochondrial oxidative stress (Maiese, 2015h).

Modulation of mTOR activity to effectively achieve metabolic homeostasis is of great importance. Either independently or in combination with other pathways, regulation of mTOR can be beneficial to treat insulin resistance, limit obesity, promote cellular protection, reduce oxidative stress, and foster tissue regeneration during DM. Further work is necessary to address these challenges to fully comprehend

Table 1 Regenerative Strategies for mTOR in Diabetes Mellitus

1. A significant non-communicable disease with limited therapeutic options, diabetes mellitus (DM) is increasing in incidence throughout the world and affects approximately 350 million individuals	of pancreatic β- cells, block neuronal cell apoptosis, protect against cognitive loss, and foster glucose homeostasis	4. A fine balance for mTOR activation is required to oversee apoptotic and autophagic pathways for cell survival and cell death as well as for control of stem cell proliferation, maintenance, and differentiation
2. The mechanistic target of rapamycin (mTOR), a principal component for mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2), offers exciting prospects for the treatment of DM since mTOR is tightly linked to DM cellular metabolism and can involve regeneration and protection	3. mTOR is intimately associated with phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), AMP activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), and Wnt1 inducible signaling pathway protein 1 (WISP1) to oversee metabolic homeostasis	5. Growth factors such as epidermal growth factor, fibroblast growth factor, and erythropoietin rely upon mTOR signaling to modulate insulin resistance, obesity, cellular protection, and oxidative stress during DM

the impact of the PI 3-K, Akt, and mTOR axis on metabolic homeostasis as well as to elucidate the delicate balance that mTOR and pathways of programmed cell death can exert over cellular survival and cellular metabolism to foster clinical translation of these pathways for optimal clinical success. Given its prominent role in regulating cellular metabolism, mTOR offers a unique target to open new avenues for the development of effect therapies to treat DM and the complications of this disorder.

References

Albiero M, Poncina N, Tjwa M, Ciciliot S, Menegazzo L, Ceolotto G, Vigili de Kreutzenberg S, Moura R, Giorgio M, Pelicci P, Avogaro A, Fadini GP (2014) Diabetes causes bone marrow autonomic neuropathy and impairs stem cell mobilization via dysregulated p66Shc and Sirt1. Diabetes 63:1353-1365.

Alexandru N, Popov D, Georgescu A (2012) Platelet dysfunction in vascular pathologies and how can it be treated. Thromb Res 129:116-126.

Andreucci M, Fuiano G, Presta P, Lucisano G, Leone F, Fuiano L, Bisesti V, Esposito P, Russo D, Memoli B, Faga T, Michael A (2009) Down-regulation of cell survival signalling pathways and increased cell damage in hydrogen peroxide-treated human renal proximal tubular cells by alpha-erythropoietin. Cell Prolif 42:554-561.

Aranha MM, Santos DM, Sola S, Steer CJ, Rodrigues CM (2011) miR-34a regulates mouse neural stem cell differentiation. PLoS One 6:e21396.

Arunachalam G, Samuel SM, Marei I, Ding H, Triggle CR (2014) Metformin modulates hyperglycaemia-induced endothelial senescence and apoptosis through SIRT1. Br J Pharmacol 171:523-535.

Bailey TJ, Fossum SL, Fimbel SM, Montgomery JE, Hyde DR (2010) The inhibitor of phagocytosis, O-phospho-L-serine, suppresses Muller glia proliferation and cone cell regeneration in the light-damaged zebrafish retina. Exp Eye Res 91:601-612.

Balan V, Miller GS, Kaplun L, Balan K, Chong ZZ, Li F, Kaplun A, VanBerkum MF, Arking R, Freeman DC, Maiese K, Tzivion G (2008) Life span extension and neuronal cell protection by Drosophila nicotinamidase. J Biol Chem 283:27810-27819.

Balestrieri ML, Servillo L, Esposito A, D'Onofrio N, Giovane A, Casale R, Barbieri M, Paolisso P, Rizzo MR, Paolisso G, Marfella R (2013) Poor glycaemic control in type 2 diabetes patients reduces endothelial progenitor cell number by influencing SIRT1 signalling via platelet-activating factor receptor activation. Diabetologia 56:162-172.

Barthelmes D, Zhu L, Shen W, Gillies MC, Irhimeh MR (2014) Differential gene expression in Lin-/VEGF-R2+ bone marrow-derived endothelial progenitor cells isolated from diabetic mice. Cardiovasc Diabetol 13:42.

Benyoucef A, Calvo J, Renou L, Arcangeli ML, van den Heuvel A, Amsellem S, Mehrpour M, Larghero J, Soler E, Naguibneva I, Pflumio F (2015) The SCL/TAL1 transcription factor represses the stress protein DDiT4/REDD1 in human hematopoietic stem/progenitor cells. Stem Cells 33:2268-2279.

Berry M, Ahmed Z, Morgan-Warren P, Fulton D, Logan A (2016) Prospects for mTOR-mediated functional repair after central nervous system trauma. Neurobiol Dis 85:99-110.

Busch S, Kannt A, Kolibabka M, Schlotterer A, Wang Q, Lin J, Feng Y, Hoffmann S, Gretz N, Hammes HP (2014) Systemic treatment with erythropoietin protects the neurovascular unit in a rat model of retinal neurodegeneration. PLoS One 9:e102013.

Cai SL, Tee AR, Short JD, Bergeron JM, Kim J, Shen J, Guo R, Johnson CL, Kiguchi K, Walker CL (2006) Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning. J Cell Biol 173:279-289.

Canto C, Auwerx J (2009) Caloric restriction, SIRT1 and longevity. Trends Endocrinol Metab 20:325-331.

Centers for Medicare and Medicaid Services (2013) National Health Expenditure Projections 2012-2022. www.cms.gov.

Chen JX, Tuo Q, Liao DF, Zeng H (2012) Inhibition of protein tyrosine phosphatase improves angiogenesis via enhancing Ang-1/Tie-2 signaling in diabetes. Exp Diabetes Res 2012:836759.

Chiara B, Ilaria C, Antonietta C, Francesca C, Marco M, Lucia A, Gilda C (2014) SIRT1 inhibition affects angiogenic properties of human MSCs. Biomed Res Int 2014:783459.

Chong ZZ, Maiese K (2012) Mammalian target of rapamycin signaling in diabetic cardiovascular disease. Cardiovasc Diabetol 11:45.

Chong ZZ, Kang JQ, Maiese K (2003) Apaf-1, Bcl-xL, Cytochrome c, and Caspase-9 form the critical elements for cerebral vascular protection by erythropoietin. J Cereb Blood Flow Metab 23:320-330.

Chong ZZ, Shang YC, Maiese K (2007) Vascular injury during elevated glucose can be mitigated by erythropoietin and Wnt signaling. Curr Neurovasc Res 4:194-204.

Chong ZZ, Shang YC, Wang S, Maiese K (2012a) A critical kinase cascade in neurological disorders: PI 3-K, Akt, and mTOR. Future Neurol 7:733-748.

Chong ZZ, Shang YC, Wang S, Maiese K (2012b) PRAS40 is an integral regulatory component of erythropoietin mTOR signaling and cytoprotection. PLoS One 7:e45456.

Chong ZZ, Shang YC, Wang S, Maiese K (2012c) Shedding new light on neurodegenerative diseases through the mammalian target of rapamycin. Prog Neurobiol 99:128-148.

Chong ZZ, Shang YC, Wang S, Maiese K (2012d) SIRT1: New avenues of discovery for disorders of oxidative stress. Expert Opin Ther Targets 16:167-178.

Chong ZZ, Shang YC, Zhang L, Wang S, Maiese K (2010) Mammalian target of rapamycin: hitting the bull's-eye for neurological disorders. Oxid Med Cell Longev 3:374-391.

Chong ZZ, Hou J, Shang YC, Wang S, Maiese K (2011) EPO Relies upon Novel signaling of Wnt1 that requires Akt1, FoxO3a, GSK-3beta, and beta-Catenin to Foster vascular integrity during experimental diabetes. Curr Neurovasc Res 8:103-120.

Choo HJ, Kim JH, Kwon OB, Lee CS, Mun JY, Han SS, Yoon YS, Yoon G, Choi KM, Ko YG (2006) Mitochondria are impaired in the adipocytes of type 2 diabetic mice. Diabetologia 49:784-791.

Choudhery MS, Khan M, Mahmood R, Mohsin S, Akhtar S, Ali F, Khan SN, Riazuddin S (2012) Mesenchymal stem cells conditioned with glucose depletion augments their ability to repair-infarcted myocardium. J Cell Mol Med 16:2518-2529.

Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR (2012) Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med 172:761-769.

Costa DC, Alva N, Trigueros L, Gamez A, Carbonell T, Rama R (2013) Intermittent hypobaric hypoxia induces neuroprotection in kainate-induced oxidative stress in rats. J Mol Neurosci 50:402-410.

D'Onofrio N, Vitiello M, Casale R, Servillo L, Giovane A, Balestrieri ML (2015) Sirtuins in vascular diseases: emerging roles and therapeutic potential. Biochim Biophys Acta 1852:1311-1322.

De Bonis ML, Ortega S, Blasco MA (2014) SIRT1 is necessary for proficient telomere elongation and genomic stability of induced pluripotent stem cells. Stem Cell Reports 2:690-706.

Deblon N, Bourgoin L, Veyrat-Durebex C, Peyrou M, Vinciguerra M, Caillon A, Maeder C, Fournier M, Montet X, Rohner-Jeanrenaud F, Foti M (2012) Chronic mTOR inhibition by rapamycin induces muscle insulin resistance despite weight loss in rats. Br J Pharmacol 165:2325-2340.

Du J, Klein JD, Hassounah F, Zhang J, Zhang C, Wang XH (2014) Aging increases CCN1 expression leading to muscle senescence. Am J Physiol Cell Physiol 306:C28-36.

Du LL, Chai DM, Zhao LN, Li XH, Zhang FC, Zhang HB, Liu LB, Wu K, Liu R, Wang JZ, Zhou XW (2015) AMPK activation ameliorates Alzheimer's disease-like pathology and spatial memory impairment in a streptozotocin-induced Alzheimer's disease model in rats. J Alzheimers Dis 43:775-784.

Easley CA, Ben-Yehudah A, Redinger CJ, Oliver SL, Varum ST, Eisinger VM, Carlisle DL, Donovan PJ, Schatten GP (2010) mTOR-mediated activation of p70 S6K induces differentiation of pluripotent human embryonic stem cells. Cell Reprogram 12:263-273.

Esser N, Paquot N, Scheen AJ (2015) Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expert Opin Investig Drugs 24:283-307.

Estep PW, 3rd, Warner JB, Bulyk ML (2009) Short-term calorie restriction in male mice feminizes gene expression and alters key regulators of conserved aging regulatory pathways. PLoS One 4:e5242.

Favero G, Franceschetti L, Rodella LF, Rezzani R (2015) Sirtuins, aging, and cardiovascular risks. Age (Dordr) 37:9804.

Fonseca BD, Smith EM, Lee VH, MacKintosh C, Proud CG (2007) PRAS40 is a target for mammalian target of rapamycin complex 1 and is required for signaling downstream of this complex. J Biol Chem 282:24514-24524.

Foster KG, Acosta-Jaquez HA, Romeo Y, Ekim B, Soliman GA, Carriere A, Roux PP, Ballif BA, Fingar DC (2010) Regulation of mTOR complex 1 (mTORC1) by raptor Ser863 and multisite phosphorylation. J Biol Chem 285:80-94.

Fraenkel M, Ketzinel-Gilad M, Ariav Y, Pappo O, Karaca M, Castel J, Berthault MF, Magnan C, Cerasi E, Kaiser N, Leibowitz G (2008) mTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes 57:945-957.

Francois A, Rioux-Bilan A, Quellard N, Fernandez B, Janet T, Chassaing D, Paccalin M, Terro F, Page G (2014) Longitudinal follow-up of autophagy and inflammation in brain of APPswePS1dE9 transgenic mice. J Neuroinflammation 11:139.

Frederick C, Ando K, Leroy K, Heraud C, Suain V, Buee L, Brion JP (2015) Rapamycin ester analog CCI-779/Temsirolimus alleviates tau pathology and improves motor deficit in mutant tau transgenic mice. J Alzheimers Dis 44:1145-1156.

Frias MA, Thoreen CC, Jaffe JD, Schroder W, Sculley T, Carr SA, Sabatini DM (2006) mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s. Curr Biol 16:1865-1870.

Fu D, Wu M, Zhang J, Du M, Yang S, Hammad SM, Wilson K, Chen J, Lyons TJ (2012) Mechanisms of modified LDL-induced pericyte loss and retinal injury in diabetic retinopathy. Diabetologia 55:3128-3140.

Gangloff YG, Mueller M, Dann SG, Svoboda P, Sticker M, Spetz JF, Um SH, Brown EJ, Cereghini S, Thomas G, Kozma SC (2004) Disruption of the mouse mTOR gene leads to early postimplantation lethality and prohibits embryonic stem cell development. Mol Cell Biol 24:9508-9516.

Garcia-Martinez JM, Alessi DR (2008) mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem J 416:375-385.

Glidden EJ, Gray LG, Vemuru S, Li D, Harris TE, Mayo MW (2012) Multiple site acetylation of Rictor stimulates mammalian target of rapamycin complex 2 (mTORC2)-dependent phosphorylation of Akt protein. J Biol Chem 287:581-588.

Gomes MB, Negrato CA (2014) Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. Diabetol Metab Syndr 6:80.

Gomez-Brouchet A, Blaes N, Mouledous L, Fourcade O, Tack I, Frances B, Girolami JP, Minville V (2015) Beneficial effects of levobupivacaine regional anaesthesia on postoperative opioid induced hyperalgesia in diabetic mice. J Transl Med 13:208.

Gu Y, Lindner J, Kumar A, Yuan W, Magnuson MA (2011) Rictor/mTORC2 is essential for maintaining a balance between beta-cell proliferation and cell size. Diabetes 60:827-837.

Guan FY, Gu J, Li W, Zhang M, Ji Y, Li J, Chen L, Hatch GM (2014) Compound K protects pancreatic islet cells against apoptosis through inhibition of the AMPK/JNK pathway in type 2 diabetic mice and in MIN6 beta-cells. Life Sci 107:42-49.

Guertin DA, Stevens DM, Thoreen CC, Burds AA, Kalaany NY, Moffat J, Brown M, Fitzgerald KJ, Sabatini DM (2006) Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. Dev Cell 11:859-871.

Gulhati P, Bowen KA, Liu J, Stevens PD, Rychahou PG, Chen M, Lee EY, Weiss HL, O'Connor KL, Gao T, Evers BM (2011) mTORC1 and mTORC2 regulate EMT, motility, and metastasis of colorectal cancer via RhoA and Rac1 signaling pathways. Cancer Res 71:3246-3256.

Hadamitzky M, Herring A, Keyvani K, Doenlen R, Krugel U, Bosche K, Orlowski K, Engler H, Schedlowski M (2014) Acute systemic rapamycin induces neurobehavioral alterations in rats. Behav Brain Res 273:16-22.

Haldar SR, Chakrabarty A, Chowdhury S, Haldar A, Sengupta S, Bhattacharyya M (2015) Oxidative stress-related genes in type 2 diabetes: association analysis and their clinical impact. Biochem Genet 53:93-119.

Hamada S, Hara K, Hamada T, Yasuda H, Moriyama H, Nakayama R, Nagata M, Yokono K (2009) Upregulation of the mammalian target of rapamycin complex 1 pathway by Ras homolog enriched in brain in pancreatic beta-cells leads to increased beta-cell mass and prevention of hyperglycemia. Diabetes 58:1321-1332.

Hamed S, Bennett CL, Demiot C, Ullmann Y, Teot L, Desmouliere A (2014) Erythropoietin, a novel repurposed drug: an innovative treatment for wound healing in patients with diabetes mellitus. Wound Repair Regen 22:23-33.

Harris MI, Eastman RC (2000) Early detection of undiagnosed diabetes mellitus: a US perspective. Diabetes Metab Res Rev 16:230-236.

He C, Zhu H, Li H, Zou MH, Xie Z (2013) Dissociation of Bcl-2-Beclin1 complex by activated AMPK enhances cardiac autophagy and protects against cardiomyocyte apoptosis in diabetes. Diabetes 62:1270-1281.

He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, An Z, Loh J, Fisher J, Sun Q, Korsmeyer S, Packer M, May HI, Hill JA, Virgin HW, Gilpin C, Xiao G, Bassel-Duby R, Scherer PE, Levine B (2012) Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature 481:511-515.

Heitman J, Movva NR, Hall MN (1991) Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. Science 253:905-909.

Hou J, Chong ZZ, Shang YC, Maiese K (2010a) FoxO3a governs early and late apoptotic endothelial programs during elevated glucose through mitochondrial and caspase signaling. Mol Cell Endocrinol 321:194-206.

Hou J, Chong ZZ, Shang YC, Maiese K (2010b) Early apoptotic vascular signaling is determined by Sirt1 through nuclear shuttling, forkhead trafficking, bad, and mitochondrial caspase activation. Curr Neurovasc Res 7:95-112.

Hou J, Wang S, Shang YC, Chong ZZ, Maiese K (2011) Erythropoietin employs cell longevity pathways of SIRT1 to Foster endothelial vascular integrity during oxidant stress. Curr Neurovasc Res 8:220-235.

Hu P, Lai D, Lu P, Gao J, He H (2012) ERK and Akt signaling pathways are involved in advanced glycation end product-induced autophagy in rat vascular smooth muscle cells. Int J Mol Med 29:613-618.

Hua J (2015) miR-204 regulated the proliferation of dairy goat spermatogonial stem cells via targeting to Sirt1. Rejuvenation Res doi:10.1089/rej.2015.1719.

Huang J, Dibble CC, Matsuzaki M, Manning BD (2008) The TSC1-TSC2 complex is required for proper activation of mTOR complex 2. Mol Cell Biol 28:4104-4115.
Hung CH, Chan SH, Chu PM, Tsai KL (2015) Quercetin is a potent anti-atherosclerotic compound by activation of SIRT1 signaling under oxLDL stimulation. Mol Nutr Food Res 59:1905-1917.
Ignacio ZM, Reus GZ, Arent CO, Abelaira HM, Pitcher MR, Quevedo J (2015) New perspectives on the involvement of mTOR in depression as well as in the action of antidepressant drugs. Br J Clin Pharmacol doi: 10.1111/bcp.12845.
Inoki K, Zhu T, Guan KL (2003) TSC2 mediates cellular energy response to control cell growth and survival. Cell 115:577-590.
Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, Hall MN (2004) Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat Cell Biol 6:1122-1128.
James MF, Stivison E, Beauchamp R, Han S, Li H, Wallace MR, Gusella JF, Stemmer-Rachamimov AO, Ramesh V (2012) Regulation of mTOR complex 2 signaling in neurofibromatosis 2-deficient target cell types. Mol Cancer Res 10:649-659.
Janku F, Wheler JJ, Westin SN, Moulder SL, Naing A, Tsimberidou AM, Fu S, Falchook GS, Hong DS, Garrido-Laguna I, Luthra R, Lee JJ, Lu KH, Kurzrock R (2012) PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol 30:777-782.
Jia G, Aroor AR, Martinez-Lemus LA, Sowers JR (2014) Over-nutrition, mTOR signaling and cardiovascular diseases. Am J Physiol Regul Integr Comp Physiol 307:R1198-206.
Jiang T, Yu JT, Zhu XC, Wang HF, Tan MS, Cao L, Zhang QQ, Gao L, Shi JQ, Zhang YD, Tan L (2014) Acute metformin preconditioning confers neuroprotection against focal cerebral ischaemia by pre-activation of AMPK-dependent autophagy. Br J Pharmacol 171:3146-3157.
Jin X, Chen M, Yi L, Chang H, Zhang T, Wang L, Ma W, Peng X, Zhou Y, Mi M (2014) Delphinidin-3-glucoside protects human umbilical vein endothelial cells against oxidized low-density lipoprotein-induced injury by autophagy upregulation via the AMPK/SIRT1 signaling pathway. Mol Nutr Food Res 58:1941-1951.
Johnson SC, Sangesland M, Kaeberlein M, Rabinovitch PS (2015) Modulating mTOR in aging and health. Interdiscip Top Gerontol 40:107-127.
Jung CH, Lee DH, Ahn J, Lee H, Choi WH, Jang YJ, Ha TY (2015) gamma-Oryzanol enhances adipocyte differentiation and glucose uptake. Nutrients 7:4851-4861.
Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, Kundu M, Kim DH (2009) ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol Biol Cell 20:1992-2003.
Kalender A, Selvaraj A, Kim SY, Gulati P, Brule S, Viollet B, Kemp BE, Bardeesy N, Dennis P, Schlager JJ, Marette A, Kozma SC, Thomas G (2010) Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell Metab 11:390-401.
Kamada Y, Funakoshi T, Shintani T, Nagano K, Ohsumi M, Ohsumi Y (2000) Tor-mediated induction of autophagy via an Apg1 protein kinase complex. J Cell Biol 150:1507-1513.
Kamarudin MN, Mohd Raflee NA, Syed Hussein SS, Lo JY, Supriady H, Abdul Kadir H (2014) (R)-(+)-alpha-Lipoic acid protected NG108-15 cells against H2O2-induced cell death through PI3K-Akt/GSK-3beta pathway and suppression of NF-kappabeta-cytokines. Drug Des Devel Ther 8:1765-1780.
Kapogiannis D, Boxer A, Schwartz JB, Abner EL, Biragyn A, Masharani U, Frassetto L, Petersen RC, Miller BL, Goetzl EJ (2015) Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease. FASEB J 29:589-596.
Katz O, Stuible M, Golishevski N, Lifshitz L, Tremblay ML, Gassmann M, Mittelman M, Neumann D (2010) Erythropoietin treatment leads to reduced blood glucose levels and body mass: insights from murine models. J Endocrinol 205:87-95.
Khamzina L, Veilleux A, Bergeron S, Marette A (2005) Increased activation of the mammalian target of rapamycin pathway in liver and skeletal muscle of obese rats: possible involvement in obesity-linked insulin resistance. Endocrinology 146:1473-1481.
Kim DH, Sarbassov DD, Ali SM, Latek RR, Guntur KV, Erdjument-Bromage H, Tempst P, Sabatini DM (2003) GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol Cell 11:895-904.
Kim JA, Jang HJ, Martinez-Lemus LA, Sowers JR (2012) Activation of mTOR/p70S6 kinase by ANG II inhibits insulin-stimulated endothelial nitric oxide synthase and vasodilation. Am J Physiol Endocrinol Metab 302:E201-208.
Kim KA, Shin YJ, Akram M, Kim ES, Choi KW, Suh H, Lee CH, Bae ON (2014) High glucose condition induces autophagy in endothelial progenitor cells contributing to angiogenic impairment. Biol Pharm Bull 37:1248-1252.
Kim S, Kang IH, Nam JB, Cho Y, Chung DY, Kim SH, Kim JS, Cho YD, Hong EK, Sohn NW, Shin JW (2015) Ameliorating the effect of astragaloside IV on learning and memory deficit after chronic cerebral hypoperfusion in rats. Molecules 20:1904-1921.
Kimura R, Okouchi M, Kato T, Imaeda K, Okayama N, Asai K, Joh T (2013) Epidermal growth factor receptor transactivation is necessary for glucagon-like peptide-1 to protect PC12 cells from apoptosis. Neuroendocrinology 97:300-308.
Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, Adachi H, Adams CM, Adams PD, Adeli K, Adhihetty PJ, Adler SG, Agam G, Agarwal R, Aghi MK, Agnello M, Agostinis P, Aguilar PV, Aguirre-Ghiso J, Airoldi EM, et al. (2016) Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy 12:1-222.
Kopp C, Hosseini A, Singh SP, Regenhard P, Khalilvandi-Behroozyar H, Sauerwein H, Mielenz M (2014) Nicotinic acid increases adiponectin secretion from differentiated bovine preadipocytes through g-protein coupled receptor signaling. Int J Mol Sci 15:21401-21418.
Korpi ER, den Hollander B, Farooq U, Vashchinkina E, Rajkumar R, Nutt DJ, Hyytia P, Dawe GS (2015) Mechanisms of action and persistent neuroplasticity by drugs of abuse. Pharmacol Rev 67:872-1004.
Krupska I, Bruford EA, Chaqour B (2015) Eyeing the Cyr61/CTGF/NOV (CCN) group of genes in development and diseases: highlights of their structural likenesses and functional dissimilarities. Human genomics 9:24.
Lai CS, Tsai ML, Badmaev V, Jimenez M, Ho CT, Pan MH (2012) Xanthigen suppresses preadipocyte differentiation and adipogenesis through down-regulation of PPARgamma and C/EBPs and modulation of SIRT-1, AMPK, and FoxO pathways. J Agric Food Chem 60:1094-1101.
Leclerc GM, Leclerc GJ, Kuznetsov JN, DeSalvo J, Barredo JC (2013) Metformin induces apoptosis through AMPK-dependent inhibition of UPR signaling in ALL lymphoblasts. PLoS One 8:e74420.
Lee JH, Lee JH, Jin M, Han SD, Chon GR, Kim IH, Kim S, Kim SY, Choi SB, Noh YH (2014) Diet control to achieve euglycemia induces significant loss of heart and liver weight via increased autophagy compared with ad libitum diet in diabetic rats. Exp Mol Med 46:e111.
Lee K, Hu Y, Ding L, Chen Y, Takahashi Y, Mott R, Ma JX (2012a) Therapeutic potential of a monoclonal antibody blocking the Wnt pathway in diabetic retinopathy. Diabetes 61:2948-2957.
Lee Y, Hong Y, Lee SR, Chang KT (2012b) Autophagy contributes to retardation of cardiac growth in diabetic rats. Lab Anim Res 28:99-107.
Lemarie CA, Shbat L, Marchesi C, Angulo OJ, Deschenes ME, Blostein MD, Paradis P, Schiffrin EL (2011) Mthfr deficiency induces endothelial progenitor cell senescence via uncoupling of eNOS and downregulation of SIRT1. Am J Physiol Heart Circ Physiol 300:H745-753.
Li Y, Xu S, Giles A, Nakamura K, Lee JW, Hou X, Donmez G, Li J, Luo Z, Walsh K, Guarente L, Zang M (2011) Hepatic overexpression of SIRT1 in mice attenuates endoplasmic reticulum stress and insulin resistance in the liver. Faseb J 25:1664-1679.
Lim HW, Lee JE, Shin SJ, Lee YE, Oh SH, Park JY, Seong JK, Park JS (2002) Identification of differentially expressed mRNA during pancreas regeneration of rat by mRNA differential display. Biochem Biophys Res Commun 299:806-812.
Lim YM, Lim H, Hur KY, Quan W, Lee HY, Cheon H, Ryu D, Koo SH, Kim HL, Kim J, Komatsu M, Lee MS (2014) Systemic autophagy insufficiency compromises adaptation to metabolic stress and facilitates progression from obesity to diabetes. Nat Commun 5:4934.
Liu DJ, Hammer D, Komlos D, Chen KY, Firestein BL, Liu AY (2014a) SIRT1 knockdown promotes neural differentiation and attenuates the heat shock response. J Cell Physiol 229:1224-1235.
Liu H, Dong W, Lin Z, Lu J, Wan H, Zhou Z, Liu Z (2013a) CCN4 regulates vascular smooth muscle cell migration and proliferation. Mol Cells 36:112-118.

Liu Q, Li J, Cheng R, Chen Y, Lee K, Hu Y, Yi J, Liu Z, Ma JX (2013b) Nitrosative stress plays an important role in wnt pathway activation in diabetic retinopathy. Antioxid Redox Signal 18:1141-1153.
Liu Y, Palanivel R, Rai E, Park M, Gabor TV, Scheid MP, Xu A, Sweeney G (2014b) Adiponectin stimulates autophagy and reduces oxidative stress to enhance insulin sensitivity during high fat diet feeding in mice. Diabetes 64:36-48.
Liu YW, Zhang L, Li Y, Cheng YQ, Zhu X, Zhang F, Yin XX (2015) Activation of mTOR signaling mediates the increased expression of AChE in high glucose condition: in vitro and in vivo evidences. Mol Neurobiol doi: 10.1007/s12035-015-9425-6.
Liu Z, Stanojevic V, Brindamour LJ, Habener JF (2012) GLP1-derived nonapeptide GLP1(28-36)amide protects pancreatic beta-cells from glucolipotoxicity. J Endocrinol 213:143-154.
Ma L, Dong W, Wang R, Li Y, Xu B, Zhang J, Zhao Z, Wang Y (2015) Effect of caloric restriction on the SIRT1/mTOR signaling pathways in senile mice. Brain Res Bull 116:67-72.
Maiese K (2013) Therapeutic targets for cancer: current concepts with PI 3-K, Akt, & mTOR. Indian J Med Res 137:243-246.
Maiese K (2014a) Cutting through the complexities of mTOR for the treatment of stroke. Curr Neurovasc Res 11:177-186.
Maiese K (2014b) Driving neural regeneration through the mammalian target of rapamycin. Neural Regen Res 9:1413-1417.
Maiese K (2014c) WISP1: Clinical insights for a proliferative and restorative member of the CCN Family. Curr Neurovasc Res 11:378-389.
Maiese K (2014d) Taking aim at Alzheimer's disease through the mammalian target of rapamycin. Ann Med 46:587-596.
Maiese K (2015a) SIRT1 and stem cells: in the forefront with cardiovascular disease, neurodegeneration and cancer. World J Stem Cells 7:235-242.
Maiese K (2015b) FoxO proteins in the nervous system. Anal Cell Pathol (Amst) 2015:569392.
Maiese K (2015c) Paring down obesity and metabolic disease by targeting inflammation and oxidative stress. Curr Neurovasc Res 12:107-108.
Maiese K (2015d) Stem cell guidance through the mechanistic target of rapamycin. World J Stem Cells 7:999-1009.
Maiese K (2015e) Programming apoptosis and autophagy with novel approaches for diabetes mellitus. Curr Neurovasc Res 12:173-188.
Maiese K (2015f) Novel applications of trophic factors, Wnt and WISP for neuronal repair and regeneration in metabolic disease. Neural Regen Res 10:518-528.
Maiese K (2015g) MicroRNAs and SIRT1: a strategy for stem cell renewal and clinical development? J Transl Sci 1:55-57.
Maiese K (2015h) New insights for oxidative stress and diabetes mellitus. Oxid Med Cell Longev 2015:875961.
Maiese K (2015i) FoxO transcription factors and regenerative pathways in diabetes mellitus. Curr Neurovasc Res 12:404-413.
Maiese K (2015j) Targeting molecules to medicine with mTOR, autophagy, and neurodegenerative disorders. Br J Clin Pharmacol doi: 10.1111/bcp.12804.
Maiese K (2015k) mTOR: driving apoptosis and autophagy for neurocardiac complications of diabetes mellitus. World J Diabetes 6:217-224.
Maiese K (2015l) Erythropoietin and diabetes mellitus. World J Diabetes 6:1259-1273.
Maiese K (2016) Regeneration in the nervous system with erythropoietin. Front Biosci (Landmark Ed) 21:561-596.
Maiese K, Chong ZZ, Shang YC (2007) Mechanistic insights into diabetes mellitus and oxidative stress. Curr Med Chem 14:1729-1738.
Maiese K, Chong ZZ, Shang YC (2008a) Raves and risks for erythropoietin. Cytokine Growth Factor Rev 19:145-155.
Maiese K, Chong ZZ, Hou J, Shang YC (2008b) Erythropoietin and oxidative stress. Curr Neurovasc Res 5:125-142.
Maiese K, Li F, Chong ZZ, Shang YC (2008c) The Wnt signaling pathway: Aging gracefully as a protectionist? Pharmacol Ther 118:58-81.
Maiese K, Chong ZZ, Shang YC, Hou J (2009a) FoxO proteins: cunning concepts and considerations for the cardiovascular system. Clin Sci (Lond) 116:191-203.
Maiese K, Chong ZZ, Hou J, Shang YC (2009b) The vitamin nicotinamide: translating nutrition into clinical care. Molecules 14:3446-3485.
Maiese K, Shang YC, Chong ZZ, Hou J (2010) Diabetes mellitus: channeling care through cellular discovery. Curr Neurovasc Res 7:59-64.
Maiese K, Chong ZZ, Shang YC, Hou J (2011) Novel avenues of drug discovery and biomarkers for diabetes mellitus. J Clin Pharmacol 51:128-152.
Maiese K, Chong ZZ, Shang YC, Wang S (2012a) Erythropoietin: new directions for the nervous system. Int J Mol Sci 13:11102-11129.
Maiese K, Chong ZZ, Shang YC, Wang S (2012b) Targeting disease through novel pathways of apoptosis and autophagy. Expert Opin Ther Targets 16:1203-1214.
Maiese K, Chong ZZ, Shang YC, Wang S (2013a) Novel directions for diabetes mellitus drug discovery. Expert Opin Drug Discov 8:35-48.
Maiese K, Chong ZZ, Wang S, Shang YC (2013b) Oxidant stress and signal transduction in the nervous system with the PI 3-K, Akt, and mTOR cascade. Int J Mol Sci 13:13830-13866.
Maiese K, Chong ZZ, Shang YC, Wang S (2013c) mTOR: on target for novel therapeutic strategies in the nervous system. Trends Mol Med 19:51-60.
Malla R, Wang Y, Chan WK, Tiwari AK, Faridi JS (2015a) Genetic ablation of PRAS40 improves glucose homeostasis via linking the AKT and mTOR pathways. Biochem Pharmacol 96:65-75.
Malla R, Ashby CR, Jr., Narayanan NK, Narayanan B, Faridi JS, Tiwari AK (2015b) Proline-rich AKT substrate of 40-kDa (PRAS40) in the pathophysiology of cancer. Biochem Biophys Res Commun 463:161-166.
Marchand A, Atassi F, Gaaya A, Leprince P, Le Feuvre C, Soubrier F, Lompre AM, Nadaud S (2011) The Wnt/beta-catenin pathway is activated during advanced arterial aging in humans. Aging Cell 10:220-232.
Marfia G, Madaschi L, Marra F, Menarini M, Bottai D, Formenti A, Bellardita C, Di Giulio AM, Carelli S, Gorio A (2011) Adult neural precursors isolated from post mortem brain yield mostly neurons: an erythropoietin-dependent process. Neurobiol Dis 43:86-98.
Martinez de Morentin PB, Martinez-Sanchez N, Roa J, Ferno J, Nogueiras R, Tena-Sempere M, Dieguez C, Lopez M (2014) Hypothalamic mTOR: the rookie energy sensor. Curr Mol Med 14:3-21.
Martino L, Masini M, Novelli M, Beffy P, Bugliani M, Marselli L, Masiello P, Marchetti P, De Tata V (2012) Palmitate activates autophagy in INS-1E beta-cells and in isolated rat and human pancreatic islets. PLoS One 7:e36188.
Miao XY, Gu ZY, Liu P, Hu Y, Li L, Gong YP, Shu H, Liu Y, Li CL (2013) The human glucagon-like peptide-1 analogue liraglutide regulates pancreatic beta-cell proliferation and apoptosis via an AMPK/mTOR/P70S6K signaling pathway. Peptides 39:71-79.
Mikhed Y, Daiber A, Steven S (2015) Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction. Int J Mol Sci 16:15918-15953.
Minino AM (2013) Death in the United States, 2011. NCHS data brief:1-8.
Moon HE, Byun K, Park HW, Kim JH, Hur J, Park JS, Jun JK, Kim HS, Paek SL, Kim IK, Hwang JH, Kim JW, Kim DG, Sung YC, Koh GY, Song CW, Lee B, Paek SH (2015) COMP-Ang1 potentiates epc treatment of ischemic brain injury by enhancing angiogenesis through activating AKT-mTOR pathway and promoting vascular migration through activating Tie2-FAK pathway. Exp Neurobiol 24:55-70.
Morgan-Warren PJ, Berry M, Ahmed Z, Scott RA, Logan A (2013) Exploiting mTOR signaling: a novel translatable treatment strategy for traumatic optic neuropathy? Invest Ophthalmol Vis Sci 54:6903-6916.
Murahovschi V, Pivovarova O, Ilkavets I, Dmitrieva RM, Döcke S, Keyhani-Nejad F, Gögebakan Ö, Osterhoff M, Kemper M, Hornemann S, Markova M, Klöting N, Stockmann M, Weickert MO, Lamounier-Zepter V, Neuhaus P, Konradi A, Dooley S, von Loeffelholz C, Blüher M, et al. (2015) WISP1 is a novel adipokine linked to inflammation in obesity. Diabetes 64:856-866.
Murakami M, Ichisaka T, Maeda M, Oshiro N, Hara K, Edenhofer F, Kiyama H, Yonezawa K, Yamanaka S (2004) mTOR is essential for growth and proliferation in early mouse embryos and embryonic stem cells. Mol Cell Biol 24:6710-6718.
Nakka VP, Prakash-Babu P, Vemuganti R (2016) Crosstalk between endoplasmic reticulum stress, oxidative stress, and autophagy: potential therapeutic targets for acute CNS injuries. Mol Neurobiol 53:532-544.
Neasta J, Barak S, Hamida SB, Ron D (2014) mTOR complex 1: a key player in neuroadaptations induced by drugs of abuse. J Neurochem 130:172-184.

Newsholme P, Gaudel C, Krause M (2012) Mitochondria and diabetes. An intriguing pathogenetic role. Adv Exp Med Biol 942:235-247.
Okada M, Kim HW, Matsu-Ura K, Wang YG, Xu M, Ashraf M (2016) Abrogation of age-induced microRNA-195 rejuvenates the senescent mesenchymal stem cells by reactivating telomerase. Stem Cells 34:148-159.
Ou X, Lee MR, Huang X, Messina-Graham S, Broxmeyer HE (2014) SIRT1 positively regulates autophagy and mitochondria function in embryonic stem cells under oxidative stress. Stem Cells 32:1183-1194.
Parmar MS, Syed I, Gray JP, Ray SD (2015) Curcumin, hesperidin, and rutin selectively interfere with apoptosis signaling and attenuate streptozotocin-induced oxidative stress-mediated hyperglycemia. Curr Neurovasc Res 12:363-374.
Parvin A, Pranap R, Shalini U, Devendran A, Baker JE, Dhanasekaran A (2014) Erythropoietin protects cardiomyocytes from cell death during hypoxia/reperfusion injury through activation of survival signaling pathways. PLoS One 9:e107453.
Pearce LR, Sommer EM, Sakamoto K, Wullschleger S, Alessi DR (2011) Protor-1 is required for efficient mTORC2-mediated activation of SGK1 in the kidney. Biochem J 436:169-179.
Pende M, Kozma SC, Jaquet M, Oorschot V, Burcelin R, Le March-and-Brustel Y, Klumperman J, Thorens B, Thomas G (2000) Hypoinsulinaemia, glucose intolerance and diminished beta-cell size in S6K1-deficient mice. Nature 408:994-997.
Peng N, Meng N, Wang S, Zhao F, Zhao J, Su L, Zhang S, Zhang Y, Zhao B, Miao J (2014) An activator of mTOR inhibits oxLDL-induced autophagy and apoptosis in vascular endothelial cells and restricts atherosclerosis in apolipoprotein E(-/-) mice. Scientific reports 4:5519.
Perez-Gallardo RV, Noriega-Cisneros R, Esquivel-Gutierrez E, Calderon-Cortes E, Cortes-Rojo C, Manzo-Avalos S, Campos-Garcia J, Salgado-Garciglia R, Montoya-Perez R, Boldogh I, Saavedra-Molina A (2014) Effects of diabetes on oxidative and nitrosative stress in kidney mitochondria from aged rats. J Bioenerg Biomembr 46:511-518.
Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI (2004) Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med 350:664-671.
Peterson TR, Laplante M, Thoreen CC, Sancak Y, Kang SA, Kuehl WM, Gray NS, Sabatini DM (2009) DEPTOR is an mTOR inhibitor frequently overexpressed in multiple myeloma cells and required for their survival. Cell 137:873-886.
Poulose N, Raju R (2015) Sirtuin regulation in aging and injury. Biochim Biophys Acta 1852:2442-2455.
Price RM, Tulsyan N, Dermody JJ, Schwalb M, Soteropoulos P, Castronuovo JJ, Jr. (2004) Gene expression after crush injury of human saphenous vein: using microarrays to define the transcriptional profile. J Am Coll Surg 199:411-418.
Reddy VS, Valente AJ, Delafontaine P, Chandrasekar B (2011) Interleukin-18/WNT1-inducible signaling pathway protein-1 signaling mediates human saphenous vein smooth muscle cell proliferation. J Cell Physiol 226:3303-3315.
Russo E, Andreozzi F, Iuliano R, Dattilo V, Procopio T, Fiume G, Mimmi S, Perrotti N, Citraro R, Sesti G, Constanti A, De Sarro G (2014) Early molecular and behavioral response to lipopolysaccharide in the WAG/Rij rat model of absence epilepsy and depressive-like behavior, involves interplay between AMPK, AKT/mTOR pathways and neuroinflammatory cytokine release. Brain Behav Immun 42:157-168.
Rutter MK, Massaro JM, Hoffmann U, O'Donnell CJ, Fox CS (2012) Fasting glucose, obesity, and coronary artery calcification in community-based people without diabetes. Diabetes Care 35:1944-1950.
Ryou MG, Choudhury GR, Li W, Winters A, Yuan F, Liu R, Yang SH (2015) Methylene blue-induced neuronal protective mechanism against hypoxia-reoxygenation stress. Neuroscience 301:193-203.
Sanghera KP, Mathalone N, Baigi R, Panov E, Wang D, Zhao X, Hsu H, Wang H, Tropepe V, Ward M, Boyd SR (2011) The PI3K/Akt/mTOR pathway mediates retinal progenitor cell survival under hypoxic and superoxide stress. Mol Cell Neurosci 47:145-153.
Sarbassov DD, Guertin DA, Ali SM, Sabatini DM (2005) Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science 307:1098-1101.
Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, Markhard AL, Sabatini DM (2006) Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell 22:159-168.
Sasazawa Y, Sato N, Umezawa K, Simizu S (2015) Conophylline protects cells in cellular models of neurodegenerative diseases by inducing mammalian target of rapamycin (mTOR)-independent autophagy. J Biol Chem 290:6168-6178.
Sataranatarajan K, Ikeno Y, Bokov A, Feliers D, Yalamanchili H, Lee HJ, Mariappan MM, Tabatabai-Mir H, Diaz V, Prasad S, Javors MA, Ghosh Choudhury G, Hubbard GB, Barnes JL, Richardson A, Kasinath BS (2015) Rapamycin increases mortality in db/db mice, a mouse model of type 2 diabetes. J Gerontol A Biol Sci Med Sci pii: glv170.
Sato A, Sunayama J, Matsuda K, Tachibana K, Sakurada K, Tomiyama A, Kayama T, Kitanaka C (2010) Regulation of neural stem/progenitor cell maintenance by PI3K and mTOR. Neurosci Lett 470:115-120.
Sato T, Nakashima A, Guo L, Tamanoi F (2009) Specific activation of mTORC1 by Rheb G-protein in vitro involves enhanced recruitment of its substrate protein. J Biol Chem 284:12783-12791.
Schaffer SW, Jong CJ, Mozaffari M (2012) Role of oxidative stress in diabetes-mediated vascular dysfunction: unifying hypothesis of diabetes revisited. Vascul Pharmacol 57:139-149.
Shang YC, Chong ZZ, Hou J, Maiese K (2009) FoxO3a governs early microglial proliferation and employs mitochondrial depolarization with caspase 3, 8, and 9 cleavage during oxidant induced apoptosis. Curr Neurovasc Res 6:223-238.
Shang YC, Chong ZZ, Hou J, Maiese K (2010) Wnt1, FoxO3a, and NF-kappaB oversee microglial integrity and activation during oxidant stress. Cell Signal 22:1317-1329.
Shang YC, Chong ZZ, Wang S, Maiese K (2011) Erythropoietin and Wnt1 govern pathways of mTOR, Apaf-1, and XIAP in inflammatory microglia. Curr Neurovasc Res 8:270-285.
Shang YC, Chong ZZ, Wang S, Maiese K (2012) WNT1 inducible signaling pathway protein 1 (WISP1) targets PRAS40 to govern beta-Amyloid apoptotic injury of microglia. Curr Neurovasc Res 9:239-249.
Shang YC, Chong ZZ, Wang S, Maiese K (2013) Tuberous sclerosis protein 2 (TSC2) modulates CCN4 cytoprotection during apoptotic amyloid toxicity in microglia. Curr Neurovasc Res 10:29-38.
Sheng B, Liu J, Li GH (2012) Metformin preconditioning protects Daphnia pulex from lethal hypoxic insult involving AMPK, HIF and mTOR signaling. Comp Biochem Physiol B Biochem Mol Biol 163:51-58.
Singh K, Sun S, Vezina C (1979) Rapamycin (AY-22,989), a new antifungal antibiotic. IV. Mechanism of action. J Antibiot (Tokyo) 32:630-645.
Sinha SS, Pham MX, Vagelos RH, Perlroth MG, Hunt SA, Lee DP, Valantine HA, Yeung AC, Fearon WF (2008) Effect of rapamycin therapy on coronary artery physiology early after cardiac transplantation. Am Heart J 155:889 e881-886.
Snyder C, Stefano GB (2015) Mitochondria and chloroplasts shared in animal and plant tissues: significance of communication. Med Sci Monit 21:1507-1511.
Sonnen JA, Larson EB, Brickell K, Crane PK, Woltjer R, Montine TJ, Craft S (2009) Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol 66:315-322.
Sun JJ, Ren QG, Xu L, Zhang ZJ (2015) LINGO-1 antibody ameliorates myelin impairment and spatial memory deficits in experimental autoimmune encephalomyelitis mice. Scientific reports 5:14235.
Tang AH, Rando TA (2014) Induction of autophagy supports the bioenergetic demands of quiescent muscle stem cell activation. EMBO J 33:2782-2797.
Tang Z, Baykal AT, Gao H, Quezada HC, Zhang H, Bereczki E, Serhatli M, Baykal B, Acioglu C, Wang S, Ioja E, Ji X, Zhang Y, Guan Z, Winblad B, Pei JJ (2014) mTor is a signaling hub in cell survival: a mass-spectrometry-based proteomics investigation. J Proteome Res 13:2433-2444.
Treins C, Alliouachene S, Hassouna R, Xie Y, Birnbaum MJ, Pende M (2012) The combined deletion of S6K1 and Akt2 deteriorates glycaemic control in high fat diet. Mol Cell Biol 32:4001-4011.
Tsai CF, Kuo YH, Yeh WL, Wu CY, Lin HY, Lai SW, Liu YS, Wu LH, Lu JK, Lu DY (2015) Regulatory effects of caffeic acid phenethyl ester on neuroinflammation in microglial cells. Int J Mol Sci 16:5572-5589.
Tulsulkar J, Nada SE, Slotterbeck BD, McInerney MF, Shah ZA (2016) Obesity and hyperglycemia lead to impaired post-ischemic recovery after permanent ischemia in mice. Obesity (Silver Spring) 24:417-423.

Vakifahmetoglu-Norberg H, Xia HG, Yuan J (2015) Pharmacologic agents targeting autophagy. J Clin Invest 125:5-13.
Viola G, Bortolozzi R, Hamel E, Moro S, Brun P, Castagliuolo I, Ferlin MG, Basso G (2012) MG-2477, a new tubulin inhibitor, induces autophagy through inhibition of the Akt/mTOR pathway and delayed apoptosis in A549 cells. Biochem Pharmacol 83:16-26.
Wang H, Zhang Q, Wen Q, Zheng Y, Philip L, Jiang H, Lin J, Zheng W (2012a) Proline-rich Akt substrate of 40kDa (PRAS40): a novel downstream target of PI3k/Akt signaling pathway. Cell Signal 24:17-24.
Wang L, Di L, Noguchi CT (2014a) Erythropoietin, a novel versatile player regulating energy metabolism beyond the erythroid system. Int J Biol Sci 10:921-939.
Wang L, Di L, Noguchi CT (2014b) AMPK is involved in mediation of erythropoietin influence on metabolic activity and reactive oxygen species production in white adipocytes. Int J Biochem Cell Biol 54:1-9.
Wang L, Lawrence JC, Jr., Sturgill TW, Harris TE (2009) Mammalian target of rapamycin complex 1 (mTORC1) activity is associated with phosphorylation of raptor by mTOR. J Biol Chem 284:14693-14697.
Wang P, Xing Y, Chen C, Chen Z, Qian Z (2015) Advanced glycation end-product (AGE) induces apoptosis in human retinal ARPE-19 cells via promoting mitochondrial dysfunction and activating the Fas-FasL signaling. Biosci Biotechnol Biochem:1-7.
Wang RH, Kim HS, Xiao C, Xu X, Gavrilova O, Deng CX (2011a) Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. J Clin Invest 121:4477-4490.
Wang S, Chong ZZ, Shang YC, Maiese K (2012b) WISP1 (CCN4) autoregulates its expression and nuclear trafficking of beta-catenin during oxidant stress with limited effects upon neuronal autophagy. Curr Neurovasc Res 9:89-99.
Wang Y, Liang Y, Vanhoutte PM (2011b) SIRT1 and AMPK in regulating mammalian senescence: a critical review and a working model. FEBS Lett 585:986-994.
Weckman A, Di Ieva A, Rotondo F, Syro LV, Ortiz LD, Kovacs K, Cusimano MD (2014) Autophagy in the endocrine glands. J Mol Endocrinol 52:R151-163.
Wei L, Sun C, Lei M, Li G, Yi L, Luo F, Li Y, Ding L, Liu Z, Li S, Xu P (2013) Activation of Wnt/β-catenin pathway by exogenous Wnt1 protects SH-SY5Y cells against 6-hydroxydopamine toxicity. J Mol Neurosci 49:105-115.
Weinberg E, Maymon T, Weinreb M (2014) AGEs induce caspase-mediated apoptosis of rat BMSCs via TNFalpha production and oxidative stress. J Mol Endocrinol 52:67-76.
White MF (2014) IRS2 integrates insulin/IGF1 signalling with metabolism, neurodegeneration and longevity. Diabetes Obes Metab 16 Suppl 1:4-15.
Wong DZ, Kadir HA, Lee CL, Goh BH (2012) Neuroprotective properties of Loranthus parasiticus aqueous fraction against oxidative stress-induced damage in NG108-15 cells. J Nat Med 66:544-551.
World Health Organization (2011) Description of the global burden of NCDs, their risk factors and determinants. Global status report on noncommunicable diseases 2010:1-176.
Xiao FH, He YH, Li QG, Wu H, Luo LH, Kong QP (2015) A genome-wide scan reveals important roles of DNA methylation in human longevity by regulating age-related disease genes. PLoS One 10:e0120388.
Xie Z, Lau K, Eby B, Lozano P, He C, Pennington B, Li H, Rathi S, Dong Y, Tian R, Kem D, Zou MH (2011) Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice. Diabetes 60:1770-1778.
Xin YJ, Yuan B, Yu B, Wang YQ, Wu JJ, Zhou WH, Qiu Z (2015) Tet1-mediated DNA demethylation regulates neuronal cell death induced by oxidative stress. Sci Rep 5:7645.
Xiong X, Xie R, Zhang H, Gu L, Xie W, Cheng M, Jian Z, Kovacina K, Zhao H (2014) PRAS40 plays a pivotal role in protecting against stroke by linking the Akt and mTOR pathways. Neurobiol Dis 66:43-52.
Xu E, Schwab M, Marette A (2014a) Role of protein tyrosine phosphatases in the modulation of insulin signaling and their implication in the pathogenesis of obesity-linked insulin resistance. Rev Endocr Metab Disord 15:79-97.
Xu YJ, Tappia PS, Neki NS, Dhalla NS (2014b) Prevention of diabetes-induced cardiovascular complications upon treatment with antioxidants. Heart Fail Rev 19:113-121.
Xue Q, Nagy JA, Manseau EJ, Phung TL, Dvorak HF, Benjamin LE (2009) Rapamycin inhibition of the Akt/mTOR pathway blocks select stages of VEGF-A164-driven angiogenesis, in part by blocking S6Kinase. Arterioscler Thromb Vasc Biol 29:1172-1178.
Yang Y, Li H, Hou S, Hu B, Liu J, Wang J (2013) The noncoding RNA expression profile and the effect of lncRNA AK126698 on cisplatin resistance in non-small-cell lung cancer cell. PLoS One 8:e65309.
Yu L, Liang H, Dong X, Zhao G, Jin Z, Zhai M, Yang Y, Chen W, Liu J, Yi W, Yang J, Yi D, Duan W, Yu S (2015a) Reduced silent information regulator 1 signaling exacerbates myocardial ischemia-reperfusion injury in type 2 diabetic rats and the protective effect of melatonin. J Pineal Res 59:376-390.
Yu T, Li L, Chen T, Liu Z, Liu H, Li Z (2015b) Erythropoietin attenuates advanced glycation endproducts-induced toxicity of schwann cells in vitro. Neurochem Res 40:698-712.
Yu Y, Shiou SR, Guo Y, Lu L, Westerhoff M, Sun J, Petrof EO, Claud EC (2013) Erythropoietin protects epithelial cells from excessive autophagy and apoptosis in experimental neonatal necrotizing enterocolitis. PLoS One 8:e69620.
Zhang D, Yan B, Yu S, Zhang C, Wang B, Wang Y, Wang J, Yuan Z, Zhang L, Pan J (2015a) Coenzyme Q10 inhibits the aging of mesenchymal stem cells induced by D-galactose through Akt/mTOR signaling. Oxid Med Cell Longev 2015:867293.
Zhang F, Cui J, Liu X, Lv B, Liu X, Xie Z, Yu B (2015b) Roles of microRNA-34a targeting SIRT1 in mesenchymal stem cells. Stem Cell Res Ther 6:195.
Zhang F, Hu Y, Xu X, Zhai X, Wang G, Ning S, Yao J, Tian X (2015c) Icariin protects against intestinal ischemia-reperfusion injury. J Surg Res 194:127-138.
Zhang S, Cai G, Fu B, Feng Z, Ding R, Bai X, Liu W, Zhuo L, Sun L, Liu F, Chen X (2012) SIRT1 is required for the effects of rapamycin on high glucose-inducing mesangial cells senescence. Mech Ageing Dev 133:387-400.
Zhang Y, Wang L, Dey S, Alnaeeli M, Suresh S, Rogers H, Teng R, Noguchi CT (2014) Erythropoietin action in stress response, tissue maintenance and metabolism. Int J Mol Sci 15:10296-10333.
Zhou J, Wu J, Zheng F, Jin M, Li H (2015) Glucagon-like peptide-1 analog-mediated protection against cholesterol-induced apoptosis via mammalian target of rapamycin activation in pancreatic betaTC-6 cells -1mTORbetaTC-6. J Diabetes 7:231-239.
Zhou J, Su P, Wang L, Chen J, Zimmermann M, Genbacev O, Afonja O, Horne MC, Tanaka T, Duan E, Fisher SJ, Liao J, Chen J, Wang F (2009) mTOR supports long-term self-renewal and suppresses mesoderm and endoderm activities of human embryonic stem cells. Proc Natl Acad Sci U S A 106:7840-7845.
Zoncu R, Efeyan A, Sabatini DM (2011) mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 12:21-35.