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Nicotinamide: Oversight of Metabolic Dysfunction through SIRT1, mTOR, and Clock Genes

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Abstract

Metabolic disorders that include diabetes mellitus present significant challenges for maintaining the welfare of the global population. Metabolic diseases impact all systems of the body and despite current therapies that offer some protection through tight serum glucose control, ultimately such treatments cannot block the progression of disability and death realized with metabolic disorders. As a result, novel therapeutic avenues are critical for further development to address these concerns. An innovative strategy involves the vitamin nicotinamide and the pathways associated with the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), the mechanistic target of rapamycin (mTOR), mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), AMP activated protein kinase (AMPK), and clock genes. Nicotinamide maintains an intimate relationship with these pathways to oversee metabolic disease and improve glucose utilization, limit mitochondrial dysfunction, block oxidative stress, potentially function as antiviral therapy, and foster cellular survival through mechanisms involving autophagy. However, the pathways of nicotinamide, SIRT1, mTOR, AMPK, and clock genes are complex and involve feedback pathways as well as trophic factors such as erythropoietin that require a careful balance to ensure metabolic homeostasis. Future work is warranted to gain additional insight into these vital pathways that can oversee both normal metabolic physiology and metabolic disease.

Keywords

Alzheimer's disease; AMP activated protein kinase (AMPK); autophagy; apoptosis; circadian rhythm; clock genes; coronavirus disease 2019 (COVID-19); dementia; diabetes mellitus; erythropoietin; mechanistic target of rapamycin (mTOR); metformin; oxidative stress; poly-ADP-ribose polymerase (PARP); SARS-CoV-2; silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; stem cells

1. The Global Impact of Metabolic Disease and Diabetes Mellitus

Diabetes mellitus (DM) is increasingly being targeted for the development of novel treatment strategies to limit death and disability for the world's population (1–10). At least eighty percent of adults with DM live in low- and middle-income countries and almost five hundred million individuals suffer from DM (11–16). Interestingly, an additional four

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hundred million individuals are believed to either suffer from metabolic disease or be at risk for developing DM (16–19). The number of individuals with DM is expected to rise to seven hundred million individuals by the year 2045 (16). Approximately thirty-five million individuals, representing about ten percent of the population in the United States (US), are diagnosed with DM (4). Seven million individuals over the age of 18 remain undiagnosed with DM and almost thirty-five percent of adults in the US had prediabetes based on their fasting glucose and hemoglobin A1c (HbA_{1c}) levels in the year 2018 (20). Prevalence of DM has also increased from nine and one-half percent during the period of 1999 to 2002 to twelve percent during the period of 2013 to 2016. Prevalence in the adult for DM can vary by factors that are influenced by socioeconomic status, such as education level. For example, thirteen percent of the adults with less than a high school education had DM compared to almost ten percent of individuals with a high school education and DM and seven and one-half percent of individuals with greater than a high school education and DM. Risk factors for the development of DM and its complications include tobacco consumption, physical inactivity, hypertension, and elevated serum cholesterol (6). Obesity is another risk factor for the development of DM and leads to impaired glucose tolerance (5, 21–27). Obesity and excess body fat can increase the risk of developing DM in young individuals (28) and can affect stem cell proliferation, aging, inflammation, oxidative stress injury, and mitochondrial function (23, 29–35).

In regards to the cost to care for DM, at least $20,000 United States Dollars (USD) are required to treat each individual with DM per year. The care for patients with DM equals approximately $760 billion USD (16). This care consumes more than seventeen percent of the Gross Domestic Product in the US (36). When considering the loss of function and disability that DM can cause in individuals, approximately sixty-nine billion USD are consumed from reduced productivity.

The toxic effects of DM involve all organs of the body and can affect all cellular systems (7). In the peripheral nervous system, at least seventy percent of individuals with DM can develop diabetic peripheral neuropathy. DM can result in autonomic neuropathy (37) and peripheral nerve disease (38–42). In the central nervous system, DM can cause insulin resistance and loss of cognition in patients with Alzheimer’s disease (AD) (3, 6, 7, 43–47). DM can affect several cellular pathways that lead to cognitive loss and dementia (13, 48–53). DM also has been tied to mental illness (54, 55), cerebral vascular injury (13, 18, 56–59), impairment of microglial activity (3, 43–45), and loss of stem cell development (13, 24, 48–52). DM leads to endothelial dysfunction (13, 47, 60–62), cardiovascular disease (19, 21, 61, 63–69), retinal disease (70–72), and immune and infectious disorders (73–79).

2. Novel Strategies for Metabolic Disease

With the growing prevalence of DM, the significant number of individuals that remain undiagnosed with DM, and the marked financial impact on all economies, innovative therapeutic strategies are critical for the treatment of metabolic disorders, such as DM. Although an early diagnosis of DM and quick treatment can offer limited protection and may block some progression of DM (14, 47, 80–84), tight serum glucose control does not ultimately prevent the complications that can arise during DM (6, 85). Careful nutritional

and exercise management also can be important for DM care, but in some cases these strategies may be less than beneficial depending on the degree of reduced oral intake and a decrease in organ mass through processes that involve autophagy (86). DM also has additional risk factors when one considers the development of neurodegenerative disorders and cognitive loss that can be compounded by hypertension, low education in early life, and tobacco use (3, 6, 7, 87). For example, vascular disease as a result of DM may lead to loss of memory and dementia (6, 7, 46, 47, 88–91). One innovative strategy to meet the challenges for the treatment of metabolic disease involves the vitamin nicotinamide and the pathways associated with the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), the mechanistic target of rapamycin (mTOR), mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), AMP activated protein kinase (AMPK), and clock genes.

3. Nicotinamide and Metabolic Disease

Nicotinamide, a vitamin, has an important role during metabolic dysfunction and DM (28, 81, 82, 92–95). Nicotinamide is the amide form of vitamin B_3 (niacin) and it is obtained through synthesis in the body or as a dietary source and supplement, such as from animal sources or plants (95). Nicotinic acid is the alternative form of the water-soluble vitamin B_3 (96). The primary form of niacin in dietary plant sources is nicotinic acid that is rapidly absorbed through the gastrointestinal epithelium (97). Nicotinamide is obtained through the conversion of nicotinic acid in the liver or through the hydrolysis of the coenzyme ß-nicotinamide adenine dinucleotide (NAD^+). Once present, nicotinamide functions as the precursor for NAD^+ (94, 98). In addition, nicotinamide is required for the synthesis of nicotinamide adenine dinucleotide phosphate ($NADP^+$) (99). Nicotinamide is changed to its mononucleotide form (NMN) with the enzyme nicotinamide phosphoribosyl-transferase (NAMPT). NAMPT has two forms of intracellular and extracellular. NMN then is changed to the dinucleotides NAD^+ and $NAAD^+$ through nicotinamide/nicotinic acid mononucleotide adenylyltransferases (NMNATs). $NAAD^+$ converts to NAD^+ through NAD^+ synthase (100) or NAD^+ can be synthesized through nicotinamide riboside kinase that phosphorylates nicotinamide riboside (NR) to NMN (101, 102). Nicotinamide through NAD^+ can be directly utilized by cells to synthesize NAD^+ (92–95, 103). Nicotinamide participates in energy metabolism through the tricarboxylic acid cycle by utilizing NAD^+ in the mitochondrial respiratory electron transport chain for the production of ATP, DNA synthesis, and DNA repair (104–106).

Specific concentrations of nicotinamide and NAD^+ may be a critical factor for cell survival (103, 107, 108). Nicotinamide offers protection usually in a specific concentration range (98). Administration of nicotinamide in a range of 5.0 – 25.0 mmol/L can significantly protect neurons during oxidative stress injuries and apoptosis. This concentration range is similar to other injury paradigms in both animal models (109) and in cell culture models (94, 110, 111). Elevated concentrations of nicotinamide in some experimental models may not offer protection and can be detrimental (112, 113). Yet, increased administration of nicotinamide may be useful against tumorigenesis (114) and lead to apoptotic cell death in cancer cells (115, 116). Nicotinamide affects both phases of apoptotic cell death. Nicotinamide can prevent exposure of plasma membrane phosphatidylserine (PS) residues

(117–123) to prevent inflammatory cell activation (98, 110, 111, 124). Nicotinamide can limit cardiovascular injury by blocking membrane PS exposure in vascular cells (94, 111), since membrane PS residue externalization in vascular cells can lead to hypercoagulation states (125) and cellular inflammation (126, 127). Nicotinamide can also reverse a previously sustained insult, since post-treatment studies with nicotinamide that can follow apoptotic injury in "real-time" show that early cellular apoptotic injury can be reversed (94, 110, 111, 124, 128, 129).

During cellular metabolism and DM, nicotinamide limits insulin resistance and glucose release with additional pathways to prevent the onset and progression of DM (130–132). Nicotinamide prevents skeletal muscle atrophy during DM (133), limits mitochondrial stress through AMP-activated protein kinase (AMPK) activation (134), and reduces inflammation of the brain during DM with niacin administration (135). In animal models, nicotinamide can maintain normal fasting blood glucose with streptozotocin-induced DM (136, 137) and block oxidative stress pathways that lead to cell death and apoptosis (111, 124, 138–140). In addition, nicotinamide can markedly improve glucose utilization, block excess lactate production, and improve electrophysiologic capacity in ischemic animal models (141). Oral nicotinamide administration at a dose of 1200mg/m^2/day protects pancreatic β-cell function and prevents clinical disease in islet-cell antibody-positive first-degree relatives of type-1 DM (142). Patients with recent onset type-1 DM receiving nicotinamide (25mg/kg) in combination with intensive insulin therapy for up to two years experienced significantly reduce HbA_{1c} levels (143). However, it is important to note that prolonged exposure of nicotinamide has been reported to result in impaired pancreatic β-cell function and cell growth (144, 145). Nicotinamide may block cytochromes P450 and hepatic metabolism (146). As a result, the duration of nicotinamide administration may influence the efficacy of this agent since long-term administration also has been reported to support glucose intolerance in some animal models (107).

4. Nicotinamide, SIRT1, and Autophagy

Nicotinamide is intimately tied to silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) to oversee cellular function and survival during metabolic disease (13, 24, 76, 147–151). SIRT1 is a histone deacetylase that can transfer acetyl groups from ε-N-acetyl lysine amino acids to the histones of deoxyribonucleic acid (DNA) to control transcription (13, 47, 152–161). Nicotinamide and SIRT1 function through autophagic pathways that necessitate a tight oversight of SIRT1 activity (91, 162–165). During nicotinamide administration, mitochondrial autophagy (mitophagy) can lead to an increased NAD^+/NADH ratio (107, 166, 167). In addition, chronic administration of nicotinamide can lead to skeletal muscle lipotoxicity and glucose intolerance during autophagy activation (107). As an inhibitor of SIRT1, nicotinamide through autophagy can limit cancer cell growth and in combination with chemotherapeutic agents lead to apoptotic cell death (168–171). Through SIRT1 inhibition, nicotinamide may exert anti-inflammatory properties and affect the transcriptional regulation of inflammatory genes (172). However, nicotinamide has been shown to be cytoprotective through SIRT1 to prevent palmitate-induced hepatotoxicity through SIRT1-dependent induction of autophagy (173).

Such observations for cellular protection with SIRT1 and nicotinamide are similar to work with the growth factor erythropoietin (EPO). EPO also protects against toxic metabolic environments through SIRT1 (76, 82, 174, 175). EPO increases metabolic activity and maintains adipose energy homeostasis in adipocytes to prevent metabolic dysfunction through the combined activation of PPAR-α and SIRT1 (176). EPO uses SIRT1 to modulate skeletal myogenic differentiation (177). In central nervous system endothelial cells, EPO promotes the subcellular trafficking of SIRT1 to the nucleus to promote vascular cell protection and to prevent mitochondrial depolarization, cytochrome c release, BCL2 associated agonist of cell death (Bad) activity, and caspase activation (178). EPO can increase survival of human cardiomyocytes that have mitochondrial dysfunction through the activation of SIRT1 during chemotherapy toxicity (154). EPO prevents the loss of neuronal cells in the brain through the up-regulation of SIRT1 (179). As a result, it is important to recognize the intimate relationship between nicotinamide and SIRT1. Dependent on the conditions, SIRT1 activity or inactivity with nicotinamide may promote cellular survival. In addition, through deacetylase reactions, SIRT1 can transfer the acetyl residue from the acetyllysine residue of histones to the ADP-ribose moiety of NAD^+, resulting in the production of nicotinamide. Additional studies suggest that nicotinamide, although an initial inhibitor of SIRT1, may subsequently promote SIRT activity as well as a result of the cellular conversion of nicotinamide to NAD^+ (93, 103).

5. Nicotinamide and the Mechanistic Target of Rapamycin (mTOR) Pathways

The mechanistic target of rapamycin (mTOR), a 289-kDa serine/threonine protein kinase, is increasingly being recognized as a critical pathway for nicotinamide to control cellular metabolism (6, 7, 24, 27, 79, 93, 180–182). mTOR also is termed the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 (160, 161) and is encoded by a single gene *FRAP1* (183–185). The target of rapamycin (TOR) was first discovered in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* (186). Employing rapamycin-resistant TOR mutants, *TOR1* and *TOR2* are now known to encode the Tor1 and Tor2 isoforms in yeast (187). Rapamycin is a macrolide antibiotic in *Streptomyces hygroscopicus* that blocks the activity of TOR and mTOR (18). mTOR is the primary component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (174, 188, 189). Rapamycin limits 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 (190). Although not entirely clear on how rapamycin blocks mTORC1 activity, one pathway 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) (191). mTORC1 is more sensitive to inhibition by rapamycin than mTORC2. Yet, chronic administration of rapamycin can inhibit mTORC2 activity as a result of the disruption of the assembly of mTORC2 (185, 192).

mTORC1 and mTORC2 are further divided into subcomponents. 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) (186). Binding of mTORC1 to its constituents occurs 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} (193). The inability to phosphorylate serine^{863} reduces mTORC1 activity, as shown using a site-direct mutation of serine^{863} (194). mTOR can oversee Raptor activity which can be blocked by rapamycin (194). Deptor, an inhibitor of the mTOR pathway, blocks mTORC1 activity by binding to the FAT domain (FKBP12 -rapamycin-associated protein (FRAP), ataxia-telangiectasia (ATM), and the transactivation/transformation domain-associated protein) of mTOR. If the activity of Deptor is blocked, Akt, mTORC1, and mTORC2 activities are increased (195). PRAS40 decreases 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 (196, 197). mTORC1 is active after PRAS40 is phosphorylated by Akt. This releases PRAS40 from Raptor to sequester PRAS40 in the cell cytoplasm with the docking protein 14-3-3 (198–202). mLST8, in contrast, fosters mTOR kinase activity. This involves binding of p70S6K and 4EBP1 to Raptor (203). mLST8 also controls insulin signaling through the mammalian forkhead transcription factor FoxO3 (75, 204). mLST8 is also necessary for Akt and protein kinase C-α (PKCα) phosphorylation and is required for Rictor to associate with mTOR (204).

mTORC2 consists of Rictor, mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (183, 196). mTORC2 controls cytoskeleton remodeling through PKCα and cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling (205). mTORC2 increases the activity of protein kinases that includes 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 (206, 207). The kinase domain of mTOR phosphorylates mSIN1 and inhibits lysosomal degradation of this protein. Rictor and mSIN1 are also able to phosphorylate Akt at serine^{473} and foster threonine^{308} phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) to enhance cell survival.

AMPK as part of the nicotinamide and mTOR pathways controls cellular metabolism as well (3, 64, 208, 209). AMPK prevents mTORC1 activity through the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that blocks mTORC1 (159, 210). In addition, oversight of the TSC1/TSC2 complex is controlled though phosphoinositide 3-kinase (PI 3-K), Akt, and its phosphorylation of TSC2. Extracellular signal-regulated kinases (ERKs), protein p90 ribosomal S6 kinase 1 (RSK1), and glycogen synthase kinase −3β (GSK-3β) can also modulate the activity of the TSC1/TSC2 complex. TSC2 functions as a GTPase-activating protein (GAP) that converts G protein Rheb (Rheb-GTP) into the inactive GDP-bound form (Rheb-GDP). Once Rheb-GTP is active, Rheb-GTP then associates with Raptor to control the binding of 4EBP1 to mTORC1 and increase mTORC1 activity (211). AMPK phosphorylates TSC2 to increase GAP activity to change Rheb-GTP into the inactive Rheb-GDP and block mTORC1 activity (212).

The mTOR pathway is closely linked to cellular metabolic function and disease (6, 18, 40, 213–216). Activation of mTOR may decrease cognitive loss that can be a result of DM and other toxicities (2, 6, 160, 217–219). mTOR activation can prevent microglial injury during oxidative stress and block ß-amyloid (Aß) toxicity in neurons (200, 218, 220–224). mTOR activation also can limit diabetic neuropathy (41), alleviate pain sensitization in combination with SIRT1 activity (225), and reduce ischemic stroke injury in conjunction with circadian clock genes (6, 158, 226–228). Interestingly, decreased activity of mTOR has been shown to increase mortality in murine models of DM (229). During mTOR inhibition with rapamycin, reduced β-cell function, insulin resistance, and decreased insulin secretion can lead to the progression of DM (230). The correct translocation of glucose transporters to the plasma membrane in skeletal muscle are also affected during loss of mTOR activity (231). In patients with metabolic syndrome, mTOR activation is diminished. mTOR activity also appears necessary for proper metabolic function during inflammatory conditions with rheumatoid arthritis (232) and during diabetes-induced testicular dysfunction (182). This loss of mTOR activity may be responsible for insulin resistance and the increased risk of vascular thrombosis (233). Activation of mTOR pathways that oversee p70S6K and 4EBP1 can improve insulin secretion in pancreatic β-cells and increase resistance to β-cell streptozotocin toxicity and obesity in mice (234). Loss of p70S6K activity leads to hypo-insulinemia and glucose intolerance with diminished pancreatic β-cell size (235). mTOR activity has been shown to protect pancreatic β- cells against cholesterol-induced apoptosis (236), lead to enhanced neuronal cell survival in DM cellular models (237), reduce oxidative stress (24, 27, 42, 79, 238–242), and block glucolipotoxicity (243). mTOR activity can foster the differentiation of adipocytes (244), prevent endothelial cell dysfunction during hyperglycemia (62), and maintain glucose homeostasis (245). mTOR provides protection as an integral component of the Mediterranean diet to reduce obesity in the population. The diet may reduce Aβ toxicity in astrocytes through enhanced Akt activity by consumption of polyphenol of olives and olive oil that over time may prevent the onset or progression of AD (214).

Nicotinamide, and in a similar manner trophic factors, can provide protection against oxidative stress and DM through mTOR pathways. In relation to growth factors, such as insulin-like growth factor-1 (IGF-1) (246–249) and EPO (6, 22, 70, 83, 127, 250–254), these trophic factors rely upon mTOR pathways. EPO utilizes the mTOR pathway, such as PRAS40 and Akt, to increase cell survival (198, 255–257) and limit toxic cellular environments (221, 258–260). EPO also plays a significant role as a potential cellular protectant during aging (261) and DM with the modulation of mTOR pathways, in part, to preserve cell survival (18, 70, 82, 83, 127, 252, 262–266). In regards to nicotinamide, nicotinamide maintains a fine control over cellular metabolism through mTOR pathways such as p70S6K, 4EBP1, and AMPK. Both p70S6K and 4EBP1 in the mTOR pathway are required by nicotinamide to protect against radiation-induced apoptosis (267). p70S6K and 4EBP1 activation also can improve insulin secretion in pancreatic β-cells and increase resistance to β-cell streptozotocin toxicity and obesity in mice (234). Concerning AMPK, nicotinamide can reduce intracellular mitochondrial stress in hypoxic cardiomyocytes through the activation of AMPK (134). Similar to nicotinamide, biguanides and metformin also use AMPK to maintain cellular function. Metformin inhibits mTOR activity, promotes

autophagy, and can function at times in an AMPK-independent manner (268). Through metformin, AMPK activation leads to autophagy induction and protects against diabetic apoptotic cardiac cell death (269). Metformin also has been shown to prevent lipid peroxidation in the brain and spinal cord and to reduce caspase activity during toxic insults (270). These observations of metformin to offer protection during DM may be associated with the ability of autophagic pathways to limit oxidative stress under some circumstances (22, 271). The protective role of metformin to regulate cellular metabolism through the inhibition of mTOR pathways and promotion of autophagy activation also has been recently highlighted as a novel means to lessen morbidity and mortality from the β-coronavirus family virion, SARS-CoV-2, and coronavirus disease 2019 (COVID-19) (79, 180, 272–279). Nicotinamide as well may function through such pathways and others, such as poly-ADP-ribose polymerase (PARP) (7, 81, 93, 94, 124, 148, 239, 280), to block illness from COVID-19 (281–283).

AMPK activation during metabolic disease can promote insulin sensitivity, fatty acid oxidation, and mitochondrial biogenesis. This leads to the generation of ATP and serves to limit oxidative stress (6, 93). AMPK activation can decrease disability and hyperalgesia from diabetic neuropathy in animal models (40). Diets associated with fish oil consumption can result in increased AMPK activity and block endothelial progenitor cell dysfunction and ischemic injuries (64). AMPK also can limit insulin resistance, since the loss of AMPK has been shown to lead to reduced tolerance for the development of insulin resistance (284). During periods of reduced dietary intake that may increase lifespan (285), AMPK activation also can shift to beneficial oxidative metabolism (286). This process has been shown to limit ischemic brain damage in diabetic animal models (287). In line with the vascular protective properties of nicotinamide (111, 128, 288), AMPK can limit insulin resistance (284) and protect endothelial progenitor cells during periods of hyperglycemia (64). AMPK activation also can strengthen memory retention in models of AD and DM (208), may assist with the elimination of Aß in the brain (289), facilitate tau clearance (290), and limit chronic inflammation in the nervous system (158, 164, 210).

AMPK oversees autophagy pathways and appears to require a fine control of activity similar to nicotinamide to achieve beneficial outcomes in metabolic disease. During metabolic disease, autophagy can remove misfolded proteins and eliminate non-functioning mitochondria to maintain β-cell function and prevent the onset of DM (291). Exercise in mice has been demonstrated to foster autophagy activation and regulate glucose homeostasis (292). Autophagy can improve insulin sensitivity during the administration of high fat diets in mice (284) and may protect microglia during acute glucose fluctuations (45). During periods of hyperglycemia, AMPK increases basal autophagy activity (156, 162) and prevents endothelial cell death (62, 293). AMPK can control autophagy during coronary artery disease (294), cholesterol efflux (295), endothelial dysfunction during hyperglycemia (62), and oxidative stress (296, 297). AMPK can promote anti-senescence activity and the increase of autophagic flux (298). Yet, as previously noted, activation of AMPK and autophagy pathways may require careful modulation during metabolic disease and DM (7, 9, 26, 43, 45, 75, 79). Enhanced activity of autophagy can lead to the loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification (86). During elevated glucose exposure, toxic advanced glycation end products (AGEs) can

yield autophagy activation and vascular smooth muscle proliferation that may lead to atherosclerosis (299) and cardiomyopathy (300). During elevated glucose exposure, autophagy can impair endothelial progenitor cells, lead to mitochondrial oxidative stress (301), and prevent angiogenesis (302). Chronic inflammatory conditions such as lichen planus also have been tied to mTOR inhibition and autophagy activation (303).

For cellular protection during metabolic disease, nicotinamide maintains a tight relationship with mTOR pathways and autophagy (24, 27, 79, 182, 238, 241, 304–308). Nicotinamide can reduce Aß toxicity and improve cognition (96, 309), limit metabolic dysfunction through the maintenance of mitochondria (81, 93, 134, 310), maintain metabolic homeostasis (282, 311, 312), block neural ischemic injury (313) and endothelial injury (314), and protect hypoxic myocardial cells through autophagy activation and the inhibition of mTOR (315). However, the loss of mTOR activity can be detrimental at times. During mTOR inhibition with rapamycin, reduced β-cell function, insulin resistance, and decreased insulin secretion can promote the DM progression (230). Decreased activity of mTOR can increase mortality in a mouse model of DM (229). Translocation of glucose transporters to the plasma membrane in skeletal muscle can be blocked in the absence of mTOR activity (231). Furthermore, limits in autophagy activation may be necessary. Interneuron progenitor growth in the brain requires mTOR activity with the inhibition of autophagy (316). Autophagy activation also can lead to injury of endothelial progenitor cells, result in mitochondrial oxidative stress, and prevent new blood vessel formation during elevated glucose exposure (302). Blockade of autophagy may also limit infarct size and rescue cerebral neurons during stroke and oxidative stress (307, 317). This work highlights a potential feedback mechanism with autophagy and mTOR, such as through AMPK, to block either excess AMPK or mTOR activity. As an example, if mTOR activity is unchecked during the inhibition of AMPK activity, mTOR and p70S6K can lead to glucose intolerance by inhibiting the insulin receptor substrate 1 (IRS-1) (318). In addition, mTOR inhibition may reduce stroke infarct size during models of DM (287), block cardiac hypertrophy (319), protect vascular cells from oxidative stress (241), prevent retinal degeneration (148), and also can be necessary for maintaining a balance between pancreatic β-cell proliferation and cell size (320). Therefore, feedback mechanisms involving nicotinamide, autophagy, mTOR, and AMPK, may be vital to achieve an appropriate balance of activity for cellular protection during metabolic disease.

6. Nicotinamide and Clock Genes

Circadian rhythm clock genes have a prominent role during cellular injury and metabolic disorders (6, 9, 158, 161, 321–327). Clock genes can impact endocrine metabolic disorders and cancer (228, 324, 325, 328), the development of DM (6, 322, 327, 329, 330), energy metabolism and aging (158, 321, 331–333), cellular metabolism and neurodegeneration (6, 332–337), mitochondrial energy maintenance (32, 325, 327, 338), diabetic retinal disease (9), and fasting plasma glucose release (329, 339). The mammalian circadian clock resides in the suprachiasmatic nucleus (SCN) located above the optic chiasm and receives light input from photosensitive ganglion cells in the retina. The SCN controls most overt circadian rhythms and relies upon the pineal gland, hypothalamic nuclei, and vasoactive intestinal peptide to oversee processes that involve the sleep wake cycle, release of hormones cortisol

and melatonin, oxidative stress responses (340), and the regulation of body temperature (329). In regards to the clock gene family, members of the basic helix-loop-helix -PAS (Period-Arnt-Single-minded) transcription factor family, such as CLOCK and BMAL1 (341), control the expression of the genes *Cryptochrome (Cry1 and Cry2)* and *Period (Per1, Per2, and Per3).* Oversight and feedback are provided by PER:CRY heterodimers that translocate to the nucleus to block the transcription activated by CLOCK:BMAL1 complexes. Other regulatory loops consist of retinoic acid-related orphan nuclear receptors REV-ERBα, also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1), and RORα that are activated by CLOCK:BMAL1 heterodimers. The REV-ERBα and RORα receptors bind retinoic acid-related orphan receptor response elements (ROREs) that exist in the BMAL1 promoter to repress and activate rhythmic transcription of BMAL1 by RORs and REV-ERBs, respectively. REV-ERBs can block transcription to result in circadian oscillation of BMAL1 (333, 342).

Clock gene pathways are associated with SIRT1, mTOR, and autophagy (6, 9, 158, 161, 226, 227, 325, 331, 338, 343–346). For example, melatonin, a pineal hormone that is involved in regulating circadian rhythm, relies upon autophagy pathways and mTOR to control processes of aging and neurodegeneration (331). Loss of mTOR activation has been shown to affect circadian rhythm and cognitive decline during prolonged space flight and microgravity (346). Cerebral ischemic infarction also may be influenced by an alteration in circadian rhythm genes and fluctuations in mTOR activity (226, 344). In relation to autophagy, circadian rhythm dysfunction that affects cognitive loss has been associated with autophagy induction (347). A basal circadian rhythm that oversees autophagy in animal models of AD may be required to limit cognitive decline and Aβ deposition (348). Changes in environmental homeostasis also can alter circadian rhythm that leads to depressed cognition function (158). As an example, chronic sleep fragmentation has been shown to alter autophagy proteins in the hippocampus and can impair memory and cognition (157, 190, 290, 343, 349, 350). In addition, autophagy activation with clock proteins may be required for cellular protection such as during cerebral ischemia, since loss of the PER1 circadian clock protein can worsen stroke pathology (344).

In light of the reliance of nicotinamide upon mTOR and autophagy pathways similar to clock genes, it may come as no surprise that nicotinamide can have an important role during circadian rhythm function. Nicotinamide and NAD^+ play a critical role with circadian rhythm and clock genes that is tied to SIRT1, mTOR, and autophagy. Cellular NAD^+ pools can fluctuate with circadian rhythmicity and with aging. SIRT1 can oversee clock gene expression through PER2 deacetylation (351). SIRT1 also in conjunction with CLOCK:BMAL1 can regulate the circadian expression of NAMPT that is necessary for the generation of NAD^+. SIRT1 can be recruited to the NAMPT promoter to foster the circadian synthesis of its own coenzyme (352). In addition, the NAD^+ pools can become more depressed with the loss of mitochondrial function that leads to cell injury as a result of the cellular NAD^+ pools oscillating in tandem with free nicotinamide levels and affecting overall cell function and metabolism (353). Furthermore, it has been shown that the loss of the pathways of SIRT1 and mTOR during obesity can lead to the suppression of core circadian components CLOCK and BMAL1 and result in metabolic dysfunction. Studies show that the agent metformin can protect against such processes during obesity in murine

models and can reverse impaired AMPK and SIRT1 function during the suppression of core circadian components CLOCK and BMAL1 (354). This work provides further evidence for circadian rhythm dysfunction linked to metabolic disease and the significant role of pathways associated with nicotinamide that include mTOR, AMPK, autophagy, and SIRT1. SIRT1 control of circadian rhythm and melatonin can affect glucose tolerance and DM (329) as well as inflammation during obesity (32). Through the oversight of circadian rhythms, SIRT1, an NAD^+ dependent histone deacetylase, controls lipid metabolism, liver regeneration (355), and is involved with liver metabolism, aging, and clock genes (356). Nicotinamide, NAD^+ pathways, SIRT1, mTOR can together influence circadian rhythm and clock genes to impact glucose tolerance, lipid metabolism, and cellular regeneration.

7. Future Perspectives

Metabolic disorders that include DM present significant challenges for maintaining the health of the world's population. Approximately eighty percent of adults with DM are living in low- and middle-income countries and almost five hundred million individuals have DM. Furthermore, the number of individuals with DM is expected to rise to seven hundred million individuals by the year 2045. In addition, the care for patients with DM equals approximately $760 billion USD and consumes more than seventeen percent of the Gross Domestic Product in the US. Risk factors for the development of DM and its complications include tobacco consumption, physical inactivity, hypertension, elevated serum cholesterol, and obesity. Disorders such as DM can affect all organs and systems of the body. Although current therapies that offer tight serum glucose control may offer some protection, ultimately these strategies cannot block progression of metabolic disorders. For these reasons, novel therapeutic avenues are necessary to address metabolic disorders and DM. An exciting strategy involves the nicotinamide and the pathways associated with SIRT1, mTOR, mTORC1, mTORC2, AMPK, and clock genes.

Nicotinamide plays an important role during metabolic disease and DM (Figure 1). Nicotinamide can markedly improve glucose utilization, block excess lactate production, limit mitochondrial stress, reduce inflammation of the brain during DM, and reduce oxidative stress pathways. In addition, patients with recent onset type-1 DM receiving nicotinamide have experienced significantly reduce HbA_{1c} levels and oral nicotinamide administration may protect pancreatic β-cell function to block clinical disease in islet-cell antibody-positive first-degree relatives of type-1 DM. However, it appears that specific concentrations of nicotinamide and NAD^+ are critical factors for cell survival. Nicotinamide offers protection usually in a specific concentration range to protect against oxidative stress and cell death. Elevated concentrations of nicotinamide may not be protective and can be detrimental with the exception to promote apoptotic cell death in cancer cells. In addition, prolonged exposure of nicotinamide has been reported to result in impaired pancreatic β-cell function and glucose intolerance.

Interestingly, nicotinamide controls pathways of autophagy through SIRT1 that requires a close regulation of SIRT1 activity to oversee cellular survival. As an inhibitor of SIRT1, nicotinamide through autophagy can limit cancer cell growth and in combination with chemotherapeutic agents lead to apoptotic cell death. Through SIRT1 inhibition,

nicotinamide may exert anti-inflammatory properties and affect the transcriptional regulation of inflammatory genes. Yet, nicotinamide at times may require SIRT1 since nicotinamide can prevent palmitate-induced hepatotoxicity through SIRT1-dependent induction of autophagy. Such observations for cellular protection with SIRT1 and nicotinamide are similar to studies with the growth factor EPO. For example, EPO increases metabolic activity and maintains adipose energy homeostasis through SIRT1. EPO also promotes the subcellular trafficking of SIRT1 to the nucleus to promote vascular cell protection and to prevent mitochondrial depolarization, cytochrome c release, BCL2 associated agonist of cell death (Bad) activity, and caspase activation. As a result, it is vital to appreciate the intimate relationship among nicotinamide, SIRT1, and cellular survival. Additionally, it is important to note that through deacetylase reactions, SIRT1 can transfer the acetyl residue from the acetyllysine residue of histones to the ADP-ribose moiety of NAD^+ and lead to the production of nicotinamide. Furthermore, nicotinamide, although an initial inhibitor of SIRT1, may foster SIRT activity as a result of the cellular conversion of nicotinamide to NAD^+.

Nicotinamide also is dependent upon the pathways of mTOR to influence cellular survival and metabolic disease. For example, p70S6K and 4EBP1 in the mTOR pathway are necessary for nicotinamide to protect against radiation-induced apoptosis and p70S6K and 4EBP1 activation also can improve insulin secretion in pancreatic β-cells and increase resistance to β-cell toxicity and obesity. In addition, nicotinamide can reduce intracellular mitochondrial stress through the activation of AMPK. As a downstream pathway of nicotinamide, AMPK oversees autophagy pathways and can promote insulin sensitivity, fatty acid oxidation, and mitochondrial biogenesis. Yet, the pathways of mTOR, AMPK, and autophagy require close oversight during metabolic disease and DM. During DM, toxic AGEs can promote autophagy activation and vascular smooth muscle proliferation that may lead to in atherosclerosis. Autophagy during periods of elevated glucose can impair endothelial progenitor cells, lead to mitochondrial oxidative stress, and block angiogenesis. In addition, during these periods of autophagy activation with the loss of mTOR activity, reduced β-cell function, insulin resistance, and decreased insulin secretion can promote DM progression. As a result, some biological conditions may require limits on autophagy activation since neuroprotection can be promoted at times during autophagy inhibition, such as during ischemic neuronal injury. Therefore, feedback mechanisms involving nicotinamide, autophagy, mTOR, and AMPK, may be required to achieve an appropriate balance of activity for cellular protection during metabolic disease.

Circadian rhythm clock genes also have a prominent role for nicotinamide during metabolic disorders. Clock genes can influence multiple processes for metabolism that include endocrine metabolic disorders and cancer, the development of DM, energy metabolism and aging, cellular metabolism and neurodegeneration, mitochondrial energy maintenance, diabetic retinal disease, and fasting plasma glucose release. Nicotinamide and NAD^+ play a vital function with circadian rhythm and clock genes that are tied to SIRT1, mTOR, and autophagy. Cellular NAD^+ pools can fluctuate with circadian rhythmicity. These NAD^+ pools can become more depressed with the loss of mitochondrial function that leads to cell injury as a result of the cellular NAD^+ pools oscillating in tandem with free nicotinamide levels and affecting overall cell function and metabolism. In addition, the loss of the

pathways of SIRT1 and mTOR during obesity have been highlighted to result in the suppression of core circadian components CLOCK and BMAL1 and lead to metabolic dysfunction. Nicotinamide, through its oversight of NAD^+ pathways, SIRT1, mTOR and clock genes can impact glucose tolerance, lipid metabolism, cellular regeneration, and cellular survival. Future work is warranted to gain further insight into these critical pathways that can oversee normal metabolic physiology as well as metabolic dysfunction.

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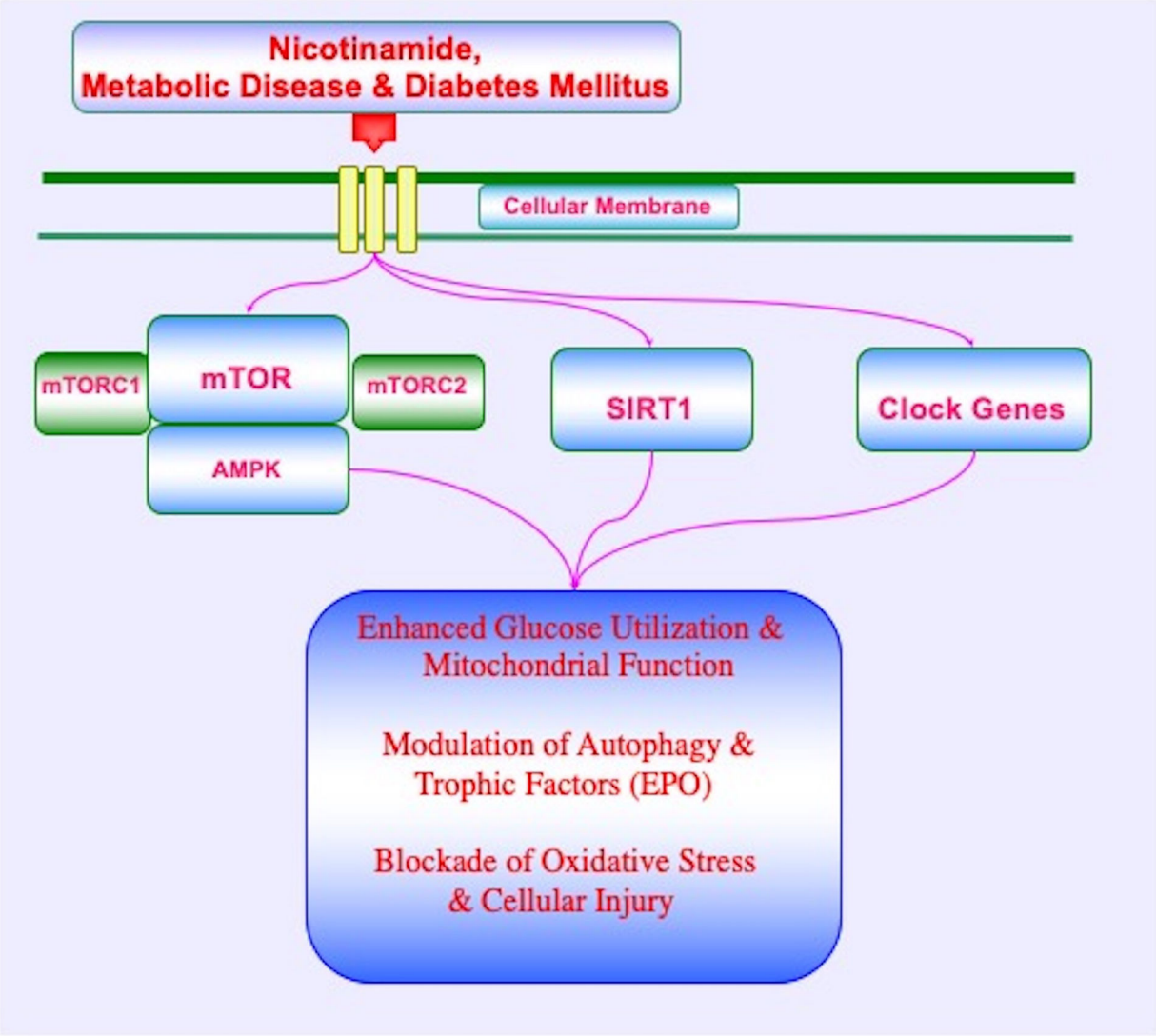

Figure 1: Downstream Nicotinamide Pathways during Metabolic Disease.

During metabolic disease and diabetes mellitus, nicotinamide employs the pathways of the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1), the mechanistic target of rapamycin (mTOR), mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), AMP activated protein kinase (AMPK), erythropoietin (EPO), and clock genes to maintain glucose homeostasis, enhance glucose utilization, oversee pathways of autophagy, and foster mitochondrial function. These pathways have complex interactions and involve feedback mechanisms that require a fine balance in activity to enhance cellular function and survival, block oxidative stress, and limit potential detrimental outcomes.