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REVIEW

Neurobiological Opportunities in Diabetic Polyneuropathy

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Abstract
This review highlights a selection of potential translational directions for the treatment of diabetic polyneuropathy (DPN) currently irreversible and without approved interventions beyond pain management. The list does not include all diabetic targets that have been generated over several decades of research but focuses on newer work. The emphasis is firstly on approaches that support the viability and growth of peripheral neurons and their ability to withstand a barrage of diabetic alterations. We include a section describing Schwann cell targets and finally how mitochondrial damage has been a common element in discussing neuropathic damage. Most of the molecules and pathways described here have not yet reached clinical trials, but many trials have been negative to date. Nonetheless, these failures clear the pathway for new thoughts over reversing DPN.

Keywords Diabetic polyneuropathy · Peripheral nerve · Diabetes mellitus · Translation

Introduction

Diabetes mellitus (DM) is a highly prevalent endocrine disorder with a substantial range of associated microvascular, metabolic, and other complications. Diabetic polyneuropathy (DPN), one of the most prevalent of these complications, is a progressive neurodegenerative condition that targets axons within the peripheral nervous system (PNS). Symmetrical loss of the most distal axons is the most common presentation of DPN rendering a stocking and glove pattern of sensory damage. Over half of patients with DM experience DPN [1]. In addition to loss of sensation and gait instability, DPN predisposes diabetic persons to refractory neuropathic pain and to foot ulcers and amputation. These features create a tremendous burden on the healthcare system and on patients' quality of life. Currently, the only treatment options available for DPN are tight glycemic control and pain management. There are no approved therapies for halting or reversing progressive damage to axons within patients suffering from neuropathy.

There is a large ensemble of cellular changes present in diabetic peripheral neurons that may contribute to the progressive loss of axons in DPN. Hyperglycemia in both type 1 and 2 DM leads to neuron oxidative damage, likely driven by overloading of metabolic pathways and elevated production of reactive oxygen species (ROS) [2]. Glucose also participates in the polyol pathway, adding osmotic stress along with depletion of NADPH that further accentuates oxidative damage [3]. Moreover, inflammatory cascades may also become activated through both intracellular hexosamine pathway activity and extracellularly from advanced glycation end products (AGEs) binding to receptors for AGEs (RAGE) [4]. These pathways are critical in the pathogenesis of DPN and are more extensively reviewed elsewhere [4–6]. We and others have postulated that the axon degeneration of DPN resembles and shares mechanisms with those of wider disorders including traumatic injury of axons or CNS neurodegenerative cascades [7, 8]. These ideas are based on the findings of morphological resemblances between the damage identified in diabetes (axonal loss and degeneration) and that of other conditions. A large body of recent work has also highlighted specific molecular cascades involved in axon degeneration, a topic not explored in depth here [9, 10]. While work dissecting potential differences in axon degeneration among these disorders is limited, new axonal signals, such as the participation of NAD + and SARM1, may be shared and may offer critical therapeutic opportunities.

In addition to the primary abnormalities of diabetic neurons and axons that may lead to polyneuropathy, there is a concurrent regenerative deficit in diabetic axons [8, 11–13]. This means that once axon damage has occurred, attempts to regenerate are compromised, even if the original cause of damage was to be removed. Injury studies in diabetic models, for example, chronic type 1 streptozotocin-treated mice,

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demonstrate a lasting deficit in histological and electrophysiological indices of regeneration. Changes in the regenerative capacity of diabetic neurons likely contributes to the overall neurodegenerative process by impaired regrowth of fibers damaged through mechanisms mentioned above [14]. This fits with the concept that sensory axons, for example, those in the epidermis, are in an ongoing "growth" mode that must be sustained in normal skin that undergoes keratinocyte turnover.

Insulin signalling applied to neurons, independent of its role in glycemic control, is an example of a pro-regenerative mechanism compromised in diabetes. There is overt loss of insulin signaling or loss of insulin sensitivity in type 1 and type 2 DM, respectively. In non-diabetic dorsal root ganglion (DRG) neuronal perikarya, there is expression of the insulin receptor, and intrathecal injection of insulin after peripheral nerve injury promotes regenerative axon regrowth [15]. To this end, chronic type 1 diabetic rats treated with low-dose intrathecal insulin reversed motor and sensory conduction velocity slowing in the absence of an impact on glycemia [16]. This is but one example from a series of cellular alterations that may be involved in pathogenesis of DPN and a lack of regenerative competency. Although treatment of DPN likely will involve multiple points of intervention, this review focuses on reversing features of DPN by promoting the intrinsic regrowth of axons.

New Targets to Support Neuron Growth: Tumor Suppressors

Tumor suppressor molecules prevent the development of oncogenesis under normal physiological conditions. They provide an important barricade for cellular growth and proliferation, a hallmark of cancer development. However, under conditions of tissue damage that require repair, the ongoing expression of this wide group of proteins may be counterproductive. In the case of stable, transmitting, and non-plastic neurons in adults, several molecules possessed of this property may hinder the regeneration of damaged axons [17]. Alternatively, strategically targeting specific tumor suppressor molecules within peripheral neurons may emerge as a strategy for the treatment of nerve injury, including that which occurs in DPN. Here, we will discuss several tumor suppressor molecules that have emerged as stably expressed in neurons after injury, but that restricts plasticity and can be manipulated to enhance intrinsic growth.

PTEN

The phosphoinositide 3 kinase (P13K) pathway is critical for axonal regeneration [18, 19]. Neurotrophin family members including nerve growth factor (NGF) and non-traditional growth factors, such as insulin, utilize this cascade to provide neurotrophic support to axons [20]. PI3K adds a phosphate group to generate phosphatidylinositol-3,4,5-triphosphate (PIP_3) from phosphatidylinositol-4,5-bisphosphate (PIP_2). PIP_3 production activates phosphoinositide-dependent kinase (PDK) which in turn activates the kinase Akt through subsequent phorphorylation, allowing downstream activation of mTOR and inhibition of GSK3 [21, 22]. Although the importance of the mTOR pathway in axon regrowth is controversial, evidence in favor of mTOR as a pro-regenerative molecule can be seen within injured axons. Increases in phospho-mTOR(S2448), along with downstream mTOR effectors p-p70S6K and EiF4b, can be observed following damage [23]. It has been previously demonstrated that inhibition of mTOR by rapamycin is sufficient to ameliorate hyperalgesia in animal models of type 1 DM [24, 25]. Along these lines, mTOR was found to be hyperactive in the skin of diabetic patients with small fiber neuropathy [25]. There is evidence implicating mTOR in the regulation of protein synthesis and growth cone formation following damage [26, 27]. Moving forward, understanding the role of mTOR in regeneration and diabetes within PNS neurons warrants further investigation.

There are also data suggesting that regeneration occurs independent of mTOR through GSK3-dependent transcription factor activation within the perikarya [22]. Furthermore, it has also been demonstrated that GSK3 has a function locally within growth cones [21]. For example, semaphophorin 3a (Sema3A) is an axonal guidance molecule that functions through activation of neurophilin-1 receptors [28]. This interaction enriches phosphatase and tensin homolog (PTEN) in growth cones and suppresses the PI3K pathway [29]. This overall increases GSK3 activation, and consequently growth cone collapse can be mitigated by GSK3 inhibition [30].

PTEN is a ubiquitously expressed tumor suppressor that controls the PI3K pathway through dephosphorylation of PIP_3 and subsequent Akt inactivation. This brake on growth is critical to prevent excessive growth and proliferation observed in tumor formation. Loss of function mutations and inactivation of PTEN are common in many types of tumors [31]. However, in the context of axon regeneration, overactivity of PTEN limits the PI3K/Akt signalling cascade resulting in suboptimal functional recovery [32].

PTEN is widely expressed in sensory neurons and is enriched in IB4-positive non-peptidergic neurons [33]. High expression of PTEN within the IB4 + population is perhaps a contributing factor for the lower growth potential of these axons following damage. In models of axonal injury, PTEN is downregulated and is coupled with a concurrent increase in miRNA-222, a PTEN-directed microRNA [32, 34]. This is the intrinsic response within peripheral neurons and likely contributes to the shift neurons undergo from a transmission to regenerative phenotype.

Despite the intrinsic declines of PTEN following injury, there is further benefit from suppressing PTEN in the damaged PNS [32]. Reductions of PTEN are correlated with enriched phosphorylated Akt and subsequent execution of regenerative programs. This indicates that the PI3K-Akt pathway can initiate axonal regrowth pathways more fully when PTEN expression is further reduced. Along these lines, deletion of PTEN in retinal ganglion cells of the CNS demonstrates enhanced growth properties [35]. Conversely, if PTEN is upregulated in regenerating axons through reduction of Nedd4, an E3 ubiquitin ligase responsible for targeting PTEN for degradation, there is impaired regeneration [36]. These studies suggest that PTEN, although important for limiting inappropriate growth and proliferation, provides an obstacle for optimal axonal growth following injury.

The growth inhibitory properties of PTEN extend to DPN as well. In vitro outgrowth assays of both diabetic and preconditioned non-diabetic cultured neurons have augmented growth potential when PTEN activity is reduced [37]. Altered PTEN expression may be linked to specific regenerative deficits in diabetic neurons [14, 38]. Consistent with this hypothesis, heightened PTEN expression has been reported in models of both type 1 and type 2 diabetic neuropathy [37, 39]. Models of DPN demonstrate behavioral differences from non-diabetic littermates, the direction depending on the strain and duration of DM including mechanical and thermal sensitivity, as well as a reduced nerve conduction velocities and alterations, albeit less consistent, in motor (CMAP-compound motor action potential) and sensory (SNAP-sensory nerve action potential) multifiber amplitudes. Histologically, epidermal axon counts are reduced attributable to their retraction from the epidermis [40]. While less commonly studied, loss of dermal axons has also been documented [8]. Administration of either siRNA directed towards PTEN or a small molecule inhibitor of PTEN in experimental DM with a superimposed injury results in improvement in behavioral deficits as well as cutaneous sensory nerve innervation [37, 39]. It is therefore not unreasonable to hypothesize that overexpression of PTEN participates in the pathogenesis and progression of DPN.

Microangiopathic changes are included in the list of potential factors contributing to the development of DPN, although their primary role is controversial [41]. The nerve blood supply has redundancies that protect them from ischemic insults, making this hypothesis problematic, and not all models demonstrate early changes in nerve blood flow. Despite this caveat, there has been microvascular pathology observed within the endoneurium in human diabetic nerves including basement membrane thickening, hyperplasia of endothelial cells, and pericyte loss [42]. Microvascular dysfunction may be a parallel early target of DM, independent of direct neuronal targeting, but in later stages adding ischemia to the endoneurium. Microangiopathic changes have been demonstrated to correlate with increased CD40 overexpression coinciding with overexpression of PTEN in endothelial and inflammatory cells, an alternative non-neuronal role for the protein [43]. The alterations also correlate with fibrin deposition within blood vessels. These findings expand the potential role of PTEN among several cell types targeted by DM. While PTEN plays a critical role in limiting tumorigenesis or aberrant axon growth in adults, in the context of nerve damage and DPN, it paradoxically may prevent the regrowth of retracted axons, a potential translational target for regenerative therapies [37] (unpublished data, Zochodne laboratory). This is based on the concept that loss of axons in DPN requires a regenerative response.

Rb1 and PPARϒ

Retinoblastoma 1 (Rb1) is a globally expressed tumor suppressor molecule that is mutated in the development of retinoblastoma, a form of childhood eye cancer. Hypo-phosphorylated Rb1 suppresses cells from inappropriately traversing the G1/S phase checkpoint by binding to the transcription factor E2F [44–46]. This interaction prevents transcription of E2F target genes, a critical requirement for cell proliferation. Conversely, hyperphosphorylation of Rb1 by cyclin-dependent kinases (CDKs) releases E2F1 from Rb1, thus allowing E2F1 to interact with DNA [44–46]. Transcription of E2F target genes enables cell cycle progression, growth, and proliferation [46]. In cancer, loss of function mutations renders Rb1 unable to control cell cycle progression and ultimately leads to unfettered growth and tumorigenesis.

Rb1 is a critical protein for embryonic development with an important role specifically in the developing nervous system. Mice deficient in Rb1 are non-viable and have critical deficits in neurogenesis with high levels of cell death in the brain and within the spinal cord [47]. If Rb1 is specifically knocked down in the telencephalon, these animals have an increased rate of neurogenesis [48]. Unlike the global Rb1 knockout, conditional knockouts do not have the same level of cell death, and as a result, the animals are viable. The knockout experiments however highlight the importance of Rb1 to neuronal survival and proliferation.

Within the regenerating PNS, Rb1 limits the growth capacity of axons following damage [49, 50]. Rb1 is expressed in the cytoplasm and nuclei of adult DRG sensory neurons and their axons with a decline following axotomy injury. Knocking down the expression of Rb1 through non-viral administration of siRNA resulted in improved functional recovery in rodent models of axonal injury**.** In adult sensory neuron DRG cultures, reductions in Rb1 led to reciprocal increases in peroxisome proliferator-activated receptor gamma (PPARϒ) expression and enhanced neurite outgrowth. Moreover, the addition of a PPARϒ antagonist to these cultured neurons appeared to attenuate the growth

benefit resulting from Rb1 knockdown. This observation indicates that an important mechanism of action of Rb1 knockdown-induced growth involves activation of PPARϒ. In agreement with this, treating cultured DRG neurons with a PPARϒ agonist resulted in increased outgrowth. Applying Rb1 knockdown in a sciatic nerve crush model of regeneration yielded improvements in sensory nerve conduction velocity and grip strength, along with mechanical and thermal sensitivity comparable to baseline values [49]. These data present Rb1 and PPARϒ as possible targets in the treatment of nerve injury and neuropathies like DPN.

Thiazolidinediones (TZDs) or glitazones are a class of approved PPARϒ agonists used clinically to treat type 2 DM [51, 52]. In the 1980s, this class of drugs was identified to have hypoglycemic and hypolipidemic effects in diabetic animals [53]. TZDs improve insulin sensitivity, induce adipocyte differentiation, and reduce inflammation [54–56]. Interestingly, TZD administration in animal models of neurodegenerative disorders including Alzheimer's and Parkinson's disease reduced brain degeneration and inflammation and protected against cognitive and behavioral changes [57, 58]. It is uncertain at this time whether TZDs might offer a benefit in DPN through its impact on glycemia or instead on intrinsic growth downstream of Rb1. Robust data connecting Rb1 knockdown, PPARγ agonists, and DPN in long-term models are not yet available. Similarly there are no known therapeutics that promote the dissociation of Rb1 from E2F1, its binding partner and transcription factor to facilitate growth.

To date, the role of Rb1 within diabetic neuropathy is largely unexplored. We have found that systemic administration of Rb1-directed siRNA is capable of reversing behavioral and electrophysiological deficits of DPN (unpublished). Given that Rb1 knockdown mediates a growth accentuating response in damaged peripheral nerves through PPARϒ, the role of PPARϒ agonists as anti-diabetic agents, and the growing evidence suggesting that PPARϒ agonist have a positive effect on neurodegeneration, indicates that Rb1 inhibitors and PPARϒ agonists warrant further investigation in DPN.

Other Tumor Suppressor Molecules

There are other tumor suppressor molecules that have demonstrated utility in models of axonal damage or neuropathy. Adenomatous polyposis coli (APC) is another tumor suppressor molecule that impedes the canonical Wnt/ β-catenin pathway through participation in the destruction of the transcription factor β-catenin [59]. APC is commonly mutated in colorectal cancer [60]. During nerve injury, APC is highly expressed, while paradoxically β-catenin expression is low [61]. Knockdown of APC increased β-catenin expression and its translocation to the nucleus and improved the regeneration of axons following damage. APC has not been extensively studied in DPN, and its role in pathogenesis is unexplored. While speculative, APC, like its tumor suppressor relatives, may enable peripheral neurons to regain their regenerative competency.

The Myc family of transcription factors has been extensively studied for their role in neoplasm formation in many different types of tumors. However, Myc is vital for the development and growth of the nervous system [62, 63]. There are regulatory mechanisms that prevent aberrant Myc signaling and subsequent tumorigenesis. Myc-associated factor X (Max) is a bHLH protein and Myc dimerization partner, and together these proteins can bind to Myc target genes [64]. Max dimerization protein 1 (Mad1/Mxd1) competitively binds to Max and will bind to the same DNA sequence as Myc-Max dimers but will have opposite effects on their transcription [65, 66]. Within the CNS, overexpression of Myc in optic nerves after crush incurs a regenerative benefit [67]. In the PNS, Myc has been largely unexplored, but recent data suggests that Myc plays a key role in upregulating regeneration-associated genes (RAGs) following a preconditioning nerve lesion [68]. Given the well-established role of Myc in oncogenesis, therapies targeting Myc have been aimed at inhibiting it rather than increasing its activity, and to our knowledge, there are no established approaches to augment Myc activity. However, we have explored Mad1 knockdown in both the injured PNS and DPN as a strategy to augment Myc activity (Unpublished and Poitras, University of Alberta MSc thesis). There are no identified therapeutics that accomplish these actions or activate Myc that might be exploited in DPN.

Non-coding RNA: miRNA + lncRNA

There are large-scale changes to global cellular expression of genes in both type 1 and type 2 DM [69–71]. Changes are not specific to mRNA, but also to non-coding RNAs, specifically microRNA (miRNA) and long non-coding RNA (lncRNA). miRNA are sequences of 18–23 nucleotides that are also non-coding. These short oligonucleotide sequences regulate post-translational gene expression through hybridization with a complementary mRNA sequence. mRNA-miRNA complexes are subsequently degraded in cytoplasmic compartments called GW/P-bodies [71–73]. There has been a diverse repertoire of miRNAs with differences in expression noted in diabetic sensory neurons compared to controls.

A microarray analyzing over 1000 miRNA targets identified 19 and 123 that were, respectively, greatly or mildly differentially regulated in the DRGs of a chronic type 1 DM model in comparison to littermates [71]. In particular, mmu-let-7i was among miRNAs found to be decreased; administration of exogenous mmu-let-7i in diabetic animals

improved NCV (nerve conduction velocity), cutaneous fiber density, and behavioral abnormalities typically observed in diabetes [71]. Another dysregulated miRNA was miR-155, upregulated in DM and coupled with a reciprocal change in the transcription nuclear factor erythroid 2-like 2 (NRF2) expression. Inhibition of miR-155 or restoration of NRF2 expression in a model of type 1 DM reversed changes to NCV and structural axonal changes [74]. Along these lines, within the trigeminal ganglia, miR-34c has demonstrated upregulation in type 1 diabetic animals [75]. High expression of miR-34c was found to be coupled to reduction of the autophagic proteins LC3-II and Atg4B. In this study, antagomir targeting miR-34c improved the growth capacity of diabetic trigeminal neurons. Taken together, these early reports highlight the potential importance of post-translational gene expression by miRNA in pathogenesis of DPN.

lncRNAs, in contrast, are long sequences of nucleotides spanning from 200 bp to many kilobases in length. These strands of RNA exhibit control over the transcriptome through interactions with transcription factors, repressors, and coactivators [76, 77]. This can result in changes to the overall landscape of the transcriptome. lncRNAs have been implicated in neurodegenerative disorders such as Alzheimer's disease through control of genes that drive amyloid production [78, 79]. lncRNA disruptions have also been implicated within diabetic animal models [76, 80–82]. The lncRNA NONRATT021972 has been positively correlated with clinical neuropathic pain scores in patients presenting with type 2 DM [83]. In this study, high levels of NONRATT021972 were coupled to levels of TNF-α, a pro-inflammatory marker that has been previously associated with DPN [84, 85]. In the same report, NONRATT021972 silencing with siRNA in type 2 DM rats resulted in decreased metrics of neuropathic pain and reduced TNF-α levels. Additionally, clinical research has identified differences in lncRNA expression between type 2 DM patients and controls and presents the lncRNA, ENST00000550339.1 as a potential diagnostic biomarker for pre-type 2 DM [86]. A more recent genome-wide screen of miRNA in sensory neurons identified 266 altered miRNAs in an animal model of type 1 DM with miR-33 and miR380 noted to be of particular importance in the development of neuropathic pain associated with DPN [87].

Non-coding RNAs and their potential therapeutic role in DPN and neuropathic pain have recently been extensively explored elsewhere [88, 89]. Here we have summarized a select few non-coding RNAs and the role they play in the pathogenesis and maintenance of DPN. Both miRNA and lncRNA are coded by sequences of DNA that were once believed to be "junk" since they are not translated into a protein product. Our current understanding of non-coding sequences including miRNAs and lncRNA demonstrates their critical role in the pathogenesis of human disease. miRNA and lncRNA present exciting novel targets for the treatment of DPN and warrant further clinical investigation.

Growth Cone Molecules: RhoGTPases

RhoA, Rac1, and Cdc42 are Rho GTPases that are constituents of the Ras super family (Figs. 1 and 2) [90]. Within this superfamily, a common characteristic is the use of guanosine triphosphate (GTP) to execute their function. Subfamilies have been identified and include Rab, Ras, ADP-ribosylation factor (ArF), RhoA, and Ran [91]. Proliferation, vesicle formation, cytoskeleton remodeling, differentiation, and apoptosis are among some of the normal cellular processes under the control of this group of molecules. The link between Ras subfamily mutations and oncogenesis is well-known [92, 93]. One of the first downstream targets of Ras to be identified was MAPK/ERK, a pathway that is frequently dysregulated in neoplasms [92, 94, 95].

The Rho GTPase proteins are most well-known for their role in actin regulation and cell migration [96, 97]. When bound to GTP, RhoA is in its activated state and in turn activates Rho-associated kinase-1 (ROCK). This subsequently activates LIM kinase which donates an inhibitory phosphate to Cofilin, an important mediator of actin turnover [98]. The overall impact of RhoA in regrowing axons is growth cone collapse and reduced regeneration [99]. Rac1 and Cdc42 have similar targets although their functions are distinct from RhoA and act to enhance lamellipodia and filipodia within growth cones, respectively. These structures allow for growth cones to sample their environment enabling navigation following injury [100].

Activation of RhoA within CNS growth cones can occur when interacting with myelin proteins Nogo-66 and Mag, in addition to other extracellular non-permissive substrates [101]. This is not the only mechanism for RhoA activation; there are other pathways by which RhoA can become active that are reviewed elsewhere [102]. In the PNS, chondroiton sulfate proteoglycans (CSPGs) are important activators [103]. RhoA-mediated growth cone collapse and retraction also impair growth cone turning, also a sign of stalled regeneration [104]. Targeting RhoA within a spinal cord injury provides a growth and neuroprotective benefit to regrowing neurons [105]. Moreover, within the PNS, after injury, there is upregulation of both the mRNA and protein for RhoA and ROCK [99]. Like the CNS, there is a regenerative benefit demonstrated in peripheral neurons when the RhoA/ROCK pathway is inhibited.

The role of RhoA in the pathogenesis and progression of complications in models of DM has been largely explored. Retinopathy, neuropathy and nephropathy all have been reported to be ameliorated in diabetics when RhoA or ROCK is inhibited [106–108]. Furthermore, inhibition of ROCK corrects insulin insensitivity [109]. The current

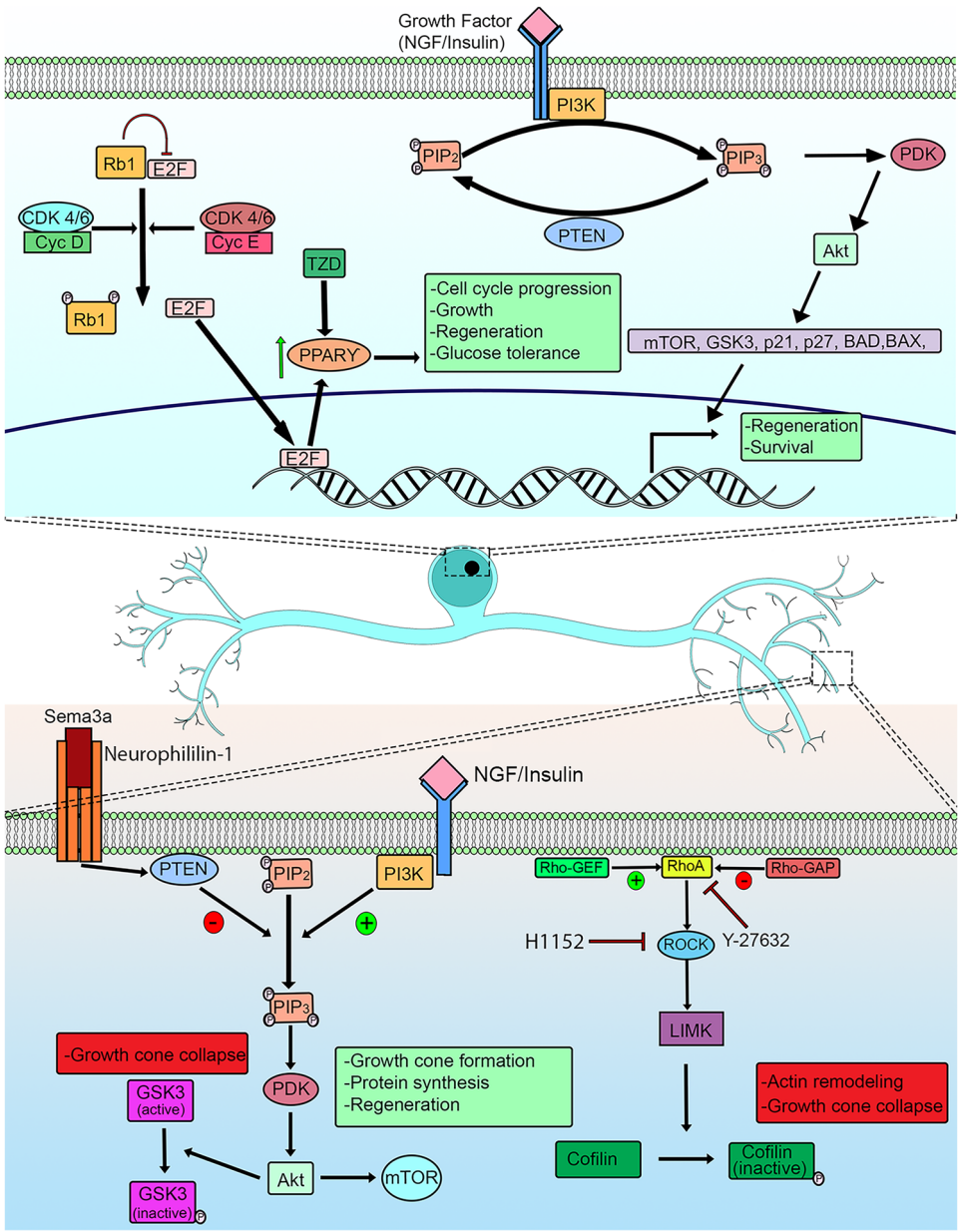

Fig. 1 Schematic summarizing RhoA, PTEN, and Rb1 signaling in the perikaryal and/or the growth cone. Within the perikarya, growth factor signaling including insulin or NGF will result in activation of PI3K and consequently, conversion of PIP_2 to PIP_3. This will activate PDK resulting in Akt activation and subsequent inhibition or activation of Akt targets. The overall neuronal response of Akt activation is regeneration and survival. PTEN antagonizes Akt activation by the conversion of PIP_3 to PIP_2 and therefore hinders Akt activation and regeneration. The pocket protein Rb1 in a hypophosphorylated state binds and sequesters the E2F family of transcription factors. However, upon hyperphosphorylation by cyclin-CDK complexes, Rb1 releases E2F where it can act in the nucleus to transduce genes. One such gene that may be upregulated by E2F is PPARϒ. Heightened PPARϒ expression or activation by agonists like thiazolidinediones (TZDs), overall result in cell cycle progression, increased glucose tolerance, axonal regeneration, and cellular growth. At the growth cone, Akt becomes activated through NGF/insulin signaling as described above. Akt will inactivate GSK3 which when active can collapse the growth cone. Akt will additionally activate mTOR resulting in growth cone formation, local protein synthesis, and generation of a pro-regenerative microenvironment. Within this pathway, Sema3a can activate neurophilin-1 receptors that enhance PTEN activity and reduce downstream Akt activity and collapse the growth cone. RhoA is a GTPase that is activated by exchanging GDP for GTP through action of a Rho guanine exchange factor (Rho-GEF). Conversely, RhoA becomes inactivated by Rho-GTPase activating proteins that cause the RhoA bound GTP to be hydrolyzed to GDP and phosphate. Activation of RhoA leads to ROCK and subsequently LIMK activation. Active LIMK phosphorylates cofilin rendering it inactive. This influences the growth cone by promoting actin remodeling and growth cone collapse. This pathway can be inhibited through H1152 or Y-27632 that inhibit RhoA and ROCK, respectively

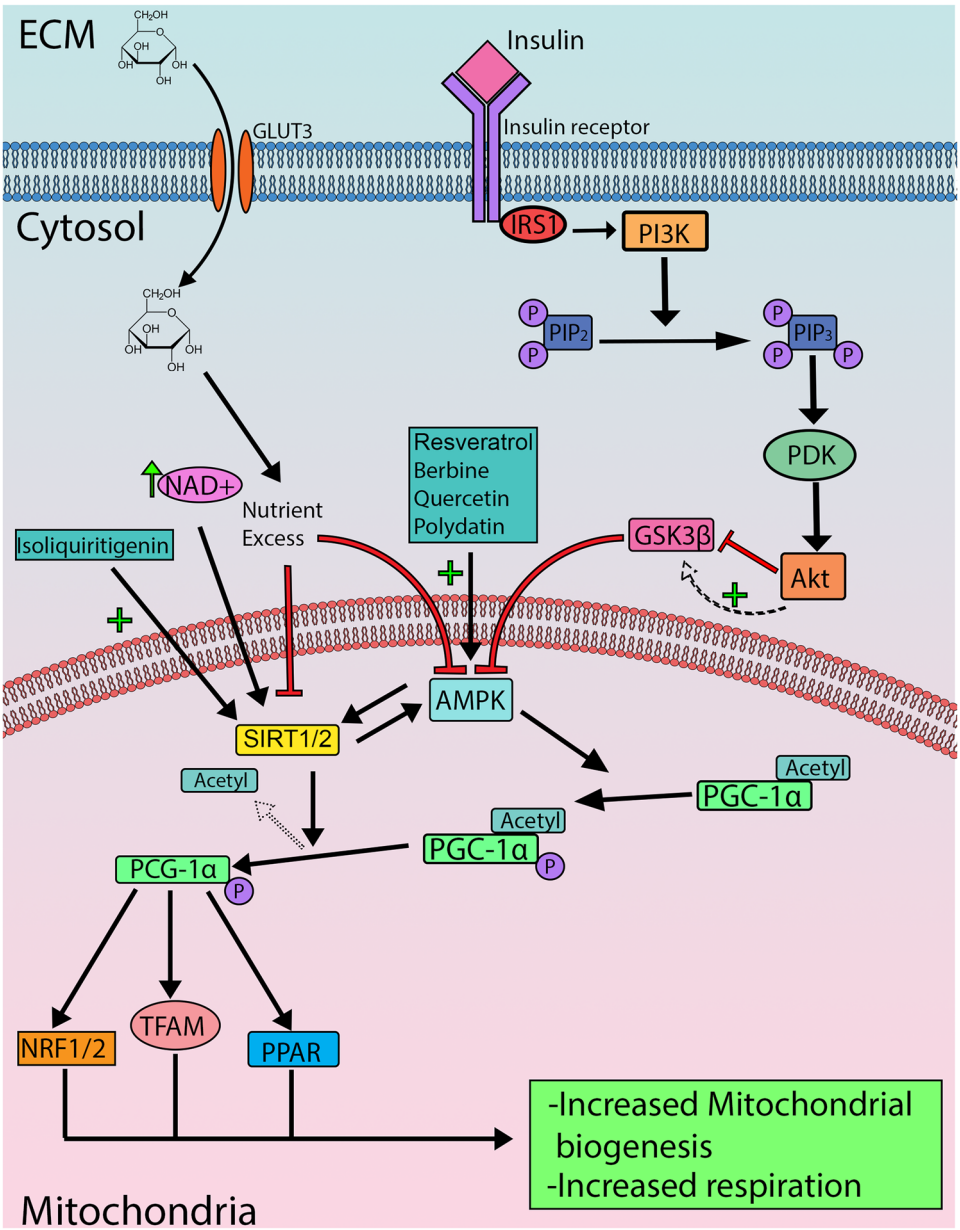

Fig. 2 Integration of insulin, Akt, AMPK, and PGC1 alpha control of mitochondrial bioenergetics. Increased insulin-mediated activation of the insulin receptor substrate (IRS-1) membrane protein results in increased intracellular activity of phosphoinositide 3-kinase (PI3K). A phosphorylation target of PI3K is phosphatidylinositol 4,5-bisphosphate (PIP2), which PI3K converts into phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 activates phosphoinositide-dependent kinase (PDK) enabling PDK to activate Akt. Akt canonically inhibits glycogen synthase kinase 3 beta (GSK3β), but it has been reported by Suzuki et al. that increased Akt activity increases GSK3β translocation to the mitochondria and repression of adenosine monophosphate protein kinase (AMPK) in a non-canonical manner. Glucose freely flows down its concentration gradient into neurons through the insulin-independent glucose transporter 3, allowing for cytoplasmic nutrient excess. Increased intracellular nutrients result in a decreased adenosine monophosphate/adenosine triphosphate ratio, which further reduces AMPK activity. The activity of SIRT1 is also decreased in conditions of nutrient excess. AMPK and Sirtuin-1/2 (SIRT1/2) work synergistically to initiate peroxisome proliferator-activated receptor-gamma coactivator (PGC-1alpha) activity in the mitochondria through phosphorylation and deacetylation respectively. AMPK and SIRT1 have a positive reciprocal relationship, where AMPK activity is enhanced through increases in SIRT1 activity as a consequence of high concentrations of nicotinamide adenine dinucleotide (NAD+), and SIRT1 activity increases downstream AMPK phosphorylation. Resveratrol interacts with this pathway through SIRT1 activation. PGC1alpha is a transcription coactivator that works in concert with including transcription factor A, mitochondrial (TFAM), nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 (NRF2), and peroxisome proliferator-activated receptor (PPAR) to increase mitochondrial biogenesis and respiration capacity. Notably, increased activity of AMPK, SIRT1, SIRT2, PGC1alpha, and TFAM has all been correlated with beneficial outcomes in models of DPN. Resveratrol, polydatin, berberine, and quercetin potentiate this pathway via increasing AMPK activity, while isoliquiritigenin potentiates this pathway through SIRT1 activation

literature indicates that RhoA and ROCK are mediators of the pathogenesis and progression of diabetes.

Patients with DPN may experience profound neuropathic pain that can be disabling and can greatly impact their quality of life. Neuropathic pain arising from peripheral nerve damage has been shown to be mediated in part by RhoA/ROCK signaling within the spinal cord [110]. Moreover, neuropathic pain can be prevented in animal models through intrathecal administration of the ROCK1 inhibitor H1152 or RhoA inhibitor Y-27632 [110, 111]. Addition of these inhibitors prevented activation of p38 mitogen-activated protein kinase (MAPK) in microglia, a pathway that participates in post-injury neuropathic pain [110, 112]. Interestingly statins, a class of cholesterol lowering drugs, can lower the amount of RhoA isoprenylation and localization to the plasma membrane rendering RhoA functionally inactive [113]. Simvastatin specifically has been associated with improved features of neuropathic pain in animal models including thermal and mechanical hypersensitivity [111, 114].

Similar to injury-induced neuropathic pain models, the spinal cord of diabetic animals has been found to have enriched active membrane bound RhoA [107]. Moreover, the development of thermal hyperalgesia in diabetics is associated with RhoA/ROCK and can be ameliorated with simvastatin [107, 115]. A clinical trial evaluating the utility of statins in DPN has revealed that patients' neuropathic pain scores can be improved with simvastatin and rosuvastatin treatment [116]. Although proposed mechanisms in this trial focused on oxidative stress, RhoA signaling should also be considered. Given the literature supporting a role for RhoA/ROCK signaling in complications of DM as both a regenerative target and a mediator of thermal hyperalgesia, this pathway may also offer translational opportunities for diabetic patients (Table 1).

On the Diversity of Sensory Neurons

Before considering direct Schwann cell targets in this review, it is worth offering a short pause to put "neuronal" therapies into further context. DRG sensory ganglia comprise diverse cell types and constituent molecules that may require separate consideration. Recent RNA seq work has highlighted how specific neuron subtypes have specificity clusters of differentially expressed mRNAs [117, 118]. While there have been attempts, with varying success, to subclassify human DPN into predominant "small fiber" or "large fiber" disease, most patients have mixed involvement. Small unmyelinated axons or smaller Aδ myelinated axons classically transmit pain and thermal sensation [119]. These neurons express differing peptide content and receptors for growth factors likely to influence their response to molecular manipulation. For example, small isolectin "IB4" non-peptidergic neurons mentioned earlier, also known as Mrgprd (Mas-related G-protein coupled receptor member D) or P2X3 (Purinoceptor 2X3) neurons, express high levels of PTEN and may be slower growing [32, 120]. They may also penetrate more superficially into the epidermis to act as thermal or pain sensors. They are distinguished

Table 1 A selective listing of molecular targets in models of DPN discussed in this review

Regenerative targets	
PTEN	·PTEN is a negative regulator of the P13K/ Akt pathway, a critical growth, and survival pathway [262, 263] ·Knockdown of PTEN within diabetics restores the regenerative capacity of axons after injury [37]
Rb1	·Rb1 is a critical cell cycle control protein that prevents inappropriate cellular growth by sequestering E2F proteins [44–46, 264] ·Our unpublished data indicates that siRNA directed towards Rb1 can improve features of DPN in animal models of type1 DM
RhoA/ROCK	·RhoA is a GTPase and member of the Ras superfamily of proteins responsible for actin regulation and cellular migration and activation in neurons results in growth cone collapse and retraction [96, 97, 99] ·Blocking RhoA/ ROCK in DM animal models prevents the development of neuropathic pain [108, 110]
miRNA	·miRNA are short nucleotide sequence that are involved in the post-translational regulation of target genes with complementary sequences [72, 73] ·miR-155 and miR-34c are upregulated in DPN, and their knockdown improves features of DPN [74, 75] ·mmu-let-7i expression is reduced in DM animals. Exogenous replacement of mmu-let-7i restores NCV and behavioral deficits observed in a DPN model [71]
lncRNA	·lncRNA regulate transcription through interactions with transcription machinery [76, 77] ·NONRATT021972 expression in DM patient is correlated to neuropathic pain and heightened levels of the pro-inflammatory cytokine TNFα [83]
PGC-1α	·PGC-1α is an important regulator in the biogenesis and homeostasis of mitochondria through interactions with the regulatory factors TFAM, NRF1/2, and PPAR [170–175] ·Knockout of PGC-1α further accentuates features of DPN, while overexpression improves the capacity for oxidative stress [216]
HSPs	·HSPs are chaperone proteins involved in the protein folding in addition to targeting misfolded proteins for degradation[265] ·Inhibition of HSP90 using small molecules offer improvements in behavioral and electrophysiologic deficits observed in DPN [233] ·Overexpression of HSP27 prevents axonal damage in models of peripheral neuropathy including DPN [255–257]

from more classical SP (substance P) containing peptidergic nociceptive unmyelinated axons that express TrkA, the high affinity receptor for nerve growth factor (NGF). The latter appear to terminate within and innervate deeper epidermal layers. Moreover, "large fiber" sensory neurons that are mechanoreceptors and subserve touch have a yet wider diversity of types that include large and small receptive field afferents and those that innervate hair follicles [121]. In general, these axons interface with receptor organelles such as Merkel discs, Ruffini endbulbs, Pacinian corpuscles, and Meissner's corpuscles, each of which also has unique physiological properties. All of this diversity impacts therapeutics that target specific molecules and pathways, although many explored to date act widely on adult sensory neurons. The differential anatomical distribution of sensory endings and their relative targeting in DPN has not been extensively examined in models of DPN. If a topical therapeutic were to be identified for DPN, the accessibility of axon terminals in the skin may become relevant.

Schwann Cell Therapeutics

Schwann cells (SCs) are the critical supporting glial cells of the PNS. Given this intimate partnership, their viability may be critical in discovering new translational approaches to DPN. They form an important supporting partnership with axons in uninjured nerves, but also play a critical role in recovery after damage. These glial cells can be categorized into myelinating SCs that wrap large calibre axons in electrically insulating myelin enabling saltatory conduction and non-myelinating SCs which are associated with many unmyelinated fibers that together form Remak bundles [122]. They play a key role in the development of the PNS during embryogenesis through axon-SC communication, critical for the survival of both the axon and the SC [123–125]. During development, SCs provide support to axons through neurotrophins, in addition to signalling nearby connective tissue to organize into the peri-, epi-, and endoneurium [124].

SCs also play an essential role in axonal regrowth after injury. When peripheral axons become damaged through transection, for example, SCs undergo change in phenotype that involves enhanced mobility and participation in axonal degeneration. SCs breakdown myelin debris through a recently characterized form of autophagy termed myelinophagy [126, 127]. Pharmacologic inhibition of autophagic pathways results in sluggish myelin debris removal after injury [127]. This may be important given the role of myelin in inhibiting growth cone advancement. Furthermore, in diabetic SCs, there are reductions in the autophagic capabilities, perhaps contributing to the lack of reinnervation in DPN [128]. The autophagic process is necessary for clearance of myelin and axonal debris following damage, and impairment of this process results in poor regenerative outcomes [129]. Additionally, SCs coordinate release of signaling molecules like neurotrophic factors to support regrowing axons, as well as cytokines and chemokines to attract hematologic immune cells to aid in promoting axonal and myelin degradation distally to the injury site [130–132].

Augmenting nerve repair has mainly been focused on enhancing axon capacity to regenerate. However, the pivotal role of SCs in the regenerative response in combination with their close partnership with axons presents a unique approach to supporting recovery after damage by injury or neuropathy. For example, SCs acquire attractive and repulsive netrin-DCC-Unc signaling capabilities in adulthood. During development, this pathway is important in signaling attraction or repulsion of axon growth. Expression of the netrin-1 receptor deleted in colorectal cancer (DCC) is upregulated, while the uncoordinated (Unc) 5H2 receptor is reciprocally downregulated in SCs following axotomy [133]. siRNA-induced reduction of DCC reduces SC activation, consequently reducing axon regrowth, while siRNA targeting of Unc5H2 coincided with improved regenerative outcomes. Another target specifically within SCs is the transcription factor c-Jun. Lack of c-Jun within SCs prevents their transition to a repair cell phenotype that overall compromises regeneration [130, 134, 135]. Therefore, blocking mechanisms that repress c-Jun like HDAC2 are viable strategies to alter SC behavior and improve axonal regrowth [136].

Given the close and interconnected function of SCs with axons in the uninjured PNS, it is not surprising that within DPN there are morphological and functional disruptions within SCs. Examination of the ultrastucture of human diabetic SCs reveals basement thickening and aggregate formation within the cell in combination with myelin sheath abnormalities [137]. SCs cultured in mild hyperglycemic conditions lose their proliferative capacity, even when neuregulin-β1 is included in the media [138]. Functionally, neurotropic support is impaired in diabetic SCs with reductions present in NGF and NT-3 [139]. A clinical trial evaluating the efficacy of recombinant human NGF replacement showed no improvement in DPN patients, indicating that the underlying pathophysiologic factors are multifactorial [140].

Targeting diabetic SCs in models of DPN have shown promise. Exosomes purified from non-diabetic SCs and delivered intravenously to db/db mice showed improvements in epidermal nerve fiber density, NCV, and sensitivity to mechanical and thermal stimuli [141]. These SC-derived exosomes contained miRNAs including miR-21, -27a, and -146a predicted to target PTEN, NFκB, RhoA, and SEMA and were internalized by SCs and axons. Treatment normalized RhoA and PTEN, among other mediators. It is likely that reducing expression of these proteins through miRNAs delivered by the exosomes is the underlying mechanism for

the improvement in features of DPN associated with exosome treatment. To further support this, a similar experiment was performed in a nerve injury model where SC-derived exosomes improved nerve regeneration following a crush injury [142]. Moreover, there was improved growth cone morphology achieved by attenuating RhoA. Given these results, perhaps delivery of SC-derived exosomes in diabetic patients may be a viable approach to change the molecular landscape within diabetic neurons, favoring regrowth and recovery. These findings underscore the requirement for normally functioning SCs to support regrowth of retracted axon fibers in DPN.

Mitochondria and DPN

As the sources of metabolic energy support to neurons, mitochondria have long been an appropriate source of attention in understanding diabetic pathophysiology. Deficits in their depolarization, fission, and fusion and protein function have all been considered, briefly reviewed here.

Mitochondrial abnormalities have been documented in both human patients as well as experimental models of diabetic polyneuropathy (DPN). Abnormal mitochondria are present in the intraepidermal and dermal nerve fibers responsible for innervating the skin in patients with neuropathies such as DPN. These alterations appear prior to the onset of nerve degeneration [143, 144]. Further, axonal swellings which are thought to contain mitochondria are present both prior to degeneration and during regeneration in human DPN patients [145–148]. Findings of abnormal mitochondria are mirrored in several experimental models of DPN. In a feline model of DPN, swellings containing accumulations of neurofilaments and mitochondria are present in peripheral sensory axons, with mitochondria developing inner membrane inclusions [149]. Moreover, mitochondrial accumulations precede the onset of autonomic fiber degeneration in the Akita mouse [150]. Finally, the development of axonal swellings may not be exclusively linked to hyperglycemia or inflammation but instead represent an early and common feature of slowly progressive axonal degeneration [151]. Therefore, it can be concluded that the pathogenesis of DPN includes alterations in mitochondrial morphology.

Hyperglycemia in diabetes is thought to contribute to mitochondrial dysfunction and to be central to the pathogenesis of DPN. Acute hyperglycemia results in an increase in mitochondrial fission, which is compensated for by increased biogenesis in chronic hyperglycemia. The imbalance between fission and biogenesis may play a role in the abnormal mitochondrial findings documented in DPN patients and animal models [152]. Notably, neurons are particularly sensitive to hyperglycemia due to the presence of GLUT3, an insulin-independent glucose transporter that allows extracellular glucose to flow down its concentration gradient into neurons, which is of particular concern in hyperglycemic states like DM [153, 154]. Elevated concentrations of several nutrients have been linked to abnormal mitochondrial function. High concentrations of palmitate, a fatty acid, impaired mitochondrial trafficking in DRG axons, highlighting that glucose is not the only nutrient factor impacting the mitochondria in diabetic neuropathy [155, 156]. An excess of nutrients, including glucose, leads to reduced mitochondrial respiratory activity through the downregulation of adenosine monophosphate-activated protein kinase (AMPK) [157]. The excess extracellular nutrients present in DM likely play an important role in the dysregulation of mitochondrial activity.

Expression of proteins important for mitochondrial respiration and homeostasis is also relevant in models of DPN [158–162]. For example**,** mitochondrial uncoupling protein 3 (UCP3) is an uncoupling protein that is downregulated in DRG mitochondria during hyperglycemia. UCP3, along with other uncoupling proteins, play integral a role in preventing inner membrane hyperpolarization, reducing ROS production, and decreasing cell death [162]. The citric acid cycle (CAC) and the mitochondrial electron transport chain (ETC) are essential for aerobic ATP production and respiratory capability in the mitochondria through the production of high-energy molecules, and key enzymes and complexes of the ETC are downregulated in diabetic neuropathy [158–161]. Reduced protein expression in these fundamental respiratory pathways contributes to a reduction in the respiratory activity of mitochondria in diabetic neurons.

Further impacting respiratory rate is depolarization of the mitochondrial inner membrane, since the proton gradient present across the mitochondrial inner membrane is essential for generation of adenosine triphosphate (ATP) through the electron transfer complex V [163–166]. In several studies, reversal of mitochondrial inner membrane depolarization was sufficient to rescue conduction defects in diabetic neurons [163, 164]. Taken together, downregulation of key citric acid cycle enzymes, mitochondrial electron transport chain complexes, and mitochondrial inner membrane depolarization contribute to reduced mitochondrial respiration in DPN. Reduced mitochondrial respiratory activity is, in turn, linked to reduced ROS production, indicating that mitochondria are likely not the source of increased ROS present in DPN [158, 167]. However, reduced mitochondrial respiration pushes glucose towards the polyol and hexosamine pathways which are the likely sources of ROS and inflammation in DPN [168].

Excessive nutrient availability leads to poorly functioning mitochondria with reduced respiratory activity, leading neurons to turn to the polyol and hexosamine pathways to satisfy their large energy demands. The energy demand at the terminus of long axons is hypothesized to be significantly

greater than demand in the DRG, and therefore, the abnormal mitochondria produced in the perikarya are thought to be insufficient to meet the energy demands of the nerve ending, leading to degeneration [169]. Compounding this, mitochondrial morphological abnormalities increased in severity with increased distance along the axon in the legs of DPN patients [143]. In conclusion, the inability of abnormal mitochondria to satisfy high axonal energy requirements is an essential component of DPN pathophysiology.

SIRT1/AMPK/PGC-1α Signaling

An interesting target for manipulation in diabetic neuropathy is the transcription coregulator PPARγ coactivator 1 alpha (PGC-1α), which is an essential regulator of mitochondrial respiratory activity and transcription. PGC-1α exerts its control over mitochondrial respiration through regulating factors relevant to mitochondrial transcription and biogenesis, including transcription factor A mitochondrial (TFAM), nuclear respiratory factor 1 and 2 (NRF1/2), and peroxisome proliferator-activated receptor(PPAR) [170–175]. TFAM, for example, functions to protect mitochondrial DNA (mtDNA) from free radicals by playing a histone-like role in mitochondrial genome packing [176, 177]. It is notable that an increase in TFAM activity elevates mtDNA transcription, which is in turn linked to increased respiratory activity [170, 172, 176, 178, 179]. Furthermore, increased PPAR signaling results in an increased expression of genes related to mitochondrial fatty acid oxidation [175]. As a compensatory mechanism to increase mitochondrial respiration, PGC-1α activity upregulates the expression of free radical scavengers such as superoxide dismutase 2 (SOD2) and thioredoxin 2 (Trx2) to tolerate increased free radical production associated with increased respiration [180].

Thioredoxin-interacting protein (TXNIP) is a protein that reduces the activity of the antioxidant thioredoxin [181]. Interestingly, TXNIP miRNA is upregulated in the DRG of diabetic rats in a manner that precedes the onset of DPN symptomology, including reduced nerve conduction [71, 182]. Of note, there is an interaction between TXNIP and PGC-1α in hepatocytes, where TXNIP signals through PGC-1α to regulate lipid metabolism [183, 184]. Abnormal TXNIP/PGC-1α signaling is implicated in the development of non-alcoholic fatty liver disease (NAFLD)[183]. Given the associations between metabolic syndrome, NAFLD, and type 2 DM, this interaction is of particular importance.

Upstream regulation of PGC-1α is multifactorial. Key players are sirtuin 1 (SIRT1) and sirutin 2 (SIRT2), which increase the activity of PGC-1α through deacetylation, and AMPK, which increases PGC-1α activity through phosphorylation [185–190]. AMPK/SIRT1/PGC-1α signaling is tightly regulated by nutrient availability and metabolic signaling. AMPK is activated by an increase in the AMP/ATP ratio, which occurs due to reduced respiration in circumstances of nutrient deficiency, driving the cell towards catabolic activities [191, 192]. Similarly, SIRT1 activity is also increased during periods of nutritional deficiency [193]. Elevated levels of nutrients such as glucose will decrease AMPK/SIRT1 activity both through a decreased AMP/ATP ratio, but also through elevated insulin signaling contributing to AMPK inhibition mediated by AKT/GSK3 [194–200]. Contrary to insulin, insulin-like growth factor 1 (IGF-1) increases AMPK activity in diabetic neurons [201]. There is a reciprocal signaling dynamic present between SIRT1 and AMPK. A target of SIRT1 deacetylation is liver kinase B1 (LKB1) that targets AMPK through phosphorylation to enhance its activity [202, 203]. Conversely, high levels of NAD + as seen during periods of nutritional deficiency directly increase SIRT1 activity and consequently AMPK activity [202]. In summary, an increase in nutrients and insulin signaling will drive cells towards anabolic metabolism through inhibition of AMPK/SERT1 signaling, allowing for increased mTOR-mediated protein synthesis, while nutrient deficiency leads to an increase in PGC-1α-mediated catabolic metabolism and therefore increased mitochondrial respiration [204, 205]. As PGC-1α is integral for increasing aerobic mitochondrial respiration, its regulation is contingent on nutrient availability and catabolic signaling.

PGC-1α has been linked to the pathogenesis of DM itself. In South Asian and Caucasian populations, a single-nucleotide polymorphism in PGC-1α was correlated with an increased risk of the development of type 2 DM [206, 207]. Mechanistically, a decrease in the activity of AMPK leads to a reduction of PGC-1α-mediated mitochondrial gene expression and therefore a reduction in oxidative phosphorylation [208, 209]. In particular, type 2 DM patients have impaired mitochondrial fatty acid oxidation, which is directly linked to reduced PGC-1α activity [208]. To further highlight the importance of this pathway, SIRT1 activity is decreased in experimental models of hyperglycemia and DPN [210]. Therefore, manipulation of PGC-1α signaling has become a common target to ameliorate DPN in experimental models.

AMPK/SIRT/PGC-1α/TFAM Manipulations

Modulation of the AMPK/SIRT/PGC-1α/TFAM signaling pathway has been demonstrated to be beneficial in various experimental models of DPN. Resveratrol is a naturally occurring phenol that has been observed to increase the activity of AMPK, and has been demonstrated to improve various indices of diabetic neuropathy in vitro and in vivo, including a rescue of mitochondrial biogenesis, reductions in oxidative stress, increased neurite outgrowth, improved nerve conduction velocity, and improved thermal hyperalgesia [157,

211–213]. Along these lines, SIRT1 and SIRT2 overexpression are both sufficient to prevent and reduce features of DPN in an AMPK/PGC-1α-dependent manner [214, 215]. Further downstream, PGC-1α overexpression has been demonstrated to reduce oxidative stress in DPN, while knockout increases the severity of DPN. Knockouts demonstrate increased lipid levels and decreased TFAM and NRF1 expression [216]. TFAM overexpression is also protective in diabetic mice and prevents the development of nerve conduction deficits, hyperalgesia, and the loss of intraepidermal nerve fibers [217]. Moreover, the development of neuropathic pain in DPN can be ameliorated through activation of the mGluR2/3 presynaptic glutamate autoreceptor which leads to downstream SIRT/PGC-1α activation [218]. This finding is particularly significant given the suspected role of glutamate in the development of neuropathic pain.

Clinically, resveratrol has demonstrated several promising treatment effects for neurological disorders and DM. A number of clinical trials have demonstrated that resveratrol appears safe for human patients with mild or moderate Alzheimer's disease and can cross the blood–brain barrier. Resveratrol treatment is associated with reduced matrix metalloprotease 9 (MMP-9) activity and increased amyloid-beta (Aβ) in the cerebrospinal fluid, which respectively imply reduced cerebral ECM degradation and brain Aβ accumulation [219, 220]. For stroke patients, resveratrol was able to improve outcomes with delayed access to recombinant tissue plasminogen activator (r-tPa), again correlated with reductions in MMP-9 and MMP-2 activity [221]. While no clinical trials regarding resveratrol use in DPN have been completed to date, its use has been explored generally in DM with mixed results. However, a meta-analysis performed in 2015 highlighted that resveratrol supplementation was superior to placebo for control of blood pressure, hemoglobin A1c, and creatinine and therefore was suggested as an adjunct therapy for type 2 DM [222].

Recently, several other treatments have been employed to increase AMPK/SIRT1/PGC-1α activity in experimental DPN models. Isoliquiritigenin, a compound found in licorice, was able to ameliorate NCV and sensory abnormalities through increasing SIRT1 activity, in addition to reversing mitochondrial depolarization and decreasing ROS generation in vitro [210]. Polydatin, a compound related to resveratrol, and berberine, an activator of AMPK, augmented PGC-1α/Nrf2 signaling to rescue similar deficits in rats with STZ-induced type 1 DM [223, 224]. Lastly, 6 weeks of quercetin, a plant pigment, was able to restore mitochondrial counts in sciatic axons, in addition to ameliorating the above-mentioned correlates of DPN through increased AMPK signaling [225]. The apparent efficacy of AMPK/SIRT/PGC-1α pathway manipulation further highlights the integral role of mitochondria in the pathogenesis of DPN and provides an exciting target for potential treatment.

DPN is not the only neurodegenerative condition that may have benefits from modulation of AMPK/SIRT/PGC-1α/TFAM pathway. PGC-1α null mice develop lesions in substantia nigra pars compacta resembling those of Parkinson's disease [226]. Moreover, PGC-1α overexpression is beneficial against the MPTP-induced experimental model of Parkinson's disease [227]. The pathophysiologic changes in the SIRT1/TFAM/PGC-1α pathway presented in DPN are mirrored in hippocampal degeneration present in Alzheimer's disease, and indeed, overexpression SIRT1 and PGC-1α is protective against degeneration in an experimental model of Alzheimer's disease [216, 227, 228]. Furthermore, TFAM overexpression is protective against beta-amyloid oxidative stress in mitochondria and in CA1 hippocampal neurons following ischemia [229, 230]. Finally, autoimmune encephalomyelitis is a condition where retinal ganglion cells (RGCs) are vulnerable to damage and heightened SIRT1 activity in response to resveratrol treatment protects against RGC degeneration in experimental models [231]. Taken together, the above studies demonstrate the centrality of mitochondrial respiration to various neurodegenerative conditions and provide strong support AMPK/SIRT/PGC-1α pathway manipulation as a potential target to ameliorate neuronal impairment, including that of DPN.

HSPs and Chaperones

Due to the rises in the content of protein adducts and misfolds that result from increased oxidative stress in DPN, it has been hypothesized that chaperones are a possible therapeutic target in DPN [232–234]. Of particular note, mitochondrial proteins appear particularly vulnerable to oxidative modifications [232]. Chaperones such as heat shock protein 70 (HSP70) and heat shock protein 90 (HSP90) function to fold and stabilize proteins, as well as direct improperly folded or noxious proteins to the proteosome to be cleared [235, 236]. There is a notable interaction between HSP70 and HSP90 as well. HSP90 is bound to heat shock factor 1 (HSF1), which releases upon conditions of cellular stress to upregulate various aspects of the heat shock response and includes increased expression of various chaperones including HSP70 [237, 238]. The heat shock response is impaired in both type 1 and type 2 diabetes, correlating with a decrease in cellular stress tolerance [238–240]. The increased volume of abnormal proteins, and reduced capacity to deal with cellular stress implicates chaperones as an interesting target in the treatment of DM.

The roles of HSP70 and HSP90 have been well-characterized in models of DPN. Small molecule inhibitors that bind the c-terminus of HSP90 are sufficient to reduced hyperglycemia-mediated neuronal cell death in an HSP70-dependent manner [233]. Moreover, this treatment allows for the rescue of

mitochondrial respiratory capacity and is linked to an increase in mitochondrial chaperone expression and decrease the transcription of factors linked to cellular inflammation [233, 241–244]. Importantly, the rescue of mitochondrial biodynamics was linked to an increased expression of the free radical scavenger manganese superoxide dismutase (MnSOD)[244]. Ultimately, small molecule modulation of HSP90 led to a rescue of various features of DPN in model animals, including the reversal of sensory abnormalities and restoration of conduction velocity [233, 242, 243]. Therefore, increasing cellular stress tolerance through augmentation of the heat shock response appears to rescue the DPN phenotype in experimental models.

HSP70 has been demonstrated to be beneficial in several models of neuropathy and neurodegeneration, particularly those related to aberrant protein accumulation [245]. Exogenous HSP70 delivery is sufficient to prevent motor and sensory neuron death following sciatic nerve transection [246]. The inhibition of HSP90 was able to rescue motor impairment in a mouse model of spinal and bulbar muscular atrophy due to increased clearance of mutant androgen Receptor protein [247]. Further, it has been demonstrated that HSF1-mediated upregulation of HSP70 is beneficial in *Drosophila* models of spinocerebellar ataxia and Huntington's disease, where it reduced protein inclusions and the severity of eye degeneration [248]. Lastly, the inhibition of HSP90 is sufficient to reduced accumulation of hyperphosphorylated tau protein and maintain Tau's solubility to prevent protein inclusions, findings that are promising for Alzheimer's disease and other Tau opathies [249–251].

Another chaperone extensively studied in peripheral axon regeneration is heat shock protein 27 (HSP27). HSP27 mRNA is upregulated in the DRG following peripheral nerve injury in rats and in chronic DPN of rats and is strongly expressed in regenerating axons and partnering SCs [252, 253]. HSP27 functions to prevent apoptosis in neurons downstream of cytochrome C and plays a role in growth cone actin dynamics during axonal outgrowth [254, 255].

Our laboratory has demonstrated that transgenic human HSP27 overexpression in peripheral neurons prevents features of neuropathic pain in long-term type 1 diabetic mice up to 6 months following the induction of diabetes as well as features of epidermal innervation and nerve conduction velocity [256]. These findings are supported in human patients with DPN that exhibit an increased serum HSP27 level associated with better neurological functionality, including reduced neuropathic signs and improved conduction velocity [257].

HSP27 has been targeted in various models of peripheral nerve disease. Overexpression of human HSP27 in a mouse model of chemotherapy-induced peripheral neuropathies preserved mitochondrial respiratory function and prevented axonal loss, SC cell loss, and apoptosis [258]. Further, increased HSP27 resulted in expediated reinnervation of motor endplates following sciatic crush and increased motor unit recovery following peripheral nerve injury [259, 260]. HSP27's pro-regenerative effect on motor axons was mirrored in a rodent model of Guillain–Barre Syndrome [261]. Therefore, HSP27 appears to be a viable target to preserve mitochondrial function and encourage axonal regeneration in DPN and other peripheral neurodegenerative conditions. To our knowledge, there are no direct therapies yet available aimed to enhance activity or expression of HSP27.

Oxidative stress leads to protein modifications in diabetic neurons, particularly proteins localized to the mitochondria. As such, potentiating the heat shock response is an interesting target to preserve mitochondrial biodynamics, encourage axon regeneration, and reverse negative clinical aspects of diabetic neuropathy such as nerve conduction and sensory abnormalities.

Conclusions

No single mechanism or target has been identified in the pathogenesis of DPN despite several decades of work in the field. Nonetheless, pathways explored in diabetic neurons and SCs have included many that are common to other disorders and other diabetic complications. Mitochondrial dysfunction is an important example of this despite the lack of a myopathic phenotype in diabetic persons, unlike other mitochondriopathies. A separate approach emphasizes the molecules and pathways that support neurons and their regrowth and how they may bypass the variety of abnormalities that DM imposes on them. While this review emphasizes selected regenerative therapeutic approaches, we believe these will be of potential therapeutic relevance; it is a large list and only addresses some of the possibilities. High priority might also be placed on specific targeting that may treat human neuropathic pain, probably among the most important disabilities with DPN. For example this might include specific targeting of aberrant ion channels. Not discussed in depth here are alternative therapies to interrupt not only the metabolic mediators of damage but also intrinsic pathways within axons to lead to their degeneration. An open-minded approach toward directing new clinical trials should emerge from the variety of targets available, guided by findings from separate research programs and verified in rigorous preclinical studies using longer term models of more than one species. Our list is by definition not comprehensive but emphasizes several newer targets that we have focused on in this review.

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