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Review

mTOR Signalling in Diabetic Peripheral Neuropathy: Balancing Neuropathic Pain and Schwann Cell-Mediated Repair

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Abstract: Diabetic peripheral neuropathy (DPN) is a prevalent secondary complication of diabetes mellitus, characterised by nerve fibre degeneration, neurosensory deficits, and chronic neuropathic pain, all of which have significant clinical impact by increasing disability, reducing quality of life, and complicating diabetes management. While oxidative stress and neuroinflammation are established contributors to DPN pathogenesis, the specific involvement of the mammalian target of rapamycin (mTOR) signalling pathway in DPN remains incompletely defined. Recent findings indicate cell-type-specific dysregulation of mTOR signalling in diabetic peripheral nerves, with direct implications for targeted clinical interventions. This review outlines the pathophysiology, clinical manifestations, and therapeutic approaches for DPN, with a particular emphasis on the differential regulation of mTOR signalling in sensory neurons and Schwann cells. A greater understanding of these molecular mechanisms could improve diagnosis and refine treatment plans for DPN patients in clinical settings. Literature published from 1990 to 2025 was systematically reviewed to enhance understanding of the mTOR pathway's contributions to DPN pathogenesis. This review clarifies that mTOR operates differently in sensory neurons and Schwann cells during persistent hyperglycaemia in DPN. Overactive mTOR in sensory neurons increases neuropathic pain by enhancing neuron excitability, altering ion channels, and disrupting synapses. *In vitro* studies indicate reduced mTOR activity in Schwann cells, likely impairing repair processes such as dedifferentiation, survival, myelin production, and nerve support. Human tissue studies yield mixed results, leaving the consistency of these changes across patients unresolved. Consequently, further research is essential to clarify the precise and consistent impact of mTOR alterations in specific cell types.

Keywords: diabetic peripheral neuropathy; mTOR signalling; Schwann cells; neurons; neuropathic pain; demyelination; hyperglycaemia

1. Introduction

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes, affecting about 50% of people with diabetes. It can cause foot ulcers, amputations, falls, and chronic pain [1]. Pathogenic mechanisms of

DPN have been thoroughly documented over the past decades, including oxidative stress, mitochondrial dysfunction, advanced glycation end products (AGEs), vascular damage, and neuroinflammation [1,2]. Although the role of mTOR signalling in DPN pathology has been explored in recent years, the specific dysregulation of mTOR in different cell types remains incompletely understood.

Existing reviews briefly mention mTOR in the context of autophagy, but few provide detailed mechanistic insights into the mTOR signalling pathway. Moreover, no review has systematically addressed the paradox of cell-type-specific dysregulation of mTOR in DPN. 'Schwannopathy', the dysfunction of Schwann cells in DPN, has recently gained recognition, prompting a number of recent reviews focused on Schwann cell-specific mechanisms.

Evidence suggests that hyperglycaemia induces mTOR hyperactivation in sensory neurons, causing hyperexcitability and neuropathic pain. In contrast, while *in vitro* studies indicate that inhibiting mTOR signalling in Schwann cells can trigger apoptosis, demyelination, and reduced neurotrophic support, findings from human tissue studies do not consistently align with these *in vitro* results. This potentially bidirectional pattern of mTOR dysfunction in different cell types is an underexplored aspect of DPN pathogenesis. However, the nature and consistency of this dysregulation across different experimental models and clinical settings remain to be established. Understanding these cell-type-specific effects may inform the development of more precise therapies that selectively modulate mTOR activity, thereby improving DPN treatments. This review addresses a key gap by providing a comprehensive synthesis of mTOR signalling in peripheral nerves. It systematically examines the mechanisms and consequences of mTOR dysregulation in both neurons and Schwann cells, and discusses the therapeutic implications for DPN management.

Peripheral neuropathy affects about 1% of adults worldwide. Symptoms range from mild numbness in the toes to severe neuropathy that affects motor nerve functions and muscle weakness, and balance issues, which may lead to wheelchair dependence. The underlying causes of peripheral neuropathy are diverse, but DPN is the most common subtype. It can cause complications ranging from sensory changes to amputations and life-threatening conditions. The number of people with diabetes worldwide is projected to rise by 46%, from 589 million in 2025 to 853 million in 2050, representing approximately 1 in 8 adults [3]. DPN has a lifetime prevalence of roughly 50% among people with diabetes, making it the most common diabetic complication [1,4]. It raises the risk of foot ulcers, lower limb amputations, falls, death, and chronic pain in 10–34% of affected patients [5,6]. Population studies consistently show that DPN prevalence differs by diabetes type, disease duration, and glycaemic control. The Rochester Diabetic Neuropathy Study found that 66% of type 1 and 59% of type 2 diabetes patients had objective evidence of any neuropathy. DPN specifically affected 54% of type 1 and 45% of type 2 patients [7]. The EURODIAB IDDM Complications Study, including 3,250 patients in 16 European countries, reported a prevalence of DPN in type 1 diabetes of 28% with no significant geographic differences [8]. Duration of diabetes, glycaemic control, smoking, elevated triglycerides, and ketoacidosis emerged as key determinants of DPN. A 2020 systematic review and meta-analysis identified a pooled global DPN prevalence of 30% among people with diabetes, where patients with type 2 diabetes showed a higher rate (~31.5%) compared to those with type 1 diabetes (~17.5%) [9]. DPN prevalence varied by age, ranging from approximately 5% in individuals aged 20–29 years to 44% in those aged 70–79 years [10]. Longitudinal data from EURODIAB showed a 23.5% incidence of neuropathy progression in initially unaffected patients over 7.3 years [11]. The Natural History of Type 2 Diabetes Study found prevalence rates of DPN rose from 8.3% at diagnosis to 41.9% after ten years [12]. The DCCT/EDIC study showed DPN prevalence in type 1 diabetes rose from less than 10% early to 34% after 25 years [13,14]. A cost burden model by Borrelli estimated that direct US healthcare costs for DPN exceed $45 billion annually, including more than $30 billion for DPN treatment and $15 billion for the management of DPN complications and disease progression. As DPN prevalence increases, the associated cost burden is expected to rise correspondingly [15]. Wang et al. examined the economic impact of diabetic peripheral neuropathic pain (DPNP) in China and found that the total costs for all DPNP patients increased from baseline to follow-up. The average cost per DPNP patient increased from approximately RMB 4000 to RMB 7500, primarily due to higher expenses related to hospitalisation and medication. The observed rise in healthcare resource utilisation and costs indicates that the burden on Chinese patients increases after being diagnosed with DPNP [16].

2. Methodology

This narrative review was conducted in accordance with established guidelines for comprehensive literature synthesis. A systematic search of the peer-reviewed literature was conducted across multiple databases, including PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, Springer, Taylor & Francis, and ScienceDirect. The search encompassed publications from 1990 through January 2025 to capture both foundational studies and the most recent advances in the field. The search strategy employed Medical Subject Headings (MeSH) terms and

free-text keywords connected by Boolean operators (AND, OR) to optimise retrieval. The primary search string was structured as follows: ("diabetic peripheral neuropathy" OR "DPN" OR "diabetic neuropathy") AND ("mTOR" OR "mammalian target of rapamycin" OR "mTORC1" OR "mTORC2" OR "mechanistic target of rapamycin") AND ("Schwann cells" OR "Schwannopathy" OR "neurons" OR "sensory neurons" OR "dorsal root ganglion"). Secondary searches were conducted using additional terms, including "peripheral nerve", "neuropathic pain", "demyelination", "hyperglycaemia", "autophagy", and "myelin", to ensure comprehensive coverage of the relevant literature. The reference lists of identified articles and relevant review papers were manually screened to identify additional studies not captured by the electronic database searches, and citation tracking in Google Scholar was performed to identify more recent publications citing key foundational studies. Studies were included if they were original research articles, conference papers, or systematic reviews published in peer-reviewed journals that investigated the pathophysiology, molecular mechanisms, epidemiology, clinical features, or treatment of DPN; examined mTOR signalling pathways in the context of peripheral nerve biology, diabetes, or neuropathy; or investigated Schwann cell biology and dysfunction in diabetic or hyperglycaemic conditions. Both *in vitro* studies using Schwann cell or neuronal cultures under high-glucose conditions and in vivo studies using validated animal models of diabetes (e.g., STZ-induced diabetic rats/mice, *db*/*db* mice, or transgenic models) were considered eligible. Clinical studies and human tissue analysis relevant to diabetic neuropathy and mTOR signalling were also included. Only articles published in English or with English abstracts providing sufficient methodological and outcome data were considered. Studies were excluded if they focused exclusively on central nervous system disorders without relevance to peripheral neuropathy, or if they examined non-diabetic neuropathies (e.g., chemotherapy-induced, inherited, or idiopathic neuropathies) without comparative relevance to DPN mechanisms. Case reports, editorials, letters to the editor, opinion pieces lacking primary research data, and studies with insufficient methodological detail were also excluded. In cases of duplicate publications or studies with overlapping datasets, the most comprehensive or recent publication was retained. Conference abstracts without full-text availability or sufficient outcome data were not considered.

3. Clinical Features and Presentation of DPN

DPN is typically characterised by symmetrical, length-dependent dysfunction of the sensory, motor, and autonomic nervous systems. It usually presents first in the toes and feet, then progresses upward in a 'stocking and glove' distribution. Sensory symptoms are the predominant phenotype in DPN and include both positive and negative symptoms; the former, also known as excitatory symptoms, include tingling sensations, sensory abnormalities, and nociceptive abnormalities, as well as an increased response to nociceptive stimuli, which may be exacerbated at night. Pain characteristics vary among patients and may include burning, tingling, electric shock-like sensations, or feelings similar to stepping on broken glass [17]. Negative symptoms include loss of sensation, such as numbness and hypoalgesia. These symptoms can cause patients, especially older individuals, to fail to notice recurrent trauma, blisters, or foreign bodies. This can lead to chronic trauma and infections, increasing the risk of foot ulcers and other complications. Raputova et al., using quantitative sensory test profiling in a large cohort of diabetic patients with and without polyneuropathy and pain, found that those with painful polyneuropathy exhibited more pronounced sensory hyperalgesia, as well as greater nerve fibre degeneration compared to patients without polyneuropathy or pain [18]. These findings highlight the heterogeneity among patients with diabetic neuropathy.

Although sensory symptoms predominate in the later stages of DPN, significant motor symptoms, such as weakness of distal muscles, particularly the ankle dorsiflexors and plantarflexors, may also occur, resulting in foot drop, gait abnormalities, and atrophy of the intrinsic muscles of the foot. In addition, a decrease or loss of deep tendon reflexes may occur, especially Achilles tendon reflexes. Some patients develop muscle weakness or myasthenia, and this motor neurological disorder can even involve the proximal muscles in severe cases [19]. Autonomic neuropathy often also occurs in DPN and can involve multiple organ systems, such as cardiovascular autonomic neuropathy, manifested by resting tachycardia, decreased exercise tolerance, postural hypotension, and even an absence of sensation to myocardial ischemia. In addition, gastrointestinal autonomic neuropathy may also occur, which manifests itself as gastroparesis, with nausea, vomiting, and diarrhoea, or intestinal dyskinesias that lead to constipation. There are also genitourinary dysfunctions, including neurogenic bladder and erectile dysfunction, as well as abnormalities in sweat gland function, including decreased sweating in the extremities, pupillary abnormalities, diminished light response, and impaired night vision. All of the above may occur as part of autonomic involvement [18]. Whilst distal symmetrical polyneuropathy is the most common pattern of presentation, DPN can also present with atypical presentations such as diabetic amyotrophy, or what is known as diabetic myopathy. This condition is characterised by severe asymmetric thigh pain and muscle atrophy, primarily

involving the quadriceps. Unlike distal symmetric neuropathies, diabetic myopathies usually have an acute onset and can be associated with significant weight loss, usually slow and often incomplete recovery [20]. Currently, the diagnosis of DPN relies on a combination of clinical assessment, neurophysiological examination, and imaging or pathological techniques. Early diagnosis of DPN is crucial for preventing complications and improving patient outcomes. The Michigan Neuropathy Screening Instrument (MNSI) is one of several standardised tools that have been developed to assess the severity of neuropathy. It combines a questionnaire with a brief physical exam to assess the appearance of the foot, foot ulceration, ankle reflexes, and vibratory sensation [21]. The Neuropathy Disability Score (NDS) is another test that assesses multiple senses and reflexes to provide a comprehensive assessment of neuropathy severity [10]. Vibration testing with a 128 Hz tuning fork on the bony elevations of the foot is a typical protective sensory test in clinical practice. Loss of vibratory feeling could indicate a higher risk of ulceration [22]. In DPN, both sensory and motor nerve conduction velocities are typically reduced, accompanied by decreased amplitudes of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). Notably, SNAPs in the common peroneal nerve are often among the first to be involved, making them a sensitive marker of early neuropathy [23]. The quantitative sensory testing (QST) uses standardised methods to assess sensory thresholds for vibration, temperature, and pain, enabling detection of early sensory dysfunction, including small fibre neuropathy. However, QST requires patient cooperation and relies on subjective responses, which may limit its reliability in certain clinical contexts [7].

Skin biopsy is a valuable tool for assessing small fibre neuropathy. This technique involves obtaining a 3 mm puncture biopsy sample from the distal calf, which is then immunohistochemically stained for protein gene product 9.5 (PGP 9.5), a widespread axonal marker, to quantify intraepidermal nerve fibre (IENF) density. Quantification of IENF density allows for objective evaluation of small fibre integrity, with a reduction in IENF density correlating with increasing severity of clinical neuropathy [24].

Alternatively, the use of corneal confocal microscopy (CCM), allows for the direct visualisation and quantitative analysis of small nerve fibres in the cornea, including measurements of nerve fibre density, length, and branching. This non-invasive technique can detect early nerve fibre loss, often preceding the appearance of clinical signs [25]. In addition, peripheral nerve imaging, such as magnetic resonance neuroimaging, enables visualization of nerve structure and integrity, while advanced techniques like diffusion tensor imaging (DTI) can detect alterations in myelin sheaths or fibre density of nerve microstructures. Although these MRI-based techniques are valuable for assessing atypical or focal neuropathies, they have not yet become routine in clinical practice [26].

4. Pathophysiology of DPN

The pathogenesis of DPN involves multiple biochemical pathways that converge to produce neuronal dysfunction and progressive neurodegeneration. These pathways stem from a complex interplay of metabolic, vascular, and inflammatory mechanisms triggered by persistent hyperglycaemia. One of the earliest recognised mechanisms is the polyol pathway, which converts excess glucose to sorbitol via the enzyme aldose reductase, depleting nicotinamide adenine dinucleotide phosphate (NADPH), which is needed for glutathione regeneration and antioxidant defence [27]. Studies in aldose reductase-deficient mice demonstrated protection against diabetes-induced reductions in motor and sensory nerve conduction velocities. These mice showed significant attenuation of c-Jun N-terminal kinase activation, glutathione depletion, and superoxide accumulation compared to controls [28]. Transgenic mice overexpressing human aldose reductase also exhibited significantly more severe reductions in motor nerve conduction velocity and nerve fibre atrophy when becoming diabetic [29]. Schwann cells express particularly high levels of aldose reductase, making them vulnerable to hyperglycaemia-induced damage [30]. In addition, AGEs gradually accumulate in diabetic tissues and exert neurotoxic effects. Bierhaus et al. demonstrated that RAGE, the receptor for AGEs, ligands, RAGE itself, activated nuclear factor kappa B (NF-κB) p65, and interleukin-6 co-localise in human diabetic gastrocnemius nerve biopsy samples, particularly within the endoneurial microvasculature [31]. RAGE knockout mice showed markedly attenuated NF-κB activation and were largely protected from the loss of pain perception despite prolonged diabetes. Oxidative stress represents another key pathogenic mechanism in DPN. Russell et al. found that high glucose rapidly induced the production of reactive oxygen species (ROS) in dorsal root ganglion (DRG) neurons, with an average of 50% increase in mitochondrial size occurring within six hours of exposure [32]. This mitochondrial swelling phenomenon was preceded by loss of membrane potential, partial ATP depletion, and activation of caspases 3 and 9, while inhibition of electron transport chain complexes III and IV prevented glucose-induced mitochondrial dysfunction and neuronal apoptosis. Another study using stable isotope labelling by amino acids in cell culture (SILAC) to compare mitochondrial protein expression in the DRG of STZ-induced diabetic rats versus insulin-treated diabetic rats

revealed significant down-regulation of respiratory chain components, including a 29% reduction in cytochrome c oxidase subunit IV (COX IV) and a 36% reduction in NADH dehydrogenase Fe–S protein 3 (NDUFS3) [33]. These protein reductions correlate with reduced mitochondrial respiration and complex activity [34]. The AMP-activated protein kinase (AMPK)/ peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signalling axis is also impaired in diabetic DRG, linking nutrient excess to defective mitochondrial biogenesis and the characteristic distal axonal lesions of DPN [35]. Mitochondrial dysfunction impairs the sirtuin 1 (SIRT1)/PGC-1α/ mitochondrial transcription factor A (TFAM) signalling pathway, disrupting energetic homeostasis and contributing to the characteristic "dying-back" pattern of distal axonal degeneration. Accumulated mitochondrial DNA damage impairs DNA polymerase-γ function, and mitochondrial DNA mutations and deletions are associated with severe mitochondrial dysfunction in nerves of diabetic patients [36]. Beyond direct DNA damage, emerging evidence suggests that epigenetic modifications also contribute to oxidative stress and mitochondrial dysfunction in DPN, potentially explaining the phenomenon of metabolic memory. Studies have demonstrated that increased histone acetylation and DNA methylation in tissues of diabetic patients, which is associated with heightened ROS accumulation, altered the expression of genes regulating redox balance, and facilitated mitochondrial damage [37].

Vascular mechanisms and endothelial dysfunction also play key roles in the pathogenesis of DPN. Diabetic peripheral nerve biopsies show pathological changes in the microvasculature, including endothelial cell thickening, basement membrane proliferation, and luminal narrowing of the nutrient vessels that perfuse peripheral nerves. These changes lead to endoneurial hypoxia and endothelial dysfunction [38]. Reduced nitric oxide (NO) bioavailability is a hallmark of vascular dysfunction. In animal models of diabetes, both the expression and activity of endothelial nitric oxide synthase (eNOS) are significantly diminished, which occurs in parallel with reductions in neural blood flow and slowed nerve conduction velocities [39]. Vascular endothelial growth factor (VEGF) signalling is critical for supporting the neurovascular unit. In diabetic rats, neural VEGF is downregulated, accompanied by reduced vascular density and nerve conduction deficits [40]. Recombinant VEGF administration restores neural blood flow and improves electrophysiological parameters. Neuroinflammation is another hallmark of DPN, in which immune and inflammatory mechanisms actively contribute to nerve injury and dysfunction. Pro-inflammatory cytokines are up-regulated in the DRG and peripheral nerves. NF-κB is aberrantly activated in diabetic peripheral nerves, particularly in Schwann cells, vascular endothelial cells, infiltrating monocytes, and even neurons in the peripheral and central nervous systems. Blocking NF-κB activation by inhibiting the inhibitor of kappa B (IκB) kinase (IKK) protected diabetic rats from deficits in nerve conduction velocity, abnormal sensory thresholds to mechanical and thermal stimuli, and reduced nerve blood flow [41]. Classical pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), are elevated in diabetic nerves and correlate with disease severity [42]. These cytokines activate downstream pathways such as p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), which promote neuronal apoptosis and axonal degeneration. Macrophages and microglia have also been found to infiltrate the diabetic DRG and peripheral nerves, exacerbating neuronal damage and further propagating inflammatory cascades. In addition, several key neurotrophic factors also show reduced expression in DPN. Nerve growth factor (NGF) supports the survival of small-diameter sensory neurons that mediate pain and temperature sensation. In animal models of diabetes, NGF levels are reduced in peripheral tissues, leading to atrophy and dysfunction of these neurons [43]. By contrast, insulin-like growth factor-1 (IGF-1) is a potent neurotrophic factor for sensory and motor neurons. In DPN, IGF-1 signalling is impaired, partly due to increased levels of IGF-binding proteins that sequester IGF-1 and prevent it from activating neuronal receptors [44]. Notably, IGF-1 supplementation in diabetic animals improves nerve conduction velocities and structural parameters.

5. Treatment of DPN

DPN management requires a multifaceted approach that includes optimal glycaemic control, symptomatic pain management, diligent foot care, and prevention of complications. To date, available therapies mainly focus on symptom management and halting progression. No established disease-modifying treatments target the underlying nerve damage in DPN. Intensive glycaemic control remains fundamental to preventing the onset and progression of DPN. The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes clearly demonstrated that intensive insulin therapy reduced the risk of developing diabetic retinopathy by 54% for the secondary intervention cohort [14]. This benefit persisted in the long-term follow-up of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, demonstrating a "metabolic memory" effect whereby early intensive treatment provides protection many years after return to usual care [45]. In type 2 diabetes, the impact of glycaemic control on neuropathy is less pronounced. The ACCORD and VADT trials showed no significant

difference in the incidence of neuropathy between intensive and standard glycaemic control arms [46,47]. These trials enrolled patients with long-standing diabetes, many of whom already had neuropathy. The results suggest that once neuropathy is established, stringent glycaemic control may have limited benefit. Likely, earlier and aggressive glycaemic management in newly diagnosed type 2 diabetes could be more effective in preventing neuropathy. Glycaemic targets should be individualised based on patient factors, including age, comorbidities, and hypoglycaemia risk. In general, a glycated haemoglobin (HbA1c) goal of <7% (53 mmol/mol) is appropriate for most non-pregnant adults, though more stringent targets (e.g., <6.5%, 48 mmol/mol) may be reasonable for younger, healthier patients if achievable without significant hypoglycaemia. The management of painful DPN requires a structured approach. Several classes of medications have shown efficacy in randomised controlled trials (RCTs) and are recommended as first- or second-line treatments.

5.1. Gabapentinoids

Gabapentin and pregabalin are α2-δ calcium channel ligands that reduce neuronal excitability by decreasing calcium influx. Multiple RCTs have demonstrated that pregabalin reduces pain and improves sleep compared to placebo. Effective doses typically range from 300–600 mg/day in two or three divided doses. Gabapentin is similarly effective but requires higher doses (1200–3600 mg/day) and lacks FDA approval specifically for painful DPN. Common side effects of gabapentin and pregabalin include dizziness, somnolence, and peripheral oedema. Both drugs are renally excreted and thus require dose adjustments in patients with renal insufficiency [48].

5.2. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine is an FDA-approved SNRI for DPN. Duloxetine at 60–120 mg/day significantly reduces pain without affecting glycaemic control [49]. A 2023 meta-analysis confirmed the efficacy and favourable safety profile of duloxetine, with common side effects including nausea, drowsiness, and dry mouth [50]. Venlafaxine, another SNRI, has also shown efficacy for neuropathic pain, though it is not FDA-approved for DPN. SNRIs should not be used concurrently with monoamine oxidase inhibitors, and tapering is recommended when discontinuing to avoid withdrawal symptoms.

5.3. Tricyclic Antidepressants (TCAs)

Amitriptyline and nortriptyline are traditional treatments for neuropathic pain. Max et al. showed amitriptyline to be superior to placebo in reducing diabetic neuropathic pain, independent of its antidepressant effect. TCAs are typically started at low doses (10–25 mg at night, up-titrated to 75–150 mg/day as tolerated) [51]. Anticholinergic side effects often limit their use, especially in older patients. These include dry mouth, constipation, urinary retention, and tachycardia. TCAs are contraindicated in patients with certain cardiac conduction abnormalities due to the risk of arrhythmia.

5.4. Opioid Analgesics

Although opioids (such as tapentadol) can alleviate neuropathic pain, they are generally considered third-line due to risks of dependency, tolerance, and adverse effects. Tapentadol, a μ-opioid receptor agonist and norepinephrine reuptake inhibitor, provided pain relief in DPN in clinical trials [52] but carries the class risks of nausea, constipation, dizziness, and potential for abuse. Opioids should be reserved for patients who do not respond to or cannot tolerate other treatments, and even then, used at the lowest effective dose and for the shortest duration necessary.

5.5. Topical Therapies

High-concentration capsaicin patches (8% capsaicin) deplete substance P from nociceptive fibres and can provide localised pain relief for up to 3 months following a single application, though initial application causes intense burning discomfort requiring management. Lower-dose capsaicin creams (0.075%) are available for home use but are often limited by skin irritation. Lidocaine 5% patches or gels provide local anaesthesia and can be helpful for focal neuropathic pain areas with allodynia. A recent narrative systematic review of topical capsaicin in DPN suggests it can yield meaningful pain relief in some patients, especially when systemic treatments are contraindicated [53].

5.6. Interventional Therapy

When conservative treatments fail, interventional approaches may be necessary. For painful DPN that is refractory to pharmacological treatment, interventional approaches may be considered. Spinal cord stimulation

(SCS) has shown promising results in reducing neuropathic pain and improving quality of life in DPN. A randomised clinical trial of high-frequency (10 kHz) SCS reported significantly greater pain reduction, with 79% of SCS patients achieving pain reduction versus 5% in the conventional management group [54]. While SCS is an invasive therapy requiring surgical implantation of epidural electrodes and a pulse generator, it can provide substantial benefit in carefully selected patients who have not achieved adequate pain relief with conventional treatments.

5.7. Other Emerging Therapies

Several new therapeutic strategies targeting the underlying pathophysiological mechanisms of DPN are under investigation. α-lipoic acid, an antioxidant, is approved for the treatment of diabetic neuropathy in some countries (e.g., Germany). The NATHAN 1 trial evaluated oral α-lipoic acid (600 mg/day) over 4 years and found modest improvements in neuropathy impairment scores but no significant effect on the primary endpoint, and it has not received FDA approval in the U.S. [55]. In recent years, anti-inflammatory agents aimed at NF-κB, MAPK, and other inflammatory pathways have also been explored in preclinical models [56].

5.8. Lifestyle Intervention

In addition, lifestyle interventions, including smoking cessation, weight management, and regular exercise, can also positively manage DPN [57], and regular aerobic exercise can also enhance peripheral blood flow, which is beneficial to fight against the development of DPN [58].

6. Schwann Cell Responses to Nerve Injury under Normal Metabolic Conditions and to DPN

Schwann cells are the major glial cells of the peripheral nervous system and play a key role in the maintenance and regeneration of damaged nerves. They form myelin sheaths that facilitate rapid saltatory conduction of peripheral axons while providing metabolic and nutritional support to neurons. Schwann cell biology has become increasingly important in peripheral neuropathy research, particularly DPN. Under normal metabolic conditions, Schwann cells undergo remarkable reprogramming after nerve injury. Peripheral nerve injury triggers Schwann cells to undergo significant plasticity through dedifferentiation, proliferation, and ultimately transdifferentiation into the repair phenotype [Figure 1]. Arthur-Farraj et al. demonstrated that the transcription factor c-Jun is a global regulator of Wallerian degeneration and the post-injury response in Schwann cells [59]. In the Schwann cell-specific c-Jun knockout mice, they found that c-Jun regulates the expression of neurotrophic factors, adhesion molecules, regenerative trajectory formation, and myelin scavenging, and c-Jun deletion resulted in Schwann cell dysfunction, failure of functional recovery, and neuronal death, establishing that c-Jun regulates myelin sheaths and the process of transdifferentiation of Remak Schwann cells to the repair phenotype essential for regeneration. The Notch signalling pathway is also an important factor in Schwann cell plasticity, as Woodhoo et al. found that Notch signalling promotes Schwann cell generation from precursor cells, maintains Schwann cell pool homeostasis by regulating proliferation, and inhibits myelin formation. Upregulation of Notch expression after nerve injury accelerates cellular dedifferentiation, while dysregulation of adult Notch signalling leads to demyelinating features [60]. The microenvironment at the injury site further affects Schwann cell reprogramming, where Clements et al. revealed that Schwann cells acquire mesenchymal properties during the process of dedifferentiation, and also demonstrated that the TGF-β signalling pathway promotes Schwann cell invasion and migration, which is critical for neural bridging during the regeneration process [61]. Schwann cells can also re-express type I neuregulin-1 (NRG1) themselves after injury, which promotes cell differentiation and myelin regeneration through autocrine and paracrine effects [62]. Additionally, conditional knockout mice demonstrated that axon-derived NRG1 is dispensable for daily myelin maintenance but required for myelin regeneration after nerve injury [63].

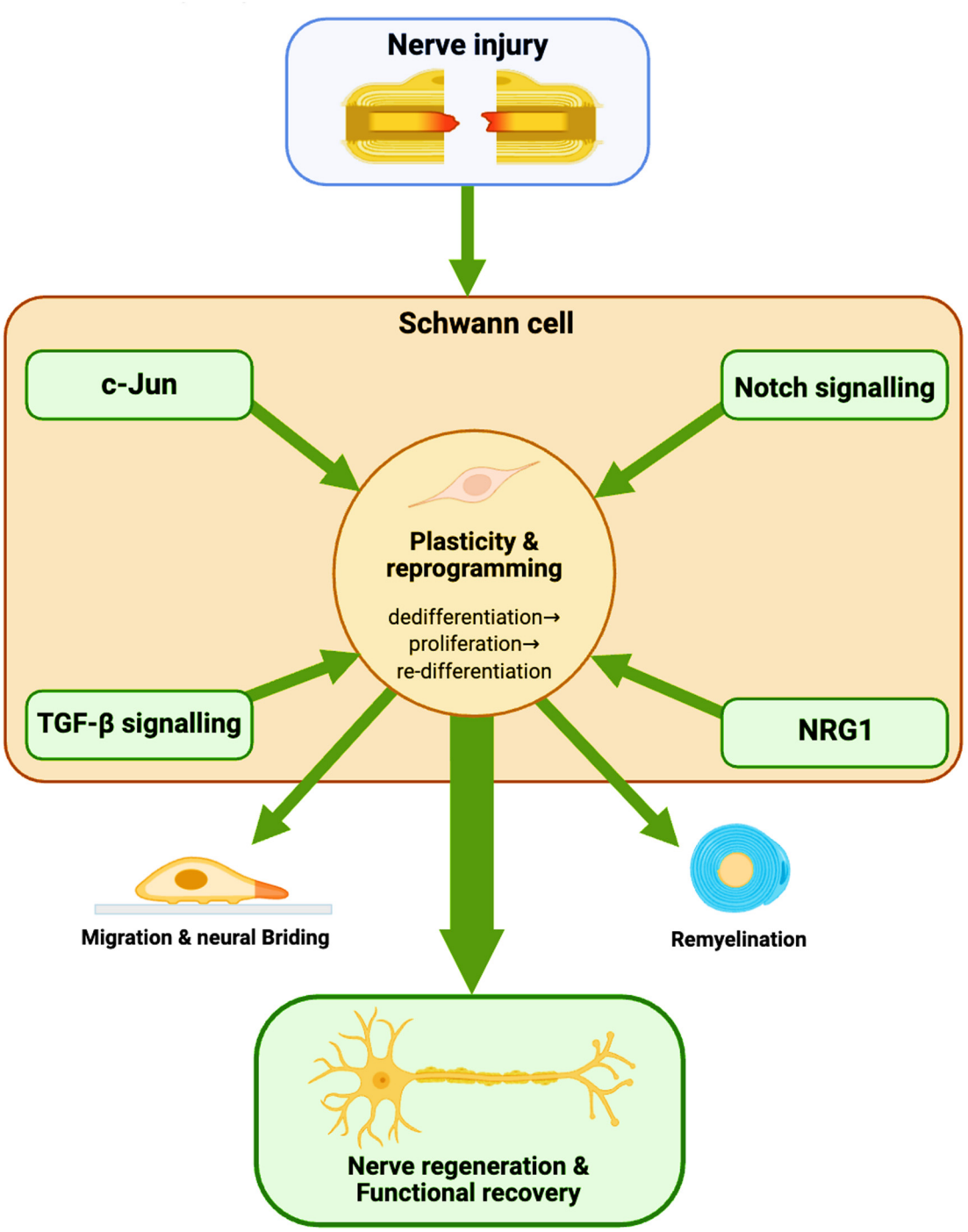

Figure 1. Schwann cell plasticity and reprogramming during peripheral nerve regeneration under physiologically normal metabolic conditions. Following nerve injury in non-diabetic conditions, Schwann cells undergo a well-characterised dedifferentiation process that enables nerve repair and functional recovery. This schematic illustrates key regulatory pathways identified through animal studies (primarily rodent models) and *in vitro* experiments. The transcription factor c-Jun acts as a master regulator of Schwann cell dedifferentiation and transdifferentiation to a repair phenotype, controlling expression of neurotrophic factors, adhesion molecules, and myelin scavenging [59]. Notch signalling promotes Schwann cell generation from precursor cells, maintains cell pool homeostasis by regulating proliferation, and inhibits premature myelin formation; upregulation of Notch after injury accelerates dedifferentiation [60]. TGF-β signalling promotes Schwann cell invasion and migration, critical for neural bridging during regeneration [61]. Neuregulin-1 (NRG1), re-expressed by Schwann cells after injury through autocrine and paracrine mechanisms, promotes cell differentiation and myelin regeneration [62,63].

6.1. Evidence from In Vitro Studies Using Cultured Schwann Cells

The diabetic microenvironment, especially hyperglycaemia, affects Schwann cell function through multiple pathways. These include metabolic dysregulation, oxidative stress, and impaired cell signalling [Figure 2]. *In vitro* experiments have provided detailed mechanistic insights into hyperglycaemia-induced Schwann cell dysfunction. Zhang et al. used stable isotope labelling of amino acids in cell culture (SILAC) to confirm that hyperglycaemia promotes mitochondrial dysfunction and expression of oxidative phosphorylation-related proteins in primary rat Schwann cells. Although hyperglycaemia increased overall oxygen consumption, it paradoxically reduced coupled respiratory efficiency, indicating mitochondrial dysfunction [64]. Also, Kato et al. demonstrated that glucose fluctuations induced apoptosis and oxidative stress in Schwann cells via the endoplasmic reticulum stress response, and the endoplasmic reticulum stress inhibitor 4-PBA significantly reduced cell death [65]. Another noteworthy mechanism studied *in vitro* is the polyol pathway, which is a major trigger of oxidative stress in diabetic Schwann cells. Sango et al. showed that a high-glucose environment promotes up-regulation of aldose reductase expression and increases intracellular sorbitol and fructose in immortalised mouse Schwann Cells (IMS32) [66]. High glucose decreases glutathione levels and activates NF-κB, changes that can be reversed by treatment with an aldose reductase inhibitor [66,67]. In addition to this, Sekido et al. showed that glyceraldehyde-derived AGEs (AGE-2) and glycolaldehyde-derived AGEs (AGE-3) were associated with a decrease in mitochondrial membrane potential, activation of the p38 MAPK signalling pathway, and promotion of TNF-α and IL-1β release, which significantly induced apoptosis and reduced the survival rate of Schwann cells [68]. Furthermore, hyperglycaemia also impairs Schwann cell secretion of neurotrophic factors, which are essential for neuronal survival and axonal regeneration, and further disrupts the regeneration of nerves that have already been damaged in the diabetic environment. *In vitro* experiments using an immortalised mouse Schwann cell line cultured under high-glucose conditions confirmed a significant reduction in nerve growth factor (NGF) secretion, which directly affects neurite outgrowth in dorsal root ganglion neurons [69]. Through the polyol pathway, neurotrophin-3-induced nerve growth factor production was also found to be suppressed in Schwann cells exposed to a high-glucose environment [67]. Epigenetic modifications may also be downstream effectors of hyperglycaemia, as high-glucose treatment reduced BDNF expression in Schwann cells and caused DNA hypermethylation of the BDNF gene [70].

6.2. Evidence from In Vivo Studies

To investigate the functional consequences of mitochondrial damage in Schwann cells *in vivo*, Viader et al. investigated the effects of mitochondrial damage in Schwann cells by constructing Schwann cell-specific Tfam knockout mice (Tfam-SCKOs), which progressively developed peripheral neuropathy, with an early preferential loss of unmyelinated small fibres, followed by demyelination and degeneration of large-diameter axons, which is highly similar to the progression of diabetic neuropathy [35]. Viader et al. in their study in 2013 supplemented with the mechanistic aspects of axonal degeneration, who noted that mitochondrial dysfunction in Schwann cells activates maladaptive integrated stress responses via heme-regulated inhibitor kinase (HRI) and shifts lipid metabolism away from fatty acid synthesis to the oxidative pathway, which leads to depletion of the lipid components of the myelin sheaths and the accumulation of neurotoxic acylcarnitines, as well as the induction of axonal degeneration [71]. Schwann cells collected from type 1 and type 2 diabetic mice also showed significantly lower levels of NGF and neurotrophin-3 and were less able to myelinate co-cultured axons [72].

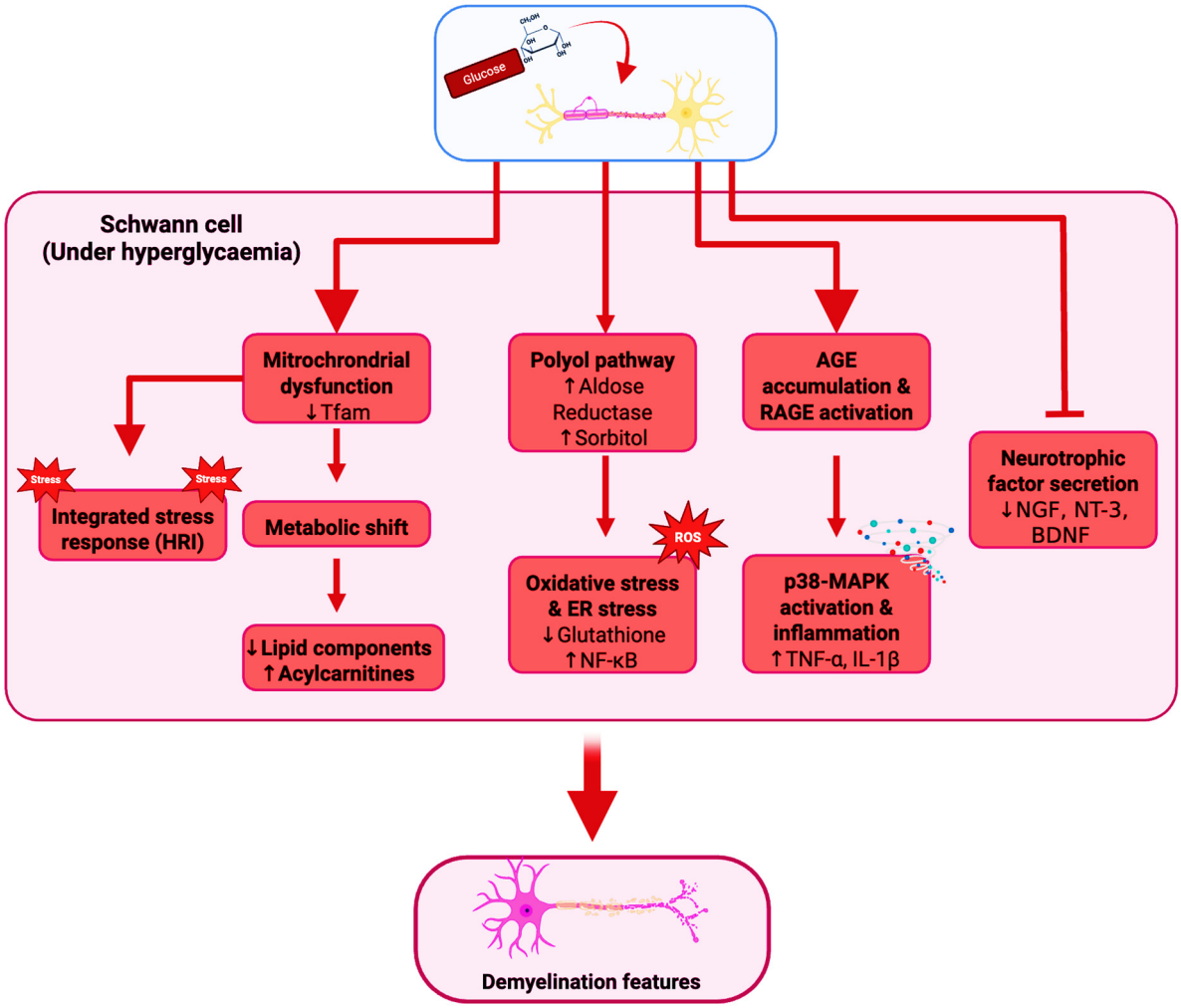

Figure 2. Multiple pathological mechanisms contribute to Schwann cell dysfunction in diabetic peripheral neuropathy, as evidenced by convergent findings from *in vitro* high-glucose studies, animal models, and human tissue analyses. Under hyperglycaemic conditions, Schwann cells experience damage through several interconnected pathways: (1) MITOCHONDRIAL DYSFUNCTION: Reduced Tfam expression (demonstrated in Tfam-SCKO mice) [35] leads to activation of the heme-regulated inhibitor kinase (HRI)-mediated integrated stress response and metabolic shift toward oxidative pathways, depleting lipid components and accumulating neurotoxic acylcarnitines [71]. SILAC proteomics of primary rat Schwann cells under high-glucose conditions revealed altered mitochondrial protein expression and reduced coupled respiratory efficiency [64]; (2) POLYOL PATHWAY ACTIVATION: High-glucose upregulates aldose reductase, increasing intracellular sorbitol and fructose in IMS32, depleting glutathione and activating NF-κB—effects reversible with aldose reductase inhibitors [66,67]. Schwann cells express particularly high levels of aldose reductase, rendering them vulnerable to hyperglycaemia [29]; (3) AGE ACCUMULATION AND RAGE ACTIVATION: AGE-2 and AGE-3 induce mitochondrial membrane potential loss, p38 MAPK activation, and TNF-α/IL-1β release, significantly promoting Schwann cell apoptosis [68]; (4) IMPAIRED NEUROTROPHIC FACTOR SECRETION: High-glucose reduces NGF and NT-3 secretion from Schwann cells (demonstrated in IMS32 cells and confirmed in Schwann cells from type 1 and type 2 diabetic mice), impairing neurite outgrowth of co-cultured DRG neurons and reducing myelination capacity [67,69,72]. High glucose also reduces BDNF expression through DNA hypermethylation [70].

7. mTOR Signalling Network in DPN

mTOR is a serine/threonine protein kinase belonging to the phosphatidylinositol 3-kinase-related kinase (PIKK) family. This highly conserved protein serves as a central hub for regulating cell growth, metabolism, proliferation, and survival across a wide range of biological systems [73]. mTOR protein has a molecular weight of 289 kDa and an extremely complex conformation. Its structure includes an N-terminal tandem HEAT repeat, a FAT structural domain, an FRB structural domain that mediates rapamycin binding, a catalytic kinase structural domain, and a FATC structural domain at the C-terminal end [74]. mTOR functions through two distinct multiprotein complexes. One of them, mTOR complex 1 (mTORC1), binds to regulatory-associated protein of

mTOR (RAPTOR), mammalian lethal with SEC13 protein 8 (mLST8), proline-rich Akt substrate of 40 kDa (PRAS40), and DEP domain-containing mTOR-interacting protein (DEPTOR) to transmit nutrient-sensitive growth signals. Meanwhile, mTOR complex 2 (mTORC2) assembles with rapamycin-insensitive companion of mTOR (RICTOR), mammalian stress-activated protein kinase interacting protein 1 (mSIN1), protein observed with RICTOR (PROTOR), mLST8, and DEPTOR, and mainly undertakes functions related to cell survival and cytoskeleton organisation [73,75,76]. The activation of mTORC1 necessitates the integration of several signalling pathways. Growth factors, for instance, activate the PI3K/AKT axis, which causes the tuberous sclerosis complex (TSC) to be phosphorylated and releases the GTPase Ras homolog enriched in brain (Rheb), which is located on the surface of the lysosome [77,78]. mTOR is also highly regulated by energy levels; when energy levels are reduced in cells, AMPK phosphorylates TSC2 and RAPTOR, thereby inhibiting mTORC1 activity during metabolic stress [79]. When mTORC1 is activated, downstream targets such as ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) are phosphorylated to drive protein synthesis or to inhibit autophagy by phosphorylating unc-51-like autophagy activating kinase 1 (ULK1) [73]. The regulation and full range of mTORC2 functions remain incompletely characterised. Existing evidence shows that mTORC2 phosphorylates protein kinase B (AKT) at Ser473, enabling it to regulate metabolism, cell survival, and cytoskeletal reorganisation [75]. The major difference between mTORC1 and mTORC2 is pharmacological, as mTORC1 responds rapidly to rapamycin, whereas mTORC2 is usually resistant to the effects of rapamycin treatment [75,80,81]. The mTOR/autophagy axis also plays a role in the pathophysiology of DPN, where damaged organelles and proteins accumulate in peripheral nerves as diabetes persists [73,82]. Oxidative stress further exacerbates the issue by impairing mTOR signalling and promoting both mitochondrial dysfunction and apoptosis [83]. Furthermore, Yao et al. provide evidence from single-cell transcriptomic analysis using human tibial nerve biopsies obtained during amputations for diabetic foot ulcer (n=4 DPN patients, 35,137 cells) versus traumatic limb amputation controls (n=3, 26,114 cells) [84]. This study identified aberrant mTOR hyperactivity specifically in mast cells from DPN nerves, with a GLUT3-ERK1/2-mTOR cascade driving mast cell activation. Further western blot from mice models confirmed increased phospho-mTOR (p-mTOR) and p-ERK1/2 under high-glucose conditions, linking mTOR hyperactivity to ER stress, mitochondrial oxidative stress, and mast cell degranulation, releasing inflammatory mediators. In peripheral nerve injury without metabolic disturbances, mTOR is transiently activated, with neurones swiftly activating mTOR within hours post-injury to facilitate local protein translation and retrograde signalling, and mTOR activity gradually reverting to baseline levels as nerve repair advances. Schwann cells also exhibit a transient surge in mTOR activity to facilitate dedifferentiation from a mature to an undifferentiated state, but as nerve repair advances, mTOR activity in Schwann cells diminishes, promoting remyelination [85].

7.1. mTOR Overactivation in Sensory Neurons and Neuropathic Pain in DPN

DPN mainly involves sensory neurons, especially those located in the DRG. The mTOR signalling system is a key regulator of neuronal metabolism, protein synthesis, and autophagy, but this pathway is significantly dysregulated during the pathological process of DPN, and mTOR overactivation in sensory neurons has become a core pathogenic mechanism underlying neuropathic pain and neuronal dysfunction [Figure 3]. Hyperactivation of mTOR in sensory neurons has become one of the central pathogenic mechanisms leading to neuropathic pain and neuronal dysfunction.

7.1.1. Clinical Evidence from Human Studies

Clinical evidence shows that serum mTOR levels are positively correlated with glycated haemoglobin, fasting glucose, and insulin resistance, suggesting that mTOR may serve as a predictive biomarker for microvascular complications, including neuropathy [86].

7.1.2. Evidence from Animal Models

Multiple animal models have demonstrated mTOR overactivation in diabetic sensory neurons through convergent pathways. Liu et al. showed that after three weeks in a STZ-induced diabetic rat model, the levels of p-PI3K, p-Akt, and p-mTOR were significantly elevated in the spinal cord region, while at the same time, Beclin1 and LC3-II levels decreased, indicating that autophagy was impaired [82]. Roy Chowdhury et al. found that levels of phosphorylated AMPK and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1α) were significantly reduced in DRG neurons of STZ-induced diabetic rats as well as in *db*/*db* mice with a disease duration of 8–14 weeks, suggesting that mitochondrial membrane depolarisation and respiratory chain activity, or even mitochondrial dysfunction, occurred [35]. A study found that the adaptor protein 1 (APPL1) also regulates the

AMPK-mTOR axis [87]. In diabetic spinal dorsal horn neurons, inhibition of APPL1 disrupts the Rab5/Akt and AMPK signalling pathways and leads to mTOR activation. In diabetic rats, mRNA levels of IGF-1, AMPKα2, and PGC-1β were altered, whereas IGF-1 treatment reversed thermal hyperalgesia and restored mitochondrial respiratory chain complex activity [88]. In terms of downstream effects, phosphorylation of the tetrodotoxin-resistant sodium channel Nav1.8 was particularly critical in animal studies. He et al. showed that levels of p-mTOR and phosphorylated Nav1.8 were significantly elevated in the DRG even before the threshold for mechanical withdrawal was decreased [89]; whereas after intrathecal injection of rapamycin for 7 days, the intervention inhibited Nav1.8 phosphorylation, reduced the tetrodotoxin-resistant current density, and alleviated behavioural hypersensitivity. This suggests that mTOR-mediated local protein synthesis induces neuronal hyperexcitability, which in turn leads to neuropathic pain. Wang et al. further elucidated the functional relationship between impaired AMPK and pain transmission in animal models, revealing that reduced pAMPK levels in DRG neurons of diabetic *db*/*db* mice are associated with membrane-associated transient receptor potential ankyrin 1 (TRPA1) channel expression and enhanced mechanical tenderness. These effects were corrected by the AMPK agonists metformin and AICAR [90]. Liu et al. demonstrated that in diabetic sciatic nerves, mTOR levels were significantly elevated, accompanied by decreased levels of autophagy markers LC3-II and Beclin1 and increased p62 accumulation [91]. They also found that LBP treatment reduced mTOR/p70S6K pathway activity, restored autophagy, and improved neurological function. He et al. found that in a high-glucose environment, TNF-α activates mTOR in spinal cord dorsal horn neurones, leading to synapsin II (Syn II) overexpression and abnormal neurite outgrowth, which results in reduced sensory sensitisation in diabetic rats [92].

7.1.3. Evidence from *In Vitro* Studies

In vitro experiments have also provided mechanistic insights into mTOR activation in sensory neurons. Aghanoori et al. observed that treating cultured DRG neurons with IGF-1 significantly increased the phosphorylation of Akt, p70S6K (a downstream target of mTORC1), and AMPK [88]. When the AMPK/PGC-1α signalling pathway is dysfunctional, it leads to reduced activity of NDUFS3 and COX IV, reduced oxidative phosphorylation, and impaired mitochondrial physiology within axons, which in turn results in the ‘energy deficit paradox’ of low intracellular ATP levels despite elevated glucose availability [34].

7.2. Therapeutic Implications from Preclinical Studies

The main cause of neuronal mTOR overactivation in DPN is inextricably linked to the metabolic environment of diabetes, where chronic hyperglycaemia-induced overnutrition triggers energy surpluses that inhibit AMPK activity and activate the pro-growth PI3K/Akt signalling pathway, and the overactivation of mTOR is a pathological response to glycaemic stress. Rapamycin and a PI3K inhibitor (LY294002) have been shown to attenuate damage sensitisation by promoting autophagy and reducing mTOR pathway activation. In contrast, resveratrol treatment promotes neural protrusion growth, restores mitochondrial membrane polarisation, and reverses thermal nociceptive sensitisation by elevating AMPK levels, and also reduces intraepidermal nerve fibre loss in diabetic rats [35,82].

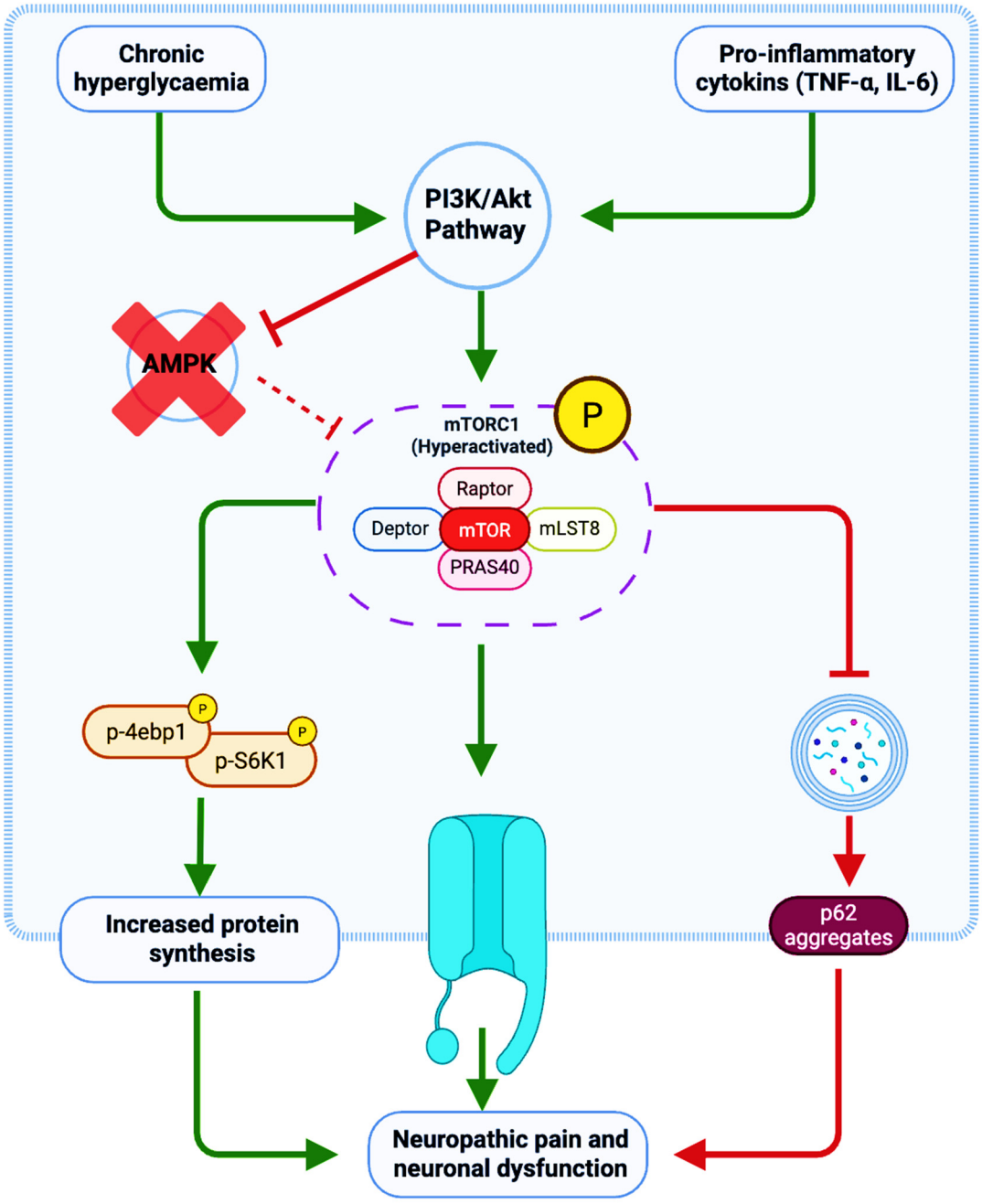

Figure 3. Mechanisms of mTOR hyperactivation in sensory neurons contributing to neuropathic pain in DPN, synthesised from animal models, *in vitro* studies, and limited human data. Most mechanistic insights derive from STZ-induced diabetic rats, *db*/*db* mice (8–14 weeks diabetes duration), and cultured DRG neurons under high-glucose conditions; human validation is limited to serum mTOR correlations with glycaemic markers [85]. Upstream activation: Chronic hyperglycaemia induces energy surplus that inhibits AMPK activity (demonstrated by reduced p-AMPK in diabetic DRG) [35] while activating the PI3K/Akt pathway. Pro-inflammatory cytokines (TNF-α, IL-6) elevated in diabetic conditions further activate PI3K/Akt signalling. This dual mechanism drives mTORC1 hyperactivation, evidenced by elevated p-PI3K, p-Akt, and p-mTOR in the spinal cord after 3 weeks in STZ rats [82]. Downstream effects: (1) mTORC1 phosphorylates 4E-BP1 and S6K1, driving increased protein synthesis, including overexpression of synapsin II (Syn II), which promotes abnormal neurite outgrowth and sensory sensitisation in diabetic rats [92]; (2) mTORC1 directly phosphorylates the tetrodotoxin-resistant sodium channel Nav1.8, with elevated p-Nav1.8 detected in DRG even before mechanical withdrawal threshold decreases; intrathecal rapamycin inhibits Nav1.8 phosphorylation, reduces tetrodotoxin-resistant current density, and alleviates behavioural hypersensitivity [89]; (3) mTORC1 hyperactivation inhibits autophagy through ULK1 phosphorylation, evidenced by decreased Beclin1 and LC3-II with increased p62 accumulation in diabetic sciatic nerves [82,91]. Impaired autophagy prevents the clearance of damaged organelles and misfolded proteins, contributing to cellular dysfunction.

7.3. mTORC1 in Schwann Cells in DPN: mTORC1 Inhibition and Schwann Cell Apoptosis

The mTOR signalling pathway plays a central role in Schwann cell function and peripheral nerve myelination [Figure 4]. In fact, mTOR dysregulation has been increasingly linked to the pathogenesis and clinical symptoms of DPN, although the precise direction and magnitude of this dysregulation may vary depending on diabetes type, disease duration, and the experimental models employed.

7.3.1. Evidence from Genetically Modified Mouse Models

Under physiological conditions, mTORC1 controls myelin formation in the peripheral nervous system by regulating lipid biosynthesis via sterol regulatory element–binding proteins (SREBPs). For example, the nuclear receptor RXRγ acts downstream of mTORC1 to regulate SREBP1c, and complete loss of mTORC1 in Schwann cells results in abnormally thin myelin and decreased nerve conduction velocity [85]. Furthermore, mTORC1 activity is progressively suppressed as Schwann cells mature. Studies have shown that while high mTORC1 activity promotes the proliferation of immature Schwann cells, an appropriate level of mTORC1 is required later for proper myelin growth in differentiated Schwann cells [93]. Disruption of insulin/IGF signalling in Schwann cells results in diminished mTOR–SREBP activity, decreased expression of genes involved in fatty acid and cholesterol synthesis, and thinner myelin sheaths during development, culminating in a sensory neuropathy phenotype similar to that seen in diabetic mice [94]. Recent research has highlighted a dual role of the PI3K-Akt-mTORC1 axis in Schwann cell myelination. During nerve development, high mTORC1 activity keeps Schwann cells in an immature state by inhibiting the pro-myelination transcription factor Krox20, and a decline in mTORC1 activity is crucial to allow Schwann cells to fully differentiate and initiate myelination. However, residual mTORC1 activity after differentiation synergistically drives myelin growth in concert with lipid synthesis via the RXRγ–SREBP1c axis [95].

7.3.2. Evidence from *In Vitro* High-Glucose Experiments

Under diabetic conditions, hyperglycaemia inhibits mTOR activity in Schwann cells. In one study, high-glucose treatment resulted in a 35.95% decrease in the p-mTOR/mTOR ratio and a 65.50% decrease in the p-S6K1/S6K1 ratio, triggering Schwann cell apoptosis via a Bcl-2/Bax-mediated mitochondrial pathway in cultured Schwann cells [96]. Silencing experiments further showed that specific inhibition of mTORC1 via RAPTOR knockdown, but not mTORC2, activated the apoptotic pathway under high-glucose conditions [96]. Additionally, sustained hyperglycaemia can lead to upstream inhibition of the PI3K/Akt pathway and concurrent overexpression of the DNA methyltransferases DNMT1 and DNMT3a, resulting in upregulation of the redox regulator TXNIP. This chain of events impairs autophagy and increases apoptosis in Schwann cells [70]. Notably, some of these high-glucose-induced changes can be pharmacologically reversed. For instance, melatonin treatment prevents oxidative stress–induced mitochondrial dysfunction and apoptosis in high-glucose-treated Schwann cells by restoring mTOR signalling and reducing oxidative stress [97]. In the pathological context of diabetes, by contrast, enhancing mTORC1 signalling can be beneficial. For example, activation of mTORC1/S6K1 with the small-molecule activator MHY1485 has been shown to prevent high-glucose-induced Schwann cell apoptosis, while sustained S6K1 activation similarly averts hyperglycaemia-induced cell death [96].

7.3.3. Clinical Evidence from Human Tissue Studies and Translational Considerations

The therapeutic benefits of mTOR activation or inhibition for Schwann cell functions and neurological recovery in DPN remain controversial. For example, Wu et al. paradoxically noted that, in human diabetic skin biopsies, patients with diabetic small fibre neuropathy exhibited higher Semaphorin 3A expression and reduced intraepidermal nerve fibre density (IENFD) compared to controls [98]. Notably, these patients also demonstrated over-activation of the mTOR signalling pathway as evidenced by increased levels of phosphorylated mTOR, phosphorylated p70S6K, and phosphorylated 4E-BP1. Meanwhile, rapamycin attenuated DPN pain and restored IENFD in a diabetic rat model [98], where IENFD is closely linked to Schwann cell function, given that healthy Schwann cells are essential for nourishing and supporting nerve fibres, particularly small unmyelinated fibres. These findings suggest that modulation of mTOR signalling may influence Schwann cell-mediated nerve repair in DPN. The study utilised STZ to induce diabetes in rats, resulting in a model that more closely resembles type 1 diabetes. Consequently, the findings may not fully reflect the mTOR activation state of Schwann cells under conditions of insulin resistance, which is a key contributor to DPN and is closely linked to mTOR activity [94]. The peripheral nerve microenvironment comprises distinct anatomical compartments with divergent metabolic responses. In the epidermal compartment, keratinocytes respond to hyperglycaemia with robust mTOR

hyperactivation, driving Semaphorin 3A secretion that mediates paracrine chemorepulsive effects on intraepidermal nerve fibres, causing growth cone collapse and axonal retraction [98]. This mechanism is extrinsic to Schwann cells yet contributes significantly to small fibre pathology. Conversely, within the endoneurial compartment, Schwann cells experience fundamentally different signalling responses to hyperglycaemia. Direct glucose exposure suppresses the PI3K-Akt-mTORC1 axis, leading to marked reductions in phospho-mTOR and phospho-S6K1 levels, shifting the Bcl-2/Bax ratio toward apoptosis [96]. Additionally, genetic disruption of insulin and IGF-1 signalling in Schwann cells recapitulates this pathway collapse, impairing lipid biosynthesis and myelination [94]. Thus, a patient with DPN may simultaneously harbour hyperactive mTOR signalling in their epidermis (driving small fibre retraction) while experiencing mTOR suppression in their nerve trunks (driving demyelination and Schwann cell apoptosis), presenting a therapeutic challenge for mTOR-modulating interventions. Based on current evidence, it can be hypothesised that within Schwann cells, mTOR activity may follow a biphasic temporal trajectory mirroring disease progression, although direct longitudinal validation of this model has not been studied and remains essential for future validation. In early DPN, the initial metabolic insult, characterised by ROS, lipid peroxidation, and inflammatory cytokines, may damage mitochondria [99] and potentially trigger non-canonical stress-induced mTORC1 activation. Evidence from in vivo models demonstrates that mitochondrial dysfunction in Schwann cells activates both mTORC1 and c-Jun, driving pathological demyelination [100]. This response superficially resembles the physiological repair phenotype observed following traumatic nerve injury, in which transient reactivation of mTORC1 promotes c-Jun-mediated dedifferentiation during normal regeneration [85]. However, in the diabetic context, this activation appears maladaptive, driving active demyelination rather than regeneration, a proposed state of 'frustrated repair' in which the Schwann cell may continuously attempt dedifferentiation without completing the regenerative cycle [101]. As the disease progresses to a chronic state, *in vitro* and cross-sectional evidence suggests that cumulative mitochondrial damage and sustained hyperglycaemia may contribute to the suppression of mTORC1/S6K1 signalling in Schwann cells [96]. Genetic knockout studies demonstrate that sustained loss of insulin/IGF-1 receptor signalling in Schwann cells reduces PI3K-Akt-mTOR pathway activity and causes thin myelin and sensory neuropathy phenocopying DPN [94]. Therefore, it can also be hypothesised that basal mTORC1 activity may fall below the threshold required for myelin maintenance, as established evidence shows that mTORC1 is essential for myelin protein synthesis and lipid biosynthesis via the mTORC1-RXRγ-SREBP pathway [85,102]. This putative anabolic collapse may manifest as impaired synthesis of myelin proteins (myelin protein zero (MPZ), myelin basic protein (MBP)) and SREBP-mediated lipids, potentially culminating in Bcl-2/Bax-mediated mitochondrial apoptosis [96]. In addition, the apparent discrepancy between *in vitro* findings demonstrating mTOR inhibition in high-glucose-treated Schwann cells [70,96] and human tissue studies showing mTOR overactivation [97] may be reconciled through several non-mutually exclusive interpretations. First, the cellular composition of analysed tissues differs substantially: while *in vitro* studies examine isolated Schwann cells, human skin biopsies contain multiple cell types, including keratinocytes, in which Wu et al. specifically demonstrated mTOR overactivation [98]. The observed elevation in mTOR markers in human tissue may therefore reflect contributions from non-Schwann cell populations and may not directly contradict the Schwann cell-specific findings from *in vitro* studies. Second, the temporal dynamics of mTOR signalling may differ across disease stages. Given that mTOR signalling tends to be activated and then downregulated in metabolically normal peripheral nerve injury tissues, it is plausible that mTOR activity in Schwann cells may similarly fluctuate during DPN progression, with potential early activation followed by later inhibition as the disease becomes chronic. Third, the metabolic context may distinctly influence mTOR regulation differently: STZ-induced diabetes models, which more closely resemble type 1 diabetes and are characterised by absolute insulin deficiency, may elicit different mTOR signalling responses compared to type 2 diabetes, which is characterised by insulin resistance. Since Schwann cells are heavily dependent on insulin and IGF-1 receptor signalling to maintain mTOR activity, variations in these metabolic states could have significant implications for Schwann cell function and the pathogenesis of DPN [94]. These considerations suggest that the proposed cell-type-specific mTOR dysregulation in DPN is a working hypothesis, requiring further validation through studies that carefully control for diabetes type and disease duration, and that employ cell-type-specific analyses in both human tissues and animal models.

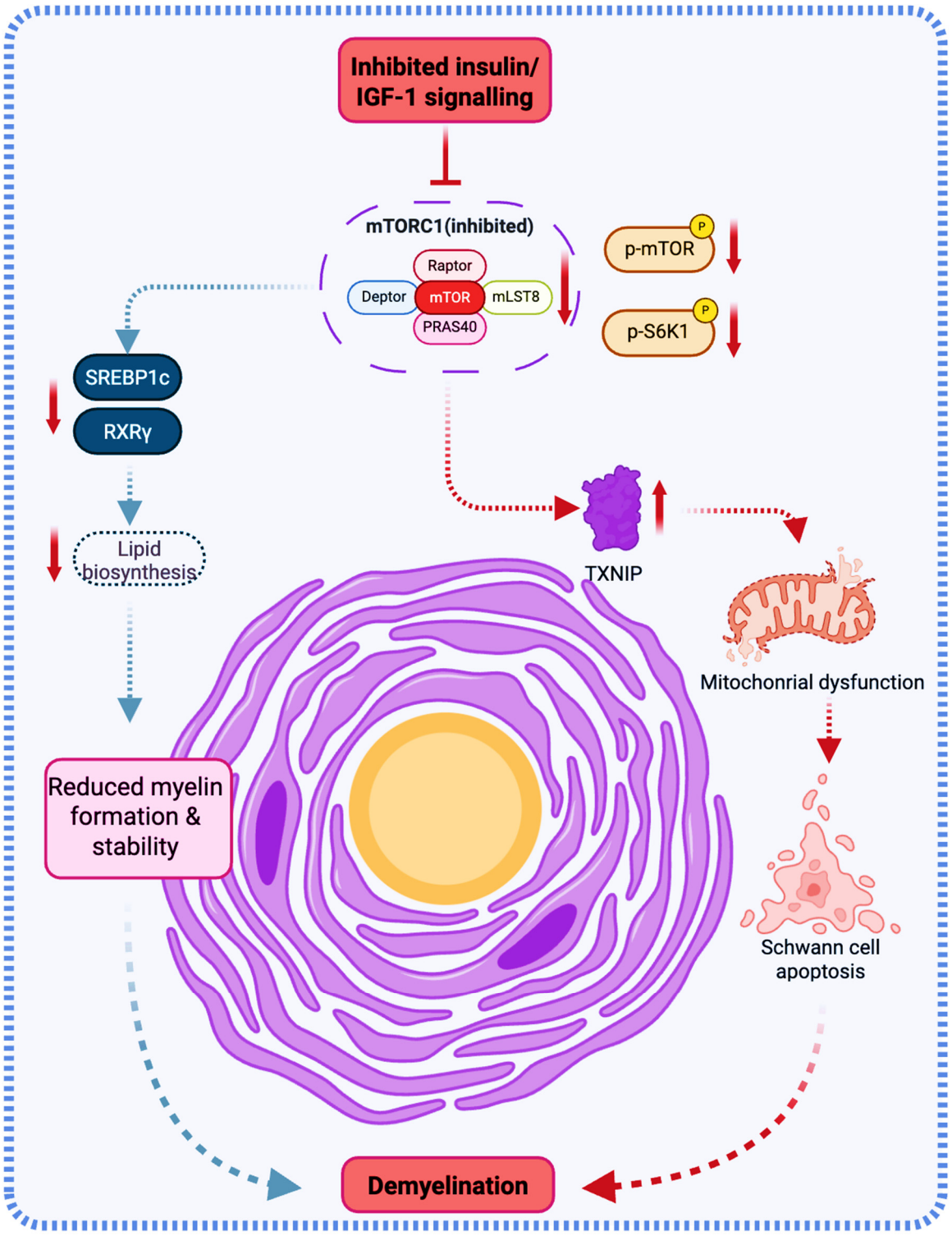

Figure 4. mTOR suppression in Schwann cells under diabetic conditions, based predominantly on *in vitro* high-glucose studies with important caveats regarding human disease relevance. Mechanism from *in vitro* studies: (1) Inhibited Insulin/IGF-1 signalling: Genetic disruption of insulin/IGF-1 receptors in Schwann cells reduces PI3K-Akt-mTORC1 activity, impairing lipid biosynthesis and myelination in mice [94]. High-glucose treatment of cultured Schwann cells produces a 35.95% decrease in p-mTOR/mTOR ratio and a 65.50% decrease in p-S6K1/S6K1 ratio [96]; (2) Downstream consequences of mTORC1 suppression: Reduced SREBP1c and RXRγ activity impairs lipid biosynthesis essential for myelin formation (established in genetic models) [85]; RAPTOR knockdown (specific mTORC1 inhibition) activates Bcl-2/Bax-mediated mitochondrial apoptosis pathway under high-glucose [96]; Sustained hyperglycaemia induces DNMT1/DNMT3a overexpression, upregulating TXNIP, impairing autophagy, and increasing apoptosis [70]. Collectively, these mechanisms result in reduced myelin formation and stability, Schwann cell apoptosis, and ultimately demyelination.

7.4. Limitations of the Current Evidence

The mechanistic understanding of mTOR dysregulation in DPN, particularly in Schwann cells, relies heavily on *in vitro* high-glucose culture models, which pose significant limitations for extrapolation to human disease. Cultured Schwann cells exposed to elevated glucose concentrations cannot fully recapitulate the complex pathophysiology of DPN, which develops over years of fluctuating hyperglycaemia in the context of systemic metabolic derangements, including dyslipidaemia, insulin resistance, chronic inflammation, and microvascular dysfunction. Isolated cell culture systems lack critical components of the in vivo diabetic environment, such as bidirectional neuron-glia signalling, immune cell interactions, paracrine factors from the neurovascular unit, extracellular matrix remodelling, and systemic hormonal influences. Furthermore, acute or subacute high-glucose exposure *in vitro* may trigger cellular responses that differ substantially from the chronic metabolic stress characteristic of long-standing diabetes. The apparent discrepancy between *in vitro* findings demonstrating mTOR inhibition in high-glucose-treated Schwann cells and human tissue studies showing elevated mTOR markers underscores these limitations and warrants careful consideration. Several factors may contribute to this disconnect. Human skin biopsies contain multiple cell types beyond Schwann cells, complicating the interpretation of bulk tissue analyses, where different cellular populations may exhibit opposing patterns of mTOR activity. Additionally, mTOR activity may vary across disease stages, with potential early activation followed by later suppression as neuropathy progresses and becomes chronic. The metabolic context also matters considerably, as STZ-induced diabetes models resembling type 1 diabetes may elicit different mTOR responses than type 2 diabetes with insulin resistance, particularly given that Schwann cells depend heavily on insulin and IGF-1 signalling to maintain mTOR activity. Therefore, while *in vitro* studies provide valuable mechanistic hypotheses and have identified potential therapeutic targets, these findings should be interpreted as hypothesis-generating rather than definitive evidence of disease mechanisms operating in human DPN. The proposed cell-type-specific mTOR dysregulation represents a working model that requires validation through cell-type-specific analyses of human diabetic nerve tissue using advanced techniques such as laser capture microdissection or single-cell RNA sequencing, longitudinal studies tracking mTOR activity across different stages of disease progression, conditional and cell-type-specific mTOR modulation in animal models, and careful consideration of diabetes type, duration, and metabolic control in both experimental designs and clinical studies. Despite these limitations, the convergent evidence from multiple experimental systems suggests that mTOR dysregulation likely contributes to DPN pathogenesis, justifying continued investigation of this pathway for therapeutic development, albeit with appropriate caution regarding target selection and patient stratification strategies.

8. Advances in Therapeutic Strategies Targeting Schwann Cell Dysfunction in Neuropathies

Recognition of Schwann cells' importance in nerve regeneration has prompted investigation of multiple therapeutic strategies targeting Schwann cell pathophysiology in DPN. Eid et al. first demonstrated the involvement of NADPH oxidase-4-derived ROS in diabetes-induced neuropathy. Targeted activation of hepatic X-receptors or specific inhibition of NADPH oxidase 4 (Nox4) attenuated diabetes-induced ROS production and restored myelin gene expression in Schwann cells [103]. α-lipoic acid antioxidant therapy also protected against glucose-induced Schwann cell damage by modulating the mitochondrial apoptotic pathway while inhibiting oxidative stress and apoptosis in Schwann cells exposed to intermittent or sustained high-glucose [104]. Recently, Majd et al. used an established DPN disease model platform derived from human pluripotent stem Schwann cells and found that bupropion, a psychotropic drug, unexpectedly exerted glucotoxicity-protective effects on Schwann cells through a high-throughput screening. Treatment of hyperglycaemic mice with bupropion prevented sensory dysfunction, Schwann cell death, and myelin damage. Additionally, a retrospective analysis of medical records showed a lower incidence of neuropathy in diabetic patients treated with bupropion [105]. Beyond pharmacological approaches, several emerging technologies have shown promise in specifically targeting Schwann cells for gene therapy, e.g., Kagiava et al. used an MPZ promoter-driven adeno-associated virus (AAV) vector carrying the gap junction beta-1 protein (GJB1) gene, a key gene that is mutated to cause X-linked Charcot-Marie-Tooth (CMT1X) demyelinating neuropathy. In Gjb1-null mice, this treatment improved motor performance, increased sciatic nerve conduction velocity, and promoted myelin formation in peripheral nerve tissue [106]. The team then used two serotypes of AAV, AAV9 and AAVrh10, also driven by the MPZ promoter, to target Schwann cells via intramedullary and intravenous administration, where they demonstrated both vectors were highly effective in targeting the peripheral nervous system (PNS) and transducing Schwann cells [107] with similar expression rates. However, the safety of these AAV approaches requires confirmation in non-human primates. To date, however, no viral vector system has been reported to target specific Schwann cell subtypes in DPN. A major reason is that DPN has a complex pathology and is a metabolic disease not caused by mutations in

a single or a few genes; therefore, gene modification using viral vectors may have limited therapeutic effect on DPN. Nevertheless, viral vectors may promote proliferation and redifferentiation of damaged Schwann cells in DPN, facilitating remyelination and neural repair. This remains an important area for investigation. For example, Zhang et al. promoted the maturation of neoplastic hair cell-like cells induced by Atoh1 overexpression through the co-regulation of multiple genes of the AAV-mediated transcription factor Atoh1 and its coordinators Gfi1, Pou4f3, and Six1 (GPAS). The AAV treatment also enhanced the transdifferentiation of supporting cells into outer HCs (OHCs) and inner HCs (IHCs)-like cells in vivo [108]. Similarly, Sun et al. used AAV-ie-mediated overexpression of Gpm6b, which was found to promote Lgr5+ SC-to-HC transformation in murine cochleae and to enhance supporting cell proliferation in cochlear organoids [109]. Specific to mTOR signalling, studies have also proved the feasibility of inhibiting mTOR via AAV-delivered shRNA or siRNA [110,111]. AAV-based modulation of mTOR in Schwann cells represents a promising therapeutic strategy that warrants investigation in DPN models.

9. Therapeutic Targeting of mTOR in DPN

Considering the likely cell-type-specific dysregulation of mTOR signalling in DPN, characterised by hyperactivation in sensory neurones contributing to neuropathic pain and suppression in Schwann cells hindering repair, therapeutic approaches must confront the distinct challenge of selectively modulating mTOR activity in various cellular compartments of peripheral nerves.

9.1. Challenges and Therapeutic Considerations

Therapeutic manipulation of mTOR in DPN presents a cell-type-specific challenge. Assessing treatment efficacy requires examining multiple functional metrics, including nerve conduction velocity, intraepidermal nerve fibre density, and pain behaviour. Given that mTOR suppression in diabetic Schwann cells has been observed *in vitro*, therapeutic strategies that restore mTOR activity have been hypothesized and, in animal models, shown to improve nerve conduction velocity, suggesting a potential avenue for intervention in DPN. Exogenous administration of insulin or insulin-like growth factor-1, both potent activators of the PI3K/Akt pathway, has been shown to reverse deficits in nerve conduction velocity in STZ-induced diabetic rats [43]. Intrathecal AAVrh10-IGF-1 delivery to STZ-diabetic mice restored both sensory and motor nerve conduction velocity through activation of Akt/PI3K signalling, which is directly relevant to mTOR pathway modulation, while increasing VEGF and enhancing myelination [112]. Given the strong correlation between myelin protein abundance and conduction velocity, these findings support the notion that pharmacological reactivation of glial mTOR signalling could be a promising therapeutic approach for restoring nerve conduction in diabetic neuropathy [113]. Beyond conduction velocity, a second critical metric of functional repair is the preservation of intraepidermal nerve fibre density [24,114]. Experimental evidence confirms that inhibiting neuronal mTOR hyperactivation preserves fibre density, as demonstrated by the direct AMPK activator AICAR, which produced striking results in diabetic neuropathy prevention. In high-fat diet mice, AICAR restored sciatic motor nerve conduction velocity from 29 ± 1.2 m/s to approximately 41 m/s and tail sensory nerve conduction velocity from 29 ± 1.4 m/s to 34.6 ± 0.9 m/s. In STZ mice, AICAR significantly increased intraepidermal nerve fibre density from 11.5 ± 1.8 to 25.1 ± 2.9 fibres/mm [115]. However, interpreting intraepidermal nerve fibre density as a repair outcome is complicated by the distinct roles of mTOR in regenerative versus degenerative contexts. Classical nerve regeneration studies using optic nerve crush models demonstrate that massive mTOR activation is required to drive axon regrowth across a lesion. For example, genetic deletion of TSC2, a negative regulator of mTORC1, in DRG neurons enhanced axonal growth capacity both *in vitro* and *in vivo*, mimicking the conditioning lesion effect through increased GAP-43 expression and phospho-S6 activation [116,117]. However, DPN pathology is not a transection but chronic metabolic stress, and in this context, the mTOR growth signal appears maladaptive, driving the neuron toward exhaustion and pain rather than orderly structural repair [89,98]. This may also hint that functional repair in diabetic neuropathy is not a monolithic endpoint but requires weighing competing cellular needs across distinct functional domains.

As mentioned in the previous sections, the proposed cell-type-specific dysregulation of mTOR signalling in DPN, if validated across different clinical contexts, would pose a unique therapeutic challenge. This potentially bidirectional dysregulation suggests that systemic modulation of mTOR, whether by activation or inhibition, may have opposing effects across different cellular compartments of peripheral nerves, potentially ameliorating one aspect of DPN pathology while exacerbating the other. However, given the conflicting evidence from different experimental models and human tissue studies, therapeutic strategies targeting mTOR should be approached with caution until the precise nature of mTOR dysregulation in specific cell populations is more definitively established. For example, administration of rapamycin attenuates neuropathic pain and restores intraepidermal nerve fibre density in a diabetic

rat model by inhibiting mTOR overactivation in sensory neurons and promoting autophagy [82,98]. The PI3K inhibitor LY294002 reduces injury pain through a similar mechanism [82]. Notably, it was observed that rapamycin treatment improved IENFD in diabetic rats, suggesting that mTOR inhibition may not necessarily be detrimental to Schwann cell-supported nerve fibre maintenance *in vivo* [98]. Nevertheless, based on *in vitro* evidence that inhibition of mTORC1 under high-glucose conditions triggers Schwann cell apoptosis via the Bcl-2/Bax mitochondrial pathway [96], the possibility that systemic mTOR inhibition may exacerbate Schwann cell dysfunction under certain conditions cannot be excluded, and this potential risk warrants careful consideration in therapeutic development. In contrast, pharmacological activation of mTORC1/S6K1 using the small-molecule activator MHY1485, which prevents high-glucose-induced Schwann cell apoptosis [96], may exacerbate DPN-induced pain following systemic administration, as it results in mTOR activation in neurons.

Therefore, several therapeutic strategies are worth considering, the first being to avoid direct modulation of mTOR signalling. Indirect modulation of the mTOR pathway through upstream modulators, such as AMPK activation, for example, may be a better option. AMPK activators such as metformin and resveratrol have shown promise. For example, metformin has been demonstrated to correct reduced levels of phosphorylated AMPK in diabetic DRG neurons and attenuate the mechanical hypersensitivity associated with TRPA1 channel expression [90], while resveratrol promotes neuronal synaptic growth that restores mitochondrial membrane polarisation, reverses thermal hyperalgesia, and reduces intraepidermal nerve fibre loss [36]. It is also reported that the knockdown of PRKAG1, a regulatory γ subunit of AMPK, inhibits AMPK and leads to mTOR hyperactivation, as well as elevated glucose-stimulated insulin secretions (GSIS) in the rat insulinoma cell line (INS-1E) [118]. Given that glucose-stimulated insulin secretion (GSIS) is a hallmark of pancreatic beta-cell function and that both GSIS and insulin translation are impaired under persistent hyperglycaemia [119], potentially exacerbating DPN and considering that overactive SGK1 (serine/threonine-protein kinase) inhibits GSIS, while SGK1 has been identified as a molecular switch in Schwann cells regulating axonal and glial regeneration during peripheral nerve injury (facilitating Schwann cell differentiation and maturation when inhibited) [120], it is plausible to speculate that AMPK inhibition may promote the recovery of nerve function via mTOR activation in Schwann cells, potentially correlating with SGK1/GSIS levels in peripheral nerve tissue. However, experimental validation is essential for this hypothesis, as there is no evidence whatsoever suggesting that mTOR activation in DPN can be achieved by modulating SGK1/GSIS levels. These approaches that avoid direct modulation of mTORC1 or mTORC2 may restore physiological mTOR activity to baseline levels appropriate for physiological states. Secondly, compounds with multifunctional properties may simultaneously target mTOR in multiple ways. For example, melatonin restores mTOR signalling in Schwann cells while reducing oxidative stress-induced mitochondrial dysfunction, thereby preventing apoptosis under high-glucose conditions [97]. In addition, our group has previously isolated a new protein, HKUOT-S2, from *Dioscorea opposita* Thunb, which can activate mTOR signalling in MSC-derived osteoblasts and facilitate bone defect repair [121]. It is also worth noting that such natural compounds may also facilitate nerve repair within the complex context of DPN, as our recent studies have demonstrated their neuromodulatory properties [122,123]. Thirdly, cell-type-specific drug delivery systems could selectively modulate mTOR signalling in neurons or Schwann cells. Several promising delivery platforms enable selective targeting of either Schwann cells or sensory neurons, depending on therapeutic goals.

9.2. Nanoparticle-Based Delivery Systems

Liposomal formulations composed of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC)/Poloxamer 188/cholesterol represent a significant advance in peripheral nerve targeting. These neurophilic liposomes cross the blood-nerve barrier via lipid-raft-mediated endocytosis and exhibit preferential uptake by myelinated peripheral nerves compared with muscle tissue [124]. Importantly, these systems accumulate in Schwann cells of the sciatic nerve after systemic administration, without penetrating the central nervous system. The incorporation of cholesterol into delivery systems mimics the natural composition of myelin membranes, thereby enhancing their affinity for myelinating Schwann cells. Furthermore, internalisation through caveolae-mediated endocytosis allows these systems to bypass lysosomal degradation, preserving sensitive cargoes such as siRNA or mRNA. For neuron-specific targeting, conjugation to the tetanus toxin C fragment is among the most validated approaches [125]. This ligand binds ganglioside receptors on neuronal terminals and exploits retrograde axonal transport, enabling peripherally administered nanoparticles to selectively reach dorsal root ganglion cell bodies. Chitosan/PEG-TTC nanocomplexes delivered intramuscularly achieved the first successful neuron-specific gene delivery via the peripheral route, with significantly increased brain-derived neurotrophic factor expression in dorsal root ganglia and spinal cord alongside meaningful sensorimotor functional recovery [126]. Poly(ethylene imine)-tetanus toxin (PEI-HC) nanoparticles achieved transfection of 56% to 64% of L4 and L5 dorsal root ganglion neurons after

footpad injection with spatially restricted transgene expression [127]. Lectin-functionalized gold nanoparticles (IB4-AuNP) provide subset-specific targeting with three- to four-fold higher accumulation in lumbar dorsal root ganglia through specific binding to non-peptidergic C fibre neurons [128]. For diabetic neuropathy specifically, aptamer-modified extracellular vesicles loaded with sinomenine achieved 7.2% spinal cord accumulation, compared with less than 2% with conventional delivery, and resulted in 60% to 70% reductions in inflammatory markers and improved dorsal root ganglion neurite outgrowth [129]. However, no nanoparticle system has yet achieved truly selective delivery to Schwann cells over neurons, representing an important opportunity that could be addressed by exploiting Schwann cell-specific surface receptors, such as ErbB2/ErbB3 or GPR126.

9.3. Viral Vector-Based Gene Delivery

Adeno-associated virus vectors offer the most advanced platform for achieving cell-type-specific gene expression in peripheral nerves, with serotype selection and promoter choice enabling selective targeting of either Schwann cells or sensory neurons. For Schwann cell targeting, AAV8 demonstrates preferential transduction via intrasciatic injection with sustained expression up to 10 weeks and particularly low neutralising antibody titres [130]. AAV8-mediated ciliary neurotrophic factor delivery upregulated myelin proteins MPZ and PMP22 in the injured sciatic nerve. AAV9 is highly effective at crossing the blood-nerve barrier following systemic or intrathecal injection and robustly transduces Schwann cells when accessible. AAVrh10 may outperform AAV9 in biodistribution to distal peripheral nerves [106]. Novel engineered variants have been specifically evolved for enhanced transduction of human Schwann cells. The MPZ promoter achieves highly specific Schwann cell expression throughout the peripheral nervous system. Intrathecal AAV9 with MPZ promoter delivering connexin 32 restored expression specifically in paranodal myelin areas and produced 60% improvement in root and femoral nerve pathology in Charcot-Marie-Tooth disease type 1X mouse models, accompanied by improved nerve conduction velocity and reduced inflammation [107]. For sensory neuron targeting, AAV5 achieves over 90% transduction of DRG at 12 weeks via direct ganglionic injection, affecting both large- and small-diameter populations [131]. AAV6 shows high specificity for small-diameter peripherin-positive nociceptive neurons in both rodent and primate models, making it suitable for pain-related applications [132,133]. The engineered variant AAV-PHP.S enables systemic intravenous delivery and transduction of more than 80% of DRG [134]. Regarding promoter specificity, human Synapsin is a pan-neuronal promoter that restricts expression to neurons while excluding glial cells [135]. Advillin is highly specific to sensory neurons in dorsal root ganglia [136,137]. Clinical translation of viral vector approaches has shown promise in the treatment of peripheral neuropathies. Sahenk et al. reported an AAV1. NT-3 gene therapy for the treatment of Charcot-Marie-Tooth disease, achieving a 52% increase in compound muscle action potential at 40 weeks in preclinical studies. Based on these encouraging results, a phase I/IIa clinical trial of scAAV1.tMCK. NTF3 for treatment of Charcot-Marie-Tooth disease type 1A (CMT1A) is expected to commence in April 2027 (NCT03520751), representing an important step toward translating cell-type-specific gene therapy approaches to clinical application in peripheral neuropathies [138].

9.4. Molecular Targets for Cell-Type-Specific Delivery

Beyond the delivery platforms themselves, successful implementation of cell-type-specific mTOR modulation requires exploiting differential surface marker expression between Schwann cells and sensory neurons. For Schwann cell-specific targeting, the ErbB2/ErbB3 receptor tyrosine kinase heterodimer represents a promising target [139–141]. These receptors bind neuregulin-1 and are expressed on Schwann cells but not on neurons, which, conversely, express the neuregulin-1 ligand but lack its receptors. Neuregulin-1 delivery promotes remyelination through PI3K pathway activation at low concentrations [142]; however, this effect is dose-dependent, as higher concentrations inhibit myelination by activating the Ras/Raf/Erk pathway. GPR126 is an adhesion G protein-coupled receptor essential and specific for Schwann cell myelination [143–145]. Small molecule screens have identified compounds that restore myelination in GPR126 hypomorphic models, and the Stachel peptide agonist promotes MBP expression. These findings highlight GPR126 as a promising druggable target for Schwann cell-directed therapies [146]. The low-affinity neurotrophin receptor p75NTR, while expressed on both neurons and Schwann cells during development, is downregulated in mature myelinating Schwann cells but re-expressed during demyelination and repair, potentially enabling targeting of repair Schwann cells specifically in neuropathic conditions [147]. For neuron-specific targeting, TRPV1 expression is restricted to nociceptive neurons and increases in diabetic neuropathy, enabling subset-specific targeting through capsaicin-conjugated delivery systems [148]. TrkA, the high-affinity nerve growth factor receptor expressed on peptidergic nociceptors, enables neurotrophin-based targeting, though cross-reactivity with Schwann cell p75NTR should be considered [149,150]. Investigating whether mTOR activity and its downstream effects vary throughout the

progression of DPN, and whether this necessitates distinct therapeutic approaches at different disease stages, represents a crucial direction for future research. Despite the large number of studies revealing the complex pathophysiological mechanisms of DPN, treatments to modify the disease process remain limited in clinical application. The lack of effective neuroprotective treatments for DPN may be due to several factors, including the multifactorial nature of the disease and the interrelated metabolic, vascular, inflammatory, and neurotrophic pathways involved. In addition, nerve damage continues to progress even when glycaemic control improves. Although many studies have reported neuroprotective effects of interventions with antioxidants (e.g., α-lipoic acid) and modulation of the mTORC1/S6K1 axis, data on their role in promoting neural regeneration and reversal of pre-existing neuropathy remain insufficient, and the exact mechanisms remain unclear. Overall, mTOR-targeted therapy in DPN requires a rational approach that considers its distinct roles in sensory neurons and Schwann cells while achieving balanced regulation. Future therapeutic development should consider strategies that restore physiological mTOR activity rather than direct, systematic inhibition or activation, or develop strategies that achieve cell-type-specific targeting to reduce neuronal hyperexcitability while promoting the survival and myelin-forming capacity of Schwann cells, thereby promoting nerve repair while avoiding exacerbation of DPN-induced pain.

10. Conclusions

DPN is a complex, multifactorial disease that poses a significant and growing clinical and economic burden worldwide. Emerging evidence suggests that cell-type-specific dysregulation of mTOR signalling may play an important role in DPN pathogenesis. Specifically, mTOR overactivation in sensory neurons appears to drive neuropathic pain through enhanced neuronal excitability and synaptic dysfunction. In contrast, *in vitro* studies indicate that mTOR suppression in Schwann cells may impair dedifferentiation capacity, promote apoptosis, disrupt myelin formation, and reduce neurotrophic factor secretion. However, findings from human tissue studies indicate a more complex picture that warrants further investigation. This potentially divergent pattern of mTOR dysregulation may partly explain the coexistence of persistent pain and progressive neurodegeneration characteristic of DPN. Further investigation to clarify these cell-type-specific mechanisms and reconcile discrepancies across different experimental models and clinical contexts could open new therapeutic avenues. If validated, strategies that selectively modulate mTOR signalling in specific cell populations may offer benefits beyond the existing symptomatic treatments and contribute toward disease modification.

Author Contributions

K.H.C. and J.A.K.: writing, editing, and reviewing of the original draft; A.S.B.: drawing figures; M.Y.A. and Y.Z.: editing and reviewing; K.W.K.Y.: reviewing and supervising. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Grammarly and ChatGPT5.2 to proofread. After using this tool/service, the authors reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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