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High glucose up-regulates Semaphorin 3A expression via the mTOR signaling pathway in keratinocytes: a potential mechanism and therapeutic target for diabetic small fiber neuropathy

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Abbreviations: 4E-BP1, Eukaryotic initiation factor 4E-binding protein 1; CPT, cold perception threshold; DPN, diabetic peripheral neuropathy; DRG, dorsal nerve root ganglia; FPG, fasting plasma glucose; HG, high glucose; IENFD, intraepidermal nerve fiber density; mTOR, mammalian target of rapamycin; NSS, neuropathy symptom score; OCT, optimal Cutting Temperature compound; p70 S6K, p70 ribosomal protein S6 kinase; PMWT, paw mechanical withdrawal threshold; PTWL, paw thermal withdrawal latency; QST, quantitative sensory testing; Sema3A, Semaphorin 3A; rSema3A, recombinant Semaphorin 3A; SFN, small fiber neuropathy; SNAP: sural nerve amplitude; SNCV: sural nerve conduction velocity; STZ, Streptozotocin; WPT, warm perception threshold.

Abstract

Small fiber neuropathy (SFN) is a common complication in diabetes, and is characterized by decreased intraepidermal nerve fiber density (IENFD). Semaphorin 3A (Sema3A), which is produced by keratinocytes, has a chemorepulsive effect on intraepidermal nerve fibers. mTOR signaling can mediate local protein synthesis that is critical for growth of axons and dendrites. Therefore, this study aimed to investigate whether Sema3A is up-regulated in diabetic keratinocytes via the mTOR-mediated p70 S6K and 4E-BP1 signaling pathways, and furthermore whether it is involved in the pathogenesis of diabetic SFN. IENFD, expression of Sema3A, and mTOR signaling, were evaluated in the skin of diabetic patients