

Intraneural VSMC dissimilation drives mast cell infiltration to exacerbate neurological deficits in T2DM

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Abstract

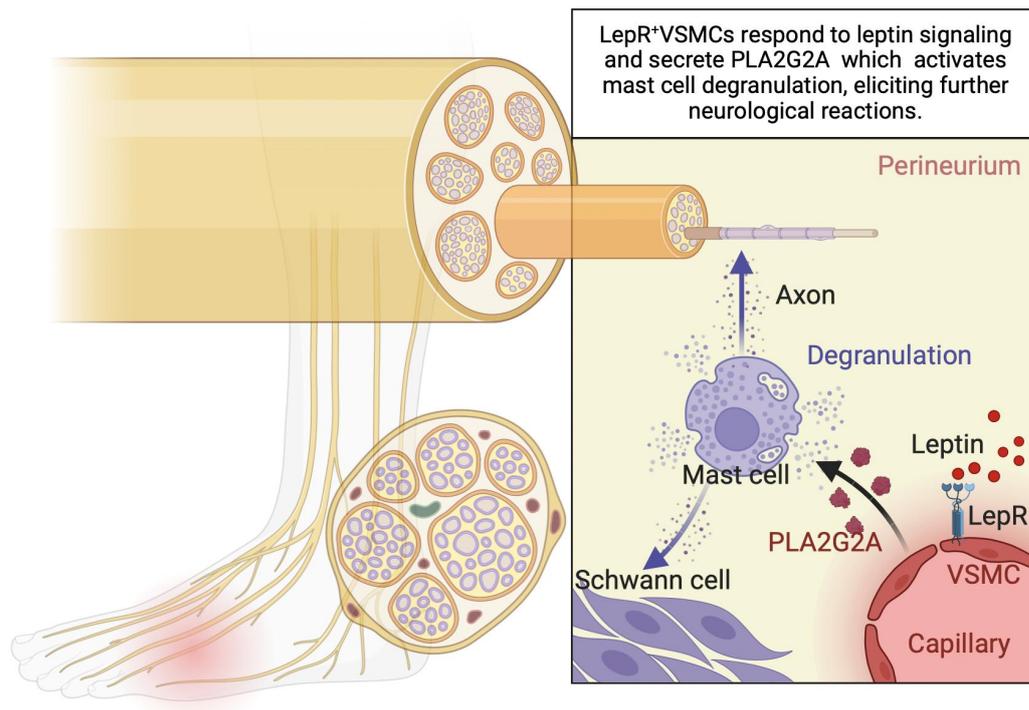
Introduction Diabetic neuropathy (DPN) occurs in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) with same typical symptoms of pain, numbness and tingling. Glycemic control effectively halts the DPN progression in T1DM patients, but the disease-modifying effects are modest in those with T2DM. This difference suggests the distinct mechanisms underlying DPN in T1DM and T2DM. However, the pathogenic mechanism of DPN remains poorly understood.

Methods We first evaluate the identities of different cell clusters within tibial nerves of T2DM-DPN and traumatic limb amputation (TLA) patients using single-cell RNA sequencing (scRNA-seq) data. Having discovered the microvascular abnormalities in T2DM-DPN patients, we next track the mural cell (vascular smooth muscle cells and pericytes) transdifferentiation in peripheral nerves during DPN progression. By crossing *ROSA26^{ZsGreen1/+}* mice with *Myh11-CreER^{T2}* mice, we generate a mural cell-lineage tracing murine model, in which mural cells and their progenies permanently express ZsGreen1. To seek the potential signaling pathways and metabolic perturbation that regulate the mural cell-mast cell interaction, we perform RNA-seq on mural cells and untargeted metabolomics analyses on mast cells. To extend our findings of angiocrine-induced mast cell activation and DPN progression, we generated a conditional knockout DPN mouse model.

Results We find a population of dissimilated intraneural mural cells in tibial nerves of T2DM patients by single-cell sequencing. Lineage tracing demonstrates that these mural cells lost their canonical markers and transitioned to leptin receptor (LepR)-positive phenotype. Ectopic LepR expression responds to leptin signal in circulation and further upregulates MAPK activities in mural cells. As a result, mural cells drive mast cell recruitment and degranulation in perivascular niche by releasing stem cell factor (SCF) and secretory calcium-dependent phospholipase A2 (PLA2G2A). Genetic interference with PLA2G2A production in murine nerves modifies mast cell activities and thus attenuates the axon degeneration and demyelination. Taken together, during T2DM-related DPN progression, dissimilated mural cells promote mast cells infiltration and activation, thereby exacerbating neuropathy progression in T2DM.

Discussion In this study, we uncover an unprecedented involvement of vascular dissimilation in the development of T2DM-DPN via mast cell recruitment and activation. We initially observe phenotypic switch of mural cells induced by elevated peripheral leptin levels during DPN progression. These LepR⁺ cells sense the leptin signal and upregulate MAPK signaling, which leads to the increased SCF and PLA2G2A production. SCF and PLA2G2A render mast cell infiltration and activation in perivascular niche. Chronic exposure to inflammatory states provided by mast cells finally leads to the axonopathy and myelinopathy in peripheral nerves. We therefore propose that LepR signaling can be targeted therapeutically to reduce pathological changes in T2DM-DPN.

Graphical abstract



Disclosure The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.