Schwann cell necroptosis in diabetic neuropathy

Alexia Belavgeni[a,b] , Francesca Maremonti[a,b], Marlena Stadtmüller[c] , Stefan R. Bornstein[a,c,d,e,f,g], and Andreas Linkermann[a,b,1]

Diabetic neuropathy (DN) is clinically characterized by a "stocking and glove" pattern of symptoms such as sensory loss, numbness, pain, and burning sensations. This pattern implicates that Schwann cells, required to maintain the myelin sheath and the nodes of Ranvier, rather than the neurons themselves, represent the primary site of injury (Fig. 1). In PNAS, Guo et al. (1) explain how the necroptosis protein, mixed-lineage kinase domain–like protein (MLKL), causes Schwann cells to lose their function.

DN is not a classical form of demyelinating neuropathy, such as Guillain-Barré syndrome. However, chronic hyperglycemia in type 1 and type 2 diabetes mellitus patients may induce typical features of demyelination, especially in severely affected patients (2–4). Therefore, understanding the death of Schwann cells might help unravel their mechanistic role in the associated loss of the myelin sheath and clinical progression of DN.

Necroptosis is a form of regulated necrosis that is associated with phosphorylation of MLKL (5, 6), a pseudokinase (7, 8). Although activation of MLKL is not sufficient to kill a cell (9), it is required for necroptosis. The only known kinase to phosphorylate MLKL is receptor-interacting protein kinase 3 (RIPK3) (5, 6) which is controlled by death receptors through RIPK1 (10–13), Toll-like receptors through the protein TIR domain–containing adapter inducing interferon-beta (TRIF) (14–16), and nucleotide sensors such as Z-DNA-binding protein 1 (ZBP1) (13, 17–23). Interaction with these proteins requires the RIP homotypic interacting motif of RIPK3 (24, 25) which is also interfered with by viruses such as cytomegalovirus (25–27), mechanistically highlighting the well-established role for necroptosis in viral defense.

In their current work, Guo et al. (1) first establish a transmission electron microscopy–based readout system of myelin decompaction following streptozotocin (STZ)–induced loss of pancreatic beta cells, thereby inducing diabetes. They demonstrate colocalization of MLKL with a known myelin sheath marker, indicating localization in the Schwann cells. Next, the authors investigate MLKL-deficient mice which exhibit less myelin decompaction and higher nerve conduction velocity in the STZ model, indicating MLKL to mechanistically induce DN. Further, they generate Schwann cell–specific MLKL-deficient mice employing a tamoxifen-inducible Plp1 promotor and confirm the above-mentioned findings. In yet another independent approach, they replace the MLKL gene with an S441A point mutation of MLKL in mice and, once again, reverse the diabetic phenotype in this setting when compared to MLKL wild-type mice. Finally, and clinically most importantly, an MLKL inhibitor (TC013249) is tested. As this inhibitor was generated to ultimately treat humans, human MLKL knock-in mice (hMLKL-KI) are employed for this important set
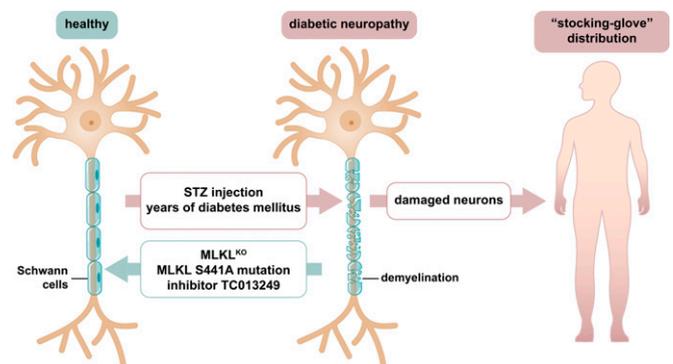

Fig. 1. Demyelination during DN involves MLKL-mediated damage of Schwann cells. In healthy individuals, the speed at which an electrochemical impulse propagates down a neural pathway, referred to as nerve conduction velocity, requires Schwann cells for electric neuronal isolation. In DN, demyelination of Schwann cells was recognized decades ago and is well known to clinically associate with the stocking-and-glove pattern frequently observed in diabetic patients. Currently, no treatment for DN is clinically available. Guo et al. (1) set out to investigate how Schwann cells lose their function. They report a critical pathophysiological contribution of MLKL, a pseudokinase and key mediator of necroptosis. In the STZ-induced murine model of diabetes and in patients suffering from DN, Schwann cell degradation is a common feature. In that model, MLKL-deficient or MLKL-mutant mice, and wild-type mice treated with the MLKL inhibitor TC013249, exhibited less demyelination.

of experiments. The authors carefully confirm that the hMLKL-KI mice do not express traces of mouse MLKL and control for equal hMLKL expression levels compared to wild-type mice. Intraperitoneal osmotic pumps are used to continuously deliver TC013249 to the hMLKL-KI mice. Upon treatment, significantly mitigated myelin sheath decompaction is observed. This functionally correlates with significantly less STZ-induced decreases in nerve conduction velocity.

MLKL inhibition, however, should be interpreted within a bigger picture. Within the field of neurology, other conditions

that include demyelination include multiple sclerosis, Marchiafava Bignami disease, central pontine myelinolysis, and others. It will be interesting to investigate the role of MLKL in these disorders. In addition, RIPK1 was demonstrated to play critical roles in diverse pathologies of the central nervous system (28). Interestingly, and somehow in contrast to a proactive role, MLKL-deficient patients may present with features of neurodegeneration (29). Beyond the field of neurology, MLKL was reported to be involved in acute conditions such as ischemia-reperfusion injury (9, 28, 30–34). In the preclinical limelight of the growing body of evidence for MLKL as a mediator of diseases, clinical trials employing MLKL inhibitors will be considered. Naturally, however, inhibiting the downstream target of necroptosis will result in the functional loss of necroptosis upon MLKL inhibition. Although most primary data indicate a viral inhibition of the kinase RIPK3 (11, 27, 35–37) rather than MLKL directly, it must be predicted that viral infections, known to be cleared by necroptosis (38), may appear more frequently. Clinical trials for testing MLKL inhibitors should therefore be designed to include more-detailed assessments than usual of safety from viral infections and associated complications.

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It is estimated that the annual cost of DN is higher than US$10 billion in the United States (39). In type 2 diabetes mellitus, improvement of glycemic control is thought to have little effect on neuropathy outcomes (39). Opioids are not recommended even in painful DN, owing to the potential for abuse. Novel treatment strategies, therefore, are of paramount clinical importance. In conclusion, the data presented by Guo et al. (1) indicate a therapeutic target in a rodent model that may be of potential future interest and clearly warrants further preclinical and clinical investigations.

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