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Ablation of Argonaute 2 in Schwann cells accelerates the progression of diabetic peripheral neuropathy

***Aim*:** In a recent paper published in *GLIA*, Fan and colleagues investigated the role of Argonaute 2, the key effector protein of miRNA-mediated silencing, in Schwann cell function in the absence of a metabolic dysfunction as well as in the setting of diabetic neuropathy.
***Methods*:** To that end, the authors assessed pain behaviors, electrophysiological changes, and nerve histopathology in a Schwann cell-specific Argonaute 2 knockout mouse model, which was induced with type 2 diabetes using the low dose streptozotocin/high-fat diet approach. The authors also examined the effect of Argonaute 2 silencing on mitochondrial structure and function in the presence or absence of type 2 diabetes. Lastly, RNA immunoprecipitation in combination with miRNA sequencing identified how Argonaute 2 deletion in Schwann cells impacted miRNAs, along with their target genes.
***Results*:** Schwann cell-specific deletion of Argonaute 2 in mice, even in the absence of type 2 diabetes, resulted in nerve damage, with mechanical and thermal allodynia, and nerve conduction velocity delays. Argonaute 2 deletion also caused demyelination and axonal loss. When type 2 diabetes was induced, Schwann cell-specific Argonaute 2 deletion worsened peripheral neuropathy. These changes were accompanied with compromised mitochondrial function and altered miRNA profiles in sciatic nerves. Specifically, the authors found a downregulation in miRNA206, a modulator of the RAGE/NF-κB pathway and mitochondrial function, to mediate at least in part Schwann cell injury.
***Conclusions*:** These findings suggest that Argonaute 2 maintains mitochondrial and Schwann cell function under normal conditions. However, when dysregulated, it may lead to demyelination and peripheral nerve degeneration, potentially through miRNA 206 downregulation.

Comments. miRNAs are increasingly recognized as major players in the development of diabetic neuropathy. Argonaute 2, a key component of miRNA-dependent gene regulation, has been implicated in many disorders, including neurodegeneration. However, preclinical research examining the role of Argonaute 2 in peripheral nerve (patho)physiology is lacking. The study by Fan et al. provides new, direct evidence that Argonaute 2 is essential for maintaining Schwann cell function under homeostatic conditions. Their findings also indicate that Argonaute 2-miRNA 206 downregulation may contribute to nerve pathology in type 2 diabetes through enhanced RAGE/NF-κB activity, reduced mitochondrial function, and Schwann cell apoptosis. Overall, this study suggests that the Argonaute 2-miRNA 206 complex serves as a promising therapeutic prospect for the treatment of diabetic neuropathy. It also opens many new avenues of research concerning Argonaute 2-mediated gene regulation in Schwann cells during metabolic dysfunction.

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Reference. Fan B, Chopp M, Zhang Y, Wang X, Kemper A, Zhang ZG, Liu XS. Ablation of Argonaute 2 in Schwann cells accelerates the progression of diabetic peripheral neuropathy. Glia. 2023 Sep;71(9):2196-2209. doi: 10.1002/glia.24387. Epub 2023 May 13. PMID: 37178056.
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