

Novel proteomic data identify energetic deficiency as an early pathogenetic mechanism in a murine model of type 2 diabetes and peripheral neuropathy

Aim: To profile the proteome of lumbar dorsal root ganglia and sciatic nerve at early stages of diabetic neuropathy in the BKS-*db/db* mouse, a robust model of type 2 diabetes and neuropathy.

Methods: Metabolic and neuropathy phenotyping was performed in *db/db* mice and their lean control littermates at different ages. Then, mice with 15 weeks of diabetes, which modelled early disease stages, were selected for further proteomic characterization in dorsal root ganglia and sciatic nerves using tandem mass tag labelling and mass spectrometry analysis. Select targets were validated by western blot.

Results: Pathways dysregulated in the *db/db* nerve included glycolytic and TCA cycle metabolism, lipid catabolism, the inflammatory response, as well as glutathione metabolism and oxidative stress related proteins. The authors also found an upregulation of muscle-related proteins in dorsal root ganglia and a downregulation in sciatic nerve of *db/db* mice. Further, major urinary protein (MUP), one of the differentially expressed proteins, was validated, confirming decreased protein expression in peripheral nerves in parallel to diabetes progression.

Conclusions: These findings support and extend existing transcriptomic and metabolomic reports, particularly regarding energy deficiency as a key pathomechanism contributing to neurodegeneration and diabetic neuropathy in type 2 diabetes.

Comments: This study characterizes for the first time the proteomic profile of peripheral nerves using the BKS-*db/db* mouse model, which faithfully recapitulates essential features of human diabetic neuropathy. The molecular alterations reported are detected even before morphological changes are observed and suggest that low ATP bioavailability has a key role in inducing nerve damage in early stages of type 2 diabetes. Subsequently, therapeutic strategies aimed at preserving ATP levels in peripheral nerves may be beneficial for the treatment of diabetic neuropathy.

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Reference: Leal-Julià M, Vilches JJ, Onieva A, Verdés S, Sánchez Á, Chillón M, Navarro X, Bosch A. Proteomic quantitative study of dorsal root ganglia and sciatic nerve in type 2 diabetic mice. *Mol Metab.* 2022. Jan;55:101408. doi: 10.1016/j.molmet.2021.101408.

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