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CORRESPONDENCE

Letter to the Editor (Correspondence): Re: genetic loss-of-function of activating transcription factor 3 but not C-type lectin member 5A prevents diabetic peripheral neuropathy

Laboratory Investigation (2022) 102:1292; https://doi.org/10.1038/s41374-022-00820-9

Dear Dr. Siegal

We reviewed with interest a relatively recent publication in Laboratory Investigation by Kan et al. entitled "Genetic loss-of-function of activating transcription factor 3 but not C-type lectin member 5 A prevents diabetic peripheral neuropathy". Laboratory Investigation (2021) 101: 1341–1352[1]. Given that LI has been an uncommon destination for papers in this field, we thought it important to make a few important points about the published work. While the molecules ATF3 and CLEC5A are of undoubted interest in experimental diabetic polyneuropathy (DPN) as newly explored in the paper, there are several issues around their evaluation in this paper that are worth discussion.

Firstly we believe that the one month duration of this model is too short for robust conclusions. DPN develops over the course of years to decades in diabetic human subjects, and we and others, including in a consensus paper, have long argued that the models should reflect that important feature of translation[2]. Early models as described by Kan et al., may theoretically have lingering impacts of streptozotocin and at one month, the model simply reflects an acute state generated by new and severe hyperglycemia. This form of acute hyperglycemia is uncommon in human diabetic subjects. Given the acute exposure to hyperglycemia, conclusions about inflammation, cytokines and ER stress may be premature. We believe that models of minimum duration 3–4 months and up to 6–9 months are more valid reflections of chronic human disease. The models by Kan et al. do not include electrophysiological characterization, i.e. multifiber motor and sensory recordings, considered by many to be essential features. A more concerning issue is the lack of information concerning nondiabetic control mice among the genetic models tested. Given that ATF3, for example, is a critical regeneration molecule[3,4], we do not know if nondiabetic models have epidermal axon loss or pain behaviour. Electron microscopy images of nerves and ganglia, as shown, but not quantitated, by Kan et al. in Figure 5 can also be problematic. Changes as depicted can overlap with handling and drying artifact in these small tissues and their significance is not established[5]. Unfortunately, the transverse sectioned morphometrically analyzed sections of sural nerve in Figure 6 also identify hyperosmolar fixative and handling artifact as well, as seen by irregular, nonrounded profiles and infolded myelin profiles. See the long established literature on avoidance of hyperosmolar fixative by Dyck and colleagues[6]. Although not also analyzed in this work, myelin thickness would not be ideally measured in these images. Finally, while the authors do show changes in microglia, these can occur simply from axonal degeneration without a need to invoke unique neuroinflammation.

Overall we would suggest that the work represents a model of acute exposure in vivo of mice to hyperglycemia rather than diabetic peripheral neuropathy as stated in the title. DPN is a chronic neurodegenerative disorder and while the molecules studied are of interest, further work would be required to put them into the context of other experimental DPN work.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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