OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
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Title: Genome-wide interrogation of transfer RNA-derived small RNAs in a mouse model of traumatic brain injury
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COMMENTS TO AUTHORS

This is a very good paper with which I have very little argument.

My following comments are more out of interest as to where this research leads us. My comments are not recommendations for alterations in the text, but may interest the authors just for their own sake. They could acknowledge a couple of possibilities if they wish.

The authors use a mouse TBI model. My own interest is in the symptomatology of electrical injury (EI), especially psychiatric symptomatology. One theory is that the symptomatology seen in electrical injury is actually a final common pathway of similar presentations of a number of injuries. These include TBI (van Zomeren, AH, ten Duis, HJ, Minderhoud, JM, Sipma, M. Lightning stroke and neuropsychological impairment: cases and questions. J Neurol Neurosurg Psychiatry. 1998;64(6):763-9), autoimmune injuries, viral illnesses, and several others.

It may be that the present paper is relevant to all these areas, and it is uncertain whether their secondary pathology is one step on the TBI pathway, or the actual final common pathway itself. By refining their findings, a number of problems beyond TBI may benefit.

The authors draw attention to chronic neurobehavioural sequelae, psychiatric, and cognitive deficits, with emotional and personality changes. These are delayed and protracted, and just what is also seen in EI. They point to excitotoxicity, oxidative stress, cerebral metabolic dysfunction, cerebrovascular pathology, chronic inflammatory events, and mitochondrial dysfunction. These have been noted in EI perhaps particularly affecting the hippocampus.

The reason for understanding the pathology is to tailor therapy. I wonder if the authors might add a paragraph on what therapy their findings point to. To me, they underline the need for anti-inflammatory modalities, among many others.

They note the recent tsRNA family, which are regulatory. They are derived from Pre-tRNAs and are transcribed by RNA Polymerase III and generate mature tRNA after cleavage and addition of CCA. The structure is known but the function is less known. The cleavage of tRNA is a response to genetic and environmental stress of the type mentioned above. Abnormality in tsRNA may lead to neurodegenerative disease, and the authors speculate may be involved in TBI. I also think of spinal cord pathologies, like AMS.

We know that the hippocampus is compromised by electrical injury (and depression, ...etc etc). Perhaps it is beyond the present paper's subject to correlate the responses in tsRNA in particular areas of the brain. This is interesting, but need not necessarily hold up this paper. It may be useful in future research.

The methodology of the experiments are complex and well described.

The results ultimately indicate differential in expression of tsRNAs, both negative and positive, pointing to tsRNA difference in TBI vs control after injury. Also mRNA were both upregulated and downregulated with various mRNA-tsRNA pairs.

Does this work lead, in the author's view, to any particular treatment modality. Though this may be future work.