Sestrin 3 as a regulator of pro-epileptic agents: the knock out rat model

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Epilepsy is a serious neurological disorders affecting about the 1% of the population worldwide. Despite evidence that most epilepsies have a genetic base, both genome wide association studies (GWAS) and exome sequencing approaches have so far provided limited insights into the mechanisms underlying epilepsy development. Recently, we used a systems biology approach to investigate transcriptional networks and pathways within the hippocampus of 129 temporal lobe epilepsy (TLE) patients who underwent the surgical resection of the epileptic focus (Johnson et al, 2015). A transcription program was identified that is overexpressed in the TLE hippocampus and promotes expression of epileptogenic signaling pathways including interleukine-1beta (IL-1beta) and toll-like receptor (TLR) (Maroso et al, 2010; Vezzani et al, 2011). Moreover, the Sestrin-3 (SESN3) gene was identified as a trans-acting activator of this transcriptional program. The pro-epileptic role for SESN3 was also confirmed in vitro in different cell-types and in vivo in the zebrafish model of chemically induced-seizures (Johnson et al, 2015). SESN3 is a member of the Sestrin family of proteins. Other Sestrins have been shown to decrease intracellular reactive oxygen species and to confer resistance to oxidative stress. SESN3 might instead regulate expression of neuro-inflammatory molecules, such as IL-1beta and tumor necrosis factor alpha (TNF-alpha) that are capable to induce changes in the neuronal excitability (Balosso et al, 2009; Johnson et al, 2015).

In this study, we investigated the phenotype of SESN3 knock out (KO) rats, both under normal conditions and after pilocarpine-induced seizures. We observed a significant delay in status epilepticus (SE) onset in SESN3 KO compared to control rats. This finding confirms in vitro and in vivo evidence indicating that SESN3 may favor occurrence and/or exacerbate seizures. Further studies in acute models of seizures are ongoing to confirm these results and to provide more insights into the mechanisms of seizure onset. Because TLR-signaling and oxidative stress pathways are also involved in the pathogenesis of anxiety, depression and cognitive impairment (Maes et al, 2015), that are recognized comorbidities of epilepsy (Tchekalarova et al, 2015), we also explored the SESN3 KO phenotype related to these other neurological disorders. SESN3 KO rats proved less anxious and less prone to develop depression compared to control rats in an array of behavioral tests, suggesting that SESN3 may be involved in the mechanism underlying anxiety, depression and epilepsy.

Taken together, the present results suggest that SESN3 may be a master regulator of the expression of molecules involved in the pathogenesis of epilepsy and of its comorbidities.