Long noncoding RNA FosDT promotes ischemic brain injury by interacting with REST-associated chromatin modifying proteins

Suresh Mehta¹, TaeHee Kim¹, Raghu Vemuganti¹

¹University of Wisconsin, Neurological Surgery, Madison

Objective(s): Ischemia induces extensive temporal changes in cerebral transcriptome that influences the neurologic outcome after stroke. In addition to protein-coding RNAs, many classes of noncoding RNAs including long noncoding RNAs (LncRNAs) also undergo changes in the post-stroke brain. We currently evaluated the functional significance of an LncRNA called Fos downstream transcript (FosDT) that is cogenic with Fos gene which was observed to be significantly elevated after cerebral ischemia in rodents.

Material and methods: Focal ischemia was induced in adult SHR rats by transient middle cerebral artery occlusion (MCAO). FosDT was silenced with a siRNA cocktail. Post-ischemic motor deficits were evaluated with rotarod, beam walk and adhesive removal tests between 1 to 7 days after ischemia. Infarct volume was estimated using Cresyl violet-stained brain sections. Expression of Fos, FosDT and the down-stream genes was evaluated with real-time PCR. Binding of FosDT to CMPs was evaluated with RNA immunoprecipitation.

Results and conclusion(s): Focal ischemia induced expression of FosDT and Fos in rat. Ischemia also induced the expression of chromatin-modifying proteins (CMPs) REST and its corepressor partners, coREST and MeCP2, and increased binding of FosDT with coREST and Sin3a. Interestingly, siRNA knockdown of FosDT attenuated the post-ischemic induction of both FosDT and Fos without affecting the levels of REST. FosDT knockdown also significantly ameliorated the post-ischemic motor deficits and reduced the infarct volume. Furthermore, FosDT knockdown derepressed REST-downstream genes GRIA2, NFκB1 and GRIN1 in the post-ischemic brain. Thus, FosDT induction and its interactions with REST-associated CMPs, and the resulting regulation of REST-downstream genes might modulate ischemic brain damage. LncRNAs such as FosDT can be therapeutically targeted to minimize post-stroke brain damage.

Funded by grants from American Heart Association and US National Institute of Health.