HuR's interaction with lincBRN1a and lincBRN1b is implicated in neuronal stem cells differentiation

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LncRNAs play crucial roles in cellular processes but their regulatory effects in the adult brain and neural stem cells (NSCs) remain to be entirely characterized. Interestingly, it has been shown that genetic ablation of specific lncRNAs can cause strong impairments in mouse brain's development.

Here, we demonstrate that 10 lncRNAs (LincENC1, FABL, lincp21, HAUNT, PERIL, lincBRN1a, lincBRN1b, HOTTIP, TUG1 and FENDRR) are deregulated during murine NSCs differentiation. By RNA immunoprecipitation assay we show that they interact with the RNA binding protein ELAVL1/HuR. Furthermore, we characterized the function of two of the deregulated lncRNAs, lincBRN1a and lincBRN1b, during NSCs' differentiation. Their inhibition obtained by siRNA approach leads to the induction of differentiation, with a concomitant decrease in stemness and increase in neuronal markers, indicating that they exert key functions in neuronal cells differentiation. The treatment with the transcriptional inhibitor actinomycin D allowed the evaluation of the half-lives of these RNA molecules. Moreover, we found that the HuR's inhibition, by siRNA or by using the specific pharmacological inhibitor dihydrotanshinone I, leads to the modification of lincBRN1a and lincBRN1b's decay rates both in NSCs and in differentiated cells. We also identified six human homologs of the ten lncRNAs studied in mice and we report their deregulation during human iPSCs differentiation into neurons.

Our results show that lincBRN1a and lincBRN1b play a role in NSCs biology influencing their differentiation capabilities, as the alteration of their levels may have an effect on this process. Moreover, we report that the inhibition of HuR's interaction with the analyzed lncRNAs leads to neural differentiation, suggesting a complementary role for the lncRNAs and HuR in stemness. The study of their expression in human iPSCs differentiation into neurons suggest that our results could also be applied to human neuronal development.