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Unveiling Transcription Factors Driving Astrocyte Functional Development by Integrated Analysis

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Astrocytes are prominent glial cells within the mammalian brain that have critical functions such as metabolic support of neurons, synaptic homeostasis, circuit homeostasis, blood-brain barrier maintenance, and immune responses. In light of the functional significance of astrocytes, there is a notable gap in our understanding of the factors that regulate the acquisition and execution of their functions and their association with brain pathology. To unveil the factors driving the development of astrocyte functions, we conducted a longitudinal characterization of transcriptome and epigenome of Aldh1l1^{+} astrocyte from mouse cortices. Through integrated analysis with fine temporal resolution spanning from embryonic day 16 (E16) to postnatal day 30 (P30), we identified 50 transcription factor candidates potentially governing astrocyte development. Analysis of chromatin interaction using Hi-C on accessible regulatory DNA (HiCAR) infers the gene regulatory networks and elucidates that TF candidates including *Egr1*, *Nr3c1*, and *Stat3* drive the astrocyte functions, such as neuronal support and neuroinflammatory response. Notably, these regulatory networks highlight potential pathological associations between astrocyte differentiation and neurological diseases such as seizures, bipolar disease, and multiple sclerosis. In particular, *Nr3c1* plays a role in maturing the immune-responsive functions in astrocytes, and its dysfunction is linked to pathological conditions of multiple sclerosis. This study offers insights into molecular candidates and their roles in astrocyte development.