LEF-1 ISOFORMS IN NEURAL STEM CELL QUIESCEENCE

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In the adult mammalian brain newborns neurons are constantly generated mainly in two regions so-called neurogenic niches due to the existence of neural stem cells (NSCs) (1,2). NSCs persist in a quiescent state for long periods of time and a delicate balance between NSC quiescence and activation is required to supply the demands of the adult brain throughout life. Previously, we demonstrated that bone morphogenetic protein 4 (BMP4) acting through the canonical BMP/BMPR1A signaling is required to regulate NSC quiescence (3). Recently, our lab has described a convergence between BMP and WNT pathways at the level of the T-cell factor/lymphoid enhancer factor gene Lef1 (4). LEF1 is a transcription factor that is expressed during development and is mainly restricted to lymphocyte populations (5, 6) and other cell types of brain (7). The Lef1 mRNA is alternatively spliced to give rise to different LEF1 protein isoforms with different functions (6). Alternative Splicing (AS) is a post-transcriptional mechanism that promotes protein diversity among other functions (8). In this study, we identify that active and quiescent NSCs are enriched in different LEF1 isoforms generated through AS. It well known that AS is controlled in a negative or positive manner by several factors. CUGBP Elav-Like Family Member 2 (CELF2), a RNA binding protein that negatively regulates Lef1 AS (9, 10), is overexpressed in quiescent NSCs. On the other hand, we explore a possible role of LEF1 on the regulation of specific target genes by studying the presence of LEF1 motifs in quiescence-specific enhancers.