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BIOLOGICAL RELEVANCE OF YAP REGULATION BY WNT SIGNALING DURING NEURAL TISSUE PATTERNING OF HUMAN INDUCED PLURIPOTENT STEM CELLS

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Human induced pluripotent stem cells (hiPSCs) have special ability to self-assemble into neural microtissues or mini-organ like structures (e.g., mini-brains). In this process, Wnt signaling impacts regional patterning and positional identity of hiPSC-derived neural progenitors. One important function of Wnt signaling is to regulate Yes-associated protein (YAP) expression (nuclear or cytoplasmic), the pivotal regulator of cell proliferation and differentiation during organ growth and tissue generation. However, the crosstalk between Wnt and YAP expression during neural differentiation of hiPSCs has not been well investigated. The objective of this study is to reveal the capability of Wnt signaling in the regulation of YAP expression to modulate 3-D neural microtissue formation from hiPSCs. Human iPSK3 cells were induced toward neural lineages through embryoid body formation. Wnt signaling was activated using CHIR99021, which was found to induce nuclear localization of YAP. CHIR99021 treatment upregulated the expression of HOXB4, the marker for hindbrain/spinal cord, while in the absence of Wnt activation, the cells maintained rostral forebrain neural identity (expression of TBR1) (by RT-PCR analysis and immunocytochemistry). Modulation of YAP expression with cytochalasin D also influenced neural cell identity, indicating bi-directional interactions of Wnt signaling and YAP expression. The perturbation of neural patterning was also evaluated by incorporating the neural spheres with microparticles. This study should advance our understanding on the biological processes regulated by Wnt signaling and YAP activity during neural tissue patterning. The results have the significance in neurological disease modeling, drug screening, and neural tissue regeneration.

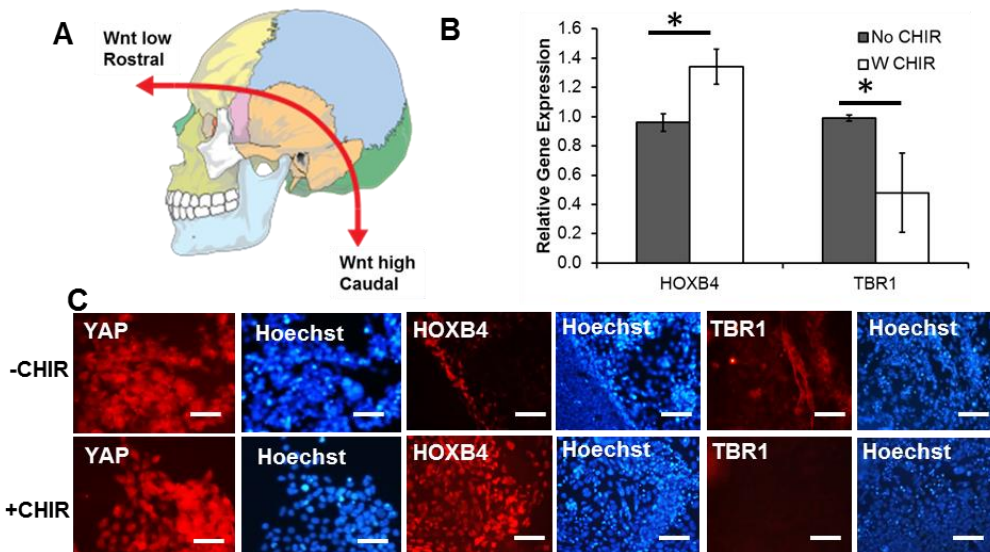


Figure 1 – The influence of Wnt signaling on neural tissue patterning. (A) Illustration of the effect of Wnt signaling on neural tissue identity. (B) RT-PCR analysis of TBR1 and HOXB4 gene expression (day 23). (C) Expression of HOXB4 (hindbrain marker) and TBR1 (forebrain cortical marker) in neural cells derived from human iPSK3 cells regulated by Wnt activator CHIR99021 (CHIR). Scale bar: 50 μ m. * p -value <0.05.