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Rapid induction and long-term self-renewal of primitive neural precursors from human embryonic stem cells by small molecule inhibitors.

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Abstract

Human embryonic stem cells (hESCs) hold enormous promise for regenerative medicine. Typically, hESC-based applications would require their *in vitro* differentiation into a desirable homogenous cell population. A major challenge of the current hESC differentiation paradigm is the inability to effectively capture and, in the long-term, stably expand primitive lineage-specific stem/precursor cells that retain broad differentiation potential and, more importantly, developmental stage-specific differentiation propensity. Here, we report synergistic inhibition of glycogen synthase kinase 3 (GSK3), transforming growth factor β (TGF- β), and Notch signaling pathways by small molecules can efficiently convert monolayer cultured hESCs into homogenous primitive neuroepithelium within 1 wk under chemically defined condition. These primitive neuroepithelia can stably self-renew in the presence of leukemia inhibitory factor, GSK3 inhibitor (CHIR99021), and TGF- β receptor inhibitor (SB431542); retain high neurogenic potential and responsiveness to instructive neural patterning cues toward midbrain and hindbrain neuronal subtypes; and exhibit *in vivo* integration. Our work uniformly captures and maintains primitive neural stem cells from hESCs.

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