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Article

Functional Maturation of hPSC-Derived Forebrain Interneurons Requires an Extended Timeline and Mimics Human Neural Development

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Highlights

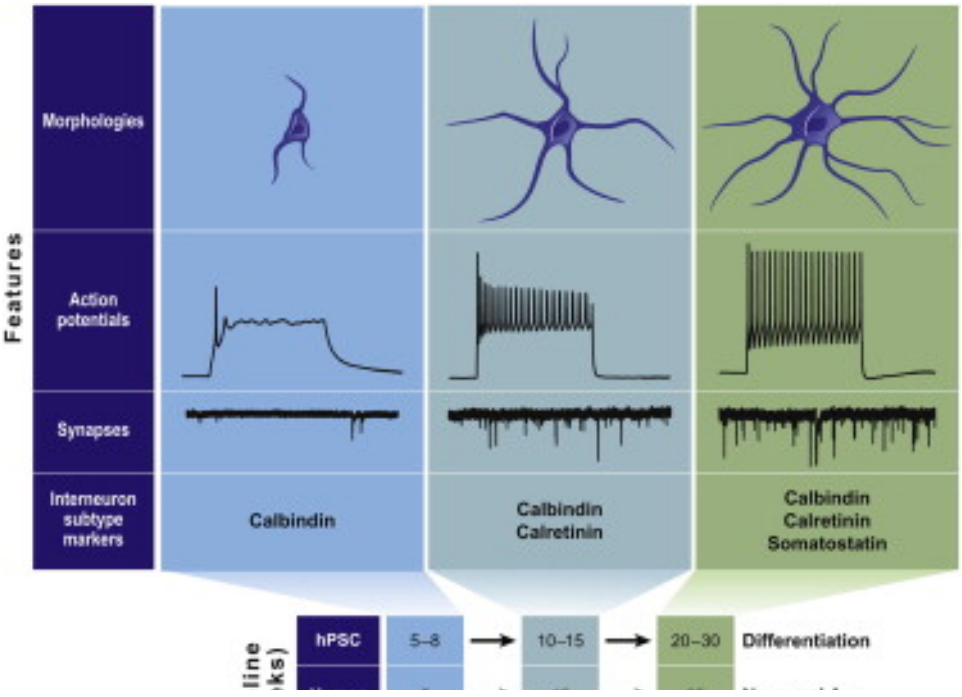
- â€¢ hPSC-derived MGE-like GABAergic interneurons model human neural development
- â€¢ MGE-like progenitors display human-enriched radial glial stem cell complexity

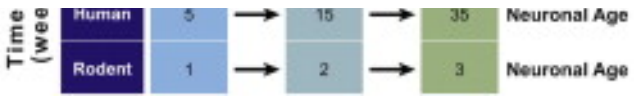
- â€¢ MGE-like cells exhibit protracted maturation into functional interneuron subtypes
- â€¢ MGE-like cells mature and functionally integrate postinjection in the mouse brain

Summary

Directed differentiation from human pluripotent stem cells (hPSCs) has seen significant progress in recent years. However, most differentiated populations exhibit immature properties of an early embryonic stage, raising concerns about their ability to model and treat disease. Here, we report the directed differentiation of hPSCs into medial ganglionic eminence (MGE)-like progenitors and their maturation into forebrain type interneurons. We find that early-stage progenitors progress via a radial glial-like stem cell enriched in the human fetal brain. Both inÂ vitro and posttransplantation into the rodent cortex, the MGE-like cells develop into GABAergic interneuron subtypes with mature physiological properties along a prolonged intrinsic timeline of up to 7Â months, mimicking endogenous human neural development. MGE-derived cortical interneuron deficiencies are implicated in a broad range of neurodevelopmental and degenerative disorders, highlighting the importance of these results for modeling human neural development and disease.

Graphical Abstract





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