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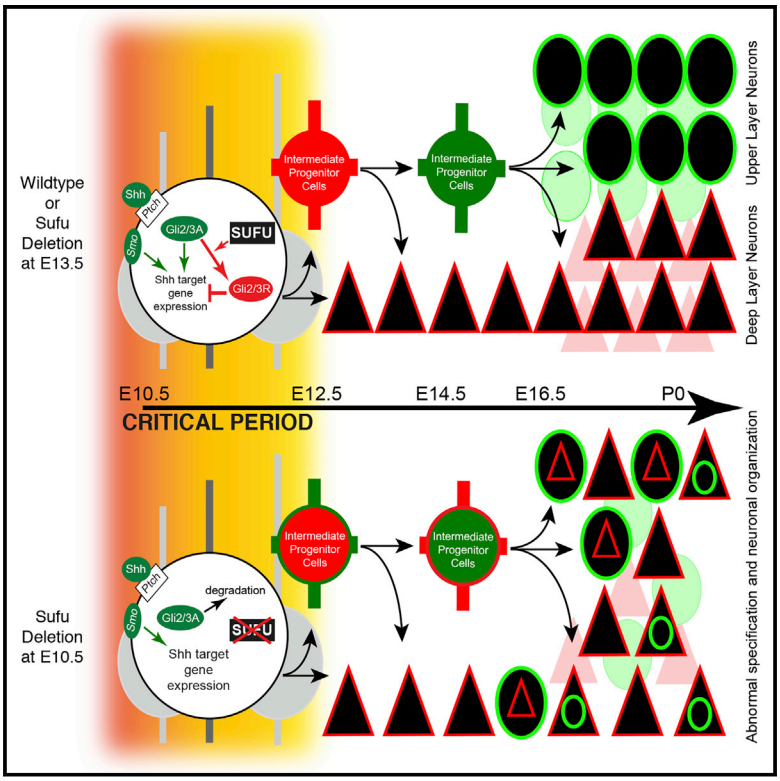
Suppressor of Fused Is Critical for Maintenance of Neuronal Progenitor Identity during Corticogenesis

Graphical Abstract



Highlights

- Sufu maintains cortical progenitor identity
- Sufu inhibits Shh signaling to specify cortical progenitors and its neuronal progenies
- Early inhibition of Shh signaling is needed to generate distinct neuronal lineages

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In Brief

Specification of cortical progenitors and subsequent differentiation into specific neuronal lineages requires execution of unique molecular programs at precise time points. In this study, Yabut et al. identify a critical role for Suppressor of Fused (Sufu) early in corticogenesis to maintain neocortical progenitor identity by regulating Shh signaling.

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Suppressor of Fused Is Critical for Maintenance of Neuronal Progenitor Identity during Corticogenesis

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SUMMARY

Proper lineage progression and diversification of neural progenitor cells (NPCs) ensures the generation of projection neuron (PN) subtypes in the mammalian neocortex. Here, we show that Suppressor of Fused (Sufu) controls PN specification by maintaining the identity of NPCs in the embryonic neocortex. Deletion of Sufu in NPCs of the E10.5 mouse neocortex led to improper specification of progenitors and a reduction in intermediate progenitors (IPs) during corticogenesis. We found that Sufu deletion resulted in unstable Gli2 and Gli3 activity, leading to the ectopic activation of Sonic hedgehog (Shh) signaling. The role of Sufu in maintaining progenitor identity is critical at early stages of corticogenesis, since deletion of Sufu at E13.5 did not cause similar abnormalities. Our studies revealed that Sufu critically modulates Shh signaling at early stages of neurogenesis for proper specification and maintenance of cortical NPCs to ensure the appropriate generation of cortical PN lineages.

INTRODUCTION

The mammalian neocortex consists of six cortical layers (layers I–VI) of molecularly and functionally distinct glutamatergic excitatory neurons (projection neurons, or PNs) controlling cognition, sensory perception, and motor control. PNs are generated in a tightly regulated inside-out order in the embryonic dorsal telencephalon, such that deep layer PNs are generated prior to upper layer PNs. Whereas deep layer PNs are derived directly from multipotent radial glial cells (RGCs) within the ventricular zone (VZ) or indirectly from intermediate progenitors (IPs) residing within the subventricular zone (SVZ), upper layer PNs largely originate from IPs (Englund et al., 2005; Kowalczyk et al., 2009; Noctor et al., 2004; Vasistha et al., 2014). To date, questions remain on the mechanisms regulating PN specification from RGCs or IPs.

Recent studies indicate that unique transcriptional programs exist and contribute to the heterogeneity of RGCs in the dorsal telencephalon to influence the fate of its progenies. For example, the basic-helix-loop-helix (bHLH) transcription factors Neurogenin1 and Neurogenin2 (Neurogenin1/2) control the specification of RGCs into deep layer PNs early in neurogenesis but require the transcription factors Pax6 and Tlx for specification of upper layer PNs (Schuurmans et al., 2004). The transcription factor Fezf2 is required in RGCs to specify corticofugal PNs that eventually populate layers V and VI (Chen et al., 2008; Molyneaux et al., 2005). A subset of Cux2-expressing RGCs has also been identified; these RGCs divide to generate IPs and give rise to layer II/III neurons (Franco et al., 2012), although whether this represents a distinct subset of limited-fate progenitors is controversial (Eckler et al., 2015). Thus, the fates of RGC progenies are, at least partially, determined prior to terminal differentiation by molecular events that regulate progenitor behavior that are yet to be completely elucidated.

Suppressor of Fused (Sufu) is a cytoplasmic protein with critical roles in mammalian development. Sufu knockout mice fail to survive past embryonic day 9.5 (E9.5), indicating an essential role in early mammalian development (Cooper et al., 2005; Svärd et al., 2006). At later stages, Sufu plays an important role in the development of specific CNS structures. In the mid-hindbrain, Sufu regulates the processing of the transcription factor Gli3 into its repressor (Gli3R) to influence cerebellar patterning, morphogenesis, and neuronal migration (Kim et al., 2011). In the developing spinal cord, Sufu regulates the stability of full-length Gli2 and Gli3 (Gli2A and Gli3A) and their cleavage into repressor forms (Gli2R and Gli3R) to regulate dorsoventral patterning and neuronal differentiation (Liu et al., 2012). Additionally, Sufu is a known target of Sox10 transcription factors to regulate the generation of oligodendrocyte lineages (Pozniak et al., 2010).

Sufu regulates Gli proteins primarily to antagonize Sonic hedgehog (Shh) signaling, an evolutionarily conserved pathway crucial in CNS development (Matise and Wang, 2011). Shh signal transduction begins when extracellular Shh binds to the transmembrane protein Patched (Ptch), relieving its repressive effects on Smoothened (Smo). Smo is a primary positive signaling element triggering a cascade of intracellular events that lead to