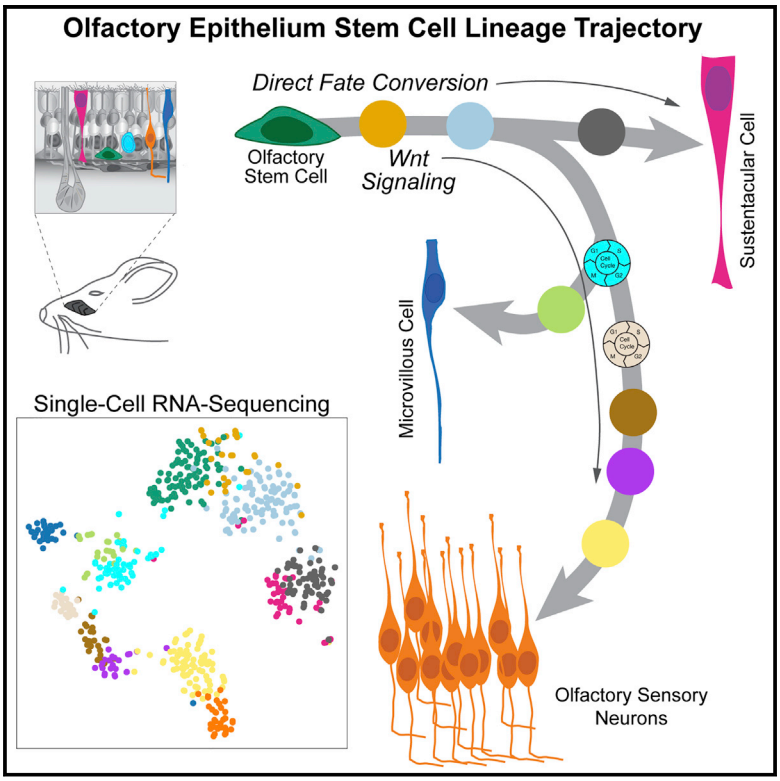
Article

Cell Stem Cell

Deconstructing Olfactory Stem Cell Trajectories at Single-Cell Resolution

Graphical Abstract



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In Brief

The olfactory epithelium is a site of active neurogenesis. Fletcher et al. combine single-cell transcriptomics and clonal lineage analysis to trace cell fates from the multipotent olfactory stem cell and identify multiple mechanisms controlling cell fate, including direct conversion of quiescent stem cells into support cells without cell division.

Highlights

- Multiple lineage trajectories were mapped from olfactory stem cells
- Sustentacular cells can arise by direct fate conversion without cell division
- Multipotency is generated through unipotent fate decisions of single stem cells
- Canonical Wnt signaling activates stem cells toward the neuronal fate

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Deconstructing Olfactory Stem Cell Trajectories at Single-Cell Resolution

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SUMMARY

A detailed understanding of the paths that stem cells traverse to generate mature progeny is vital for elucidating the mechanisms governing cell fate decisions and tissue homeostasis. Adult stem cells maintain and regenerate multiple mature cell lineages in the olfactory epithelium. Here we integrate single-cell RNA sequencing and robust statistical analyses with in vivo lineage tracing to define a detailed map of the postnatal olfactory epithelium, revealing cell fate potentials and branchpoints in olfactory stem cell lineage trajectories. Olfactory stem cells produce support cells via direct fate conversion in the absence of cell division, and their multipotency at the population level reflects collective unipotent cell fate decisions by single stem cells. We further demonstrate that Wnt signaling regulates stem cell fate by promoting neuronal fate choices. This integrated approach reveals the mechanisms guiding olfactory lineage trajectories and provides a model for deconstructing similar hierarchies in other stem cell niches.

INTRODUCTION

A fundamental challenge in stem cell biology is to define both the cell fate potential of a given stem cell and where cell fates are specified along a developmental trajectory. Moreover, detailed lineage trajectory maps are necessary for identifying the regulatory networks that govern the cell fate transitions underlying tissue maintenance and regeneration and are essential for designing strategies to manipulate cells for therapeutic applications. Lineage tracing—a technique for permanently labeling the descendants of a targeted cell—has long been established as a powerful tool for elucidating the cell fate potential of progenitor cells (Dymecki and Tomasiewicz, 1998; Le Douarin and Teillet, 1974; Price et al., 1987; Weisblat et al., 1978; Zinyk et al., 1998). However, this approach alone cannot readily identify all intermediate stages in a lineage or pinpoint when, in a branching lineage, multiple cell fates arise.

Whole-transcriptome profiling of single cells by RNA sequencing (single-cell RNA-seq) has recently emerged as a powerful method for discriminating the heterogeneity of cell types and cell states in a complex population (Wagner et al., 2016). New statistical approaches have further enabled the ordering of cells along developmental lineages based on gradual changes in gene expression detected at the single-cell level (Trapnell et al., 2014). However, current approaches struggle to overcome the challenge of identifying where lineages diverge in more complex branching trajectories of multipotent progenitors, a problem that is only beginning to be addressed (Setty et al., 2016). Importantly, even the most sophisticated analysis of single-cell RNA-seq data can only provide predictions that require independent experimental validation.

The olfactory epithelium maintains a steady-state population of mature olfactory sensory neurons via continual neurogenesis in the postnatal animal (Graziadei and Graziadei, 1979b; Mackay-Sim and Kittel, 1991). Olfactory neurogenesis is normally sustained through differentiation of globose basal cells (GBCs), which are the actively proliferating neurogenic progenitor cells in the niche (Caggiano et al., 1994; Graziadei and Graziadei, 1979b; Schwob et al., 1994). Upon targeted destruction of the sensory neurons or more severe injury to the entire tissue, the olfactory epithelium can regenerate (Graziadei and Graziadei, 1979a). Following such injury, horizontal basal cells (HBCs)—the normally quiescent, reserve stem cells of the niche—become activated to differentiate and reconstitute all major cell types in the epithelium (Iwai et al., 2008; Leung et al., 2007; Figure 1A).