NEUROGENESIS

Same path, different beginnings

An extensive single-cell transcriptomic collection of over 30,000 cells of the developing hippocampus shows that adult hippocampal neurogenesis follows the same differentiation path as embryonic neurogenesis, but the cell of origin differs. This work provides an invaluable resource with important implications for neuronal regeneration.

Ben W. Dulken and Anne Brunet

The generation of new neurons (neurogenesis) from neural stem cells occurs both embryonically and in the adult brain, raising the intriguing question of how adult neural stem cells differ from their embryonic counterparts. Adult neurogenesis is critical for aspects of learning and memory and for repair after stroke[1], but it is restricted to a few discrete regions, including the dentate gyrus of the hippocampus, which is involved in aspects of spatial learning and memory, and the subventricular zone, which gives rise to neurons in the olfactory bulb[1]. Adult neural stem cells are relatively quiescent and restricted in their progeny. The limited nature of adult neurogenesis contrasts with that of embryonic neurogenesis. Indeed, embryonic neural stem cells (called radial glia) rapidly proliferate to expand the neural pool during embryogenesis, and they are responsible for generating the full complement of diverse neuronal subtypes found in the adult brain[2]. Previous work in the subventricular zone has shown that radial glia give rise to adult neural stem cells, though there are profound transcriptomic differences between radial glia and adult neural stem cells[3,4]. In the hippocampus, however, the relationship between the embryonic and adult stem cells is still a puzzle[3], and solving it could help harness the potential of these regenerative cells in adults.

Here Hochgerner and colleagues[5] provide important insight into the relationship between developmental and adult hippocampal neurogenesis. Using two different single-cell RNA-sequencing platforms (10x Genomics Chromium and Fluidigm C1) at over 20 different developmental time points, they sequenced over 30,000 cells from developing and adult mouse hippocampi (a previous study had profiled the hippocampal neurogenic region[6], but with only hundreds of cells and only in adults). They then used state-of-the-art clustering methods to identify cell types and assess how they change over time, establishing the relationship between embryonic, postnatal and adult hippocampal neurogenesis. The authors show that the state of neural stem cells transforms at a critical juncture after birth, from radial glia to 'radial glia-like' cells, but that their immediate progeny and differentiation paths are strikingly similar (Fig. 1). The authors show this not only via conducting clustering analysis but also by performing differential expression between key cell types in the embryonic and adult states. For example, differential expression between radial glia cells in the embryo and radial glia-like cells in the adult revealed distinct expression patterns, including the upregulation of genes associated with astrocytes, such as *Atp1a2* and *Gstm1*, in the radial glia-like state. In contrast, differential expression between neural stem cell progeny (proliferating neural progenitors) in embryonic, postnatal and adult states reveals very few transcriptional differences between these states. Although the sensitivity of single-cell RNA-sequencing may not be sufficient to identify differences between progenitor cells, these results indicate a striking similarity in the differentiation path between embryonic and adult states.

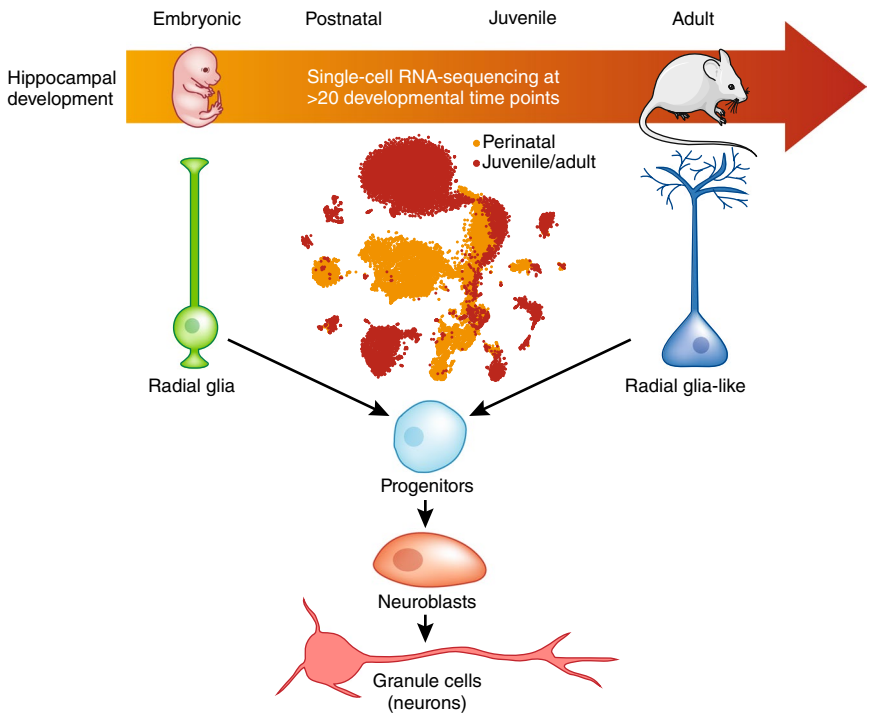

Fig. 1 | Relationship between embryonic and adult hippocampal neurogenesis as defined by single-cell RNA-sequencing technology.

Another fascinating question that can be addressed by single-cell technology is whether subtypes of cells were previously missed. Hochgerner and colleagues identify heterogeneity within what was previously thought to be a homogenous cell population: the hippocampal progenitor cells. They demonstrate that proliferative hippocampal progenitors exist in several states of differentiation. This is similar to what was previously found in the adult hippocampal and subventricular zone

neurogenic niches[6–8], supporting the notion that heterogeneity exists within populations previously believed to be homogeneous. This study also highlights the power of single-cell technology to identify more specific markers to identify these new states. For example, the authors identify novel marker combinations to mark radial glia-like cells and proliferative progenitors in vivo in the hippocampus, including *Tfac2c*, a transcription factor involved in morphogenesis and cell cycle control[9]. The ability to selectively mark specific cell populations in the neurogenic lineage, especially those with stem cell potential, could ultimately be instrumental for the therapeutic use of these cells, including transplantation.

Although single-cell RNA-sequencing is an incredibly powerful tool for profiling the transcriptomic composition of a niche or tissue at a single point in time, it is hard to infer direct lineage relationships from single-cell data. More work will be needed to support the relationships between the cell types identified in this study, for example by performing lineage tracing or by coupling single cell analysis with CRISPR–Cas9 tagging technology[10]. The present datasets in fact provide several markers that could be used in lineage tracing experiments and can serve as a tool kit for genetically tracing the source of adult neural stem cells.

This study also has important implications for aging and disease. During aging, neurogenesis declines, and this is associated with an age-related cognitive and sensory deterioration[11]. Could adult neurogenesis be stimulated in aged individuals to counter neurodegeneration or injury? Knowing the molecular relationships between neural stem cells at different stages could suggest mechanisms by which adult neural stem cells could be reverted into a more youthful, regenerative state. Conversely, glioblastoma, an aggressive cancer of glial cells in the adult brain, may represent a reversion of adult astrocytes or stem cells to a more embryonic-like proliferative state[12], and the datasets presented in this study may facilitate the development of strategies to suppress malignant proliferation of these cells and return them to a more dormant state. This work may also provide insight into infectious diseases, such as Zika virus. In mouse models, Zika virus infection causes severe microcephaly in developing fetuses by inhibiting the proliferation of radial glia cells and inducing early differentiation[13]. Due to the similarities between embryonic and adult neurogenesis identified by Hochgerner and colleagues[5], Zika infection postnatally may also impair neurogenesis, thereby triggering cognitive defects that may not yet be fully appreciated. On the other hand, the differences between embryonic radial glia cells and adult neural stem cells may impact susceptibility to Zika infection or downstream effects, and those differences could perhaps be exploited to develop new therapies.

This work also raises the crucial question of whether this developmental timeline is conserved in humans. Sustained neurogenesis in the hippocampus in humans is believed to be important for maintaining cognitive and memory function[14], but the study of human adult neurogenesis has been challenging. Consensus on the extent and importance of adult neurogenesis in humans has been elusive, perhaps because the structure and behavior of neurogenic niches is not directly equivalent between humans and mice[15,16]. Single-cell sequencing technologies have been applied to human neuronal differentiation[14], but so far only in prenatal states, and of course in vivo lineage tracing cannot be done in humans. Thus, applying single-cell technologies to postmortem human brains from individuals of different ages might help resolve these long-standing controversies about human neurogenesis and perhaps even uncover new populations with neurogenic potential.

By providing a comprehensive molecular characterization of the cell types present in the hippocampal formation across many life stages, this study illuminates how the processes of embryonic and adult neurogenesis are related. This work also provides the community with an invaluable transcriptomic account of hippocampal neurogenesis through time, and this will undoubtedly inspire novel hypotheses and experiments to examine how adult neurogenesis could be harnessed to counter aging, brain injury or disease. ❐

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Published online: 25 January 2018
https://doi.org/10.1038/s41593-017-0063-3

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Competing interests

The authors declare no competing financial interests.