The crucial difference is that in the work of Barik *et al.*, the transport is topological, and photons can be routed through bends with negligible backscattering. This feature opens up an exciting new playground for the implementation of integrated quantum networks. Efficient manipulation of photons at the quantum level requires low-loss routers and beam splitters, which are now easily accessible owing to the technology developed by Barik *et al.* Possible upcoming steps based on this kind of topological circuit include on-chip optical isolation, generation of emitter-emitter entanglement, and the implementation of integrated quantum gates (*13*).

Before getting to these applications, some challenges must be overcome. The topological protection of the phase discovered by Kane and Mele (*5*) actually relies on the fermionic nature of electrons, which flip their spin under a fermionic time-reversal transformation. This is not the case for photons, which are bosons. To circumvent this problem, Wu and Hu (*9*) introduced an additional symmetry in the system, a hexagonal geometry. The combination of time-reversal symmetry and the hexagonal C_{6v} geometry mimics the fermionic time-reversal behavior. A price must be paid, in that the topological channel is not immune to disorder in the shape of the hexagons forming the lattice. Only those bends with C_{6v} symmetry (60°, 120°, 240°, and 300°) are immune to backscattering. How these constraints affect the extension to larger and more elaborate quantum networks remains an open question.

Haldane ended his Nobel prize lecture in December 2016 (*14*) by pointing out that "a large experimental and theoretical effort is underway to find and characterise [...] new [topological] materials, study entanglement, and dream of new 'quantum information technologies.'" The work of Barik *et al.* is an important step in this direction. ■

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DEVELOPMENT

Revising concepts about adult stem cells

Imaging adult neurogenesis reveals surprising behavior of progenitor cells

By **Magdalena Götz**

The term "stem cells" is one of the most disputed terms in science. The general definition that stem cells are at the origin of a lineage, self-renewing and multipotent—generating all cell types of a given tissue or even organism (if totipotent)—is agreed upon. But how many cell divisions are required to be called a stem cell? Among the adult stem cells, hematopoietic stem cells are the champions because they can repopulate the immune systems of five generations of mice, living beyond the life of the organism from which they originated. But what about neural stem cells (NSCs), the founder cells of all cells in the central nervous system? Are a few cell cycles of self-renewal, such as nine in embryonic neurogenesis of the neocortex (*1*), sufficient to call them stem cells? And how many different cell types need to be generated by a stem cell? Do cells making only neurons, as occurs in embryonic neurogenesis, qualify as stem cells (*2*)? However, when cultured in vitro, they generate neurons and several other glial cell types, which qualifies them as multipotent (*2*). This is also the case for adult NSCs, but their behavior in vivo is even less well understood. On page 658 of this issue, Pilz *et al.* (*3*) track, for the first time, adult NSCs live in the mammalian brain, gaining exciting new insights that prompt revision of how we define stem cells.

During development, NSCs are radial glial cells (RGCs) defined by their radial morphology and glial hallmarks. Interestingly, adult NSCs also resemble RGCs in morphology and share traits with mature astroglial cells (*2*). However, the adult mammalian brain is largely devoid of NSCs, which are restricted to a few niches, such as the dentate gyrus (DG). This poses the fascinating question of when and how it is determined that neurogenesis continues in one region of the brain but not another. Adult NSCs persist, owing to RGCs dividing in specific modes and becoming quiescent (nondividing) at surprisingly early developmental stages (*4*). This highlights one of many differences between embryonic and adult neurogenesis, namely the speed of cell division (*5*). Adult RGCs divide slowly and generate neurons in specific niches, whereas the generation of glial cells prevails in the remaining adult brain. Conversely, embryonic neurogenesis is widespread and precedes gliogenesis. During developmental neurogenesis, the newly generated neurons connect and mature together, whereas neurons generated in adulthood need to integrate into a preexisting network. This integration serves as a role model for neuronal replacement therapies, such as those aiming to replace degenerated neurons in Parkinson's disease or after stroke (*6*, *7*).

> ***"TAPs are key not only for regulating the output of adult neurogenesis but also in development and evolution when they become more frequent."***

But how does all this occur? How often do RGCs truly self-renew? How hierarchical is lineage progression, and are RGCs the only cells to self-renew? From analyses in fixed brains, it is predicted that RGCs generate an intermediate, transit-amplifying progenitor (TAP). These cells amplify their own population before going on to generate neurons. TAPs have lost the radial morphology and glial hallmarks of NSCs, but little is known about how often they divide and in which mode.

These processes can best be understood by direct observation. Because regions of adult neurogenesis are buried deep in the brain of mammals, live imaging of adult neurogenesis was first performed in zebrafish, a species with an everted telencephalon that exposes adult NSCs to the brain surface (*8*). This revealed the unexpected direct conversion of an RGC into a neuron without any cell divi-

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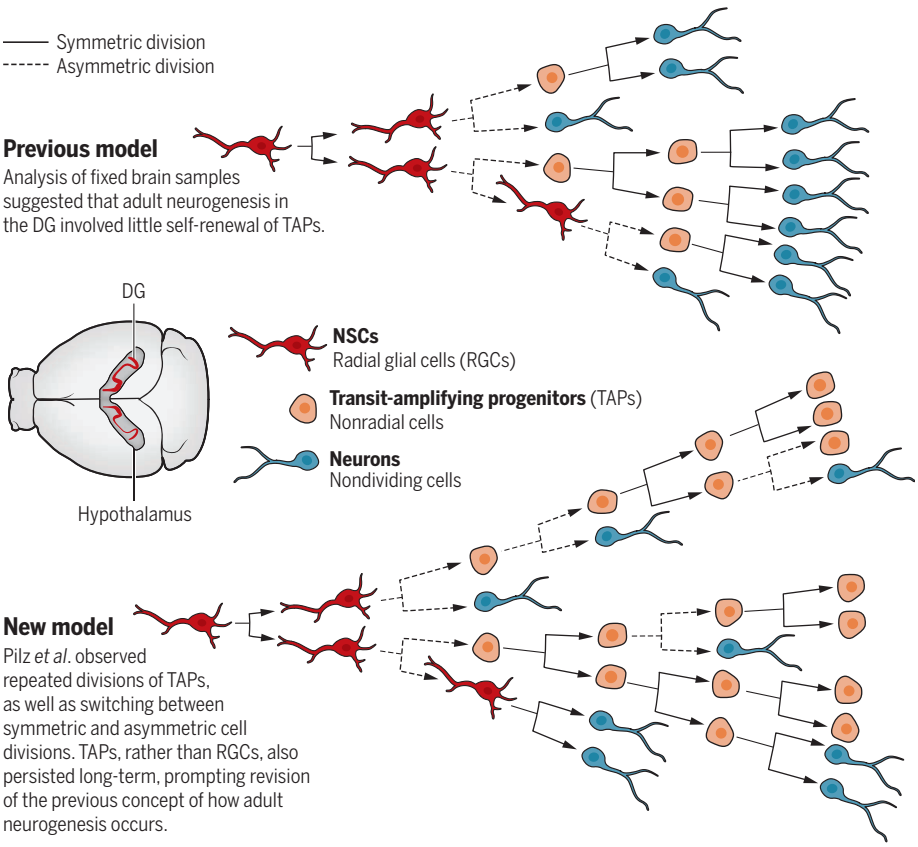
Constructing neural cell lineages

Adult neurogenesis is restricted to a few niches in the mammalian brain, including the DG. RGCs are NSCs, the origin of neural lineage trees that are capable of asymmetric or symmetric divisions to self-renew. However, Pilz *et al*. reveal that RGC progeny, nonradial cells or TAPs, can also undergo asymmetric or symmetric divisions to self-renew or amplify the cell population. Thus, these TAPs have some stem cell characteristics.



sion, but the extent to which this also occurs in mammals is unknown.

Pilz *et al*. imaged adult neurogenesis in the mammalian DG by removing the overlying neocortex to get visual access to RGCs sparsely labeled by Achaete-scute homolog 1 (Ascl1)–driven expression of green fluorescent protein. Dividing RGCs and all their progeny were followed by daily imaging for up to several months. The RGCs underwent typically two to three cell divisions with initial symmetric or asymmetric self-renewing divisions (producing two or one RGCs, respectively), followed by a final self-depleting symmetric division generating two nonradial daughter cells (see the figure). This is consistent with previous clonal analysis in mouse brain sections (*9*, *10*), whereas others have proposed long-term RGC self-renewal (*11*). Importantly, the imaging analysis followed Ascl1-expressing RGCs, whereas other subtypes of RGCs that do not express Ascl1 may be more prone to long-term self-renewal.

The biggest surprise came when observing the direct progeny of the RGCs that were expected to amplify the population by dividing symmetrically. However, Pilz *et al*. demonstrated that they also divide asymmetrically, producing a neuronal daughter and an apparently self-renewing mother cell. As they divided much more than RGCs and with the ability to stochastically switch between asymmetric (with one differentiating daughter) and symmetric (self-renewing or amplifying) division, their behavior may qualify them as NSCs. Thus, TAPs are becoming more similar to stem cells, as in other organs (*12*). These findings also have repercussions for the part of the definition that asserts that stem cells are the origin of a lineage. Because cells not at the top of the lineage tree, like TAPs, meet some criteria of stem cells, this part of the definition may also need to be revisited, including reconsidering the unidirectional aspect of lineage trees.

Another interesting observation was an early wave of cell death during adult neurogenesis, apparently regulated by intrinsic factors. This is deduced from the observation that entire branches of a lineage are prone to die and that cell death occurs independent of location. This fascinating finding provokes questions about what these intrinsic factors might be.

These data also allow for further comparisons between neurogenesis in development and adulthood. No in vivo imaging is available for neurogenesis in mammalian embryos, but in the developing zebrafish, amplification by TAPs is rare, and if TAPs exist, they divide only once (*13*, *14*). However, the sequence of symmetric self-renewing divisions of RGCs followed by asymmetric divisions generating a neuron and an RGC is also prevailing in developmental neurogenesis. Interestingly, while RGCs in adult neurogenesis obey this rule, TAPs do not.

However, especially in the developing mammalian brain, there are some regions with a large population of TAPs, such as in the telencephalon. In these regions, TAPs also exhibit an intriguing behavior, with increasingly faster cell cycles in each subsequent round of cell division, whereas RGCs divide much slower (*15*). In the adult DG, RGCs divide as fast as TAPs, which do not change their cell cycle duration with subsequent divisions. Moreover, adult DG TAPs switch between symmetric and asymmetric division—a behavior unprecedented in the nervous system so far. Thus, the behavior of TAPs is another difference between embryonic and adult neurogenesis.

TAPs are key not only for regulating the output of adult neurogenesis but also in development and evolution when they become more frequent. Indeed, there is little lineage amplification in adult zebrafish forebrain neurogenesis, allowing the direct conversion of RGCs to neurons that was not observed in the adult mammalian DG. Thus, the mechanisms regulating the emergence of indirect neurogenesis with an ever-enlarging and stem cell–like TAP population are of prime importance for brain expansion and for neuronal output in adult neurogenesis. Given that such TAPs can readily replenish the stem cells at the origin of the lineage tree in some organs (*12*), such as the intestine, it is important to watch them in an injury paradigm and be prepared for further surprises. ■

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