Geminin halts DNA synthesis

Once is enough when it comes to DNA replication—for every cell cycle, chromosomes are replicated just one time to prevent genomic instability. On page 473, Melixetian et al. identify a protein that polices this limitation in human cells. The replication police officer is Geminin, which prevents replication origins in *Xenopus* from recruiting licensing proteins that can give the replication go-ahead. In frogs, Geminin does not work alone, as its loss does not induce rereplication. But in human cells, the authors find, Geminin runs the show.

Rereplicating cells accumulated foci of proteins that bind to double-stranded DNA breaks. The foci might be a result of colliding replication forks that are recognized as breaks. Whatever their genesis, they resulted in activation of the DNA damage checkpoint controlled by the CHK1 kinase, thus preventing entry into mitosis.

If the checkpoint was then turned off, the cells entered mitosis but died before division was complete. If cells lacking Geminin couldn’t somehow escape the checkpoint and yet survive (through other unknown mutations), they would be a cancerous nightmare, complete with genomic instability and uncontrolled proliferation.

Slingshot to the lamellipod

The actin cytoskeleton at the front of migrating cells is an ever-changing species. Although actin is polymerized in the lamellipod, the filaments that are built remain dynamic. Their turnover is mediated by cofilin, which stimulates filament disassembly at or near the pointed ends, thus providing monomers for further polymerization. On page 465, Nagata-Ohashi et al. show that actin filaments take care of their own dynamic behavior via Slingshot-1L (SSH1L), a phosphatase that activates cofilin.

In vitro, F-actin activated SSH1L 10-fold. Migrating epithelial cells accumulated SSH1L (and thus dephosphorylated and active cofilin) in the lamellipod, and this depended on an intact actin assembly.

To bind to F-actin and activate cofilin, SSH1L must first be released from an interaction with 14–3-3 proteins, which sequester SSH1L in the cytoplasm. SSH1L escaped this interaction when it was dephosphorylated. This dephosphorylation could be induced with the extracellular migratory signal, NRG.

Restricting SSH1L activity to the F-actin–rich lamellipod may help to maintain polarized migration by allowing more stable actin structures, such as stress fibers, to persist at the rear of the cell. Cofilin was recently shown to be capable of defining the direction of cell migration (Ghosh et al. *Science*. 304:743–746). Now, the authors need to determine whether this function requires the F-actin–mediated activation of SSH1L.

NG2+ cells feed the brain

The brain is a rapidly changing landscape. After birth, its alterations require a source of progenitors that can form different cell types. In an attempt to characterize these progenitors, Aguirre et al. (page 575) have identified a population of neural stem cells (NSCs) that make inhibitory neurons in the postnatal mouse brain.

Neurogenesis is common in an area of the brain known as the subventricular zone (SVZ), so this seemed like a likely place to find NSCs. The same laboratory had previously shown that cells expressing the NG2 proteoglycan, once thought to give rise only to oligodendrocytes, could form active neurons in vitro. They now find that a portion of NG2-expressing cells that reside in the SVZ are these NSCs, which contribute to neurogenesis in the postnatal brain.

Some of the SVZ NG2+ cells also expressed proteins that mark stem cell populations. These cells were the progenitors of hippocampal neurons. The group isolated NG2+ cells from the brain of one mouse and transplanted them into the lateral ventricle of a host mouse. Weeks later, progeny of the transplanted cells that ended up in the white matter had formed oligodendrocytes. But those found their way to the hippocampus had become fully functional and integrated inhibitory interneurons.

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The inhibitory neurons formed by NG2+ NSCs are the same type of cells that degenerate in a common childhood form of epilepsy. The next step is to determine whether transplanted NG2+ cells can regenerate these lost neurons in a mouse model of the disease.