nonhematopoietic tumors although we first need to identify the specific growth and differentiation factors for such tissues. Furthermore, we know very little about the signals that control self-renewal and proliferation of pluripotent stem cells (*22*, *23*). If, indeed, PTEN controls self-renewal and proliferation of neuronal stem cells, then this protein could be used to harvest increased numbers of these cells for research. The Groszer *et al.* findings also provide insight into how neuronal stem cells remain pluripotent. Perhaps stem cell pluripotentiality could be maintained by expressing activated PKB/AKT or other components of signaling pathways that are suppressed by PTEN. PTEN may also be important for maintaining the pluripotentiality of other types of stem cells.

One striking feature of stem cells is their ability to self-renew, a property that also defines cancer cells. Tumors often originate through the transformation of stem cells, and it has been postulated that stem cell transformation, self-renewal, and proliferation may be controlled by the same signaling pathways (*22*). The notion that the tumor suppressor PTEN, which is mutated in many different human tumors, may regulate neuronal stem cell renewal and proliferation is very exciting. One could speculate that loss of PTEN in tumors would help them to become pluripotent, although PTEN loss is often a late event in tumor formation (*21*). The conditional PTEN-mutant mice develop macrocephaly and perturbed neuronal patterning, so loss of PTEN alone is insufficient to drive transformation and there must be an additional mutational event for brain tumors to develop. If this hypothesis is correct, then D5 lipid phosphatases such as SHIP1, which control proliferation and differentiation of hematopoietic progenitor cells, must also have tumor suppressor activity.

From a therapeutic standpoint, transient inactivation of PTEN could provide a booster shot for a rare stem cell population needed to treat certain neurodegenerative diseases. The caveat is that such an approach would have to circumvent the procancer consequences of PTEN inactivation in other cell types. If we have indeed found our modern Holy Grail, then we must be sure that it does not harbor poison.

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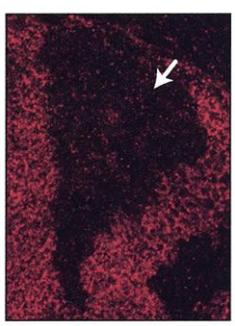
NOTA BENE: BIOMEDICINE

In the Nic of Time

Alzheimer's disease (AD), the most common neurodegenerative disease of old age, is characterized by two types of deposits in the brain: amyloid plaques and tau tangles. Amyloid plaques are composed of short, sticky β-amyloid peptides formed by aberrant cleavage of an amyloid precursor protein (APP) at a site in its transmembrane domain. The enzyme responsible for this aberrant cleavage is a mysterious γ-secretase that has yet to be fully characterized. The favored candidate is a transmembrane protein called presenilin that is mutated in some patients with an early-onset form of AD. But there are also other contenders, including nicastrin, a transmembrane protein that associates with presenilin in a giant, multisubunit complex that has γ-secretase activity. A trio of recent papers (*1*–*3*) confirms that nicastrin is indeed essential for activity of the γ-secretase complex, but the reports differ when it comes to speculating about what nicastrin actually does in the cell.



The humble fruit fly has proved to be a boon for those interested in AD because a membrane-tethered signaling protein called Notch, which is essential for normal fly development, must be cleaved by γ-secretase before it can transduce signals. Cleavage releases an intracellular fragment that moves to the nucleus and alters the transcription of target genes required for development. Using mutant flies deficient in nicastrin (*nic*), the three groups examined the effects of a lack of nicastrin on the cleavage of Notch by γ-secretase. They found that *nic* mutant flies could not cleave Notch (or other substrates including APP). This resulted in a series of developmental abnormalities—such as large notches and thickened veins in the wings, and altered segregation of neuroblasts—that were indistinguishable from the abnormalities seen in flies deficient in either Notch or presenilin.

The finding that nicastrin is essential for γ-secretase activity does not prove that it is proteolytically active. So, what does nicastrin do? Chung and Struhl (*1*) discovered that in the absence of nicastrin, presenilin could not move to the apical plasma membrane of the cell, the location where γ-secretase cleavage of Notch usually takes place (see the figure). They suggest that nicastrin may be required for the subcellular trafficking of presenilin (or another γ-secretase component) or for assembly of the complex itself. Hu *et al.* (*2*), on the other hand, propose that nicastrin (either on its own or bound to substrate) may be important for the stabilization or maturation of presenilin. Using small RNAs to interfere with nicastrin activity in cultured fly cells, this group showed that loss of nicastrin activity was accompanied by decreased accumulation of the mature form of presenilin.

Supporting the Hu *et al.* proposal is the work of López-Schier and St. Johnston (*3*), which hints that nicastrin may be important for the long-term stability of presenilin. But perhaps even more intriguing is the claim by the third group that nicastrin is necessary for maintaining the integrity of the cell's spectrin cytoskeleton. In both nicastrin-deficient and presenilin-deficient fly cells, the normal distribution of α-spectrin and β-spectrin was disrupted. The former increased in apical regions of the cell, whereas the latter disappeared from these regions altogether. Through control experiments, the investigators showed that the disruption in spectrin organization was independent of Notch signaling, suggesting that both nicastrin and presenilin do something else besides helping γ-secretase to cleave Notch and APP. That two central components of the γ-secretase complex seem to be important for another cellular process hints that γ-secretase inhibitors under development for the treatment of AD may have harmful side effects.

—ORLA SMITH

References and Notes

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