In This Issue

**RB pockets the cell cycle**

Widely used cancer therapies inflict collateral damage on normal dividing cells. But now Lohez et al. (page 67) find a way to distinguish normally cycling cells from cancer cells using actin inhibitors that cause an RB-dependent cell cycle arrest.

High levels of actin inhibitors prevent cell cleavage and thus lead to a doubling of cellular DNA and subsequent cell death. However, cells usually sense the problem and halt the cell cycle in G1.

The authors found that very low levels of actin inhibitors that do not affect most cellular processes still induce a reversible G1 arrest. This sensitive response requires the function of RB pocket proteins (RB, p107, and p130) but is independent of p53.

The arrest may arise because the drug-treated cells believe that they are contact inhibited. As in contact-inhibited cells, membrane ruffling is suppressed and levels of NF2/merlin increase. NF2/merlin is an actin-associated tumor suppressor protein that is related to the cytoskeletal linkers ezrin, radixin, and moesin. It has been shown to mediate G1 arrest in response to contact inhibition, and may function in a similar manner in response to low levels of actin inhibitors.

Low doses of actin inhibitors should selectively arrest normal cells but not tumor cells, which generally lack an RB-dependent G1 arrest. Follow-up treatments that induce the death of cycling cells should then effectively target tumor cells. Lohez et al. do not directly test this scheme, but use slightly higher actin cycling cells should then effectively target tumor cells. Lohez et al. do not directly test this scheme, but use slightly higher actin levels of actin inhibitors.

**Life in a low calcium home**

Life without Ca\(^{2+}\)—a vital enzyme cofactor and essential second messenger—is no life at all. Consider then the challenge faced by *Plasmodia*, the causal agent of malaria. These parasites spend most of their life inside red blood cells, whose cytoplasmic levels of Ca\(^{2+}\) are far too low to support their survival. On page 103, Gazarini et al. now show that *Plasmodia* get around this problem by maintaining a high Ca\(^{2+}\) level within the parasitophorous vacuole (PV), their home in the red blood cell.

Previous studies suggested that the PV membrane (PVM) was something of a sieve, and that the ionic environment inside it should be similar to the host cytoplasm. The researchers tested this by using indicator dyes to measure Ca\(^{2+}\) levels in the cytosol and inside the PVM. They found that *Plasmodia* maintain local Ca\(^{2+}\) levels that are 100–1,000 times higher than those in the red blood cell cytoplasm—easily enough to supply their internal stores. Those stores are essential for regulation of parasite activity, including a Ca\(^{2+}\)-based signaling system that responds to the host hormone melatonin. Ca\(^{2+}\) is also required for parasite maturation, as even a temporary two hour decrease in PV Ca\(^{2+}\) concentration strongly decreased the number of *Plasmodia* that developed to the infectious stage.

It is not yet clear how Ca\(^{2+}\) levels are kept so high in the PVM. The orientation of the host plasma membrane is inverted to form the PVM during parasite invagination, so inverted Ca\(^{2+}\)-ATPase pumps from the host membrane may be able to pump Ca\(^{2+}\) into the PVM. A drug that interferes with this PVM Ca\(^{2+}\) accumulation without affecting the red blood cells themselves might be a valuable tool in our arsenal against this devastating parasite.

**APP causes an energy crisis**

Although the normal occupation of the transmembrane amyloid precursor protein (APP) is not fully understood, its rogue activity is well documented. An APP cleavage product known as A\(\beta\) accumulates in plaques and tangles that are the hallmark of Alzheimer’s disease (AD). Anandatheerthavarada et al. now report that APP is also targeted to and can damage mitochondria (page 41).

The researchers realized that APP carries a dual zip code that can send a protein to either the endoplasmic reticulum or the mitochondria. Although the amount of APP that normally gets sent to mitochondria is small, they found a significant amount of it there in studies of both cultured cells and transgenic AD mice.

An acidic domain in APP causes the protein to get stuck in the mitochondrial transport channels. This impairs mitochondrial energy output, probably because it blocks the import of normal freight. These problems correlate with the mitochondrial dysfunction and sharp decrease in energy output seen in AD patients, implicating a new pathway of APP-mediated neuronal injury in AD.

Factors that increase the targeting of APP to mitochondria are under investigation. At present, APP is not known to have a normal function in mitochondria. But if targeting of APP to the cell powerhouse is something of an accident, it is certainly a very costly one.