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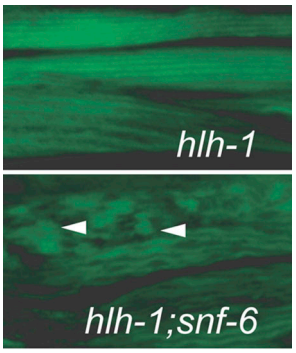


Kim/Macmillan

Without the SNF-6 acetylcholine transporter (bottom) mutant muscles fall apart.

Dystrophic muscles get overexcited

Loss of adhesion is a primary suspect for the underlying cause of muscular dystrophy (MD). Muscles from individuals with MD look like they are pulling themselves apart, and they are mutant for various members of the dystrophin-glycoprotein complex (DGC), which links intracellular actin to extracellular laminin. But now, Hongkyun Kim, Steven McIntire (University of California, San Francisco, CA), and colleagues suggest that loss of the DGC results in loss of an associated neurotransmitter transporter, thus leading to overexcitation of MD muscles.

Kim was screening for alcohol-resistant worms when he chanced upon the transporter mutants. Like worms mutant for the dystrophin homologue *dys-1*, the *snf-6* mutants bent their heads excessively when they tried to move fast. Wild-type SNF-6 protein promoted uptake of the neurotransmitter acetylcholine into transfected cells, and is needed in muscle cells, presumably to mediate similar uptake.

The *snf-6* mutants showed higher neuronal responses downstream of repeated (but not individual) electrical stimuli. Loss of dystrophin or its partner syntrophin resulted in delocalized SNF-6 in older worms, and SNF-6 coimmunoprecipitated with worm syntrophin.

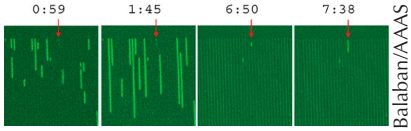
Adhesion may still be important in MD pathology, as the group does not yet know whether all DGC components are in the correct place and functioning properly in the *snf-6* mutant. Teasing apart the transporter and adhesion functions may be easier in mammalian systems, although the worm system is still a promising approach for exploring downstream effectors of MD disease. ■

Reference: Kim, H., et al. 2004. *Nature.* 430:891–896.

Slow but steady wins the drug race

Bacteria that survive antibiotic assaults fall into two groups: resistant mutants; and the more mysterious persistent cells. Persisters, a known entity since 1944, survive the intial burst of antibiotics but unlike mutants may succumb to later treatments. Nathalie Balaban (now at Hebrew University, Jerusalem, Israel), Stanislas Leibler (Rockefeller University, New York, NY), and colleagues now find that persisters are a constant presence in the population—a slow-growing minority that acts as a reserve population in case of chemical attack.

The alternative explanations for persisters are legion. They might be completely dormant, or normal cells caught in a protected part of the cell cycle when the antibiotic arrives, or a state induced in response to antibiotic treatment. Balaban and colleagues looked at the behavior of single cells immobilized in a microfluidic device and saw that the few cells surviving antibiotic treatment were growing slowly even before the drug was added.



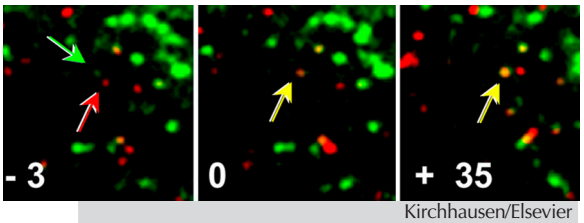
Balaban/AAAS

A slow-growing variant cell (arrow) can escape ampicillin (present at 6:50).

Extrapolating from the behavior of two mutants that produce an excess of persisters, the team deduced that wild-type cells make persisters both in response to time spent in stationary phase and at a constant rate during normal growth. Persisters escape their sluggish state at a slow but appreciable rate.

For basic researchers, the persistence pathway offers a bacterial example of an alternative phenotypic state, and one that is somehow generated at a low, constant frequency. For clinicians,the pathway may present a target for drugs that would get rid of the few bacteria left after conventional antibiotic treatments. ■

Reference: Balaban, N., et al. 2004. *Science*. doi: 10.126/science.1099390.



Kirchhausen/Elsevier

A preexisting clathrin coat (green) and cargo (red) encounter each other.

Clathrin starts off alone

A detailed visualization of clathrin dynamics by Marcelo Ehrlich, Tomas Kirchhausen (Harvard Medical School, Boston, MA), and colleagues reveals that two events—the initiation of clathrin-mediated endocytosis and recognition of cargo—are distinct. It appears that clathrin-coated pits start to form randomly but collapse unless stabilized, perhaps by cargo capture.

The Boston team marked clathrin and the AP-2 adaptor using fusions that allowed dynamic behavior, and collected complete datasets that were quantified automatically. The intensity of clathrin spots grew over time, with most reaching a critical point at ~20 s. By then the curvature of the clathrin triskelions may become unsupportable without bolstering by other proteins. If labeled cargo joined the spots by then or soon after then, the spot continued to grow; but otherwise the spot dissipated without the burst of dynamin accumulation characteristic of endocytosing vesicles.

Apart from a few large, inactive regions, placement of pits was random and did not favor sites of previous pit formation. This suggests that static pit-forming factories do not exist. An as-yet-unidentified pit-initiating protein is, however, a distinct possibility.

Kirchhausen says the random formation is reminiscent of the random probing by dynamic microtubules, which are stabilized only if they happen to encounter their target proteins. The source of stabilization for clathrin coats remains uncertain. Cargo binding may induce a conformational change in an adaptor, thus strengthening links from adaptors to clathrin or other proteins. ■

Reference: Ehrlich, M., et al. 2004. *Cell.* 118: 591–605.