Salmonella sneaks past security

Certain gut cells can leave resident bacteria alone but respond selectively to invaders. Satoshi Uematsu, Shizuo Akira, and colleagues (Osaka University, Japan) suggest that gut cells achieve this differentiation by using a special, pathogen-specific receptor called the Toll-like receptor 5 (TLR5). But the pathogenic Salmonella typhimurium turns the situation around: events triggered by the special receptor help the bug to invade its host.

TLRs, which are expressed on professional antigen-presenting cells, recognize common pathogen-associated molecules and trigger innate immunity. TLR5 on dendritic cells recognizes bacterial flagellin protein in vitro, but its function in vivo was previously unknown.

Akira’s team found that TLR5 mRNA was highly expressed in the mouse intestine particularly in a specific subpopulation of antigen-presenting lamina propria cells (CD11c+ LPCs). In these cells, TLR5 was necessary for bacterial flagellin to induce inflammatory cytokines, yet when the team infected TLR5−/− mice with Salmonella, a flagellated bacterium, these mice were unexpectedly resistant to the bug.

It was not, however, invasion of the CD11c+ LPCs that showed a difference. In the gut, Salmonella invaded the CD11c+ LPCs in both TLR5+/+ and TLR5−/− mice. However, in the TLR5−/− mice, fewer bacteria-laden CD11c+ LPCs moved from the intestinal tract to the mesenteric lymph nodes, probably because the LPCs failed to be activated by the bacteria. These mice had more resistance to systemic infection—fewer bacteria reached their livers and spleens—but it is not yet clear whether a similar tactic of TLR5 blocking would work in humans.


Transforming antibiotic treatment

Antibiotic-resistant bacteria are an ever-evolving medical concern. Now, Marc Prudhomme, Laetitia Attaiech, Jean-Pierre Claverys, and colleagues (CNRS, Toulouse, France) report that antibiotics increase genetic exchange and the chance for adaptation in Streptococcus pneumoniae by activating its transformation pathway. The findings highlight the danger of inappropriate antibiotic use.

Transformation (the uptake and genomic integration of exogenous DNA) in S. pneumoniae can only occur when the bacteria are competent. Competence is a transitory state in bacteria. Although its regulation is rather well understood, the signals that trigger it remain elusive. Recent evidence suggests that in S. pneumoniae competence is a stress response to environmental change. Claverys’s team therefore wondered whether antibiotic-induced stress might trigger competence.

Out of the dozen or so antibiotics that the team checked, six up-regulated the competence pathway when used at concentrations that killed approximately 50% of the bacteria. These antibiotics kill bacteria by either damaging DNA, inhibiting protein synthesis, or blocking DNA synthesis. Thus, the mechanism of action of a particular antibiotic cannot be used to predict its ability to induce competence.

Approximately 40% of the human population carry S. pneumoniae asymptomatically in the nose and throat. If the bacteria invade other tissues, however, severe diseases such as pneumonia, meningitis, and osteomyelitis can develop. Two of the antibiotics found to induce competence are commonly used to treat respiratory tract infections. Although the generation of antibiotic-resistant bacteria cannot be completely prevented, choosing antibiotics that do not promote genetic exchange may help to minimize future problems.

Nucleotides: saviors of the cell

Nucleotides are the building blocks of DNA and the cell’s energy currency. Now, a report by Dhyan Chandra, Dean Tang (University of Texas, Smithville, TX), and colleagues reveals that these multifunctional molecules are also bodyguards, protecting healthy cells from apoptosis.

The apoptotic cascade unfolds when failing mitochondria leak cytochrome c (cyt c), which then binds to and oligomerizes the caspase activator called Apaf1. Previous experiments showed that low concentrations of nucleotides, in the form of ATP or dATP, were needed for cyt c to bind to Apaf1.

The new results show that higher concentrations of ATP prevent apoptosis. At these higher levels, which match those found in healthy cells, the nucleotides bound up cyt c, thus preventing it from attaching to its Apaf1 partner.

The inhibition was overcome by artificially increasing cyt c levels or decreasing nucleotide concentrations. In healthy cells, sufficient nucleotide levels probably prevent small mitochondrial leaks from triggering death by sequestering the cyt c, thus preventing it from attaching to its Apaf1 partner.

Low nucleotide levels, the group also shows, are induced by apoptotic signals and anticancer drugs such as etoposide. ATP production probably drops as a result of mitochondrial injury, but what causes the levels of the other nucleotides to drop is unclear as yet.


The fragility factor

Prion proteins with the same amino acid sequence but different biophysical and biochemical structures show different pathological severities. A study of a yeast prion model, by Motomasa Tanaka, Jonathan Weissman, and colleagues (University of California, San Francisco, CA) reveals that a prion’s power is determined by aggregate stability—or, rather, lack of it.

Prions replicate by recruiting their normally folded counterparts into large aggregate fibers, which then break up to form new prion particles, capable of recruiting and converting further normal forms. A shortened version of the yeast protein Sup35, called SupNM, can misfold into various prion forms. These forms seed aggregates that result in phenotypes of reproducibly different strengths.

To investigate the basis for this difference, Weissman’s team looked at how fast the Sup-NM-derived aggregate fibers elongated. Contrary to expectations, they found that the most potent form, Sc4, had the slowest growth. However, this slow growth was accompanied by increased amyloid fragility—the fibers fell apart more often.

The potency of the Sc4 form was thus explained not by aggregate size or growth rate but instead by its propensity to break into new infectious prion particles. If the same physical basis of infectivity holds true for mammalian prions, then designing therapies that stabilize prion aggregates might slow or even stop disease progression.

It would be of interest to determine whether the specific structure of the Sc4 form could explain its increased aggregate fragility. Indeed, such experiments are “high on our list,” says Weissman.


Positioning proteasomes

Activity produces waste, so it makes sense to position waste disposal facilities close to sites of activity. Baris Bingol and Erin Schuman (California Institute of Technology, Pasadena, CA) have discovered that neurons do just that, recruiting proteasomes to active dendritic spines.

Dendritic spines must construct and destroy many proteins as they respond to synaptic excitation. Protein synthesis machinery has been shown to sit locally in spines to make protein when needed. Indication that the degradation machinery (proteasomes) might also serve its function locally came from Bingol’s discovery that adjacent synapses in the same neuron contained different amounts of proteasome.

Investigating the dynamics of this varied distribution, the team observed that excitation of neurons drove proteasomes from the shafts to the spines within minutes. Proteasome levels then remained high in the spines for up to an hour. Ubiquitinated proteins, targeted for destruction, also initially increased, but shortly thereafter decreased as the proteasomes arrived and got to work. Thus, the study shows that proteasomes are dynamic machines that are capable of moving toward their targets.

The increase in spine proteasome levels was due partly to recruitment and mostly to sequestration, and excitation led to an increased association of proteasomes with the actin cytoskeleton, suggesting a possible mechanism for activity-dependent localization. Investigating the molecular mechanics of actin binding would be the sensible next step, says Bingol.