

Fighting Fluoride

RIBOSWITCH HELPS BACTERIA TOSS OUT TOXIC FLUORIDE.

Since the early 1950s, fluoride has been added to toothpaste, mouthwash, and water to strengthen tooth enamel and prevent tooth decay by killing bacteria. Now, research by HHMI investigator Ronald R. Breaker shows how bacteria that live inside the mouth respond to this toxic ion.

Breaker's lab group at Yale University studies a type of noncoding RNA, called a riboswitch, that helps turn genes on and off. Riboswitches are attached to the genes they regulate; if a gene is involved in the production of a certain compound, the riboswitch usually is sensitive to that compound. If the level of the compound gets too high or too low, the riboswitch can cause more or less of it to be made.

Recently, Breaker and his colleagues discovered a riboswitch attached to several genes with a diverse set of functions. Curious about the riboswitch's job, the scientists put the RNA in a test tube and added different compounds, observing whether the substances bound to the riboswitch. They worked through a long list of chemicals before accidentally stumbling upon fluoride—the ion was a contaminant in one sample they were testing.

Once the team learned their riboswitch interacted with fluoride, they determined that some of the genes controlled by the RNA are involved in removing fluoride from a cell. Breaker explains that when

fluoride builds up to toxic levels in a cell, a riboswitch binds to fluoride and turns on genes that can overcome its effects by transporting it out of the cell.

Because genes associated with fluoride-sensitive riboswitches are found in many types of bacteria, fungi, and plants, the research team concluded that these RNAs and the genes they control may represent components of an ancient system that cells have evolved to deal with toxic levels of this ion. The researchers published their findings January 13, 2012, in *Science*.

“Our data not only help explain how cells fight the toxicity of fluoride, the results also give us a sense of how we might enhance the antimicrobial properties of fluoride,” says Breaker. For example, the researchers showed that deleting the fluoride channel makes cells 200 times more sensitive to fluoride. ■ —NICOLE KRESGE



Bacteria, such as streptococcus, use an RNA switch to turn on genes that fight off toxic fluoride.

IN BRIEF

That figure, Dong notes, amounts to about 10 percent of the genes in *Arabidopsis thaliana*, a member of the mustard family that she studies. The team reported its findings January 24, 2012, in *Current Biology*.

TBF1's widespread effects raise a question—how do plants turn it on and off? “TBF1 controls so many genes you don't want it around when it's not necessary,” Dong says. The mechanism is surprisingly intricate. One factor is NPR1, which has a reciprocal relationship with TBF1—each protein regulates the other's gene. Sequences in the TBF1 mRNA can also sense the metabolic changes that occur during pathogen invasion and trigger TBF1 production.

NEW WEAPON AGAINST PROSTATE CANCER

Patients with advanced forms of prostate cancer undergo treatment with drugs that suppress the growth of cancer cells by targeting the androgen receptor. Unfortunately, many patients develop resistance to the drugs, and their cancer returns. Now, a compound developed by HHMI investigator Charles Sawyers of Memorial Sloan-Kettering Cancer Center may give these patients a fighting chance.

Sawyers and his team discovered that a compound called RU59063 binds to the androgen receptor about 100 times more strongly than bicalutamide, a current drug for prostate cancer. The scientists made a series of tweaks to RU59063 and created a compound—MDV3100—that was able to shrink drug-resistant tumors in mice. In a phase III clinical trial, men treated with MDV3100 had a median survival about 5 months longer than men treated with a placebo. On the basis of the trial results, which were reported in February at the American Society of Clinical Oncology Genitourinary Cancers meeting, it is anticipated that a drug application will be filed with the FDA later this year.

Sawyers, meanwhile, is continuing his research on MDV3100. “One of the key questions we're trying to pin down is how does MDV3100 change the structure of the androgen receptor once it is bound to it,” he says. “We also want to know how tumors might escape from MDV3100, so we can be ready with the next drug.”

DELAYING ALZHEIMER'S MEMORY LOSS

New research from an HHMI investigator shows that blocking a molecule called

HDAC2 might delay the memory loss associated with Alzheimer's disease.

HDAC2 is an enzyme that turns off genes by removing chemical groups from histones—the protein spools around which DNA is wrapped. Li-Huei Tsai of the Massachusetts Institute of Technology showed that in mice with neurodegeneration and in patients with Alzheimer's disease, HDAC2 levels are increased in certain areas of the brain. In these regions, HDAC2 binds to a host of memory genes and dampens their expression. As Tsai and her team report in *Nature* on February 29, 2012, blocking the expression of HDAC2 in the brain increases the number of functioning neurons, thereby improving memory. The scientists also showed that amyloid beta and oxidative stress—key features of Alzheimer's disease—can activate a protein called glucocorticoid receptor 1, which, in turn, can switch on the expression of HDAC2.

“The striking thing is that amyloid beta has a very, very acute effect in elevating HDAC2 expression, but then the consequences can be very long term,” says Tsai. This mechanism could explain why clinical trials of drugs that clear out amyloid beta in people with Alzheimer's haven't worked very well, she adds.