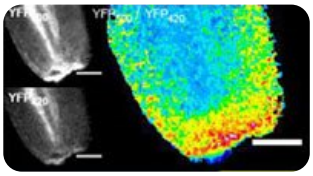
Hydrogen peroxide marshals immune system

When you were a kid your mom poured it on your scraped finger to stave off infection. When yo got older you might have even used it to bleach your hair. Now there's another possible functior for this over-the-counter colourless liquid: your body might be using hydrogen peroxide as an envoy that marshals troops of healing cells to wounded tissue.



In the zebrafish tail fin imaged here, a small wound is inflicted at the tip of the fin. Red represents high concentrations of hydrogen peroxide and blue represents low concentrations. The chemical burst far exceeds the single cell diameter and reaches well into the surrounding tissue. Click here to view video.

Using the zebrafish as an animal model, researchers in the lab of Harvard Medical School professor of systems biology Timothy Mitchison and Dana Farber Cancer Institute professor Thomas Look have discovered that when the tail fins of these creatures are injured, a burst of hydrogen peroxide is released from the wound and into the surrounding tissue. Teams of rescue-working white blood cells respond to thi chemical herald, crawl to the site of damage, and get to work.

"We've known for quite some time that when the body is wounded, white blood cells show up, and it's reall a spectacular piece of biology because these cells detect the wound at some distance," says Mitchison. "But we haven't known what they're responding to. We do know something about what summons white blo cells to areas that are chronically inflamed, but in the case of an isolated physical wound, we haven't really known what the signal is."

These findings are reported in the June 4 issue of the journal *Nature*.

Can hurt - or help

Philipp Niethammer, a postdoc in Mitchison's lab, and Clemmens Grabber, a postdoc in Look's lab, initiate this research project with no interest in wound healing. Rather, they were studying a group of molecules called reactive oxygen species, or ROS. These small oxygen-derived molecules, of which hydrogen peroxide is one, have the potential to be both helpful and hurtful. Niethammer and Grabber were simply curious to find ways to detect ROS molecules in an organism.

To do this, they took a gene engineered to change colour in the presence of hydrogen peroxide and inserted it into zebrafish embryos. Once the embryos entered the larvae stage after a few days, this synthetic gene spread throughout the entire body, essentially "wiring" the fish so that any discreet location which hydrogen peroxide appears would glow.

But how do you coax the fish to produce a reactive chemical like hydrogen peroxide in the first place?

Hydrogen peroxide arrives first

Since white blood cells have long been known to produce hydrogen peroxide, one obvious way to initiate chemical production would be to inflict a small wound onto the fish, and then, using microscopy, observe patterns of this chemical as white blood cells gathered around the wound. But much to the researchers' surprise, they found that hydrogen peroxide immediately appeared at the wound site, prior to the arrival of any white blood cell, and quickly disseminated into neighbouring tissue.

They repeated the experiment, this time in zebrafish where they'd disabled a protein that was previously discovered to produce hydrogen peroxide in the human thyroid gland. Not only did hydrogen peroxide not appear at the wound site, but white blood cells failed to respond to the injury.

Eureka!

"This was our real eureka! moment," says Niethammer. "We weren't too surprised that we could block hydrogen peroxide production through this technique, but what we didn't expect at all was that white blood cells wouldn't respond. This proved that the white blood cells needed hydrogen peroxide to sense the wound, and move towards it."

Of course, zebrafish are not people, and while our genomes share many similarities with these tiny fish, it isn't yet clear that natural selection has conserved this process throughout the evolutionary family tree. Still these findings offer something of a conceptual shift in how to view human conditions where hydrogen peroxide plays a role.

"When we look at how hydrogen peroxide works in people, this really starts getting intriguing," says Mitchison.

Worth pursuing

In the human body, hydrogen peroxide is produced primarily in three places: lung, gut, and thyroid gland. Because hydrogen peroxide, and the proteins responsible for producing other ROS molecules, are especially present in lung and gut, the researchers hypothesize that human diseases relevant to these findings would include any in the lung and gut that involve disproportionate levels of white blood cells, like asthma, chronic pulmonary obstruction, and some inflammatory gut diseases.

"Our lungs are supposed to be sterile; our guts are anything but," says Mitchison. "It's very logical that both those tissues produce hydrogen peroxide all the time. Perhaps in conditions like asthma, the lung epithelia producing too much hydrogen peroxide because it's chronically irritated, which, if our findings translate to humans, would explain inappropriate levels of white blood cells. This is certainly a question worth pursuing

Mitchison is currently laying the groundwork for investigating this hypothesis.

hms.harvard.edu