Scientists find hole in immune defenses

Researchers in Switzerland report the existence of a flaw in the body's immune system that allows some kinds of foreign material to evade that system, usually so efficient at seeking out, identifying and destroying invaders.

The flaw is associated with the body's self-protective mechanisms, which are built to distinguish between proteins that are naturally part of the body and the "nonself" proteins that come from the outside. If, for example, certain nonself proteins are present on a cell, the immune-system cells know a virus has invaded that cell and it must be destroyed.

But in order not to attack its own cells, the body has to learn which proteins belong to it and which don't. If a foreign protein is similar enough to one of the body's own proteins, the invader can escape detection by the immune system, report Damir Vidović and Polly Matzinger, of the Basel (Switzerland) Institute for Immunology, in the Nov. 17 NATURE.

Other researchers have proposed that such a flaw might exist, but Vidović and Matzinger are the first to find a foreign protein that actually mimics a native protein, Matzinger says. Two other types of holes in the immune system have been spotted before.

One type occurs when the receptor that recognizes foreign proteins is defective. Another type is found where foreign proteins physically can't combine with native proteins that mark the body's own cells. Such a foreign protein/marker protein combination is required to alert certain immune cells.

The newly discovered flaw probably doesn't allow disease-causing organisms to slip through the body's defenses, but it may help reveal how the immune system ends up attacking the body's own cells, producing painful and debilitating autoimmune diseases such as lupus and insulin-dependent diabetes, Matzinger says. Studies have linked such diseases to a group of immune-system genes called the major histocompatibility complex, but Matzinger believes other genes must also be involved.

Such attacks on native tissue, and the lack of attacks on some foreign proteins, may be the result of the difficult compromise the body makes in trying to protect itself against invaders and accept its own tissue, Matzinger says. If the immune system learned to accept a native protein and that protein mutated, attacks on native tissue could result. If, on the other hand, the immune system tolerated differences in protein structure, it could allow organisms to invade by carrying proteins that seem to be similar to proteins found in the body. — *C. Vaughan*

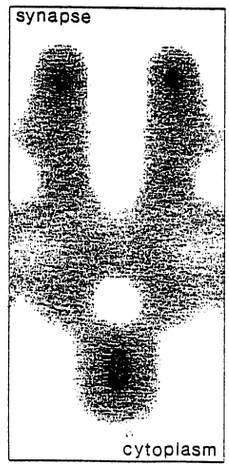
Gatekeeper protein pictured in profile

Just as it's easier to understand how a lawnmower engine works if you take it apart yourself instead of looking at a bag of the pieces, understanding how a biological structure works often requires understanding how it is put together.

For this reason, the first clear side view of a cell membrane's ion channel (right) should help clarify how the structure functions and may lead to better drug design, say the scientists who used X-ray crystallography to image the channel.

Ion channels, made of protein, regulate the flow of important ions through cell membranes, allowing muscles to contract and nerve cells to transmit signals. Scientists have imaged such channels from the top down, but the new side view is the first with enough resolution to show where ion passage through the channel may be regulated, say Chikashi Toyoshima and Nigel Unwin of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, in the Nov. 17 NATURE.

The channel is shaped like an hourglass, with the ions from outside the cell first entering the long opening at the top of the image. In the middle of the five-protein structure there is a much narrower gap, too small to be seen on the image, where ion flow is probably regulated, Unwin says. At the bottom end there sits a protein that is not part of the channel but may serve as some sort of fence, he says. "Before, we didn't know where that protein fit in," he adds. Researchers might be able to design drugs that regulate nerve signals by blocking the channel opening, Unwin suggests. — *C. Vaughan*



Toyoshima, Unwin/Nature

The air you breathe may hurt your ears

Patrons of smoky honky-tonks may subject their ears to more than just music, and mechanics who inhale exhaust while working around noisy engines may take home more than grease under their fingernails. Ongoing research suggests prolonged exposure to high carbon monoxide levels combined with loud noise can cause permanent hearing damage.

Smokers carry 300 to 400 parts per million (ppm) of carbon monoxide in their lungs during smoking, says Laurence D. Fechter of Johns Hopkins University in Baltimore. For 3½ hours, he and co-workers subjected rats to carbon monoxide concentrations of 500 ppm, a dose he says "might correspond to human smoking." During the last 2 hours, the researchers also exposed the rats to a constant noise level of 105 decibels (dB), roughly that experienced by front-row fans at indoor rock concerts.

The rats suffered permanent hearing loss averaging 20 dB from a single exposure. "Loss of the same magnitude in humans would impair their ability to hear conversation," Fechter says. The group plans epidemiologic studies to determine how human hearing responds to the combination of noise and smoke.

Presented this week in Honolulu at a meeting of the Acoustical Society of America and its Japanese counterpart, the results expand on the team's earlier finding that loud noise and 1,200 ppm of carbon monoxide together pose a far greater hearing-loss risk than either alone. Scheduled for publication this winter in FUNDAMENTAL AND APPLIED TOXICOLOGY, the new findings also suggest carbon monoxide and other chemicals cause hearing damage by restricting the flow of oxygen to nerve cells in the cochlea of the inner ear. These "hair cells" demand more oxygen as sound level increases, Fechter says.

Earlier studies have shown a few chemicals can induce temporary hearing loss without any coincident noise (SN: 5/22/82, p.347). Now the Hopkins group has demonstrated that butyl nitrite, a street drug commonly called poppers, by itself can cause longer-term hearing damage. The team's most recent measurements show rats averaged 20 dB of hearing loss one week after getting 70 microliters of the drug per 100 grams of body weight. Fechter says this dose exceeds what people probably would inhale, but butyl nitrite users tend to breathe the drug in loud environments — such as discotheques and concert halls — that compound hearing-loss risk.

The researchers also have shown that high doses of trimethyltin chloride, found in some pesticides and recently banned marine paints, by themselves can damage rats' hair cells irreversibly. The group plans experiments to determine whether butyl nitrite can permanently impair rats' hearing and to clarify the oxygen-restriction process. — *C. Knox*