Three Immune Signals Share Receptor

Three reports now establish a common link among three key immune-system messengers. That link will help researchers make sense of how a single genetic defect can derail the body's defenses and how these messengers interact with one another, comments Thomas A. Waldmann at the National Cancer Institute in Bethesda, Md. "This is a big-league finding."

Certain cells release these messenger molecules, called interleukins, to regulate the growth, differentiation, or proliferation of immune-system white blood cells that defend the body against infections. Membranes of these target cells possess docking sites, or receptors, for the appropriate interleukins. The receptors often consist of several subunits, or chains, that combine to form the docking site and relay the interleukin's message.

In the Dec. 17 SCIENCE, two research groups show that to work well, at least three interleukins must use the same chain as part of their docking site. Because researchers discovered this chain first in the receptor for interleukin-2 (IL-2), it bears the name IL-2 receptor gamma chain. However, that chain makes cells listen also to the messages carried by interleukin-4 (IL-4) and interleukin-7 (IL-7), says Warren J. Leonard, a molecular immunologist at the National Heart, Lung, and Blood Institute (NHLBI), also in Bethesda, Md.

Scientists had known that people with a form of severe combined immune deficiency disease (SCID) that is linked to the X chromosome lacked this gamma chain. Such people make few or no white blood cells called T-cells. However, other kinds of SCID patients and SCID mice — both of which have the gamma chain but lack IL-2 — still make T-cells.

Thus, Leonard began to suspect that other messengers that stimulate T-cell production also depend on the IL-2 receptor's gamma chain. To test this idea, the NHLBI group genetically engineered lab-grown cells to contain the various receptors and subunits to be studied.

Masayuki Noguchi, who works with Leonard, studied IL-7, which typically stimulates the growth of immature T-cells in the thymus and affects the development of a different white cell, the B-cell.

Until now, scientists thought IL-7's docking site consisted of just one subunit. But these experiments show that while IL-7 does attach to that subunit, it fails to get into the cell unless the gamma chain is also present, Leonard says.

Then Sarah M. Russell of Leonard's group studied the role of this gamma chain in the function of IL-4. This interleukin regulates B-cells and also stimulates the growth of T-cells. As with IL-7, IL-4 binds to its receptor's lone subunit. However, IL-4 needs the gamma chain to cause enzymes inside the target cell to take on chemical side groups called phosphates, they note.

In a separate report, a Japanese team reaches similar conclusions about IL-4. Motonari Kondo and Kazuo Sugamura from Tohoku University School of Medicine in Sendai and their colleagues made antibodies that link to the gamma chain, thus blocking its binding by IL-2. They added these antibodies to different kinds of rodent cells growing in the laboratory and observed that the antibodies inhibited the growth-stimulating activity of both IL-2 and IL-4.

"[All these results] really allow us to better understand why it is that children with [X-linked] SCID have the profound immune deficiencies that they have," says Leonard.

"Any error to gamma means you can't make any response to IL-2, IL-4, and IL-7. You lose [almost] everything," Waldmann adds.

Moreover, "Now people will have to think about how one signal can interfere with another signal," says Gerard Zurawski at DNAX Research Institute in Palo Alto, Calif. These interleukins may compete for the available gamma chains.

For example, the Japanese group calculates that its cells each possess about 2,800 gamma chains, nearly all of which become unavailable when the scientists add IL-2, leaving none for IL-4. In contrast, only about 1,200 gamma chains are tied up when the researchers expose a cell to lots of IL-4. Even so, those cells become less responsive to IL-2, says Sugamura. — *E. Pennisi*

Stressed-out platelets secrete hazards

Mental stress may enter the bloodstream almost as though injected intravenously, rapidly agitating cells responsible for blood-vessel repair and possibly promoting heart disease, according to a new study.

After individuals complete a stressful laboratory test, their blood platelets secrete much more of a substance called adenosine triphosphate (ATP). In large amounts, ATP helps trigger blood-vessel changes that may lead to heart attacks and strokes, reports a scientific team directed by Stephen B. Manuck, a psychologist at the University of Pittsburgh, and Pittsburgh psychology graduate student Susan B. Malkoff.

Their findings appear in the November/December PSYCHOSOMATIC MEDICINE.

Researchers have yet to track the long-term effects of psychological stress on platelet function, notes Thomas G. Pickering, a cardiologist at the New York Hospital-Cornell Medical Center in New York City, in an accompanying comment. But the new data add to evidence that "blood platelets may be an important link... between psychological stress and cardiovascular disease," he asserts.

A few previous studies offer inconsistent results regarding the effects of mental stress on platelets. Those studies largely involved people facing "naturalistic" forms of stress, such as elective surgery or public speaking.

The Pittsburgh investigators elicited mental stress in the laboratory in order to control for changes in diet, sleep difficulties, and other behaviors that often accompany real-life stress and can also alter platelet function. They relied on a task that has vexed volunteers in hundreds of experiments — the Stroop test (SN: 5/9/92, p.312).

In a computerized version of the Stroop test, administered to 30 healthy men, a series of four color names flashed on a screen, each printed in a color other than the name itself (such as the word "blue" in green print). Volunteers identified print color as quickly as possible by pressing one of four switches corresponding to the correct color. To make the task more difficult, a computerized voice synthesizer randomly generated a spoken color name as each word appeared on the screen.

Participants were told that they would receive up to $21 for their performance on the 21-minute trial. However, the computer allowed less time for responding as performance improved, thus ensuring an overall rate of about 60 percent correct for each volunteer.

Another 10 healthy men served as controls, sitting quietly for 21 minutes next to the computer setup.

Concentrations of ATP rose sharply only in men who completed the Stroop task. The same men also showed large jumps in heart rate and blood pressure.

The outer membranes of platelets emit several chemicals, including ATP, in response to physical or psychological stress, Pickering says. If these substances permeate blood vessels for prolonged periods, studies suggest, they promote plaque formation and other potentially fatal complications, he points out. — *B. Bower*