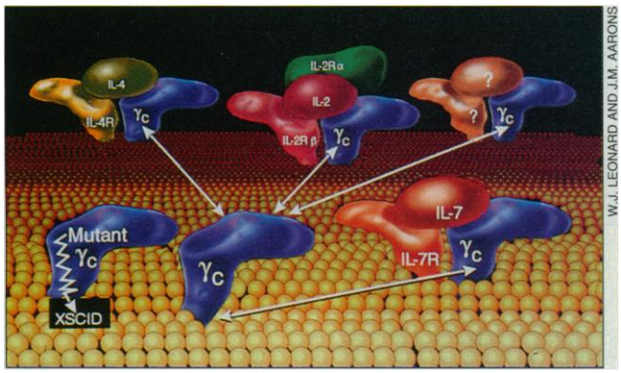
IMMUNOLOGY

'Bubble Boy' Paradox Resolved

Earlier this year, a team of researchers at the National Institutes of Health (NIH) solved a biological mystery when they identified the gene that is at fault in the hereditary disease known scientifically as X-linked severe combined immunodeficiency (XSCID)—and colloquially as "bubble boy disease." By so doing, however, they created another mystery. The defect they identified was in the gene for one of the proteins that make up the receptor for interleukin 2 (IL-2), a cytokine, or intracellular signaling protein, that helps regulate the immune system. And although the defect presumably blocks all of IL-2's effects, it did not seem capable of causing the devastating immune system failure that afflicts XSCID patients. Humans and mice that lack IL-2 entirely, for example, suffer far milder symptoms.



W.J. LEONARD AND J.M. AARONS

Common bond. The normal γ chain is part of the active forms of at least three interleukin receptors.

Now, two teams, one led by Warren Leonard of the National Heart, Lung, and Blood Institute (NHLBI), the other by Kazuo Sugamura of Tohoku University School of Medicine in Sendai, Japan, have solved this mystery (also see pages 1874, 1877, and 1880). And while their work doesn't promise an immediate cure for XSCID, it does add an important piece to an emerging picture of the structure and function of cytokine receptors.

What the two teams have shown is that the IL-2 receptor protein defective in XSCID (the γ chain) may form part of two other cytokine receptors as well: those for IL-4 and IL-7. Each of the three cytokines IL-2, IL-4, and IL-7 boosts a different stage in the growth and development of T and B cells. These cells provide both the commanders and weapons of the two major arms of the immune system —the arm based on cells that kill infected, cancerous, or damaged cells and the one based on antibodies. A defect in the three receptors should thus explain the severity of XSCID, says Leonard: "When you simultaneously inactivate multiple cytokine systems, the defect is going to be greater than when you inactivate any one alone."

The investigation that led to the new finding began in January, when Leonard, working with NHLBI colleague Masayuki Noguchi and O. Wesley McBride of the National Cancer Institute, discovered the XSCID IL-2 receptor defect. Because of the devastating nature of the XSCID immunodeficiency compared to that of IL-2 deficiency, the Leonard team immediately suspected the γ chain would turn up in receptors for other cytokines that regulate T and B cells, most of which comprise two or three protein chains. To the NHLBI team, the IL-4 and IL-7 receptors were obvious suspects. "Only a single chain for the IL-4 and IL-7 receptors had been identified," says Leonard, "so we postulated that, analogous to many other cytokine systems, a second chain would also exist."

Something else piqued the Japanese team's interest in the IL-4 receptor: The strength with which the receptors bound IL-4 appeared to vary from lab to lab. "We guessed that there must be another component to the receptor to account for this [difference]," says Tohoku University's Masataka Nakamura. Spurred on by these observations, the Sugamura team went on to demonstrate that the mouse IL-4 receptor can contain a γ chain, and the Leonard team showed that both the human IL-4 and IL-7 receptors can contain it.

According to the researchers, one chain in the multichain IL-2, IL-4, and IL-7 receptor complexes is unique to the receptor and binds its specific cytokine, while the addition of the common γ chain increases the strength of the binding between the cytokine and the receptor. The γ chain also enables the receptor to pass its signal to the cell interior.

The Leonard and Sugamura teams are now hot on the trail of other interleukin receptors that might share the common γ chain. A report in the July *EMBO Journal* from Gerard Zurawski and his colleagues at the DNAX Research Institute in Palo Alto, California, suggests one likely possibility. They found that the IL-13 and IL-4 receptors share a second chain, which they hadn't yet identified. Both Sugamura and Leonard predict this will prove to be the widespread γ. "It's very exciting, this shared receptor subunit business," says Maureen Howard, director of immunology at DNAX and a codiscoverer of IL-4. "In the last couple of years it's become a theme: Cytokines with overlapping biological properties share common receptor chains."

It now appears that cells may mix and match a limited number of receptor subunits to create a larger array of cytokine receptors. This, the researchers say, may be nature's way of upgrading the signaling systems to handle the increasingly complex interactions of the cells of higher organisms.

–Rachel Nowak

PALEOCLIMATES

Ancient Climate Coolings Are on Thin Ice

SAN FRANCISCO—Like readers nearing the end of a fascinating tale, only to find that the last chapter may have been garbled by a careless printer, climate researchers today are a frustrated bunch. For the past year, the climate community has been transfixed by the history of ancient climates gleaned from two ice cores drilled out of the thickest part of the Greenland ice sheet. First the two cores—the European Greenland Ice-Core Project (GRIP) and the U.S. Greenland Ice Sheet Program II (GISP2)—revealed that the last ice age, from about 12,000 to 110,000 years ago, was punctuated by bursts of warming that took hold in as little as 10 years. Then, in July, a preliminary analysis of the GRIP core suggested that just before the ice age, the warm interglacial period was shattered by sudden cooling pulses (*Science*, 16 July, p. 292). That, researchers thought, implied that our own warm climate—analogous to the last interglacial—may be less stable than it seems. If they obtained similar data from GISP2, it would bolster that conclusion.

Instead the two-core comparison, reported last week, has undermined it. As GRIP and GISP2 investigators announced at the fall meeting of the American Geophysical Union in San Francisco, and in papers in *Nature*, they tried to match the cores' records of two climate signals. One signal is electrical conductivity, which decreases in ice formed during cold periods because it contains more windblown dust. The second is the oxygen-isotope ratio in the water molecules, a measure of temperature. For 90% of their length, down to a depth of about 2700 meters and an age of more than 100,000 years, the records dovetail almost exactly, adding to the groups' confidence in their ice-age findings. Below that depth, however, where some of the ice probably dates from the interglacial period between about 110,000 and 130,000 years ago, the correlation between the two cores falls apart. Notes GRIP investigator Willi Dansgaard of the