both techniques still require some assumptions. The boron technique assumes that seawater composition remained roughly constant over millions of years, and the alkenone method assumes that coccolithophorids grew at a steady rate. To check the validity of the methods, says Crowley, the techniques must be applied to a time of known carbon dioxide concentrations, such as the past few hundred thousand years. Pagani is even now marching his carbon analyses up a sediment core toward the present. If the technique proves reliable, carbon dioxide may have to share its role as prime mover of long-term climate change.

–RICHARD A. KERR

IMMUNOLOGY

Elusive Interferon α Producers Nailed Down

Almost everyone agrees that recycling is a good idea. Indeed, even our immune system seems to have picked up the idea for one of its most valued assets—cells. A paper in this issue of *Science* suggests that the body uses the same set of cells to perform two immune functions, one when the cells are young, and a second after they mature.

On page 1835, a team of immunologists led by Yong-Jun Liu at the DNAX Research Institute in Palo Alto, California, reports pinning down the origins of a key component of our immune defenses. They've isolated the hitherto elusive cells, known as natural interferon-producing cells (IPCs), that churn out huge amounts of interferon α (IFN-α). This so-called cytokine has a variety of immune stimulatory effects that help protect cells against viral and bacterial infections, and it also curbs tumor growth. The IPCs turn out to be the immature forms of a special type of dendritic cell (DC), an immune system sentinel that engulfs foreign proteins, or antigens, chops them up, and displays the pieces to other immune cells, the T cells. This kicks off a fierce, specific immune response directed at the triggering antigen.

The finding links the two branches of our immune system, the innate, more primitive immunity triggered by a wide variety of pathogens and the more sophisticated, adaptive immunity based on antigen-specific cells, which can be tailored against almost any intruder. "The study suggests that this cell type—which had previously been implicated in adaptive immunity—has the potential to also be an early player in the innate part of the immune response. This enriches the capacity of DCs to control immunity," says dendritic cell expert Ralph Steinman of The Rockefeller University in New York City. And because the IPCs seem to be involved in a variety of illnesses, from AIDS to cancer to autoimmune diseases, "having identified this cell type opens an immense amount of possibilities" to try to treat or control these conditions by manipulating the cells, says immunologist Jacques Banchereau of the Baylor Institute for Immunology Research in Dallas.

IPCs first appeared on immunologists' radar screens in the early 1980s, when it became clear that only a special, very rare type of white blood cell is capable of producing huge amounts of IFN-α. But immunologists did not identify a good candidate for the job until about 3 years ago, when Gunnar Alm and his colleagues at the Swedish University of Agricultural Sciences in Uppsala showed that IPCs "have all the characteristics of an immature DC," as Alm puts it. They found, for example, that cells that stain positive for IFN-α also bear characteristic DC surface markers.

At the same time, Liu and his colleagues isolated an odd cell type from human tonsils and blood, which they couldn't classify. Yet when Liu cultured the cells, they developed into a new type of DC with unique T cell–stimulating properties. He also realized that the cells, which he designated pDC2, bore a striking resemblance to Alm's. So he wondered whether the tonsil DC2 precursors and the natural IPCs were one and the same.

To test this idea, the researchers purified more pDC2s from human blood, not a trivial endeavor given that there's only one pDC2 in every 1000 white blood cells. Under the electron microscope, Liu saw that the pDC2s have a prominent protein secretion apparatus, suggesting that the cells can produce huge amounts of protein. When the team stimulated the cells in culture with inactivated herpes simplex virus, they found that their purest pDC2 preparation did in fact make up to 1000 times more IFN-α than the same number of unpurified white blood cells. That response shows, says Liu, that the pDC2s are the natural IPCs.

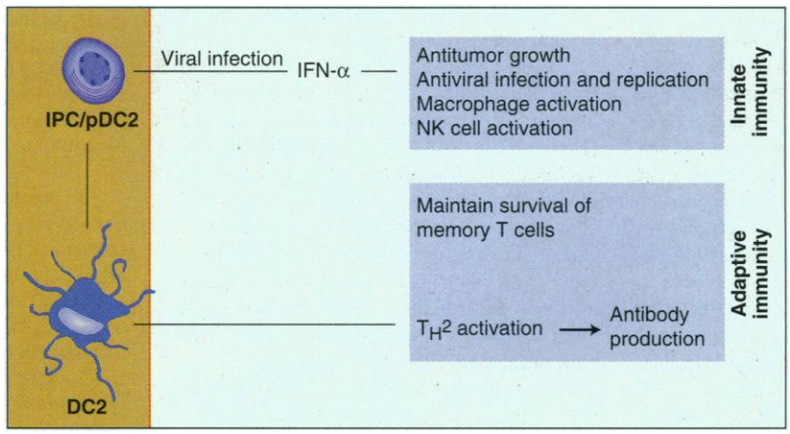
Many in the field are especially taken by the proposed versatility of the pDC2s and their mature version, the DC2s. "The cell seems to serve two masters at different stages of its [lifetime], which is quite unusual for immune cells. It's almost as if nature doesn't want to have cells just sitting around," Banchereau says. Liu adds that the shift in responsibilities as the cell ages makes sense. "If a virus invades, you need a quick response; otherwise you may die. And that's what [the pDC2s] do [by producing IFN-α] within only a few hours. After that you'd want to call in the adaptive immune system for help—and that's the job of the DC2s."

Still, Paola Ricciardi-Castagnoli, an immunologist at the University of Milano in Italy, points out that no one has shown yet that pDC2s produce the same skyrocketing amounts of IFN-α in the body as they do in cell culture. Also unknown, says Ken Shortman, a developmental immunologist at the Walter and Eliza Hall Institute in Melbourne, Australia, is whether "pDC2s ever turn into mature DCs in the body."

If the pDC2s are indeed the long-sought IPCs, their isolation may yield significant medical benefits, as researchers look for ways to stimulate them or rein them in. Boosting IPC activity could be beneficial in AIDS, which seems to correlate with a drastic drop in IPC count, as indicated by, among other things, a drop in the patients' production of IFN-α, and perhaps also in cancer. Conversely, Alm has recently found evidence that IPC activity could contribute to the abnormal immune attacks of autoimmune disorders, such as systemic lupus erythematosus, suggesting that curbing the cells might be valuable there.

The next challenge, everybody agrees, is to learn more about them. "Now we need to know how to produce these cells in large amounts and then how to modulate their function," says Banchereau. "This is going to be one of the hot spots of the future," he predicts.

–MICHAEL HAGMANN



Two-pronged attack. In response to microbial infections, type 2 dendritic cell precursors (pDC2s) produce IFN-α, which activates other immune cells such as macrophage scavengers and natural killer (NK) cells. Then, the mature cells (DC2) stimulate type 2 T helper (T_H2) cells to induce antibody production.

CREDIT: MARIBEL ANDONIAN, DNAX RESEARCH INSTITUTE