anthropologists were fighting to help them retain their culture, they realized, for the first time, that "they were special because they had a culture of their own. The work that anthropologists and others did among them did a very important job of politicizing their cultural consciousness," says Turner.

As their cultural awareness grew, the Indians of different groups in Amazonia began getting in touch with each other and started holding national meetings. Five years ago, the Indians founded the Union of Indian Nations.

"A pan-Indian consciousness has grown up in Brazil very rapidly," says Turner. "The Indians collectively pose issues, lobby, and speak out, and hold news conferences. There really has been a revolution in many respects."

Yet despite the encouragement by the anthropologist advocates, the majority of American anthropologists who work in Brazil have not become Indian advocates. One reason is that advocacy is not in the academic tradition and will not necessarily help advance a young anthropologist's career. Advocacy, says Maybury-Lewis, "may be considered seriously worth doing, but it is considered apart from your evaluation as a scholar. I have been struck by the vehemence with which younger anthropologists speak of the professional problems they face. It was brought home to me that I have a very privileged position. I have tenure at a major university and I have a base from which I can do this. For a person with a new Ph.D., advocacy work does not have much reward."

Kracke agrees. Although he too has tenure, he says he still is asked when he is going to get back to doing anthropology. To him, however, what he is doing *is* anthropology.

The situation is somewhat different for Brazilian anthropologists for whom "advocacy is still not the best way to advance a career, but there are not penalties," says Maybury-Lewis. "Here, advocacy work may be considered serious and worth doing, but it is considered apart from your evaluation as a scholar. In Brazil, anthropologists feel an obligation to make their own work relevant to the problems of the country."

Nonetheless, advocacy can have unexpected payoffs even for American anthropologists. Kracke, who says he is strongly influenced by the attitude of Brazilian anthropologists, said he learned more about the Indians' belief systems when he spent time helping them than he ever would have learned as a neutral observer. This is not an argument for advocacy, of course, but it can mean, says Kracke, that time spent helping the Indians is not necessarily time taken from a career. ■ GINA KOLATA

The T Cell Receptor Family Is Growing

Researchers have identified a second type of T cell receptor, which comes in several structural variations, and are now trying to pin down its functions

IMMUNOLOGISTS once underwent years of frustration during their quest for the Holy Grail of immunology, namely the T cell receptor. Now they have been so successful that they have two with which to contend. The original model, which was identified about 4 years ago, is the equivalent of the "on" switch for T cells. It is the cell surface molecule that recognizes and binds foreign antigens, thereby triggering the cells' activities. The function of the second model, discovered last summer, is still largely unknown. Current indications are that it might act both during T cell development and in the mature animal, perhaps in a novel type of killer cell.

The discovery of this second receptor had an immediate consequence in that it laid to rest a mystery that had cropped up during the work on the first. Early on, researchers had shown that the original, antigen-binding receptor contains two protein chains (designated α and β) that have variable structures and are linked to a third, invariant protein called T3.

During the course of the intense efforts to clone the genes for the α and β proteins, Susumu Tonegawa and his colleagues at the Massachusetts Institute of Technology (MIT) identified a clone that had all the earmarks of a gene that might encode a T cell receptor protein. Other researchers had already cloned the gene for the β chain, and the MIT workers accordingly proposed that they had cloned the α-chain gene. When subsequent work showed that this was not correct, the MIT clone became the "mystery gene" of T cell receptor research.

In July of last year, Michael Brenner, Michael Krangel, and their colleagues at Harvard Medical School were the first to report that they might have a function for the mystery gene in encoding a protein for what appeared to be a second T cell receptor. They identified a population of human lymphocytes that carried T3 proteins on their surfaces without any α or β proteins. The T3 proteins were instead associated with two different protein chains, one of them the apparent product of the Tonegawa group's gene (now called the γ gene), and the other (which has been designated the δ chain) of unknown origin.

In short order, other groups, including that of Arthur Weiss of the Howard Hughes Medical Institute at the University of California at San Francisco, Jannie Borst of the Netherlands Cancer Institute in Amsterdam, and John Coligan, Drew Pardoll, and Ronald Schwartz of the National Institute of Allergy and Infectious Diseases (NIAID), also provided evidence that the γ chain might form a part of a second type of T cell receptor in mouse and human cells.

The big question then became whether the new $\gamma\delta$ receptor works the same way the classic $\alpha\beta$ receptor does in triggering T cell activities in response to antigenic stimulation or whether it has some unique function of its own. The answer to this question is not yet in, but identifying the gene for the δ chain is a high priority for investigators because a better understanding of its nature could provide clues to the receptor function.

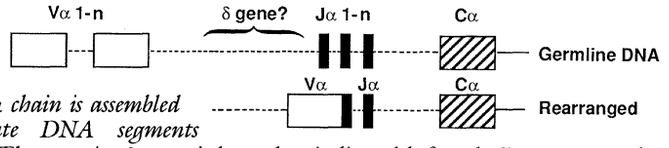
Recently, Yueh-hsiu Chien, Mark Davis, and their colleagues at Stanford University School of Medicine identified a new T cell receptor gene that may be the one coding for the δ chain.* The gene is interesting not just because of its possible function, but because of its rather surprising location—nested within the gene coding for the α chain of the T cell receptor.

The complete genes for the α and β T cell receptor proteins resemble those encoding antibody proteins in that they are assembled from separate DNA segments. It takes three such segments, designated V (for variable), J (for joining), and C (for constant), to make an α gene. The candidate δ gene is located preceding the J segments of the α gene.

The newly identified gene fits the general pattern of a T cell receptor gene. It, too, is assembled from separate segments of DNA, although it includes a fourth segment, called D (for diversity), in addition to the V, J, and C segments. In addition, the joining of the V, D, and J gene segments occurs at the

*The data were presented at a symposium on "The T Cell Receptor" that was sponsored by Smith Kline & French and the University of California at Los Angeles and held on 26 April to 1 May in Keystone, Colorado.

Gene for the α chain of the T cell receptor.



A complete gene for the α chain is assembled by joining the separate DNA segments designated V, J, and C. The putative δ gene is located as indicated before the J segments and will be excised during V-J joining.

appropriate stage of development. The gene rearrangement can be detected by day 14 of the mouse gestation period, Chien and Davis find. The Pardoll-Coligan-Schwartz group has shown that the γδ receptor is present on developing T cells from the thymus gland by day 15, and the V-D-J joining must precede the expression of the gene. Moreover, the Stanford workers find that the gene is transcribed in several different populations of T cells that have γδ receptors.

Despite all this, however, there is a problem. The molecular weight predicted for the protein product of the putative δ gene is only 31,000, whereas the molecular weight determined for the δ protein itself is 34,000 to 37,000. There is a possibility, Davis says, that some unusual feature of the protein's structure makes it appear to have a higher molecular weight than it actually does.

Nevertheless, the current discrepancy in molecular weights puts up at least a small stumbling block that will have to be removed before the gene identified by Chien and Davis is unequivocally accepted as the δ chain gene. The definitive proof that the gene encodes the δ protein can come only when the sequences of the gene and the δ protein are determined and compared.

Having both the γ and δ chain genes in hand could aid in understanding the function of the γδ receptor by providing information about its recognition capabilities. "To understand what a cell is doing, you have to understand what it is recognizing," Schwartz explains.

For example, the repertoire of αβ receptors must be large enough to recognize an essentially unlimited number of target antigens. Consistent with this need, the α and β chain genes have several alternate V segments—50 to 100 in the case of the α gene—from which to chose in assembling the complete genes. They can thus generate many different receptor proteins.

The γ gene, in contrast, has fewer V regions, roughly ten, and thus appears much less capable of generating a diverse group of proteins. "Everybody wants to know about the δ gene," Schwartz explains. "If it also lacks diversity, it would suggest a different function for the γδ receptor [than for the αβ receptor]." There is a possibility, however, of greater diversity in the δ gene if it does turn out to be the one identified by Chien and Davis. This gene may not have its own separate set of V segments but may instead use those of the α gene.

Current work suggests that cells with the γδ receptors may participate in T cell development. As previously mentioned, Pardoll, Coligan, and Schwartz found that the receptors are present on thymus cells by day 15 of the mouse gestation period, which is about 2 days before αβ receptors appear. The NIAID group's results and also those of Weiss, Lewis Lanier of the Becton-Dickinson Monoclonal Center, Inc., in Mountain View, California, and their colleagues indicate that the γδ cells are not precursors of the αβ cells, but are a separate lineage. Among other things, the γδ cells do not carry either the T4 or T8 antigen, surface markers that are found on αβ cells.

The developmental pattern of expression of the two types of receptors suggests that the γ and δ genes undergo V-J or V-D-J joining first. If these rearrangements produce functional genes, then the analogous rearrangements do not occur in the α and β genes. If functional γ and δ genes are not produced, however, then the α and β genes can rearrange. The location of the putative δ gene between the V and J segments of the α gene means that it will be excised during α gene rearrangement. In accord with this, Davis notes that the putative δ gene is not present in cells with αβ receptors.

The γδ cells might play a role in fostering the development of the αβ cells even if the two cell types are of separate lineages. Brenner, Krangel, and their colleagues have shown that the γδ cells, when they are appropriately stimulated, can release interleukin-2, which is one of the proteins that foster T cell growth and development. "These might be the cells that prime the pump and prepare the thymus for the growth and expansion of αβ cells," Schwartz postulates.

Although the γδ cells predominate in the thymus of the 15-day mouse embryo, they are a distinctly minor cell population in the adult where they constitute less than 1% of the thymus cells and less than 5% of the T cells elsewhere in the body. Nevertheless, several groups have evidence suggesting that the γδ cells may have an immune function.

In particular, the cells can kill other cells. "The finding that they have cytolytic machinery is pretty solid," Brenner notes. So far at least, the cell killing has not been antigen-specific in the same way that killing by αβ cells is, but is more like the nonspecific, spontaneous activity of "natural killer" cells. That situation could change, however, with additional work. Questions also remain about whether the nonspecific cell killing by γδ cells is an intrinsic property of the cells or an artifact of the conditions in which they are grown in the laboratory.

In addition to finding γδ receptors on the double negative T cells, investigators, including the NIAID group and also James Allison of the University of California at Berkeley and his colleagues, have found it on a type of cell located in mouse skin, but bearing a characteristic T cell marker. The function of these cells is also unknown.

Finally, the human γδ receptor shows a structural heterogeneity not seen in the murine receptor. In some human cells, the γ and δ chains are linked by covalent disulfide bonds and in others they are not. In addition, the γ chains of the nondisulfide-linked receptors vary in size. These variations occur, according to results both from the Brenner group and from Weiss, Dan Littman, who is at the University of California at San Francisco, and their colleagues, because either of two alternate C region coding sequences can be used to form a complete human γ gene.

One of the C regions has the cysteine residue needed to form disulfide bonds with the δ chain, whereas the other does not. The gene segment encoding the C region without the critical cysteine comes in two variant forms. In one, a particular coding sequence has been duplicated and in the other it is triplicated. The genes assembled from the two variants will thus produce proteins of different sizes.

Whether these structural variations influence the function of the human γδ receptors is unknown. Although the discovery of the new receptor has solved one mystery of immunology, it has clearly produced several new mysteries that will keep laboratory lights burning late into the night for some time to come. ■ JEAN L. MARX

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