Second thoughts on second genetic code

On May 13, the New York Times reported MIT scientists had "deciphered a second genetic code." Readers of that article and similar stories in other newspapers were given the impression a major breakthrough had resulted in the solution of an old scientific problem. In the weeks following the publication of the MIT findings, however, a small scientific controversy has emerged over the precise significance of the work at MIT and how the press reported these developments.

Four other scientific groups working in the same area agree the MIT work is important, but hardly most of the answer to the puzzle that some call "the second genetic code" and others call "the protein recognition problem." Rather, they say, it is one more step in a process that started in the 1950s and has moved forward quickly in the last few years: that of understanding fully how DNA directs the construction of proteins.

The first part of that understanding came in the 1960s with the deciphering of DNA's genetic code: how three-letter "words" in the DNA of cells determined which specific amino acids, the building blocks of protein, were linked together to form the proper protein. The way those DNA words are translated into amino acids is a three-step process. First the DNA passes its information to another molecule called messenger RNA, which passes the information to transfer RNA. Only transfer RNA (tRNA) interacts with amino acids and directs their assembly into proteins. There are 20 different tRNAs, each of which interacts only with a specific type of amino acid.

The question scientists at MIT and elsewhere are pursuing is: How does each tRNA recognize only one type of amino acid? This pattern of recognition, the "second genetic code," is not really a separate code at all, but part of the first genetic code discovered in the 1960s.

Transfer RNA is made up of nucleic acids, the same material that makes up DNA. What MIT scientists Paul Schimmel and Ya-Ming Hou discovered was that by changing just two nucleic acids in one kind of tRNA, they could transform it into a different type of tRNA. In effect, they said in an article in the May 12 NATURE, these two nucleic acids were enough to decide which amino acid this kind of tRNA would seek out.

Other scientists disagree with Schimmel and Hou about how big a part these two nucleic acids play. "I think they are about 50 percent of the story [of what determines what kind of amino acid this tRNA binds to], and Paul Schimmel thinks they are about 90 percent of the story," says Olke Uhlenbeck, who does tRNA research at the University of Colorado in Boulder. There probably are other sites, Uhlenbeck and other scientists say, that play a large part in determining which amino acid the tRNA binds.

These two nucleic acids might act as a guidepost to other important processes in amino acid recognition, says tRNA researcher William McClain of the University of Wisconsin in Madison. "It might be like directing someone how to get somewhere in New York and you tell them, 'First go to the Empire State Building,'" says McClain. Schimmel's nucleic acid pair might act as such an obvious starting point.

McClain also points out that although Schimmel used the nucleic acid pair to transform one kind of tRNA into a tRNA that binds to the amino acid alanine, when McClain introduced exactly the same amino acid pair into another tRNA (that for the amino acid glycine), it failed to bind alanine. Therefore, that particular nucleic acid pair may not be the most important determinant to make tRNAs specific for alanine, McClain says. California Institute of Technology scientist John Abelson, widely credited with developing the methods for recent tRNA research, comments that "clearly [Schimmel's] code is not universal." Hou disagrees, saying the tRNA McClain used is not fully understood to be a normal tRNA, and that in the MIT experiments the nucleic acid change always made tRNAs with some specificity to alanine.

All researchers, including the MIT group, agree that tRNAs other than that for alanine recognize amino acids by many means, not just the nucleic acids Schimmel and Hou pinpointed. This means that any "code" that is discovered will probably not be as simple as a changing combination of one pair of nucleic acids, scientists say. "We are in the process of defining the code," says Uhlenbeck. "As we find more determinants a few rules may emerge."

Many scientists in this field are glad to see the problem get attention, but they also criticize the way the discovery was covered in the press. Although the NATURE article received a lot of attention, an article by McClain with very similar results was published the week before in the May 6 SCIENCE and got virtually no attention. Some tRNA researchers partly fault MIT scientists for not mentioning other important research in the field and overplaying the significance of their research. "Some of the things they're quoted as saying are quite incredible, like this may lead to better computers," says Abelson. Some say they are also upset that some press accounts gave the impression that the tRNA puzzle is now solved. "In the next few years we will get a lot of new information on this," McClain says, "but what we have now is not the whole picture." *– C. Vaughan*

Cell receptors drop with HIV infection

Knowing why some immune cells in the body can harbor the AIDS-associated virus (HIV) and still survive could prove crucial in AIDS treatments. Hidden inside these cellular sanctuaries, the virus apparently lies in wait – until unknown factors reactivate it and the immune cells are destroyed. On the basis of a new study using chronically infected T4 lymphocytes, scientists now say the appearance of HIV envelope material on the surface of these immune cells after infection actually makes them "cytolysis resistant," protected from virus-induced rupture during the latent period.

After inserting the HIV-envelope gene into T4 lymphocytes to create chronic infections in the cells, scientists at the University of Nebraska Medical Center in Omaha looked at the concentration of CD4 receptors on cell surfaces. These common T-lymphocyte molecules are in part responsible for interactions between a cell and another structure, whether other cells or foreign antigens. The researchers found that, as HIV-envelope structures appeared on T4-cell surfaces, the number of CD4 receptors on HIV-gene-containing cells dropped by about 60 percent, compared with that on unaltered cells. The CD4 receptors are thought to be important in binding HIV to cells during the infection process.

When mixed with HIV in the laboratory, the gene-containing cells were resistant to killing by the virus, whereas cells that had not been injected with the envelope gene prior to HIV exposure died. The treated cells also were resistant to repeated HIV exposure. According to the scientists, this phenomenon can occur with retroviruses other than HIV, including HTLV-I, recently linked to human leukemia and lymphoma. Because this loss of receptors may postpone the HIV-mediated death of T4 lymphocytes, which correlates with the appearance of AIDS symptoms, it has "important implications for both the pathogenesis of and treatment strategies for AIDS," the group writes in the May 6 CELL.

The authors also say they disagree with current scientific opinion that the rupture of infected cells may depend on the presence of syncytia – giant cells formed when lymphocytes clump around an infected cell and their membranes fuse. After adding a chemical known to greatly enhance HIV replication, the scientists found the majority of chronically infected lymphocytes died within 96 hours. They say this effect occurred despite the absence of CD4 and syncytium formation. *– D.D. Edwards*