Gene therapy gets a boost with 'natural' regulators

A new technique for regulating gene expression in genetically altered bone marrow cells is raising hopes that a biotechnical cure may be feasible for a class of inherited blood disorders. Such disorders, which result from the defective production of hemoglobin, the oxygen-carrying substance in blood, include the most common inherited diseases in humans. While it will probably be years before the new method of gene therapy is attempted on people, recent experiments with mice demonstrate the possibility of fine-tuning the machinery of hemoglobin production. That machinery is among the most tightly regulated in the human body, and until now was believed to be far too complicated to respond to genetic manipulation.

The research involves inserting genetic material into immature bone marrow cells, or stem cells, which are destined to differentiate and grow into various types of blood cells. In certain diseases, such as the group of inherited disorders known as the thalassemias, stem cells may develop into red blood cells that fail to make some of the protein components of normal hemoglobin. Affected persons suffer varying degrees of anemia. In its most severe form the disease is fatal.

Previous attempts to insert genes for the production of normal hemoglobin into abnormal stem cells were fraught with difficulties. Stem cell gene transfer is typically accomplished by inserting the desired gene into retroviruses and allowing the viruses to infect stem cells. But an individual stem cell may develop into one of several types of cells; to prevent overproduction of hemoglobin proteins, actual production should occur only in stem cells that are destined to become red blood cells. Also, red blood cells undergo a complicated developmental process, and hemoglobin production should be programmed to occur only at the proper stages of a red cell's life. Until now, researchers have been unable to ensure that retrovirally injected genes would "turn on" only in the appropriate cells at the appropriate time.

Researchers at the Whitehead Institute for Biomedical Research in Cambridge, Mass., and the University of Washington in Seattle appear to have solved this complex regulatory puzzle by taking a gene's own regulators that are coded into its surrounding DNA and including these in the genetic "package" that gets transferred to stem cells. Their research appears in the Jan. 8 NATURE.

"Genes have their own transcriptional regulation elements that will allow them to be expressed in a certain time in development and that allow them to be expressed in particular types of cells," says Elaine A. Dzierzak, one of the Whitehead researchers. "It's an advantage to use the regulatory elements that nature provides with those particular genes," rather than relying upon the generic retroviral regulatory elements that previous researchers have used.

Dzierzak and her colleagues successfully introduced the gene for human beta-globin, a hemoglobin protein missing in some thalassemias, into mice that had an induced anemia. They detected beta-globin production in red cells as long as nine months after retroviral transfection. Although production of the protein was somewhat lower than normal, the researchers say they should be able to bring levels up to normal by including an additional, recently discovered regulator.

In an accompanying editorial, D. J. Weatherall, of the University of Oxford, England, notes that "Although these results represent a genuine advance towards gene therapy, many difficulties remain." Among these, he says, are the need to get higher percentages of stem cells infected by the gene-carrying retroviruses, or a means of ensuring preferential survival of the stem cells that have been successfully infected. — *R. Weiss*