Scripps Researchers Develop Insights into How Proteins Recognize DNA and RNA to Regulate Gene Expression

La Jolla, CA. April 21, 1993 -- Scientists at The Scripps Research Institute have determined for the first time the way in which a single class of proteins can bind both to DNA and RNA and, by so doing, have achieved a more profound understanding of the process of gene regulation. As reported in this week’s issue of the journal Science, they have shown which of the nine tandemly-repeated modules, or motifs, of a zinc finger protein recognize DNA and which recognize RNA.

By better understanding the recognition process, scientists have the potential for controlling the expression of genes at will, according to Peter E. Wright, Ph.D., and Joel M. Gottesfeld, Ph.D., two of the study’s authors, and chairman and associate member, respectively, of Scripps’ Department of Molecular Biology. Their work provides insights into how zinc finger proteins may function as a switch to turn on or off the function of a gene.

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"Many diseases arise from gene expression gone wrong; the wrong genes are expressed at the wrong times, or they’re not expressed at all, or they are expressed as mutations. Cancer, for example, is aberrant gene expression," said Wright.

"What is particularly exciting about our insight into recognition by this particular protein, " according to Gottesfeld, "is that a protein of this type is involved in Wilms’ tumor, a rather rare but potentially fatal form of kidney cancer generally found in children under 14 years of age." He continued, "In theory, the long-term implications of the study could lead us toward the development of inhibitors or activators of specific genes that could turn on a tumor suppression gene or turn off an oncogene."

The zinc finger protein was the first specific gene regulatory DNA binding protein from a higher animal isolated and cloned. What makes this protein unique is its ability not only to perform the gene regulatory function, but to bind the product of the gene it regulates, or RNA. Its role in binding the gene is in turning the gene on. It serves as a storage particle for RNA. This RNA is used by the cell in the process of protein synthesis.

The fundamental unit of the protein is its so-called zinc finger. This protein consists of nine of these units. Through the method of recombinant DNA, the TSRI scientists have found that the first three units are responsible for the recognition of DNA, and the next four for RNA. They have discovered that the regions of the protein
that give it specificity are different and perform these different functions. This was achieved by removing different regions of the gene for the protein. Then, these were expressed in bacteria, purified and tested for whether they would bind DNA or RNA using a specific assay. A painstakingly careful quantitative analysis was critical in determining how well the units bound to RNA and DNA.

The protein’s interaction with DNA and RNA may ultimately lead to the design of new molecules, potentially new therapeutics that can regulate gene function. It may be possible to reconfigure the units of the protein and bind them in different ways into new combinations that do not exist in nature. By so doing, these proteins then could recognize different genes and either activate or inhibit their functions.

Because of the work in this study, according to its authors, scientists have received the first indication that different fingers can perform different functions. This, in turn, will provide clues and insights into other large, multi-finger proteins.

Additional authors of the study in *Science*, which is titled, "Molecular Basis for Specific Recognition of Both RNA and DNA by a Zinc Finger Protein," are TSRI researchers Karen R. Clemens, Ph.D., Veronica J. Wolf, Steven J. McBryant, Penghua Zhang, Ph.D., and Xiubel Liao, Ph.D.