

A Protein Called Stat Provides a Platform for Potential Cancer Therapies

Over the last 10 years, cancer researchers have been tracking down a protein called Stat, shorthand for “signal transducers and activators of transcription.” They have found an overabundance of this protein in a wide variety of human cancers, ranging from head and neck to breast, prostate and blood.

What happens when the protein is no longer present in these cells? School of Medicine scientists showed for the first time that inhibiting the production of one type of Stat, called Stat3, made lymphoma tumors in mice disappear. They prevented production of the protein by using sophisticated genetic manipulation techniques that

selectively eliminate the gene that is responsible for producing the protein. Their findings were published in the journal *Nature Medicine*.

Lymphoma is a type of cancer of white blood cells. The NYU researchers were led by David E. Levy, Ph.D., the Dr. Louis A. Schneider Professor of Molecular Pathology and Professor of Microbiology, and Giorgio Inghirami, M.D., Associate Professor of Pathology.

The NYU research adds to growing evidence that cancer cells need an overabundance of Stat3 to survive. Dr. Levy has been studying Stat3 since the mid-1990s, when he and his colleagues cloned its gene. “Our results,” he says, “were obtained from studies in mice,

but we think our approach can be extended to the treatment of malignancies in humans. Pharmaceutical companies are interested in this approach.”

Dr. Inghirami has focused his studies on anaplastic large cell lymphoma, which mainly affects children. The NYU researchers used a snippet of DNA called an antisense oligonucleotide to scramble the cellular machinery necessary to produce Stat3. It was injected into mice transplanted with human lymphomas. Over the next few days, the tumors seemed to melt away, says Dr. Inghirami. The molecule also prevented tumor growth if it was injected at the same time that the tumors were transplanted into the mice. ■

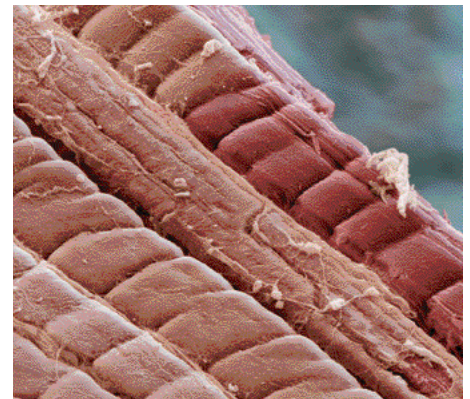
How Muscle Cells Pump It Up

Building muscles requires much more effort than just lifting weights. Using a novel combination of laboratory techniques, Brian D. Dynlacht, Ph.D., Associate Professor of Pathology, and his colleagues have identified a large network of proteins that regulate the development of mammalian muscle cells. This work, described in a recent issue of the journal *Genes & Development*, also highlights new directions for further studies of genes involved in muscle repair and response to stress and damage.

Until now, researchers have known relatively little about the transcription factors (proteins that regulate gene expression) that govern how muscle-cell precursors, called myoblasts, fuse with each other to form tubular-shaped intermediary cells, which then become full-fledged skeletal-muscle fibers.

To unearth the details of this intricate process, Dr. Dynlacht and his team used the latest techniques in molecular biology and systems biology—from genome-wide location analysis, gene-expression profiling, and gene-ablation techniques, to computational methods. This is the first time such a multifaceted approach has been used to dissect a genetic program in mammalian cells.

The team also learned that the transcription factors involved in muscle-cell development prepare myoblasts to respond to diverse types of stress. “It is surprising that genes involved in cell differentiation and in stress response would be activated by the same regulatory proteins,” says Dr. Dynlacht. He speculates that these stress-response genes may be involved in the function of the endoplasmic reticulum. This organelle in cells regulates calcium,



Rows of tightly packed myofibrils in skeletal muscle influence movement.

which is used in muscle contraction.

Now that the researchers have outlined the steps involved in normal muscle-cell development, the team can start looking at what happens when the process goes awry. He hopes that this work will lead to a greater understanding of cancer and other diseases that affect muscle tissue. “Cancer is basically a failure to properly regulate the right genetic programs,” says Dr. Dynlacht, “so these cells don’t differentiate.” ■