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New Insight Into Genetic Cause of Infant Mortality

Four years ago, researchers identified a genetic mutation associated with spinal muscular atrophy (SMA), an inherited neuromuscular disease that is the most common genetic cause of infant mortality. Now, HHMI investigator Gideon Dreyfuss and his colleagues at the University of Pennsylvania Medical Center have found two critical pieces of evidence that support the hypothesis that this gene mutation causes SMA.

Dreyfuss and colleagues Livio Pellizonni, Bernard Charroux and Naoyuki Kataoka have identified the function of the protein produced by this gene, and they have used that information to begin searching for a drug that can either replace or repair the defective protein. The results of these studies are published in the November 25, 1998, issue of the journal *Cell*.

SMA affects 1 in 6,000 newborns, causing progressive muscle weakness, wasting, or atrophy as motor neurons degenerate. In 1994, researchers discovered that the gene, *survival of motor neurons (Smn)*, is deleted or mutated in almost all SMA patients. This observation strongly suggested that reduced levels of or mutations in the SMN protein cause spinal muscle atrophy.

Dreyfuss and his colleagues have now answered two lingering questions: What is the SMN protein's normal function and how does decreased SMN protein activity cause degeneration of motor neurons? The team showed that the SMN protein is needed by all cells to produce messenger RNA (mRNA). Production of mRNA is a critical step in gene expression, and ultimately, in the production of functional proteins. Furthermore, motor neurons, the nerve cells that degenerate in SMA, are extremely sensitive to defects in SMN. Dreyfuss's research team found that SMN deficiency leads to the death of motor neurons and atrophy of the muscles controlled by those neurons.

Specifically, SMN protein plays a crucial role in the genesis of mRNA from a precursor called pre-mRNA. The conversion of pre-mRNA to mRNA takes place in the cell nucleus during a process called splicing.

Splicing requires the interaction of a large number of proteins, including a group called small nuclear ribonucleoproteins (snRNPs), nicknamed "snerps." This molecular machinery assembles and reassembles itself cycle after cycle on each of the numerous sequences that needs to be spliced out of

every pre-mRNA generated by a cell.

"Our research shows that SMN and its entourage of helper proteins are required for the proper form and function of snRNPs and for maintaining the splicing machine in an active form so that it can be used for multiple rounds of splicing," explains Dreyfuss.

It turns out that healthy human motor neurons contain some of the highest concentrations of SMN and snRNPs of any cells in the body. Perhaps not surprisingly, then, when there is a deficiency of SMN, motor neurons appear to be the first cells to suffer, and cell death eventually results.

Researchers do not know why levels of SMN are higher in normal motor neurons, but Dreyfuss suspects that this may be due to the relatively large size of these cells, which requires the nucleus to "crank out a tremendous flow of mRNA."

The description of the molecular machinery underlying the disease constitutes a real ray of hope for SMA clinicians. "This paper is an important step towards an effective treatment for spinal muscle atrophy," says Kenneth H. Fischbeck, chief of the neurogenetics branch at the National Institute of Neurological Disease and Stroke. "Now scientists will be able to work back from the biochemistry of the disease to eventually design new therapies."

Dreyfuss's team has developed a set of cell-free assays that mimic the biochemical activity of SMN in a test tube. "We know the function of the protein and can reconstitute the biological activity of SMN in vitro. This gives us the opportunity to search for potential therapeutic compounds, one that could enhance or substitute for the activity of SMN," says Dreyfuss.

He and his colleagues intend to screen compounds while continuing their study of SMN. "We want to understand the molecular function of SMN and its entourage in as much detail as we can, hopefully one day down to the atomic level," explains Dreyfuss.