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Researchers gain new insights on spinal muscular atrophy

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Researchers from the University of Pennsylvania School of Medicine discovered that the effect of a protein deficiency, which is the basis of the neuromuscular disease spinal muscular atrophy (SMA), is not restricted to motor nerve cells, suggesting that SMA is a more general disorder. This new insight will allow for better understanding of how this complex disease arises. Gideon Dreyfuss, PhD, the Isaac Norris Professor of Biochemistry and Biophysics and Investigator, Howard Hughes Medical Institute and colleagues, report their findings in last week's issue of *Cell*.

SMA is a group of hereditary diseases that causes weakness and wasting of the voluntary muscles in the arms and legs of infants and children. The disorders are a result of genetic lesions in a gene called survival of motor proteins (SMN) that cause a deficiency in the SMN protein. This protein is essential for all cells, but reduced levels of SMN cause spinal muscular atrophy. Why this seemingly cell-specific reduction happens is not known.

SMN normally works in all cells to bring small RNAs together with specific proteins to form particles called snRNPs (pronounced snurps). snRNPs are the molecular machines that splice different parts of RNA together to form the messenger RNA (mRNA) before it leaves the nucleus to travel to the cytoplasm. Here, mRNAs get translated into working proteins.

"SMN plays a key role in determining the inventory of the different

types of snRNPs in all cells, what we call the snRNP repertoire or the 'snRNPertoire,'" says Dreyfuss. "When SMN levels are reduced, the biochemical balance needed to make the snRNP complexes for splicing RNA is impaired."

The Dreyfuss lab looked at reduced SMN levels in cultured cells and mice and found that changes in levels of the snRNPs, as well as the mRNAs – their spliced products – were affected, producing numerous abnormal mRNAs. These effects varied from tissue to tissue. The findings suggest that spinal muscular atrophy is a general disease of splicing.

"Now we know that SMA is clearly a disease that not only affects motor neurons, but all cell types when the gene for SMN is damaged," says Dreyfuss. In the end, concludes Dreyfuss, this is a different way to look at the disease. Finding a way to restore SMN levels in the entire body is one therapeutic approach to aim for, based on these findings.

Source: University of Pennsylvania