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Vitamin Deficiency May Worsen Motor Neuron Disease

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the process of discovering a function for a common modification of proteins
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— **Gideon Dreyfuss**

the cell, researchers have found evidence that suggests that insufficient amounts

of folic acid and vitamin B12 in the diet may exacerbate spinal muscular atrophy (SMA), a genetic disease that attacks motor neurons.

The scientists are planning to collaborate with clinicians to explore whether these vitamins might ameliorate the severity of symptoms in some SMA patients.

In a research article published in the May 2001 issue of the journal *Molecular Cell*,

Howard Hughes Medical Institute investigator Gideon Dreyfuss

and colleagues at the University of Pennsylvania School of Medicine report new

information about how the protein, "survival of motor neurons" (SMN), which is

reduced or defective in people with SMA, attaches to other proteins with which

it interacts.

"SMN is a sort of master builder or chaperone that

helps assemble many large RNA-protein machines (RNPs) in the cell," said

Dreyfuss. "In particular, it appears to help construct complicated molecular

machines that are critical for the production of messenger RNA." Messenger RNA

plays an essential role in ensuring that the information contained in DNA is

properly translated into functional proteins.

SMA is the most common genetic cause of infant

mortality, affecting about one in 6,000 newborns. The disease causes

progressive muscle weakness, wasting, or atrophy as motor neurons degenerate.

The severity of the disease ranges from milder forms, in which people can live

into adulthood, to more severe forms that cause death a few months after birth.

SMA is caused by deletions of one of the two genes

that code for the SMN protein. Deletion of the gene reduces the level of SMN

protein, which causes damage to the nerve cells that serve major muscle groups.

Loss of nerve stimulation causes muscles to atrophy and can result paralysis.

In their studies, Dreyfuss and his colleagues probed

how SMN binds to its multiple target proteins in the cell. Using biochemical

methods, they determined that SMN binds to regions of target proteins that are

rich in the amino acids arginine and glycine. "When we tested binding of SMN to

these proteins directly *in vitro*,

however, we found a surprisingly low affinity," said Dreyfuss. "We then began

to suspect that something else must influence the binding, because when we isolated the target proteins from cells, SMN bound to them avidly."

To solve the mystery, Dreyfuss and his colleagues used

the long-known fact that the arginines contained in many proteins are modified

by the attachment of two molecules called methyl groups. "Dimethylation of arginines is a fairly common modification of proteins, especially RNA-binding

proteins, that had first been reported more than thirty years ago," said

Dreyfuss. "But the function of that modification was not known."

By using synthetic peptides with (or without) the

methylated arginines as found in the cell, the researchers established that SMN

did, indeed, bind tightly to its target proteins only when the arginines on those target proteins were dimethylated. "That alteration makes the modified protein interact with another protein — in this particular case with SMN — with much higher avidity," Dreyfuss said. The alteration of the arginines quite

likely changes the shape of the protein's surface, making it fit SMN more snugly, he explained.

The finding — which solves a three-decade-old

scientific mystery — provides a new research pathway for studying how proteins

attach to one another and might also have clinical implications for people who

have SMA, said Dreyfuss.

"These SMN target proteins obtain their methyl groups from a methyl donor called, *S*-adenosylmethionine, which itself depends on folate and vitamin B12 as part of its metabolic pathway," said Dreyfuss. Humans cannot produce or store folate and B12, so they must obtain those vitamins through their diet. "The thought is that SMA patients, who are already compromised in their levels of SMN, might be more severely affected if they are also suboptimal in their levels of protein methylation," said Dreyfuss.

"Insufficiency of folate and B12 in SMA patients is a real possibility and this could lead to under-methylation of proteins, even if only slightly," he said. "Given this possibility, it would seem prudent for these patients, in consultation with their physicians, to ensure that their diet includes the recommended daily requirement of these vitamins."

Dreyfuss is planning to collaborate with neurologists

Thomas Crawford of The Johns Hopkins University School of Medicine and Richard

Finkel of The Children's Hospital of Philadelphia to explore whether vitamin therapy might offer some relief to people with SMA.

Dreyfuss and his colleagues will also continue their

studies of arginine methylation. They plan to begin looking for the enzyme that

catalyzes attachment of methyl groups to the protein targets of SMN. Those studies, he said, could help reveal the regulatory pathway in a key cellular process that may extend to other proteins and other degenerative diseases of the nervous system.