WASHINGTON—Sporadic inclusion body myositis is a mysterious disease of unknown cause. It has some characteristics of an autoimmune disorder, but some authorities view it instead as a degenerative disorder of aging muscle with a strong inflammatory component.

The inclusion bodies that give the disease its name contain large amounts of amyloid-beta (A-beta), the same protein found in Alzheimer disease plaques, along with a variety of other proteins.

Now a new study shows that A-beta appears to trap an important lipid-related transcription factor, peroxisome proliferator-activated receptor gamma (PPAR-gamma), inhibiting its entry into the nucleus.

Anna Nogalska, PhD, described the new findings here at the annual meeting of the American Neurological Association in October. Dr. Nogalska and colleagues conducted the research in the laboratory of Valerie Askanas, MD, PhD, at the University of Southern California (USC) Keck School of Medicine Neuromuscular Center in Los Angeles.

But some experts question whether this newly identified prisoner of the inclusions actually holds the key to unlocking the mystery of the disease, or whether it is instead one more bystander in the long and growing list of molecules that are found in the inclusions.

**Why Explore PPAR-gamma?**

PPAR-gamma is a transcription factor that is held in its inactive form within the cytoplasm. It is activated when it binds a prostaglandin, becomes dephosphorylated, and links up with a co-transcription factor called retinoid X receptor. When this occurs, the complex moves from the cytoplasm to the nucleus, where it binds DNA and regulates lipid metabolism.

The PPAR family of transcription factors, including PPAR-gamma, has aroused interest among researchers in diabetes and Alzheimer disease. Rosiglitazone (Avandia), for example, is a PPAR-gamma activator, which increases insulin sensitivity and is used to treat type 2 diabetes. PPAR-gamma promotes breakdown of amyloid-beta

Dr. Anna Nogalska: “Our studies demonstrate for the first time PPAR-gamma abnormalities in s-IBM muscle fibers. It suggests that PPAR-gamma cannot function properly in these muscles. It is possible that because PPAR-gamma is bound to amyloid-beta, it can’t get properly dephosphorylated and therefore cannot get to the nucleus.”
precursor protein, and in transgenic Alzheimer disease animals, PPAR-gamma-activating drugs (called thiazolidinediones) have slowed disease progression and reduced the accumulation of A-beta plaques. In a small study of AD patients, rosiglitazone improved memory.

**Study Findings**

All these connections led Dr. Nogalska and colleagues to ask whether PPAR-gamma might be affected in sporadic inclusion body myositis (s-IBM). They studied muscle biopsies from 15 s-IBM patients and 20 controls. Among findings, PPAR-gamma messenger RNA was increased threefold in s-IBM muscle compared to controls. The inactive protein was also elevated threefold in the cytoplasm, and co-localized with A-beta in inclusions. In contrast, active nuclear PPAR-gamma was decreased by 50 percent compared to normal controls. The cytoplasmic kinases that phosphorylate—and thereby inactivate PPAR-gamma—were also increased.

“Our studies demonstrate for the first time PPAR-gamma abnormalities in s-IBM muscle fibers,” Dr. Nogalska said. “It suggests that PPAR-gamma cannot function properly in these muscles. It is possible that because PPAR-gamma is bound to amyloid-beta, it can’t get properly dephosphorylated and therefore cannot get to the nucleus.”

The investigators previously reported that an increase in kinases in s-IBM muscle may indicate an excess of phosphorylation, which may also play a role.

**Experts Comment**

But neuromuscular disease experts, who were not involved in the current study, expressed skepticism about the role of PPAR-gamma in the pathogenesis of s-IBM.

“Overexpression of ‘alien’ proteins in muscle fibers, such as A-beta, is a tantalizing aspect of this disease,” George Karpati, MD, professor of neurology at McGill University, told Neurology Today, “and A-beta may be a neo-antigen [an antigen present in tumors induced by certain types of adenoviruses and papovaviruses or in cells transformed in vitro by those viruses] that provokes an immune response.” But, he added, researchers, including those who conducted this study, “have shown upregulation or downregulation of so many diverse molecules in sporadic IBM muscle fibers that, now, to single out PPAR-gamma as the target for a ‘magic bullet’ is more like wishful thinking than a realistic expectation.”

Dr. George Karpati acknowledged that “overexpression of ‘alien’ proteins in muscle fibers, such as A-beta, is a tantalizing aspect of this disease,” but he added that other investigators “have shown upregulation or downregulation of so many diverse molecules in sporadic IBM muscle fibers that, now, to single out PPAR-gamma as the target for a ‘magic bullet’ is more like wishful thinking than a realistic expectation.”

Dr. Karpati, who was not involved in the current study, said he also does not hold much hope for rosiglitazone as a potential treatment. “To try to make a case for a drug that is supposed to be therapeutic in Alzheimer disease, and weakly at that, is stretching it,” he said.

Richard Moxley, MD, director of the Neuromuscular Disease Center at the University of Rochester, said that from his perspective, there is a “morass” of information about possible causes of s-IBM. He said these results, while intriguing, do not make an especially stronger hypothesis than some of the others. “The bottom line is that for me personally, it is still a morass.”

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