Following chronic fatigue mechanisms to the source: WASF3 and mitochondrial respiration

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Researchers at the National Heart, Lung, and Blood Institute at NIH, Bethesda, have discovered a potential breakthrough for people with

myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), marked by extreme exhaustion, post-exertional malaise and cognitive issues.

In a paper, "WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome," published in *PNAS*, the team details the influence of increased WASF3 proteins on the assembly of mitochondrial proteins, hampering energy production.

The study focused on a woman (S1) who experienced severe long-term fatigue. Measuring her muscles for phosphocreatine regeneration after exercise revealed a significant delay in mitochondrial ATP synthesis capacity. This discovery was followed up with a cell assay which found increased phospho-activation of an enzyme in a signaling pathway (MPAK).

In a large database meta-analysis, MPAK was previously associated with chronic fatigue syndrome. In that meta-data study, the gene WASF3, which produces a protein that can activate increased phospho-activation, was highlighted as a good candidate for further investigation.

The researchers tested S1's muscle tissue and revealed elevated levels of WASF3, indicating that her condition and the mechanism behind it were related to a larger pathology of chronic fatigue syndrome seen in other research.

Taking the investigation further, a genetically engineered mouse model with elevated WASF3 levels showed mice exhibiting mitochondrial dysfunction and reduced treadmill performance.

Turning once again to the scientific tool of reading previous research, the team found WASF3 reported to be regulated by BiP (GRP78), an endoplasmic reticulum (ER) chaperone for protein quality control whose

defective response can cause ER stress and metabolic disorders. With an understanding of interactions between the ER and mitochondria for muscle function, the current team reasoned that ER stress may regulate WASF3 in muscle cells.

To test the link between ER stress and WASF3, researchers treated human myoblasts with ER stress inducers and observed increased WASF3 protein. The level of WASF3 was inversely correlated with that of MTCO1, the last enzyme in the mitochondrial electron transport chain, which drives oxidative phosphorylation.

This disruption leads to reduced mitochondrial oxygen consumption, providing a molecular explanation for symptoms like exercise intolerance and post-exertional malaise in patients with chronic fatigue.

Muscle samples from ME/CFS patients also displayed higher WASF3 levels and lower levels of associated mitochondrial protein complexes.

While the research only focused on one individual, the connections to larger study cohorts, correlations to previously discovered mechanisms, along with the new findings could have broad treatment implications for chronic fatigue.

More information: Ping-yuan Wang et al, WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2302738120