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Microglia Drive Neurodegeneration in Friedreich's Ataxia

Ryan Quigley:
You're listening to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today we're exploring a study that challenges a long-standing assumption in Friedreich's ataxia—shifting the focus from neurons alone to microglia as active drivers of neurodegeneration.

Friedreich's ataxia affects roughly one in 50,000 individuals and has long been understood as a mitochondrial disease rooted in frataxin deficiency. But this study—published in *Nature Communications* in late 2025—asks if microglia are simply responding to neuronal damage, or if they could be playing a more central role in the disease process.

To explore that, the team designed a multi-layered experimental approach. They used patient-derived induced pluripotent stem cells, also called iPSCs, to generate microglia, allowing them to isolate cell-specific effects of frataxin deficiency. Cells from patients with Friedreich's ataxia were compared with healthy controls, familial carriers, and cell lines edited by CRISPR/Cas9. They then extended the work into co-culture systems with neurons and into a humanized mouse xenograft model—a way to test causality across systems rather than relying on a single model.

What emerges is a remarkably consistent picture: Friedreich's ataxia microglia are intrinsically abnormal. Even in isolation, they adopt a hyperactivated, pro-inflammatory phenotype—morphologically less ramified and increased pro-inflammatory markers like CD68 and Iba1 expression.

But the dysfunction runs deeper. Mitochondria are central to energy production and reactive oxygen species balance, but are severely impaired. The study shows increased mitochondrial reactive oxygen species, reduced membrane potential, and diminished ATP production in Friedreich's ataxia microglia. These defects are also accompanied by structural abnormalities, like increased fragmenting and spherical mitochondria.

Lysosomal systems, which normally clear damaged organelles, are also significantly compromised. Researchers showed that Friedreich's ataxia microglia had reduced mitophagy and impaired lysosomal acidification. Basically, microglia lose their ability to recycle dysfunctional cell organelles which fuels more inflammation.

These organelle-level failures ultimately converge into a broader metabolic imbalance marked by iron overload and increased lipid peroxidation, along with disrupted lipid handling. The result is accumulating DNA damage, reinforcing a chronic state of cellular stress.

But the most compelling insights came from functional interaction studies. When Friedreich's ataxia microglia were co-cultured with otherwise healthy neurons, the neurons began to suffer. They accumulated iron, showed oxidative DNA damage, and increases in markers for cell death pathways. Notably, conditioned media alone from Friedreich's ataxia microglia did not reproduce this effect which suggests that these results are from direct cell to cell interactions, not just soluble inflammatory signals.

And mouse data reinforces this. In a humanized mouse model, transplanted Friedreich's ataxia microglia preferentially accumulated in the cerebellum—particularly in the Purkinje cell layer—and triggered neuronal loss along with increased oxidative DNA damage.

And this is where it really turns translational. Using CRISPR/Cas9 to correct the genetic mutation causing Friedreich's ataxia restored frataxin levels and reversed many of these abnormalities—normalizing mitochondrial function, reducing inflammation, and preventing neuronal death both in vitro and in vivo.

So what does this all mean? This study reframes Friedreich's ataxia as more than just a neuron-centric disease, but one where microglial dysfunction may independently drive pathology. It also positions microglia—and potentially hematopoietic stem cell–based gene therapies targeting them—as a therapeutic entry point.

There's still uncertainty, particularly around the exact mechanisms of microglia–neuron interaction and long-term outcomes. But the direction is clear: microglia are not bystanders. They are active participants, and possibly key targets for intervention.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Pernaci C, Johnson A, Gillette S, et al. Microgliopathy as a primary mediator of neuronal death in models of Friedreich's Ataxia. *Nat Commun*. 2025;17(1):81. doi:10.1038/s41467-025-66710-y