Mitochondrial roles in antiviral immunity modify manifestations of neurological diseases

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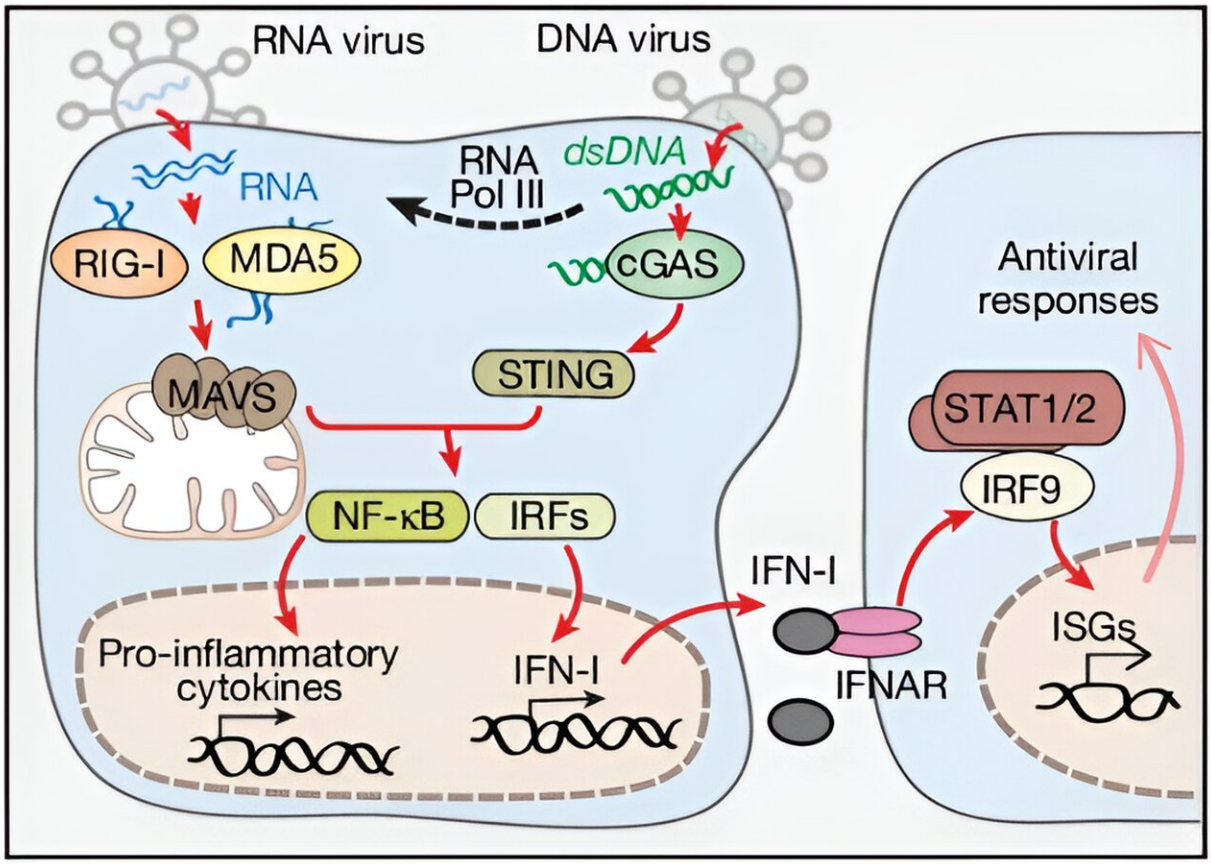

Schematic of antiviral innate immune signaling responses to viral PAMPs.
Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07260-z

A multidisciplinary team of scientists led by University of Helsinki reports that a progressive neurodegenerative disease can be triggered by a viral infection. The mechanism relates to mitochondrial roles in antiviral defense mechanisms.

The scientists report that a specific gene variant affecting the mitochondria disturb cellular antiviral defense responses. The results implicate that viral infections can trigger and modify symptoms of neurological diseases in subjects carrying genetic sensitivity. The article is published in *Nature*.

Viking-age gene mutation alters viral defense

Why a disease manifests at a certain age, and what kind of triggers may be involved, are still open questions. Recent data indicate that mitochondria, the cellular centers of energy and nutrient metabolism, have new important roles in protecting cells from both internal and external stresses. Importantly, a novel role of mitochondria in strengthening the immune system has been recognized, but the relevance of these functions for human diseases has been unclear.

The current study shows that deficient mitochondrial functions in immune defense are connected to manifestation of brain diseases and sometimes also liver dysfunction. A multidisciplinary team led by academy professor Anu Suomalainen discovered that a genetic variant affecting the function of mitochondrial POLG enzyme delays detection of viral infection, leading to delayed severe inflammatory reaction damaging the brain and liver.

The POLG variant originates from a single individual dating back to Viking times and has spread to populations of European origin. Especially Northern European countries show high carrier frequencies: one in a hundred individuals in Finland and Norway. If a subject inherits

the POLG-variant from both parents, a neurological disease, MIRAS (mitochondrial recessive ataxia syndrome), manifests. However, the ages of onset and manifestations of MIRAS are highly variable, raising the question of whether the disease is triggered by additional factors.

Using a variable set of model systems, the team shows that the POLG variant leads to a weakened initial immune activation in response to viral infection, followed by a delayed, overactivated inflammation damaging the brain and liver. The scientists suggest that this mechanism explains why some MIRAS patients manifest in teenagers with severe epilepsy, while some other patients with the same genetic background show disease signs years or even decades later, as motor coordination defects or Parkinson's disease.

"Our results indicate that external factors, such as viral infections, can modify manifestation and age-of-onset of neurological diseases," postdoctoral scientist Yilin Kang says. "Identification of susceptibility factors and triggering mechanisms are valuable targets for new therapy developments. The current findings indicate the importance of new mitochondrial functions in maintaining brain health."

More information: Yilin Kang et al, Ancestral allele of DNA polymerase gamma modifies antiviral tolerance, *Nature* (2024). DOI: 10.1038/s41586-024-07260-z

Provided by University of Helsinki

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