COMMENTARY

# Losing sleep over mitochondria: a new player in the pathophysiology of fatal familial insomnia

Markus Glatzel; Diego Sepulveda-Falla

Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg D-20246, Germany.

**Corresponding author:**
Markus Glatzel, MD, Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (E-mail: *m.glatzel@uke.de*)

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This commentary highlights the study by Frau-Mendez and coworkers in this issue of *Brain Pathology* (xxx) in which the authors show evidence for involvement of mitochondria in the pathophysiology of fatal familial insomnia (FFI). Using genetic, biochemical and morphological means, they provide a comprehensive picture of the degree of mitochondrial damage in FFI and show that this leads to increased oxidative stress. This adds FFI to the growing list of dementias with mitochondrial involvement. Future studies will have to address the causality dilemma of which came first, mitochondrial damage and subsequent neurodegeneration or vice versa. Either way, these data provide the basis to devise novel therapeutic strategies for FFI.

Human prion diseases have puzzled generations of scientists and continue to do so. A rare form of genetic prion disease termed (fatal familial insomnia, FFI) is a good example for this. This incurable and invariably fatal condition was firstly reported as a familial disease causing sleep disturbance and failure of the autonomic nervous system, later it was linked to a specific mutation (D178N) within the gene encoding the prion protein ($PrP^C$) (4). Clinicopathological correlation established that the extent of neuropathology manifesting as neuronal loss, gliosis and limited spongiosis of the thalamus, inferior olive and entorhinal cortex, is only partially parallel by deposition of pathological prion protein ($PrP^{Sc}$) (8). Evidence for transmissibility is not as clear-cut as for other human prion diseases with some studies showing transmissibility, whereas others including studies in FFI mouse models, challenge this view (2). How generation of mutated $PrP^C$ causes such a devastating disease is the topic of intense research. Structurally, the D178N mutation, located in the globular domain of $PrP^C$, affects noncovalent interactions within the molecule thus changing protein stability (4). Additionally, this mutation affects maturation of the protein and leads to retention in the biosynthetic pathway (2). But how does this lead to neurodegeneration? Similar mutations in the globular domain of $PrP^C$ impair trafficking of $PrP^C$-interacting proteins and this affects integrity of synaptic calcium channels (12). Deletions in the globular domain of $PrP^C$ lead to accumulation of mutant $PrP^C$ in intracellular compartments and activation of the p38-MAPK pathway with subsequent neurodegeneration (10).

In this issue of *Brain Pathology*, Frau-Mendez et al. (7) show evidence for involvement of mitochondria in the pathophysiology of FFI. For prion diseases, mitochondrial involvement has been suggested by a number of studies (5, 15), yet it is unclear whether $PrP^{Sc}$ directly interacts with mitochondria or if this is an indirect effect caused by astrocyte-mediated up-regulation of nitric oxide (Table 1) (14). For other neurodegenerative diseases, such as Alzheimer's disease, involvement of mitochondria is less vague (3). In fact, mitochondrial dysfunction affecting mitochondrial metabolism and dynamics or presenting with activation of mitochondria-related cellular death pathways is currently considered a common pathway of neurodegeneration in several dementias (3, 6). For Alzheimer's disease, mitochondrial involvement was shown in patient's tissue, in experimental models and in *in vitro* studies (Table 1). Here, mitochondrial damage is a consequence of intracellular aggregation of β-amyloid peptide, leading to increased production of reactive oxygen species and affecting mitochondrial dynamics (9). Mutations leading to familial Alzheimer's disease can induce disturbance

**Table 1.** Mitochondrial dysfunction and associated cell death in Alzheimer's and prion diseases.

| Disease | Altered Mitochondrial function | | | | | Cell Death pathway | | |
|---|---|---|---|---|---|---|---|---|
| | Respiration/ROS-RNS | Dynamics | MAM | mtDNA | Lipid synthesis | MPTP formation | Apoptosis signalling | Mitophagy |
| Alzheimer's disease | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Prion disease | Hamster and mouse models | Hamster model | No | Mouse model | No | No | Yes | Mouse model |

ROS/RNS = reactive oxygen species/reactive nitrogen species; MAM = mitochondrial associated membranes; mtDNA = mitochondrial DNA; MPTP= mitochondrial permeability transition pore formation.

in the function of mitochondria associated membranes leading to altered $Ca^{2+}$ homeostasis, defective lipid synthesis and damage of mitochondrial DNA (1). Whether by direct toxicity or by altered cellular pathways, mitochondrial dysfunction in Alzheimer's disease culminates in mitochondrial transition pore formation, apoptotic signaling and mitophagy (11). Finally, mitochondrial damage leading to degeneration of specific neuronal populations may translate to distinct clinical phenotypes (13).

It remains to be seen whether mitochondrial involvement is specific for FFI or if other genetic prion diseases show similar characteristics. Mitochondrial involvement in prion diseases could be relevant and should be further investigated given that it offers a novel opportunity to design therapeutics to tackle this devastating group of diseases. In this respect, genetic prion diseases are of special interest since they allow to initiate therapy before clinical onset of disease.

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