Mitochondrial preproteins as markers for Alzheimer's disease

Technology

Most mitochondrial proteins possess N-terminal presequences that are required for targeting and import into the organelle. Upon import presequences are cleaved off by matrix processing peptidases and subsequently degraded by the peptidasome Cym1/PreP that also degrades Amyloid-beta peptides (Aβ). We found that Aβ which accumulates in mitochondria of Alzheimer's disease (AD) patients early during pathogenesis inhibits peptidasome activity resulting in a feedback inhibition of presequence processing enzymes. This leads consequently to the accumulation of immature preproteins in mitochondria which causes a variety of dysfunctions that were described for AD. Due to the presence of the (non-processed) presequence these preproteins can be distinguished by their different molecular weight or by using presequence specific antibodies. Both methods revealed a specific appearance of immature preproteins in mitochondria from post mortem brain samples of AD patients. A specific accumulation of mitochodrial preproteins can also be observed in blood cells of AD patients opening the chance of a novel diagnostic tool.

Innovation

- Mitochondrial preproteins specifically accumulate in their immature form in AD patients.
- Mature and immature species can be distinguished by their size difference or using presequence specific antibodies
- This method will allow early AD diagnosis in easy available samples (e.g. blood or fibroblasts)

Application

- Early AD diagnosis in living patients
- Post mortem AD diagnosis for evaluation purposes
- Easy measurable parameter during therapy

Developmental Status

- Several presequence specific antibodies available
- Large study for test in blood cells has started
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> Mossmann *et al.* (2014) Cell Metabolism 20, 662-669

Responsible Scientist

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Diagnostic

Patent Status

EP and US patent application pending

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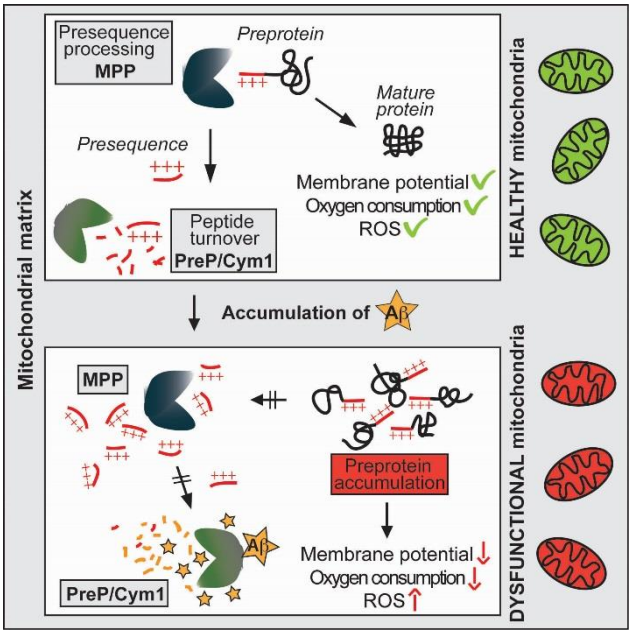

Figure 1: Model how Aβ peptide leads to accumulation of immature preproteins in mitochondria.

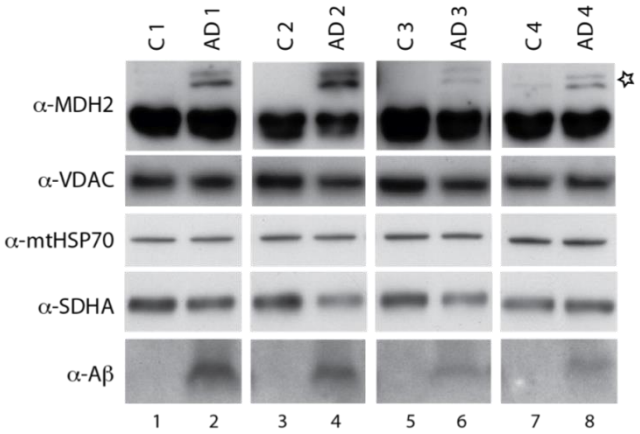

Figure 2: Accumulation of immature mitochondrial Malat Dihydrogenase (MDH2) (star) in post mortem brain mitochondria of AD patients. C1-4, age-matched controls.

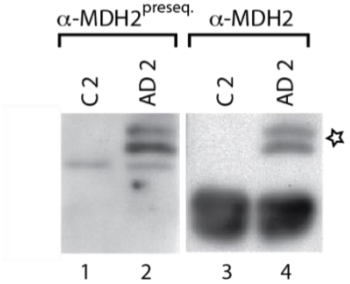

Figure 3: Specific detection of MDH2 preprotein in AD brain mitochondria using a presequence specific antibody.

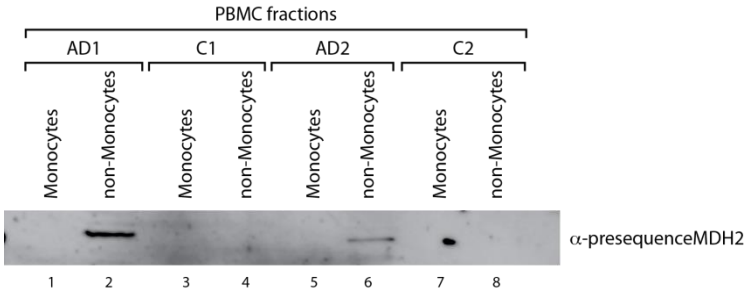

Figure 4: Specific detection of MDH2 preprotein in non-monocytes from PBMC fractions of AD and age-matched control blood samples.