Protein Mfn2 may increase the currently short therapeutic window in stroke

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Francesc Soriano, Ramón y Cajal researcher at the Department of Cell Biology of UB and member of the Research Group Celltec UB.

A new study published in the prestigious publication The *EMBO Journal* shows that the mitochondrial protein Mfn2 may be a future therapeutic target for neuronal death reduction in the late phases of an ischemic stroke. The study has been coordinated by Dr Francesc Soriano, Ramón

y Cajal researcher at the Department of Cell Biology of the University of Barcelona (UB) and member of the Research Group Celltec UB.

The study, funded by the Fundació La Marató de TV3, is part of the PhD thesis developed by Àlex Martorell Riera (UB), first author of the article. Experts Antonio Zorzano and Manuel Palacín, from the Department of Biochemistry and Molecular Biology of UB and the Institute for Research in Biomedicine (IRB Barcelona), and Jesús Pérez Clausell and Manuel Reina, from the Department of Cell Biology of UB, also collaborated in the study.

When blood flow is blocked in the brain

According to the World Health Organization (WHO), strokes are the second leading cause of death in the world. A stroke occurs when a blood vessel is blocked interrupting blood flow in the brain. Ictus damage is progressive: it begins some minutes after the attack. Recommended treatment consists in restoring blood flow to the brain, but it must be done during the first four hours after the stroke.

According to researcher Francesc Soriano, "one of the main causes of brain death in ictus events is glutamate increase; glutamate is the main excitatory neurotransmitter in the central nervous system. Glutamate extracellular concentrations remain low due to the activity of membrane transporters, which require energy to work".

When blood flow is blocked, energy levels are reduced in the affected area. This phenomenon leads glutamate transporters to work inversely, so glutamate is expelled to the extracellular space. Glutamate activates its receptors —particularly, the N-methyl-D-aspartate receptor (NMDA)— on neurons' surface, a process that triggers an excessive flux of calcium, the activation of a series of reactions and neuronal death, in a process known as excitotoxicity. "Many of these excitotoxic cascades

—points out Soriano— converge on the mitochondrion, an organelle which plays a major role not only in energy production, but also in apoptosis".

New therapeutic strategies against ischemic ictus

Specifically, Mfn2 is a mitochondrial protein involved in the regulation of organelles' morphology and function. The team led by Dr Francesc Soriano has just discovered that the reduction in Mfn2 protein levels occurs four hours after the initiation of the excitotoxic process in in vitro and in vivo animal models.

In vivo experiments proved that if Mfn2 reduction is stopped, delayed excitotoxic cell death is blocked. The research team from the Department of Cell Biology of UB found that the Mfn2 reduction is triggered by a genetic transcription mechanism (DNA is transcribed into RNA molecules). UB experts also discovered that MEF2 is the transcription factor involved in this process. Authors affirm that these findings are essential to find a strategy to reverse Mfn2 reduction.

Currently, the team led by Dr Francesc Soriano are researching on brain damage in excitotoxic conditions in animal models where the gene Mfn2 has been removed. The main objective is to design therapeutic strategic in order to reduce damage.

More information: Martorell Riera, A.; Segarra Mondejar, M.; Muñoz J. P.; Ginet, V.; Olloquequi, J.; Pérez Clausell, J.; Palacín, M.; Reina, M.; Puyal, J.; Zorzano, A.; Soriano, F. X. "Mfn2 downregulation in excitotoxicity causes mitochondrial dysfunction and delayed neuronal death." *EMBO Journal*, DOI: 10.15252/embj.201488327

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