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MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

seminar

Wednesday, 9th November, 12.00pm

Seminar Room

Host: Prof. Jesus Ruiz-Cabello

From worms to patients: learning from C. elegans survival strategies to treat neurological diseases

Dr. med.
Francisco Pan-Montojo
Facharzt für Neurologie
Klinik für Psychiatrie und Psychotherapie
LMU Klinikum der Universität München
Germany

Caenorhabditis elegans dauer larva have developed incredible survival strategies that allow them to resist desiccation. We have previously shown that the up-regulation of dir 1.1, djr1.2 and glod-4 is essential for dauer larva survival to desiccation. These genes are orthologs of human *DJ-1* (also known as *PARK-7*) and *GLOD-4*) and have been described as glyoxilases converting glyoxal and methylglyoxal into glycolic acid (GA) and D-lactate (DL). Disrupting the conversion of glyoxal and methylglyoxal into GA and DL results in a decreased tolerance to anhydrobiosis in *C. elegans* dauer larva. Interestingly, administering GA and DL was able to rescue this phenotype. As during desiccation/rehydration a metabolic stop/start with increases in oxidative stress, disruption in calcium homeostasis and mitochondrial dysfunction similar to the one observed during ischemia/reperfusion and other neurological diseases occurs, we hypothesised that GA and DL could also have protective properties in neurological diseases. We tested this hypothesis in several vitro and in vivo models of stroke, ALS and Parkinson´s disease as well as in first-in-man studies in ALS patients. Our results show that GA, alone or in combination with DL, is able to reduce ischemic damage by up to 50% in swine, delay the progression of the disease in SOD-1 mice and patients and protect dopaminergic neurons against paraquat toxicity in mice. Moreover, our results suggest that this therapeutic effect is mediated by a triple effect of GA and DL. These i) reduce intracellular calcium, ii) support mitochondrial function enhancing energy production and iii) combat oxidative stress by the production of reduced glutathione. Overall, our results suggest that GA and DL are strong drug neuroprotective candidates for the treatment of neurological diseases.