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TEMSIROLIMUS AS A NEW TREATMENT FOR X-ADRENOLEUKODYSTROPHY

INVENTIÓN DESCRIPTION

X-linked adrenoleukodystrophy (X-ALD) is a neurometabolic disease characterized the loss of function of the peroxisomal transporter ABCD1 resulting in the accumulation of very-long chain fatty acids (VLCFA). The incidence of this disease is 1:17.000 in newborns, although it is likely higher due to its poor diagnosis.

Depending of the patient age and whether brain is specially affected, X-ALD is classified in three variants: AMN (late-onset form that affects adults); cAMN (include cerebral demyelination and neuroinflammation in adults), cCALD (include cerebral demyelination and neuroinflammation in children).

Currently there is no a successful treatment although several approaches have been done in order to combat this disease, including allogenic bone marrow transplantation (low rate of survival, a new clinical trial is in process); gene therapy with transfection of the ABCD2 gene (no statistical results at this moment, a new clinical trial is in process); Lorenzo's oil dietary treatment[3] (no clinically relevant benefits) and treatments with diverse drugs such as 4- phenylbutyrate and valproic acid (not clear results), bezafibrate(no reduction of VLCFA in either plasma or lymphocytes) or sobetirome (preliminary results, in phase 1).

Constitutive autophagy is indispensable for maintaining neural tissue homeostasis and normal function. Dysfunctional autophagy has been observed during neurodegeneration in both *in vivo* animal models and *in vitro* primary neuronal cultures.

We used biochemical, morphological and functional assays to directly analyze the autophagic system status in X-ALD fibroblasts, patient brains and X-ALD mouse models (*Abcd1*− and *Abcd1−/Abcd2−/−*).

We report aberrant mTOR signaling that causes autophagy impairment as a mechanistic and pivotal component of X-ALD pathogenesis.

BUSINESS SECTORS OF APPLICATION

Pharmaceutical sector.

TECHNICAL ADVANTAGES AND BUSINESS BENEFITS

Using *in vivo* and *in vitro* models, we demonstrate that autophagic flux was impaired due to elevated mammalian target of rapamycin (mTOR) signaling, which contributed to X-ALD pathogenesis. We also show that excess VLCFAs downregulated autophagy in human fibroblasts. Furthermore, mTOR inhibition by a rapamycin derivative (*Temsirolimus*) restored autophagic flux and inhibited the axonal degenerative process as well as the associated locomotor impairment in the A*bcd1−/Abcd2−/−* mouse model. This process was mediated through the restoration of proteasome function and redox as well as metabolic homeostasis.

Temsirolimus has shown neuroprotective role in brain samples of cCALD and cAMN patients, *Abcd1− mice* and human X-ALD fibroblasts, suggesting a mechanism that attenuates oxidative stress levels.

Confirmation of these results in AMN-patient samples has not been carrying out yet due to unavailability.

DEVELOPMENTAL STATE OF THE TECHNOLOGY

In contrast to the treatments listed above, ***Temsirolimus*** has been effective for all types of X-ALD. Furthermore, ***Temsirolimus*** is a marketed drug, so its security has been already tested and this will speed up the steps needed to become a successful therapy against this disease.

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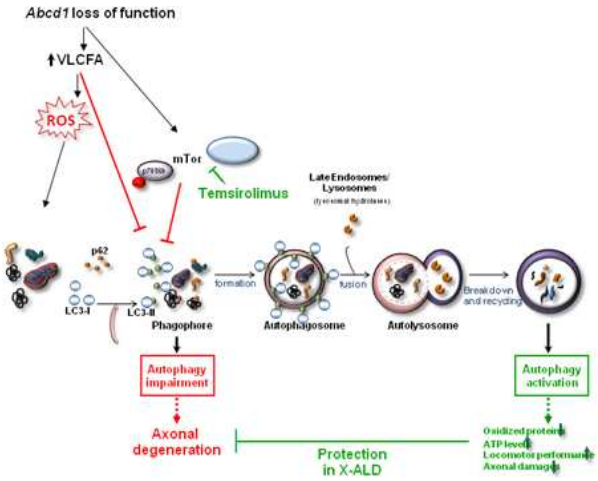
IP RIGHTS

A European patent application (EP14382353.2) has been filed.

DESIRED BUSINESS RELATIONSHIP

Based on preclinical test results from a mouse model using the rapamycin analog temsirolimus, we propose using rapamycin-related mTOR inhibitors as a potential therapeutic approach for X-ALD.
Due to Temsirolimus is a marketed drug, we request for repurposing it with the advantage that the new use of this drug can be marketed quickly.

RELATED PICTURES



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