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HERV inhibitors for use in tauopathies

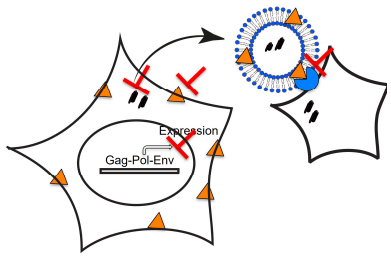
Tauopathies, HERV, Env/Gag inhibitors, spreading of Tau aggregates, inhibition of receptor binding

INVENTION NOVELTY

The deposition of intracellular fibrillar phosphorylated Tau in the central nervous system is a pathologic hallmark of tauopathies within the group of neurodegenerative diseases. Several lines of evidence suggest that transcellular spreading of distinct Tau aggregates may underlie the diversity and progression of tauopathies. Human endogenous retroviruses (HERV) in the human genome, usually epigenetically silenced, become upregulated in neurodegenerative diseases associated with protein aggregation. Increasing evidence indicates that extracellular vesicles (EVs) play a prominent role in disseminating aberrant Tau species to neighboring cells. Viral glycoprotein decoration of EVs from donor cells harboring proteopathic seeds composed of Tau strongly increased their aggregate inducing capacity in recipient cells. Thus, endogenous viral glycoproteins expressed could act as “address codes” that enable delivery, receptor binding, efficient uptake and cytosolic release of proteopathic cargo in recipient cells. So far it is unclear how exactly Tau is sorted into EVs and how these EVs target recipient cells.
Upregulation of endogenous retrovirus gene expression drastically affects the dissemination of protein aggregates between cells in culture. The present invention introduces inhibitors of HERV Env and Gag expression and maturation and inhibitors of binding of HERV Env to its receptor.

VALUE PROPOSITION

Expression of HERV Env increases Tau aggregate dissemination in human cell cocultures. Env mediates membrane association between donor and recipient cells and promotes the intercellular transfer of protein aggregates. Inhibition of expression and/or maturation of viral Env/Gag and viral ligand - receptor interactions impaired proteopathic seed spreading. These findings raise the possibility that de-repression of HERVs accelerates spreading of protein aggregates and suggests that HERVs represent potential therapeutic targets for tauopathy disease intervention.



Potential targets for therapeutic intervention. *Source: DNZE*

TECHNOLOGY DESCRIPTION

Upregulation of endogenous retroviruses, as demonstrated for endogenous Moloney leukemia virus (MLV) as surrogate virus, correlates with increased aggregate inducing capacity in recipient cells. Analyses confirmed increased expression of Env and Gag in cell lysates and EV fractions from donors upon prolonged culture. Interfering with receptor - viral ligand interactions by antibodies inhibited aggregate induction in both coculture and by EVs. MLV protease inhibitors Atazanavir and Amprenavir impairing MLV protein maturation reduced the percentage of recipient cells with induced aggregates. In addition, silencing of recipient MLV Env receptor strongly reduced aggregate induction in cocultures.

COMMERCIAL OPPORTUNITY

Elevated HERV transcripts have been reported for certain tauopathies like Alzheimer’s Disease (AD), Progressive Supranuclear Palsy (PSP) and frontotemporal dementia. The data highlight the potential influence of endogenous retroviral proteins on protein misfolding diseases and suggest that antiviral drugs could represent promising candidates for inhibiting protein aggregate spreading. The technology is open for licensing, further co-development is highly welcomed.

DEVELOPMENT STATUS

Besides data with MLV, Env proteins encoded by HERVs have been tested and similarly affected spreading of Tau misfolding. Inhibition experiments expressing such HERV Env proteins using protease inhibitors are ongoing.

PATENT SITUATION

Patent applications based on WO2021/044009 with priority of Sept. 4, 2019 are pending in US and EP.

FURTHER READING

Liu et al. (2022), bioRxiv preprint “Endogenous retroviruses promote prion-like spreading of proteopathic seeds".

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