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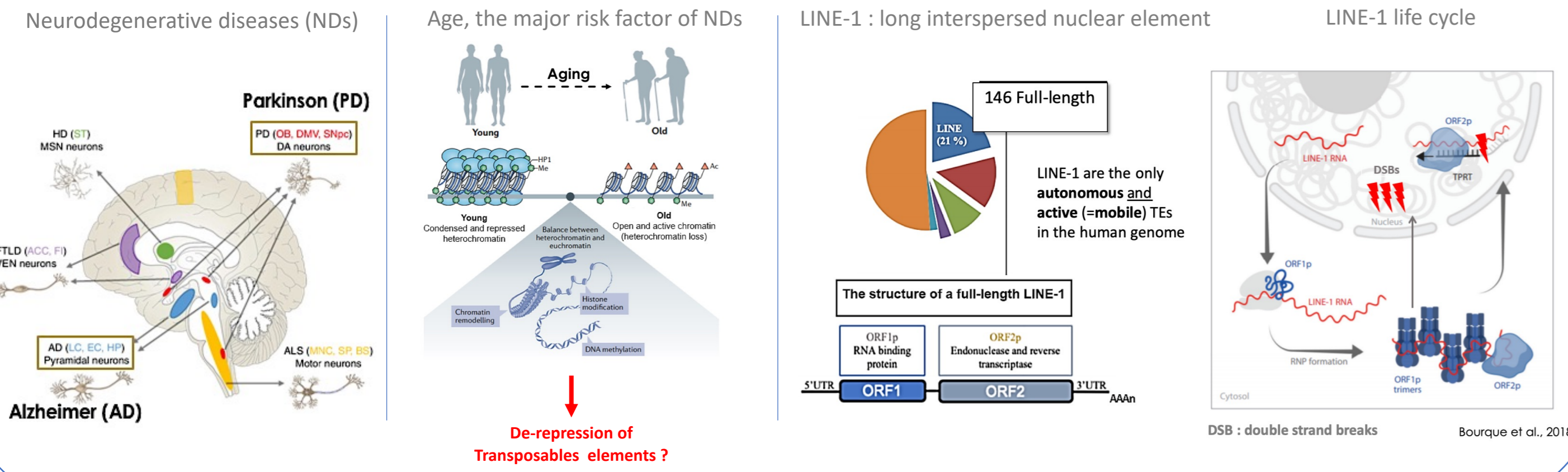
LINE-1 ORF1p is targeting nuclear envelope components in a human neuronal model of aging

Team : « Pathophysiology of transposable elements in the brain »

Rania Znaidi, Tom Bonnifet, Olivia Massiani-Beaudoin, Rajiv L. Joshi and Julia Fuchs

Introduction

Transposable elements (TEs) are emerging as novel culprits in neurodegenerative diseases (Peze-Heidsieck, et al., 2021) (Ravel-Godreuil et al., 2021). The effects of the activation of young, coding TEs from the LINE-1 family are not well known but include genomic instability and inflammation. We are studying the mechanisms through which LINE-1 RNA and proteins are linked to age-related neurodegenerative disorders like Parkinson's and Alzheimer's disease.



Objectives

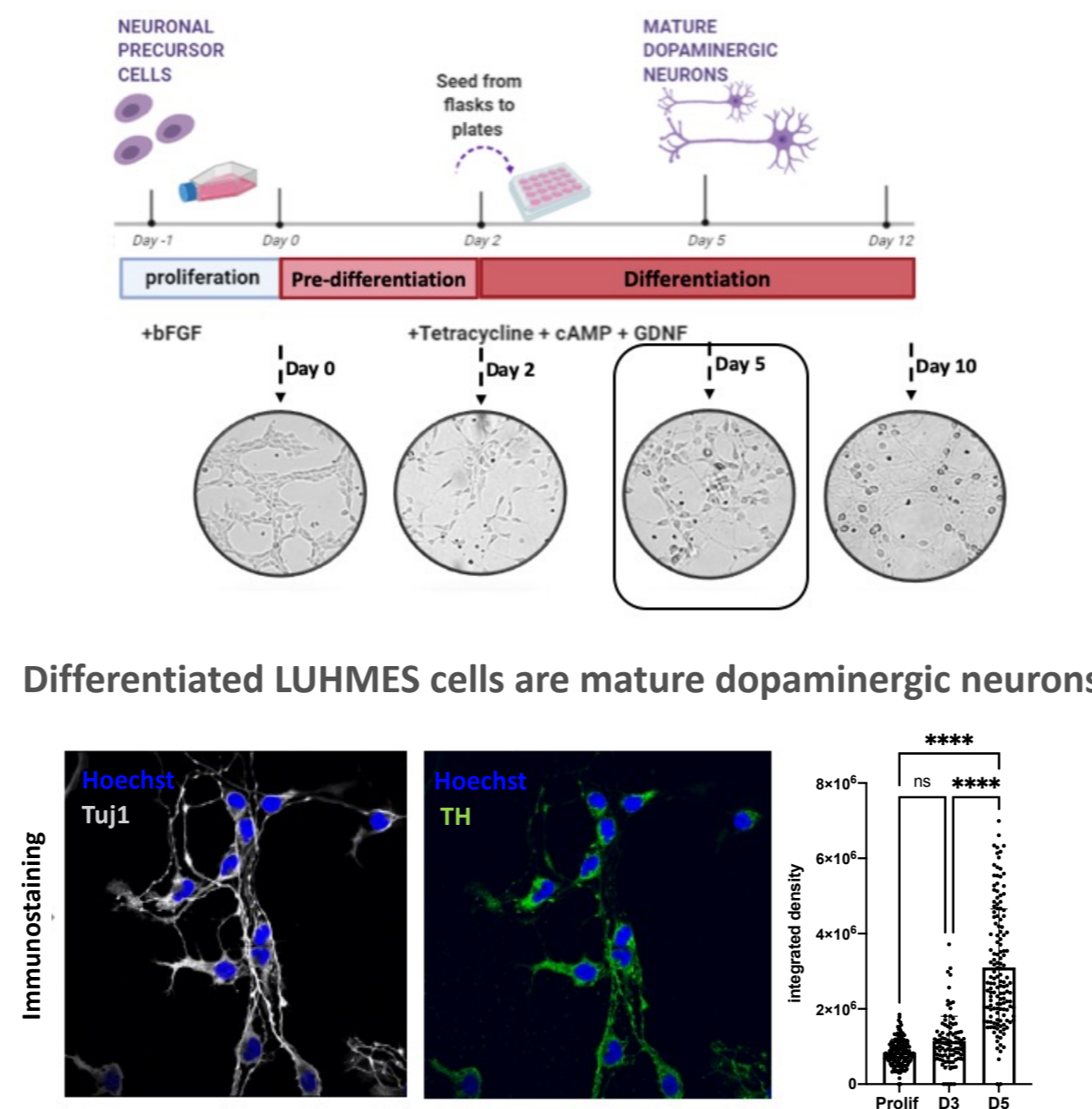
- I. Establishment of a cellular model of premature aging of human dopaminergic neurons
- II. Explore age-related nuclear dysfunctions and LINE-1 expression in the pathogenesis of PD/AD
- III. Therapeutic strategies to reverse the LINE-1-dependent aging phenotype in cell models

Models

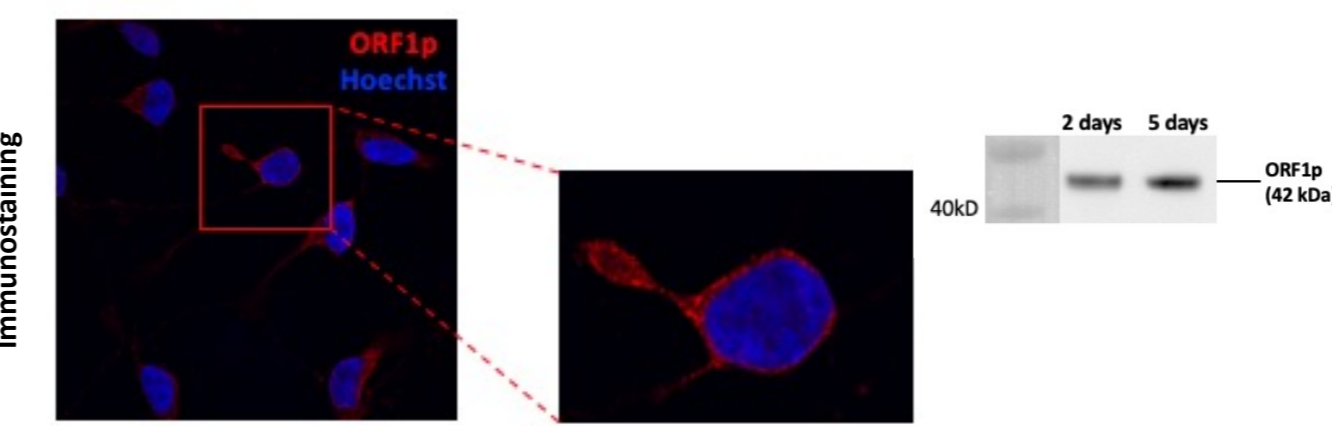
- **LUHMES** : Human Dopaminergic cell lines
 - Post-mortem human brain tissues (AD/PD)(Cingulate gyrus and frontal cortex)
-

Results

Cellular model of stress : LUHMES, human dopaminergic cell line

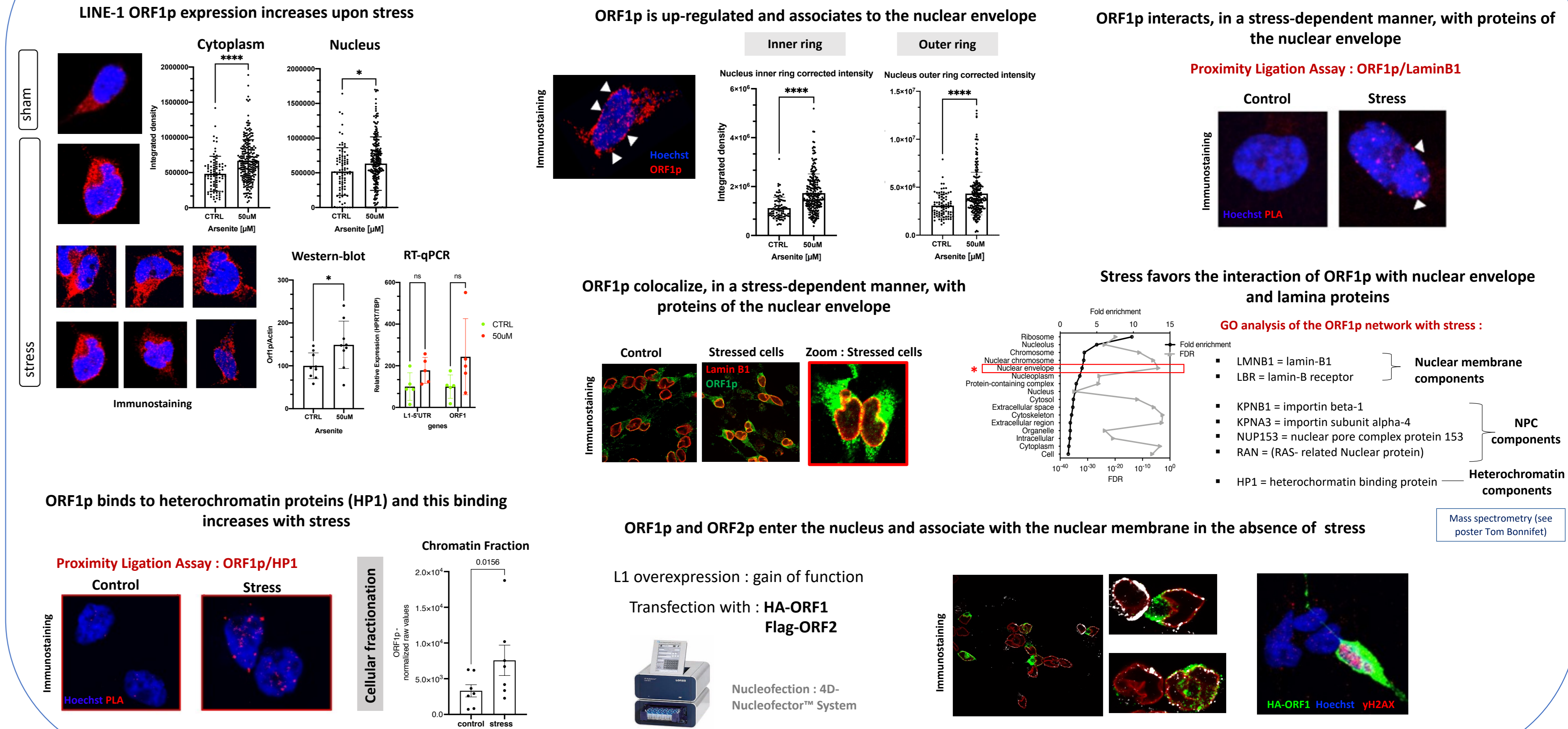


Mature human dopaminergic neurons express ORF1p at steady-state



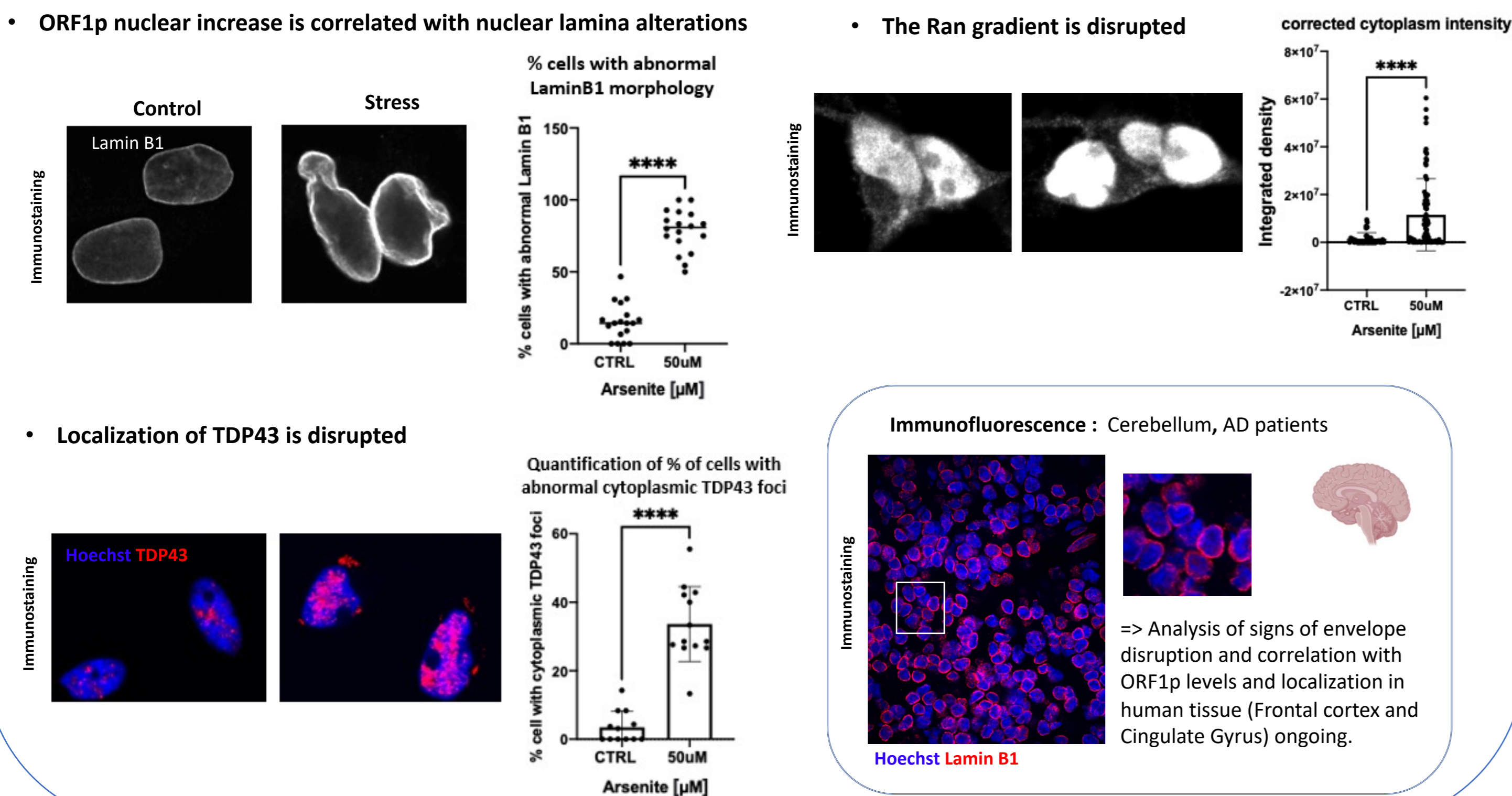
Results

ORF1p is up-regulated by oxidative stress in the cytoplasm, associates to nuclear envelope and translocates into the nucleus



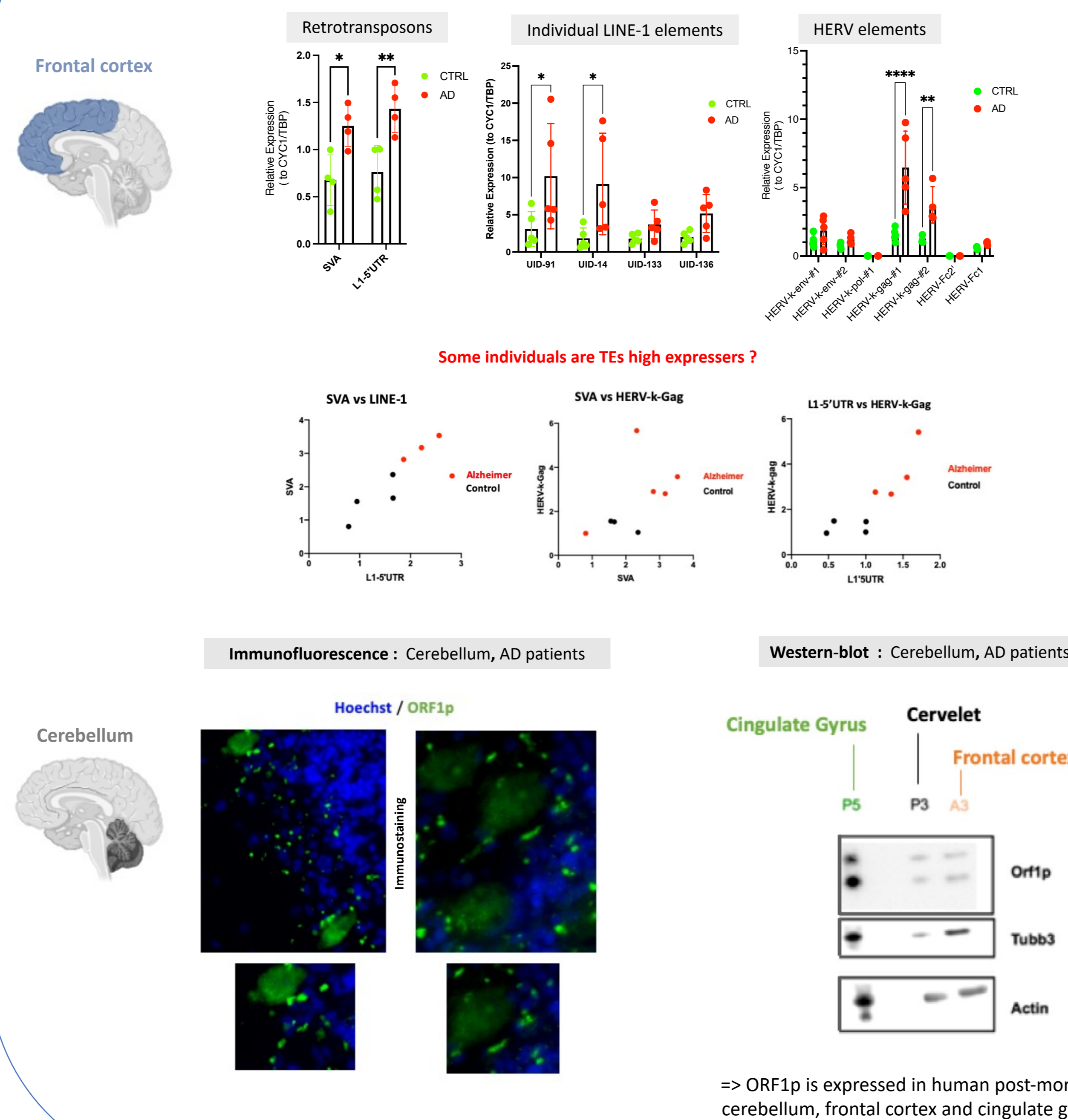
Results

ORF1p nuclear increase is correlated with nuclear lamina alterations and nucleocytoplasmic transport defects

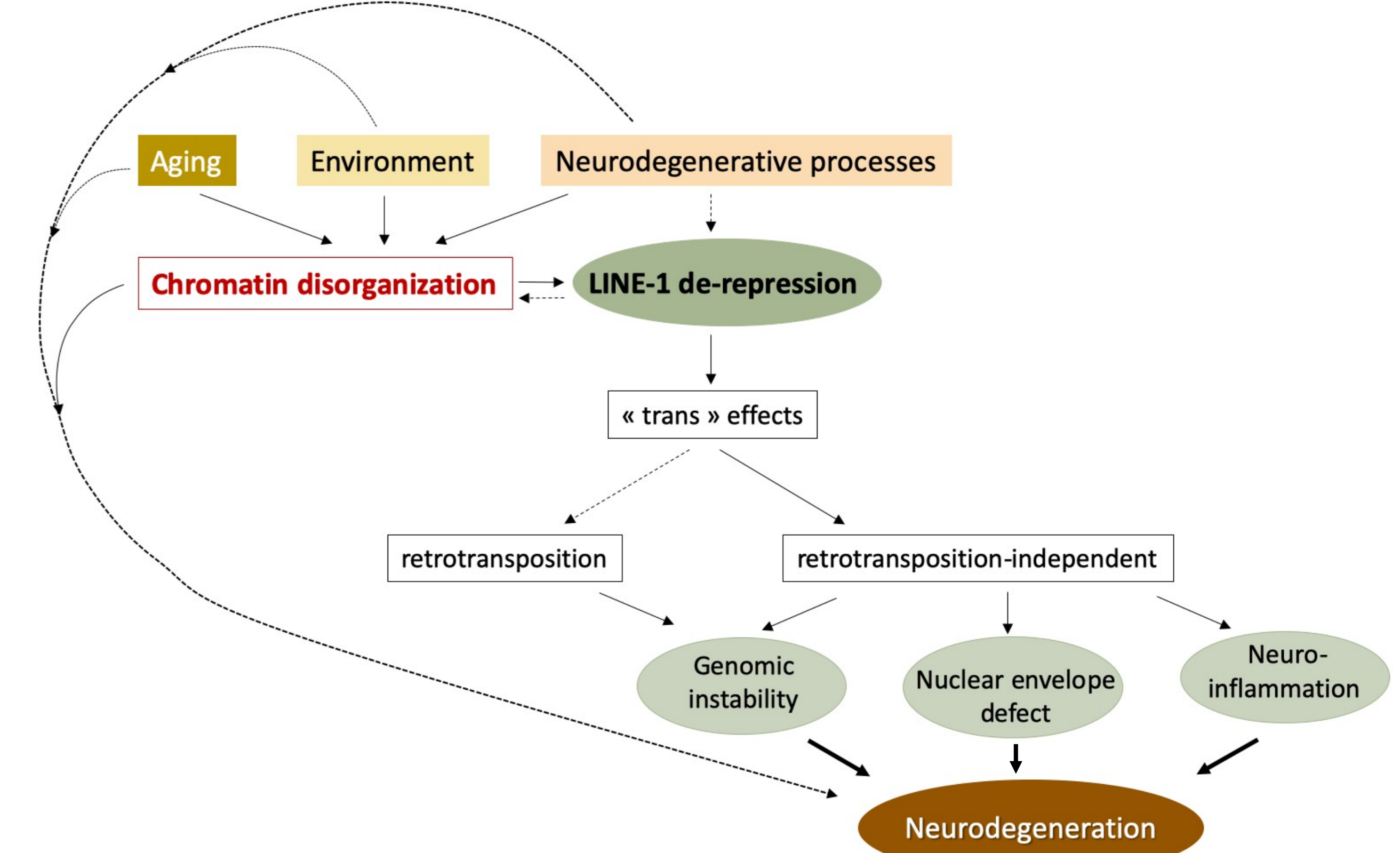


Results

Increase of TEs expression (LINE-1/HERV-k) in human frontal cortex of AD patients

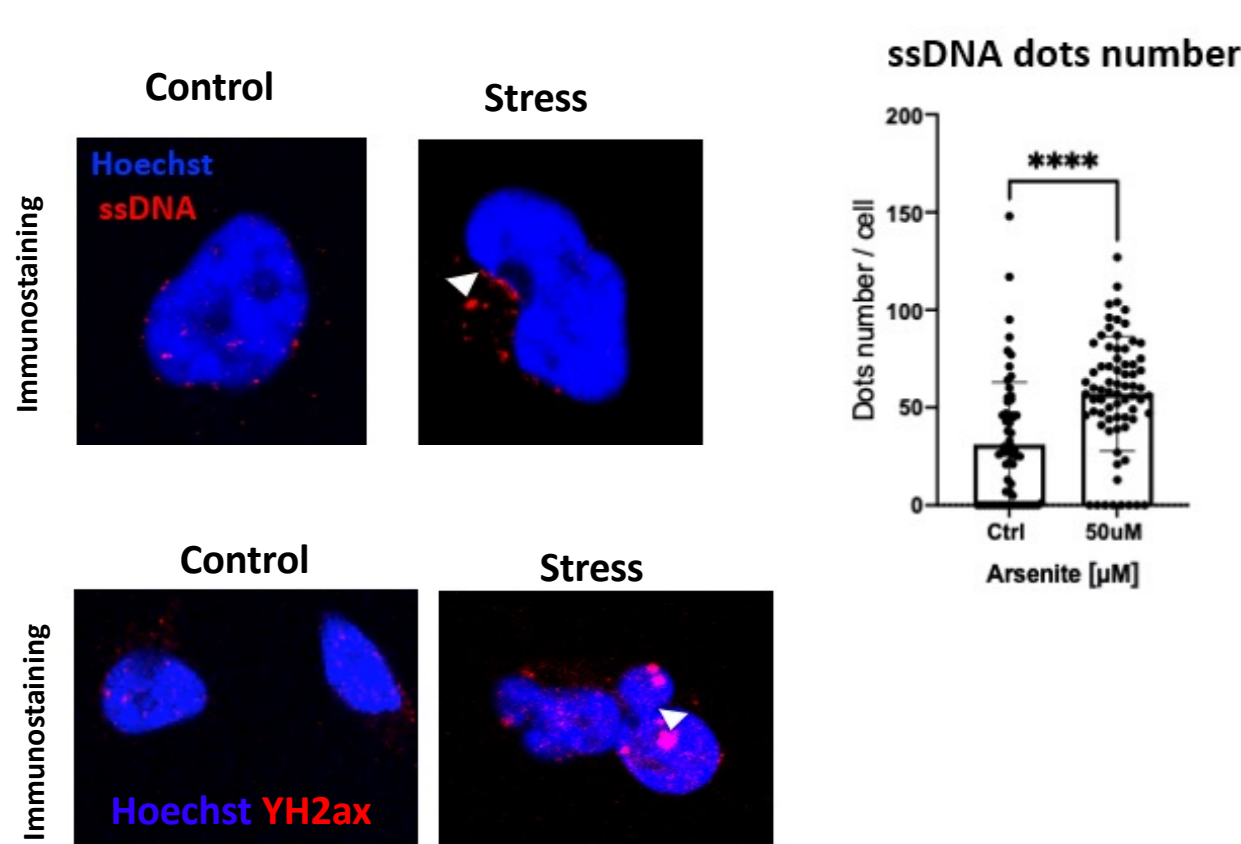


A new pathogenic axis of neurodegeneration



Results

ORF1p up-regulation correlates with ssDNA (neuroinflammation) and γH2AX accumulation (genomic instability)



Therapeutic strategies for neuroprotection

- **Anti-LINE-1 strategies** : RT inhibitors : Stavudine / siRNAs : against L1 ORF1p/ORF2p
- **Drug targeting nuclear transport** : "Ivermectin" (importin blocker)
- **Drug targeting nuclear envelope integrity** : Remodelin (Collab. R.Rodriguez, Institut Curie)

Conclusion

- Arsenite induced-oxidative stress causes LINE-1 upregulation (and other TEs : HERVs, not shown)
- ORF1p is up-regulated by ox. stress in the cytoplasm, associates to the nuclear envelope and translocates into the nucleus.
- The interaction of ORF1p with NPC and nuclear membrane components might cause disruption of nuclear envelope and nucleocytoplasmic transport.
- Altered nuclear morphology and nucleocytoplasmic transport are emerging features of neurodegenerative diseases (Liu et al., 2012 ; L. Gil et al., 2020).
- Strategies targeting LINE-1, LINE-1 import, or nuclear envelope integrity might be new therapeutic strategies for neuroprotection.

References :

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