A TDP-43 LINKED ALS MURINE MODEL

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Objectives

To characterise pathology in organotypic cultures prepared from a murine model of human TDP-43-linked ALS.

Materials

TDP-43 transgenic mice were previously created in order to assess the effect of TDP-43 expression and mutation in vivo (Mitchell et al, 2015). Mice carrying human wild-type TDP-43 (TDP-43WT) don't have a clinical or pathological phenotype, while mice carrying Q331K mutant TDP-43 (TDP-43Q331K) have a progressive non-lethal motor phenotype with a number of pathological hallmarks found in ALS patients. To see if we could recapitulate pathologic findings in vivo in organotypic slice culture model, we conducted a time course study on TDP-43Q331K mice and non-transgenic littermates.

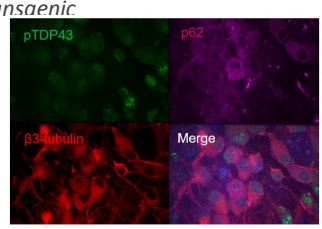
Methods

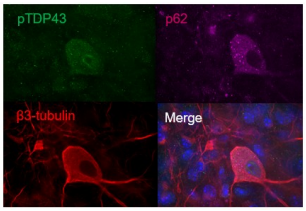
Spinal cord organotypic slice cultures were prepared from Q331K single mutant and non-transgenic (NTg) littermates and maintained for 2, 4 and 6 weeks. After 4% paraformaldehyde fixation and harvesting, an immunohistochemical analysis for pTDP and p62 was performed.

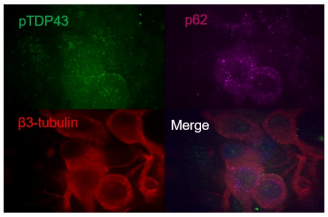
Results

Organotypic slice cultures from Q331K single mutant transgenic mice generally show an increase in the pathological markers of TDP-43-linked ALS compared to NTg mice. pTDP-43 tends to be more cytoplasmically localized in TDP-43Q331K slice cultures, compared to non-transgenic ones, and appears to form small cytoplasmic aggregates over time. In contrast, p62 shows evidence of aggregates in both NTg and TDP-43Q331K cultures at all time points, possibly due to the stress of the culture environment. However, there appears to be a marked increase in p62 aggregates over time in the TDP-43Q331K cultures compared to NTg, thus the presence of the mutant TDP transgene appears to increase pathology development

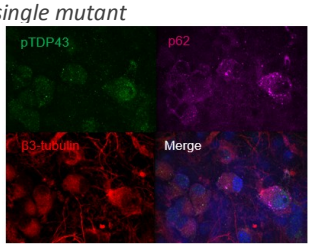
Non-transgenic

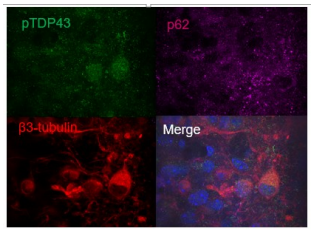


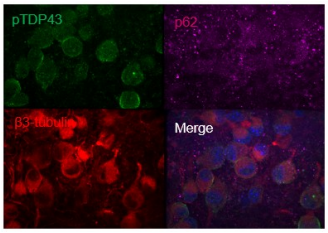




Q331K *single mutant*







2 weeks cultured *4 weeks cultured* *6 weeks cultured*

Discussion

TDP-43-linked ALS include mostly sporadic ALS cases, familial ALS cases (excluding SOD1- and FUS-associated ones) and MND-FTLD cases. It is known from post-mortem studies that the brain and the spinal cord of these patients have neuronal and glial inclusions that are immunoreactive for pTDP-43. Furthermore, TDP-43 aggregates colocalize with the adaptor protein p62. This murine model presents clinical and pathological features that resemble the human disease.

Conclusions

This model is a reliable model of the disease and organotypic slice cultures can provide useful in vivo informations about its pathological stages.

References

Mitchell JC, Constable R, So E et al., Acta Neuropath. Comm. 2015; 3:36