A NEURONAL MODEL OF THE DEMENTIA FENIB

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The serpinopathies are human pathologies caused by mutations that promote polymerisation and intracellular deposition of proteins of the serpin superfamily, leading to cell toxicity and death. The dementia FENIB (familial encephalopathy with neuroserpin inclusion bodies) is caused by mutations in the neuronal serpin neuroserpin (NS) that lead to its polymerisation within the endoplasmic reticulum (ER) of neurons. Our aim is to understand how NS polymers accumulate within the ER and what is the mechanism of their cellular toxicity, by creating a neuronal model of the dementia FENIB.
We have generated stably transfected neural progenitor cell lines from mouse brain cortex, expressing the control protein GFP (green fluorescent protein) or human NS, in three different versions: wild type, the mutant variant G392E that causes severe FENIB, and deltaNS (a control truncated version). We have characterised these cells in the proliferative state and after differentiation to neurons using RT-PCR, SDS and non-denaturing PAGE and western blot, ELISA and immunocytochemistry. Our results show that wild type NS is secreted as a monomeric protein into the culture medium, while G392E NS forms polymers that are mostly retained within the ER. DeltaNS is absent at steady state due to its rapid degradation, but it is easily detected upon proteosomal blocking. Regarding intracellular distribution, wild type NS is found in partial co-localisation with a Golgi marker, while G392E NS fully co-localises with an ER marker.
We have thus created a neuronal model system that recapitulates the main features of FENIB, which we have used to perform a transcriptomic comparison of GFP and G392E NS expressing cells by RNAseq. We have detected several genes with altered expression and we are now characterising them to discover cellular responses to the presence of NS polymers within the ER of neurons.