Alzheimer’s (AD) and Huntington’s disease (HD) display changes in the function and abundance of the Ca2+ machinery at the endoplasmic reticulum (ER) which result in alterations in Store-Operated Calcium Entry (SOCE). We hypothesized that these changes initiate or propagate the neurodegenerative process in these diseases and have so far studied the role of key players of SOCE, the Ca2+ sensing protein STIM1 (Henke et al., 2012) and the Ca2+ channel Orai1 (Henke et al., 2013), in oxidative stress which is implicated in neuronal degeneration in AD and HD. This resulted in the identification of Orai1 as a channel activated by oxidative stress which then leads to a cytotoxic Ca2+ overload ultimately causing cell death. Orai1 therefore constitutes a potential drug target. We have also investigated changes in the expression levels of the so-called calciosome in different models of HD which also resulted in the identification of Ca2+-regulated proteins that might play a role in the pathophysiological cascade leading to neuronal degeneration (Czeredys et al.). To analyze the role of these changes in vivo, we have now established a novel transgenic mouse model of HD, the Q155 mouse, in the laboratory. These mice are on the C57Bl6 background which will facilitate the future analysis of the identified target proteins by crossbreeding.

Prof. Elena Kaznacheyeva team:

Irreversible neurodegenerative disorders such as Alzheimer’s disease (AD) and Huntington’s disease (HD) had no effective treatment due to lack of specific drugs to cure these diseases or to delay their progression. It is clear that new target proteins pathways need to be addressed. We proposed to approach this problem by targeting calcium (Ca2+) homeostasis as a potential site for new treatments as both diseases are accompanied by profound changes in the intracellular Ca2+ homeostasis. We hypothesize that changes in the function or abundance of the Ca2+ machinery at the endoplasmic reticulum (ER) result in changes in Store-Operated Calcium Entry (SOCE) as well as voltage-gated calcium channels (VGCC) activity and that this initiates or propagates the neurodegenerative process in AD and HD. In current project we used electrophysiological measurements and calcium imaging experiments with AD and HD cell models to detect calcium channels activity impairments. We demonstrated that the amplitude of SOC current in MSN neurons infected with pathological expended Huntington (Htt138Q) was dramatically increased. This data was consistent with our previous data obtained in neuroblastoma SK-N-SH cell line. Moreover we detected that TRPC1 and Orai1 channels subunits had a key role in pathological SOC pathway in HD neurons. It has been found previously that familial AD presenilin-1 (PS1) gene mutants disrupt calcium homeostasis in hippocampal neurons disrupting calcium storage in the lumen of endoplasmic
reticulum (ER). In current project we detected that the loss of ER calcium sensor STIM1 activity is key event in both cases of changes in L-type and SOC channels activity due to ER calcium overload in cells with expression of familial AD mutant PS1 M146V.

**Prof. Jacek Kuźnicki team:**

The aim of our study was to investigate whether mutated HTT is responsible for the changes in the expression of calciosome genes, and if so, which of such changes might explain the alterations of calcium homeostasis observed in HD. Using custom-made TaqMan low-density arrays (Life Technologies) and individual real-time quantitative polymerase chain reaction (RT-qPCR), we studied changes in gene expression in two HD models. We found increased expression of few components of the calcium signalosome and genes indirectly involved in calcium homeostasis in YAC128 brains. We identified that approximately 32% of the analyzed genes in the striatum exhibited statistically significant changes in expression in YAC128 mice compared with control mice. To verify the significance of mRNA measurements protein analysis was done using western blotting. We found an increase in HAP1 protein in brain extracts from striatum of YAC128 mice as compared with control animals. Cellular models of HD was used to detect the early, direct effects of mutant HTT. We observed a statistically significant reduction of calcium influx during SOCE, but not calcium content in the ER, in inducible huntingtin-expressing PC12 cells as compared with control un-induced cells. Reduced activity of the SOCE in induced PC12 cells might be explained by down-regulated of some genes as shown by RT-qPCR. Thus, each of studied models exhibited characteristic features of HD, such as the deposition of HTT aggregates mainly in the nuclei of inducible PC12 cells and nuclei of MSNs in the striatum in YAC128 mice. Our data indicate that the dysregulation of calcium homeostasis correlates with changes in the gene expression of members of the calciosome, but the two models used in this study exhibit distinct changes in gene expression and may only partially resemble the human disease.

**Papers with Target-SOCE acknowledgments:**


