Linking endoplasmic reticulum stress to Autism Spectrum Disorders
Flores Lietta Favaloro, PhD student, XXVIII ciclo

Mutations linked to autism spectrum disorders are found in genes encoding for the synaptic adhesion proteins Neuroligins (NLGNs). In particular, the R451C mutation in NLGN3 causes a local misfolding followed by the retention of the protein in the Endoplasmic Reticulum (ER) (De Jaco et al, 2010). Misfolded protein accumulation in the ER leads to the activation of Unfolded Protein Response (UPR), which aims to restore normal ER function, lately implicated in the pathogenesis of several neurological diseases (Roussel et al, 2013). We have generated a PC12 Tet-On cell line with inducible expression of either wild type or R451C NLGN3 in order to investigate whether overexpression of the mutant protein would lead to the activation of the UPR. Our data (Ulbrich et al, *submitted*) show that the R451C mutation in NLGN3 activates distinct UPR signaling pathways downstream of the ATF6, IRE1α and PERK stress sensors and leads to the up-regulation of UPR target genes, such as BiP and CHOP.
In order to study the effects of the R451C mutation in vivo and a possible correlation with ER stress, we are currently focusing our work on the R451C NLGN3 Knock In (KI) mice carrying the substitution in the endogenous gene. NLGN3 KI mice have been reported to exhibit a gain of function phenotype characterized by autistic-like behaviors and changes in synaptic transmission, not observed in the NLGN3 Knock Out mice (Tabuchi et al, 2007). In order to assess whether the activation of UPR is detectable in the R451C NLGN3 mice strain, we have quantified the expression of UPR markers in adult mice brain, and compared this with the parental mice strain. Preliminary data suggest a differential regulation of key UPR target genes in the KI animals. As the onset of the autism spectrum disorders occurs early during childhood, we are currently focusing our study on the alterations induced by the R451C mutation during development.