Histone post-translational modifications in epilepsy disorders.

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Following the time interval known as the “latent” or “silent” period, animals exposed to status epilepticus develop spontaneously recurrent seizures (Avoli et al. 2002) and molecular changes in limbic circuits occur as demonstrated also by the increased expression of immediate early genes (IEGs, Biagini et al. 2005, 2008). These changes occur also in patients presenting with mono-lateral hippocampal sclerosis, a common (up to 70%) finding that is associated with antiepileptic drug resistance in approximately 35% of cases.

Recent studies in TLE kainate model have shown that starting a few minutes after kainate or pilocarpine injection, histone H3 phosphorylation and H4 acetylation changes occur in hippocampal sub-regions, and modulate the promoters of several target genes such as c-fos, jun, BDNF and CREB (Taniura 2006). Moreover, pre-treatment with curcumin, a histone acetyltransferase (HAT) inhibitor, partially blocks kainate-induced c-fos and c-jun induction as well as seizure severity. From preliminary analysis with two antibodies, one directed to acetylated H3 histone (H3K14ac) and the other directed to phosphoacetylated one (H3K14acS10P), we know that there is a widespread activation in different areas of the cortex such as entorhinal cortex, perirhinal cortex and insula, already by 24 hours.

Since we want to assess the activation of the transductional machinery induced by spontaneous seizures, we decided to analyze animal with spontaneous seizures. For this purpose I will work with histone post-translational modifications that normally are involved in transcription regulation and chromatin silencing. The different modifications of the histone N-terminal tails can be selectively recognized as epigenetic imprints, therefore leading to a unique and specific answer at the transcription level.

In order to do this I will also use a murine model of the fragile X syndrome (FXS), a syndrome characterized by many symptoms such as intellectual disability (from learning disabilities to severe mental retardation and autism), and behavioral characteristics (attention deficit disorders, speech disturbances, hand flapping, autistic behaviors). This impairment is caused by a mutation in a gene on the X chromosome (FMR1 - fragile X mental retardation 1 gene) that normally produces an important protein called FMRP; this protein regulates the trafficking of various
mRNAs and their transduction in protein products inside of dendrites and axons of neurons as well as in cells of other tissues.

We decided to use the FMR1-knockout (FMR1-KO) mouse mainly because in this model it has been possible to reproduce the principal clinical features of the human disease, including seizures. The propensity to develop seizures in FMR1-KO mice could be related with the recently demonstrated alterations in several neurotransmittorial systems, both excitatory and inhibitory.

My future PhD work will focus on the epigenetic expression of some markers in Fragile X syndrome and TLE, trying to understand what are the mechanisms involved in neuronal hyperexcitability in epilepsy.

The main goal of this project is to provide coherent evidence on the existence of an imbalance between excitatory and inhibitory systems and the propensity to develop seizures in established animal models of different epileptic syndrome.