**Induced epigenetic effects on glutamate system genes as a neurodegeneration therapy**

We developed a detailed characterization of the molecular events leading to spinocerebellar ataxia type 28 (SCA28), a rare form of cerebellar degeneration (MALTECCA et al. 2008; MALTECCA et al. 2009; MALTECCA et al. 2012) caused by mutations of the AFG3L2 gene. AFG3L2 coassembles with paraplegin into multimeric complexes, called the m-AAA proteases, in the inner mitochondrial membrane (KOPPEN and LANGER 2007). We demonstrated that the haploinsufficient Afg3l2+/- mouse recapitulates the features of SCA28 patients (MALTECCA et al. 2009). The SCA28 mouse displays motor incoordination due to dark cell degeneration (DCD) and loss of Purkinje cells (PCs). DCD of PCs in the SCA28 mouse is quite particular since it originates from mitochondrial dysfunction, while in other forms of SCA it is associated to a dysfunctional glutamatergic system. We demonstrated that the triggering event of PC-DCD in SCA28 mice is a defective calcium internalization in mitochondria, which in turn causes alteration of calcium homeostasis under normal glutamate stimulation, thus mimicking excitotoxic-mediated DCD.

We provide the first evidence of a pre-clinical treatment of this disease by leveraging on a peculiar side activity of beta-lactam antibiotics that are able to increase the expression of the glutamate transporter GLT1/EAAT2 in astrocytes (ROTHSTEIN et al. 2005). This enhanced GLT1 expression provokes the reduced glutamate stimulation of PCs and, therefore, protects Purkinje cells from calcium-excess degeneration, thus rescuing the clinical and neuropathological signs of ataxia (MALTECCA et al. 2015). This knowledge allowed us to formulate a possible treatment of the preclinical SCA28 model with ceftriaxone (CEF), a known antibiotic, which revealed to be extremely effective in preventing or ameliorating the ataxic symptoms (MALTECCA et al. 2015). Based to a strong rationale, this project proposes to test the same pharmacological approach with CEF on other forms of SCA, such as SCA2 and SCA3, which represent approximately 50% of all autosomal dominant forms of spinocerebellar ataxia.

**Cited references**


