“Role of autophagy in oligodendrocytes in perinatal cerebral hypoxia-ischemia”

Over the last years, **my group has proposed a new mechanism involved in neuronal death** after **perinatal cerebral hypoxia-ischemia** (HI), which is an abnormally elevated activation of (macro)autophagy. **Autophagy** is an essential physiological degradation process by which the cell engulfs damaged organelles, toxic agents and long lived proteins in autophagosomes before to eliminate them in lysosomes after fusion. However, we provided evidences in different neonatal models of acute brain injury, such as stroke and cerebral hypoxia-ischemia, that autophagy is excessively activated in neurons and its inhibition (by pharmacological or genetical means) provides strong **neuroprotection**.

We provided evidences that **autophagy could mediate neuronal death by two main mechanisms**. Autophagy **could act upstream of another mode of cell death**, such as apoptosis. In both *in vitro* and *in vivo* models of apoptosis and neonatal cerebral HI, we demonstrated that autophagy inhibition could influence apoptosis suggesting that autophagy inhibition has to be considered as a therapeutic strategy in neuronal pathologies involving apoptosis. Second, **autophagy**, in certain conditions, **could trigger neuronal death by itself**. We identified and characterized autosis, a Na+K+ ATPase-dependent type of autophagic cell death, in dying neurons of the CA3 hippocampal region following neonatal cerebral HI.

More clinically relevant, our group also demonstrated, for the first time, that autophagy is also enhanced in the brain (thalamus and lentiform nuclei) of died human newborns with severe hypoxic-ischemic encephalopathy (HIE) suggesting that **autophagy inhibition should be considered as a primary target for the development of neuroprotective strategies for human HIE**.

However, following perinatal brain injuries, **other cell types, such as oligodendrocytes, are affected and are associated to long term deficits**. Since previous studies (including ours) suggest to develop **neuroprotective strategies based on selective autophagy inhibition of deleterious neuronal autophagy in the context of HIE,** it appears important to evaluate the involvement and the role of autophagy in oligodendrocytes, in order to determine whether autophagy inhibition could be beneficial or deleterious for other cell types in the context of perinatal brain injuries. This appears to be a critical step to determine whether autophagy inhibition should be targeted to a specific type of brain cell or if autophagy inhibition could be widely applied to the HI brain.

Models: Primary oligodendrocytes cultures, Primary oligodendrocytes and cortical neurons co-cultures and *in vivo* models of neonatal cerebral HI

Main techniques: Western blot, immunocytochemistry and confocal microscopy, electron microscopy, plasmid transfection, virus production and infection for protein knockdown or overexpression, time lapse imaging, lysosomal enzyme activity assays, cell cultures, *in vivo* models of cerebral HI, behavioral tests.