**CONTRIBUTION OF ASTROCYTES TO NEUROGENIC DEFICITS ASSOCIATED WITH DOWN SYNDROME**

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Down syndrome (DS) is a neurodevelopmental disorder caused by the triplication of human chromosome 21 and the most common genetic cause of intellectual disability. A well characterized preclinical model for DS is the Ts65Dn mouse line, which bears segmental trisomy for a distal region of Mmu16 containing approximately 55% of Hsa21 conserved genes. This model shows reduced proliferation of neural progenitor cells (NPC), reduced neurogenesis, with, in parallel, increased gliogenesis and, importantly, cognitive impairment (Bartesaghi et al., 2011). Astrocytes provide neurons with metabolic and structural support, but also regulate neurogenesis and brain wiring. The pathological role of astroglia in DS has not been investigated to a large extent. In recent years, several groups have reported that DS astrocytes are not only more proliferative, but they also display functional alterations that can directly affect properties of NPC and their progeny (Garcia et al., 2010; Chen et al., 2014).

In our laboratory we are interested in understanding the cross-talk between NPC and astrocytes and its relevance in cell fate specification of neural progenitors. Recently, we identified novel signalling pathways which may modulate astrocyte-derived pro-neurogenic and anti-neurogenic soluble signals (Cvijetic et al., 2017).

We have prepared different primary cell cultures from Ts65Dn (Trisomic, TS) and euploid (EU) pups (1-2 DPN). In particular, we generated NPC from the subventricular zone (SVZ) and astrocytes from cortex/hippocampus of these pups. We then investigated, in vitro, the influence of TS and EU astrocyte-conditioned media (ACM) on neuronal/glial differentiation and survival of both TS/EU NPC. We showed that both TS and EU ACM increased astrogliogenesis and reduced the apoptotic rate of TS/EU NPC. Conversely, only TS ACM, but not EU ACM, negatively affected neuronal differentiation of EU NPC.

In the future we will try to identify, through a proteomic approach, the soluble factors which may be differentially released by TS and EU astrocytes. Moreover, we will investigate if such factors may also affect other NPC properties, like, for example, their proliferative potential which is known to be significantly reduced in DS. Such an effort can potentially increase our current knowledge on the pathophysiology of DS and suggest potential therapeutic targets for this neurodevelopmental disorder.

Bartesaghi et al. (2011). Reviews in the Neurosciences. 22(4), 419-455.

Chen et al. (2014). Nat Commun. 5, 4430.

Cvijetic et al. (2017). Glia. 65(1), 169-181.

Garcia et al. (2010). PLoS One. 7(11), e50724.