Stéphanie Baulac – Michael Prize 2019

Dr Baulac was awarded with the 2019 Michael Prize to acknowledge her work on the genetics of focal epilepsies with malformations of cortical development (MCD) and on functional studies to unveil their underlying pathogenic mechanisms.

In 2013, her team contributed to the identification of a novel epilepsy gene, DEPDC5, which is to date recognized as the most frequently mutated gene in familial focal epilepsies (Ishida et al., 2013). DEPDC5, as opposed to many other epilepsy genes, does not encode an ion channel, but a repressor of the mechanistic target of rapamycin (mTOR) signaling pathway, a master regulator of cell physiology regulating growth, proliferation and protein synthesis. Mutations in DEPDC5 have emerged as a major cause in a broad spectrum of focal epilepsies ranging from nonlesional focal epilepsies to severe forms associated with an MCD, in particular focal cortical dysplasia (FCD). FCDs are the cause of drug-resistant childhood-onset epilepsy and their treatment often require neurosurgery to control seizures. Pathologically-relevant brain tissues obtained from epilepsy surgery offers unique opportunities for research purposes. Why only a subset of patients among families with DEPDC5 mutations develops FCD, while other affected family members have apparently nonlesional epilepsy, led us to postulate the occurrence of Knudson's two-hit mechanism where a somatic second mutation, arising during brain development triggers a focal malformation.

To pursue the hypothesis that a somatic second-hit mutation may be responsible for the dysplastic lesion, we performed conventional Sanger sequencing of DEPDC5 in the DNA extracted from a formalin-fixed, paraffin-embedded (FFPE) resected brain tissue. We identified a brain-only mutation in DEPDC5 in addition to the germline mutation which segregated in the family. However, we were not able to assess the mosaic levels of the somatic mutation, neither to confirm it is located on trans position from the germline mutation (and thus prove a biallelic inactivation) due to the low quality of FFPE-extracted DNA (Baulac et al., 2015).

Lately, we provided the proof of concept, from postoperative human tissue, that a biallelic two-hit – brain somatic and germline – mutational mechanism in DEPDC5 causes focal epilepsy with FCD. We were able to definitively prove the existence of a somatic second-hit DEPDC5 mutation in a patient with an FCD and a DEPDC5

germline mutation by demonstrating the DEPDC5 somatic mutation was in trans configuration to the germline. We further discovered a mutation gradient with a higher brain mosaicism rate in the epileptogenic seizure-onset zone than in the surrounding epileptogenic zone. We also confirmed that the DEPDC5 mutations caused mTORC1 hyperactivation in enlarged NeuN+ neurons present in the resected brain specimen (Ribierre et al., 2018).

Subsequently, we demonstrated that biallelic inactivation in a Depdc5 brain somatic knockout mouse model, accurately recapitulates the human condition. We reported the generation of focal malformations displaying neuropathological hallmarks of FCDs (cortical dyslamination, dysmorphic neurons), as well as spontaneous seizures followed by SUDEP-like events. We further unveil a key role of Depdc5 in shaping dendrite and spine morphology of excitatory neurons. This mouse model therefore serves as a valuable novel functional platform for future clinical research directed towards the development of drugs acting on the mTOR pathway.

Overall, her studies have important implications for patients and their families, offering the possibility of genetic testing. Nowadays, DEPDC5 is routinely screened in clinical diagnostic centers. This work also emphasizes promising therapeutic avenues for treating refractory focal epilepsies with mTOR-targeting molecules. Indeed, FCD-related epilepsies remain difficult to treat. While the standard treatment is surgical resection of the epileptogenic zone, only 30–50% of these patients will properly manage their seizures following surgery, while others are not operated because of surgical inaccessibility. There is therefore an urgent need for new medical therapies.