Identification of pathogenic mechanisms involved in DEPDC5-related epilepsy

Team: Genetics and physiopathology of familial epilepsies (S. Baulac)

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Epilepsy: a major medical burden
DEPDC5 the gene the most frequently mutated in familial focal epilepsy

- Spontaneous and recurrent seizures
- Hypersynchronization of neuronal networks

- 1% of the population

Interest in genetic cause of focal epilepsy:

- 2013: **DEPDC5** mutations have been identified in focal epilepsies
  - 20% of familial forms
  - **DEPDC5** mutations are loss-of-function
  - 55% are drug-resistant
  - Increased risk of SUDEP linked to **DEPDC5** mutations
    (Sudden Unexpected Death in Epilepsy)
DEPDC5, a repressor of mTORC1

mTORC1 is an ubiquitous cellular pathway

- mTORC1 pathway acts on:
  - Cell growth
  - Proliferation
  - Apoptosis
  - Gene transcription
  - Protein synthesis

The brain function of DEPDC5 remains unknown

Adapted from Bar-Peled et al., 2013
Expression pattern of DEPDC5

Western blot and immunohistochemistry done on mouse samples

- DEPDC5 is found in organs related to SUDEP

- In the brain, DEPDC5 is mostly expressed in neurons

- SUDEP pathomechanisms

Identification of novel mechanisms in DEPDC5-related epilepsy
Which are the pathways regulated by DEPDC5 involved in development and neuronal excitability?

- Transcriptomics (by RNA-seq / Integragen)
- Preclinical mouse models of DEPDC5-deficiency:
  - Embryonic model
  - Adult model
Developmental pathways regulated by DEPDC5

Embryonic time point

- **Full Depdc5 KO**
  - Lethal at Embryonic day 14.5
  - WT | KO
    - 14.5 dpc
  - With brain and heart malformations

- **Lack of clustering for the genotype**
  - Unsupervised analysis

Collection of E14 samples

- Whole brain
- Whole heart

High morphological heterogeneity of embryos?
Cortical pathways regulated by DEPDC5

Adult time point

- Neuronal conditional Depdc5 KO
  DEPDC5-cKO display spontaneous epileptic seizures, and SUDEP

Fatal seizure occurring after 3 months

Collection of samples before seizure
  (Somatosensory cortex)
Volcano plot of protein coding genes:
> 500 genes dysregulated in KO (0.5>FC>2)

Enrichment pathways:

56 OVEREXPRESSIONED
- mTOR pathway
  \( Eif4a2, Cdkl2, blc2l11, Rps6k, \ldots \)
- GO: Receptor regulator activity
  \( Bdnf, Wnt2/9b, Nts, Calca, Adm2 \)
- Reactome signaling by GPCR
  \( Casr, Nts, Drd4, Calca, Mc4r, Adm2, Gpr55 \)

20 UNDEREXPRESSIONED
- Morphogenesis (Wnt pathway)
  \( Sfrp5, Myoc \)
THANK YOU FOR YOUR ATTENTION!
And thanks for all collaborators

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