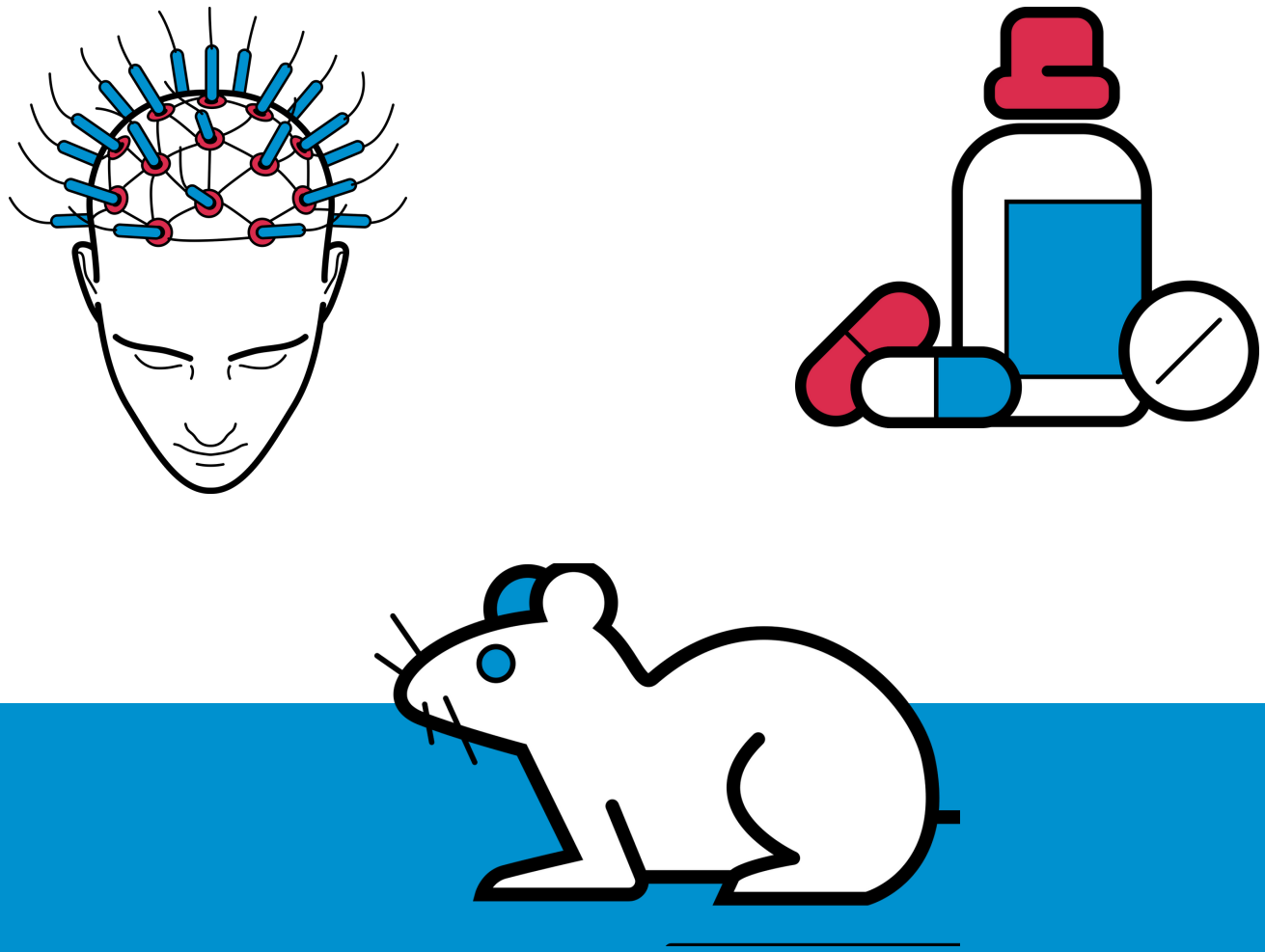
THE ROLE OF MTOR IN FOCAL EPILEPSY

FROM BEDSIDE TO BENCH AND BACK



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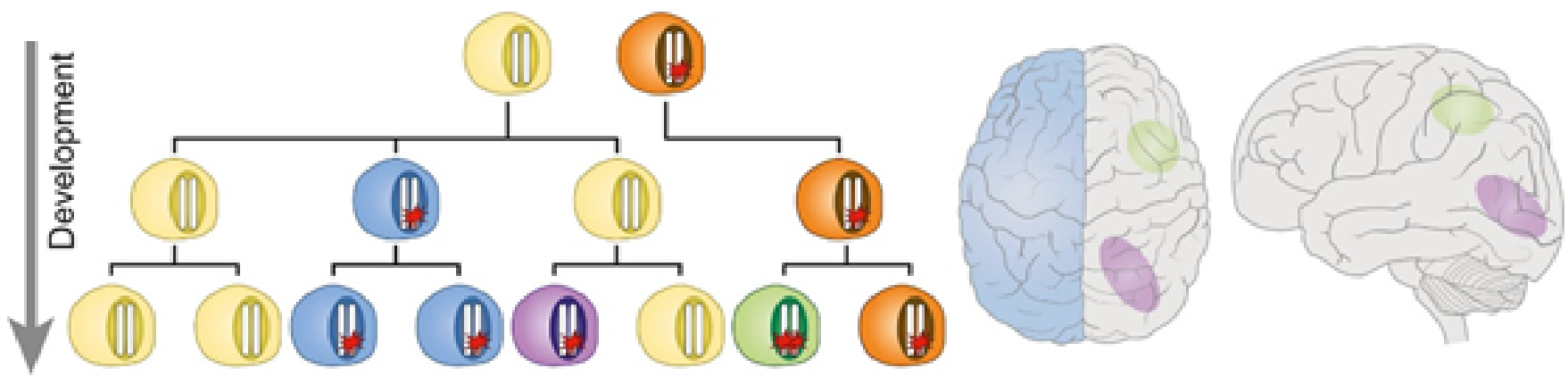
MALFORMATIONS OF CORTICAL DEVELOPMENT (MCD) are

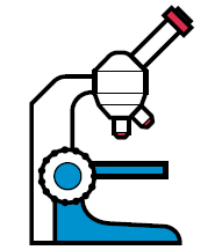
- a major cause of severe refractory epilepsy and intellectual disability
- one of the most frequent histopathology found in focal epilepsy patients that undergo surgery
- represent a wide range of lesions including hemimegalencephaly (HME), polymicrogyria (PMG), focal cortical dysplasia (FCD), macro- or microcephaly, lissencephaly, heterotopias among others.

The pathological features depend on

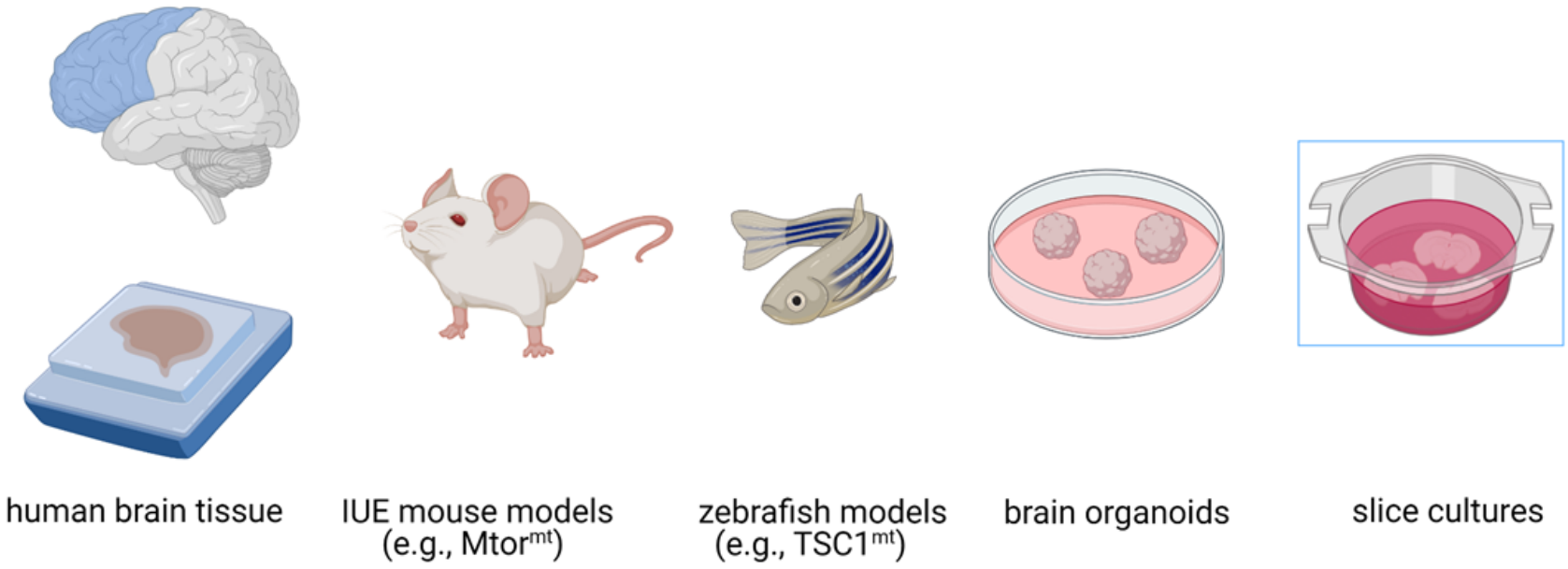
- timing during brain development: the earlier the abnormality occurs, the larger the resulting brain lesion
- the cause, e.g., abnormal proliferation, differentiation, or neuronal migration



MCD AND EPILEPSY



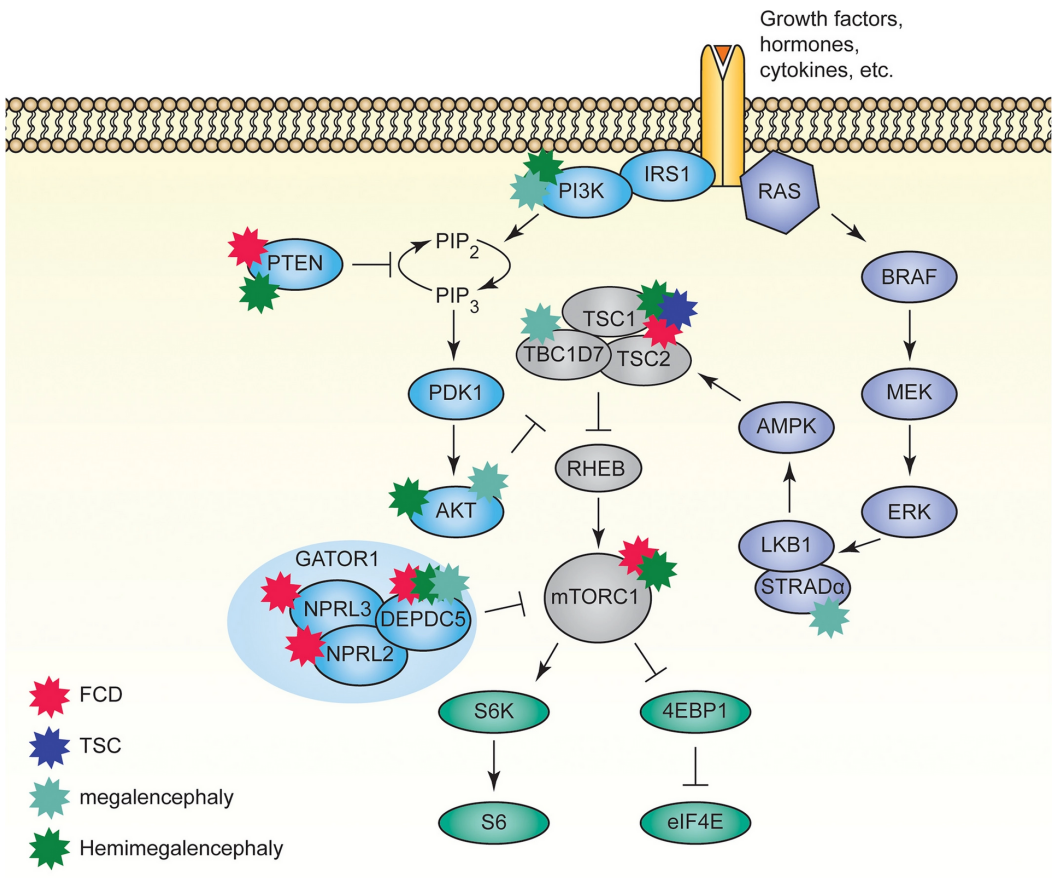
We do not know yet, how cortical malformations lead to seizure development, but much interesting research is done in brain organoids, animal models, and surgical tissue from patients. This research helps us to understand both normal and abnormal brain development.



IUE - in utero electroporation, MTOR - mammalian target of rapamycin, TSC - tuberous sclerosis complex

MTOR SIGNALING PATHWAY

1 constitutes a part of a complex network of cell signaling



2 Controls

- anabolism
- autophagy
- cell growth & survival
- proliferation
- migration

3 is essential for proper brain development and function

4 several mutations targeting the mTOR signaling pathway have been identified in MCD including FCD, TSC, and HME

MTOR MUTATIONS IN CORTICAL DEVELOPMENT AND EPILEPSY

Germline

Prototypical disorder(s):

Tuberous Sclerosis Complex (TSC)

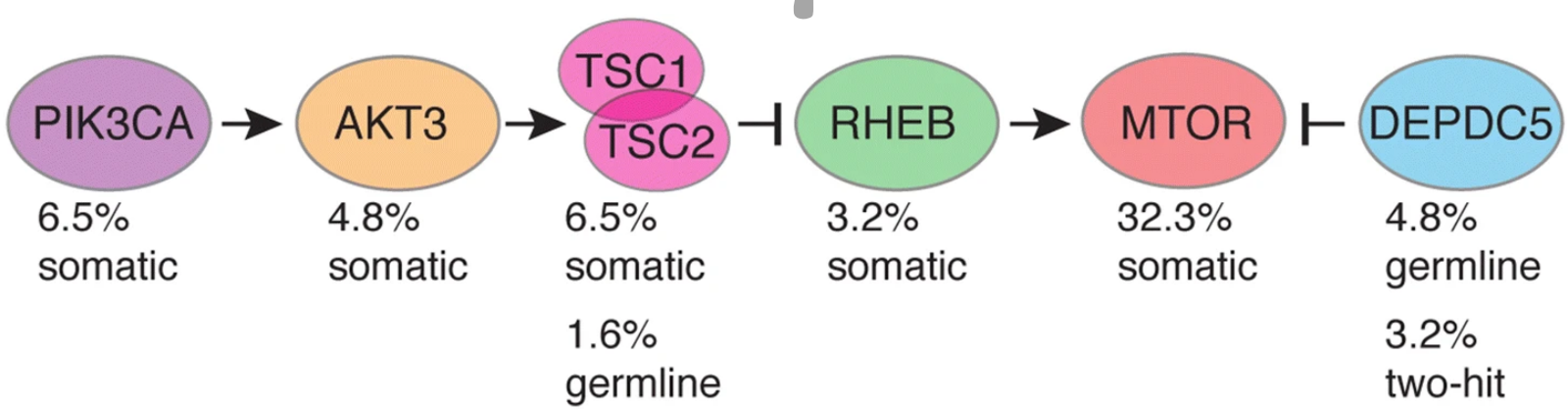
- a mutation in the TSC1 or TSC2 gene
- brain abnormalities include cortical tubers, which are highly epileptogenic
- histopathological features include dysmorphic neurons and balloon cells
  - very similar to FCD type 2B and HME

Somatic

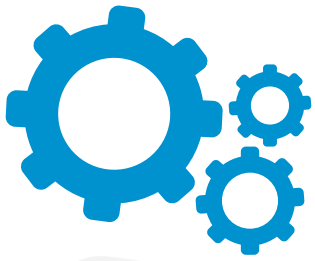
Prototypical disorder(s):

FCD type 2 and HME

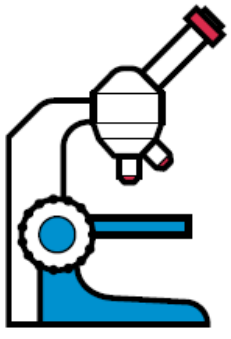
- mutations affecting mTOR pathway-related genes
- unclear how few mutated cells lead to epilepsy
- sometimes as little as 1-2% of cells seem to be affected by the mutations



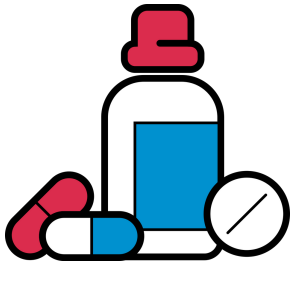
MTOR, EPILEPSY, AND PRECISION MEDICINE



Similarities in histopathological features of HME, TSC, FCD type II, and epilepsy-associated glioneuronal tumors point to a unifying molecular pathomechanism, i.e., the mTOR pathway.



Most recently, it was shown that somatic variants can be detected not only from surgical brain tissue but also from cerebrospinal fluid (CSF). If validated, this may become a new diagnostic approach and way to precision medicine prior to surgery.



The mTOR pathway may be targeted by so-called mTOR inhibitors (rapalogs, e.g., everolimus, rapamycin), but there are several side effects that need to be considered.

Malformations of cortical development

large, heterogeneous group of disorders of disrupted cerebral cortex formation caused by various genetic, infectious, vascular, or metabolic etiologies. Commonly manifest with developmental delay, cerebral palsy or seizures. Can be surgically treated if identified as underlying structural brain lesion in focal epilepsy.

Biological Relevance

mTOR signaling is essentially involved in brain development and function. Pathway seems to be hyperactivated in MCD with mTOR-related mutations.

Clinical genetics

Many mutations affecting the mTOR pathway have been identified in focal epilepsy patients with MCD. Findings support an integrated diagnostic approach based on histopathology and molecular-genetic features.

Personalized Treatment

mTOR-Inhibitors like Rapamycin and Everolimus are currently tested in clinical trials as treatment in epilepsy patients with tuberous sclerosis or FCD type 2

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