Biobanking in Tuberous Sclerosis Complex

Challenges and opportunities for understanding epilepsy and cognitive and behavioral comorbidities

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Objectives

**Biobanking in the era of personalized medicine**

- **Biobanking:** not only surgical specimens........
  - Post-mortem tissue in epilepsy research
  - *Healthy Brain* Biobank
  - Developmental Disorders Biobank (Fetal and Children’s brain)

- **Tuberous Sclerosis Complex (TSC): model disease**

  **Opportunities:**
  - Human brain tissue: to identify mechanisms that are *unique* for TSC pathology and *common* among patients with epilepsy
  - Human brain tissue: to validate emerging hypotheses on the mechanisms of epileptogenesis and *target of therapy*

- **Challenges and next steps to move forward**
The public’s awareness towards research biobanks

Biobanking in the era of personalized medicine

Patients are becoming more aware of the importance and benefits of biobanking as part of the medical infrastructure.
There is no ideal model: a model is just a model

Acquired and genetic models

The use of human tissue to increase the translational value of in vivo and in vitro studies

Validate and generate data
Banking brain tissue for epilepsy research

Not only surgical specimens……..
Banking brain tissue for epilepsy research
Not only surgical specimens…….
Healthy Brain Biobank
Developmental Disorders Biobank

Fetal Biobank (AMC-NBB)
Human astrocytes/Human neural stem cell

Neurosphere

Nestin

Tuj1/Sox2

GFAP/Sox2
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Tuberous sclerosis complex (TSC)

Neurological manifestations of TSC:

**Epilepsy**

Cognitive-behavioral and Psychiatric manifestations

TSC Associated Neuropsychiatric Disorders (TAND)

Multisystem genetic disease

Loss-of-function mutations in either TSC1 or TSC2: Constitutive mTOR activation

Tubers, SEN, SEGA
What we have learned from human tissue?

**Beyond tuber pathology**

- Tuber
- Microtuber
- Dyslamination
- "Sentinel" cells

Brain lesions are not static

Changes within the tubers
*(cystic degeneration/calcifications)*

Increased micropathology

.. Increasing seizures, autism, cognitive disability

**Dynamic disease process**
What we have learned from human tissue?

mTORC1 signalling is ACTIVATED early during brain development

Pathological neural network formation during brain development:
Cellular/Molecular Abnormalities


Tuber

Epileptogenesis: chronic process that can be triggered by **genetic** or acquired factors, and that can continue long after epilepsy diagnosis.
mTOR pathway

Commonalities in epileptogenic processes

mTOR signaling dysregulation represents a common pathogenic mechanism in a subset of malformations of cortical development.

Activating mutations: AKT3**, MTOR*, PIK3CA**, PI3KR*...
Inactivating mutations: PTEN*, STRADα*, DEPDC5**, NPRL2-3*, TSC1/2**, TBC1D7**
Cortical layer markers:

- Cux2: layers II and III (blue)
- Satb2: layers II, III, IV, and V (green)
- RORβ: layer IV and VI (orange)
- ER8: layers V and VI (purple)
- Tbr1: layers V and VI (red)

Similar histological pattern

Early and late migratory patterns (severe impairment of the late stage of maturation)
Evaluation of oligodendroglial lineage maturation indicates that the development from OPCs to myelinating oligodendrocytes is insufficient in TSC and FCD II.
In TSC and FCD II GABA_A and AMPA receptor function retain features that are typical of an immature brain.
RNA sequencing data in TSC

Epigenetic modulation of the IL-1β signaling in TSC: IL-1β promoter hypomethylation
The miR-34 family (miR-34A, miR-34B and miR-34C) target multiple genes in the neurogenesis and glutamate receptor signaling modules.
miR146a & 147b in astrocytes

Inhibitor of inflammation

IL-1β

Increased in astrocytes in human epileptic brain

Promotes neuronal differentiation

What we have learned from human tissue?

Van Scheppingen et al., Glia 2016, 2018
From human tissue to animal models

Therapeutic outcome: disease-modification

- Blockade of epilepsy progression
- Reduction of chronic seizures
Challenges and next steps to move forward

The use of human tissue increases the translational value of in vivo and in vitro studies

- The collection and use of well-documented and high quality human brain tissues from severe pediatric epilepsies requires a multidisciplinary approach embedded in international research networks.
Challenges and next steps to move forward

The use of human tissue increases the translational value of in vivo and in vitro studies

- Active, early and sustained involvement of patient and public representatives in biobanks will become increasingly important.

- Expert knowledge in neuropathological diagnostic criteria with harmonization of procedures-protocols, and implementation of common standards for ethical and legal issues is important and requires further streamlining.
Challenges and next steps to move forward

The use of human tissue increases the translational value of in vivo and in vitro studies

- The long-term sustainability of tissue collections represents a major challenge, particularly for rare genetic diseases

- There is a clear need for long-term investment in order to optimize the potential of tissue biobanking for epilepsy research within a unified and harmonized network
Thank You!

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