Understanding and Treating Autism in Tuberous Sclerosis

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Neurological manifestations

- Tumors
- Seizures
- Cognition and autism
TSC is a disease of abnormal cell size...
The TSC pathway

Growth Factors

Energy Level

↑AMP

AMPK

Protein synthesis

Cell growth

↑Protein synthesis

mTOR → S6K → S6 → Protein synthesis

rheb

TSC2

TSC1

Akt

mTOR

S6K

S6

TSC2

TSC1

Growth Factors

Akt

AMPK
Neurological manifestations

• Tumors
• Seizures
• Cognition and autism
Autism in TSC

Jeste et al., J Child Neurol, 2008
Mouse models of TSC

Meikle et al., J. Neurosci. 2007
Less myelination in the TSC brain

Meikle et al., J. Neurosci. 2007
mTOR inhibitor treatment

Meikle et al., J. Neurosci. 2008
Rapamycin Treatment Rescues the Myelin Loss

Cont | Mut | Mut+Rap

Meikle et al., J. Neurosci. 2008
Miswiring in the TSC mouse brain

Nie et al., Nat Neurosci 2010
Miswiring in the TSC mouse brain

Nie et al., Nat Neurosci 2010
Autism spectrum disorders: developmental disconnection syndromes
Daniel H Geschwind and Pat Levitt

Current Opinion in Neurobiology
Why is TSC unique in AUTISM?

• Many of the TSC patients are diagnosed pre- or neo-natally


Among fetuses or newborns with multiple cardiac tumors, the chances of having TSC is 95%.
Early Detection of Autism in TSC

Study modelled on studies of early infant development:

1. Neurocognitive assessment of infants
2. Diffusion tensor imaging
3. Neurophysiological assessment of face processing and other visual paradigms

Jeste, Nelson, Sahin, Warfield
Tracing axons in the human brain

mTOR inhibitors in TSC mouse models

1. Improves myelination and seizures (Meikle et al., 2008)

2. Prevents or stops seizures (Zeng et al., 2008)

3. Improves learning (Ehninger et al., 2008)
Cognition in TSC mice

- Hyperactive mTOR signaling leads to deficits in learning.

- A brief treatment with rapamycin in adult mice can rescue the learning deficits in TSC2 mice.

(Ehninger et al., 2008)
Randomized Phase II Trial of mTOR inhibitors in TSC

• 6-21 year olds with TSC, IQ>60
• Randomized placebo controlled, double blind, cross-over
• 55 patients
• Neurocognitive testing at baseline, 3 months, 6 months
• Secondary endpoints: autism, seizures, sleep
THANK YOU!