LAM or TSC Disease Models:

Hum Mol Genet. 2013 Oct 14. [Epub ahead of print]
Tsc1 deficiency-mediated mTOR hyperactivation in vascular endothelial cells causes angiogenesis defects and embryonic lethality.

Ma A, Wang L, Gao Y, Chang Z, Peng H, Zeng N, Gui YS, Tian X, Li X, Cai B, Zhang H, Xu KF.

Main points covered in the paper

This is a study on the role of tuberous sclerosis complex1 (TSC1) mutation and mTOR activation in endothelial cells during angiogenic and embryonic development. A mouse model was developed using conditional Cre-loxp gene knockout approach to delete Tsc1 in mice's endothelial cells. The majority of Cre/Tsc1-/- embryos died at embryonic day 14.5 in utero. Cardiovascular defects including a disorganized vascular network, defective sprouting of vessels in yolk sac and thickening of the labyrinth layer in the placenta were also observed.

What is the relevance of the study?

Given the fact that mTOR1 activation is seen in these mice, the authors treated prenatally a cohort of mice with mTOR inhibitor rapamycin. As expected, the offspring of these mutant mice survived up to 22 days after birth. This observation highlights the role TSC1-mTOR signaling in endothelial cells is crucial for vascular development and embryogenesis.

Is there a public health implication of the research described in this paper?

It does not have an immediate impact besides reinforcing the therapeutic use of rapamycin. In addition, it might help our understanding of the deranged angiogenesis seen in diseases such as TSC or LAM.

www.impactjournals.com/oncotarget/
A novel androgen-regulated isoform of the TSC2 tumor suppressor gene increases cell proliferation
Jennifer Munkley, Prabhakar Rajan, Nicholas P. Lafferty, Caroline Dalgliesh, Robert M. Jackson, Craig N. Robson, Hing Y. Leung and David J. Elliott

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Main points covered in the paper

Our current understanding of the molecular mechanism controlling the mTORC1 pathway (the signaling module found to be hyperactive in LAM cells) involves the TSC complex. TSC2 protein complexes with TSC1 and blocks the ability of the Rheb (Ras homolog enriched in brain) GTPase to activate mTOR (mammalian target of rapamycin), a crucial signal transducer which regulates protein synthesis and cell growth. Establishing both the regulatory network and the diversity of the complex components is the next level of understanding the molecular steps involved in the genesis of LAM. The authors report the identification of a novel isoform of TSC2 that is under direct control of the ligand-activated androgen receptor.

What is the relevance of the study?

The new version of TSC2, TSC2 isoform A (TSC2A) is derived from an internal androgen-regulated alternative promoter and encodes a 508-amino acid cytoplasmic protein corresponding to the C-terminal region of full-length TSC2. This unique form of TSC2 has a couple of key features: it lacks the interaction domain for TSC1 and contains an incomplete interaction domain required for Rheb inactivation. The most remarkable finding is that the expression of TSC2A is induced in response to androgens while the full-length TSC2 (the common form) is down-regulated, indicating an androgen-driven switch in TSC2 protein isoforms. The biochemical implication of this switch is that this novel form stimulates cell growth, in opposition to the function associated with the full length TSC2. This work indicates, for the first time, a novel role for a well-known tumor suppressor gene, in response to androgen stimulation.

Is there a public health implication of the research described in this paper?

Not at the present state of the research. However, the data suggests that the function of mTORC1 is tuned depending on the hormonal balance and that an integrative view of the action of androgens (as well as estrogens) is warranted in order to understand the exquisite gender selectivity of LAM.

Clinical Trials/Clinical Studies:

Biologics. 2013;7:211-221. Epub 2013 Oct 10.
Everolimus in the treatment of subependymal giant cell astrocytomas, angiomyolipomas, and pulmonary and skin lesions associated with tuberous sclerosis complex.

Franz DN.

Main points covered in the paper

Mutations in either the TSC1 or TSC2 genes lead to the development of multiple, benign tumors in several organs throughout the body. Lesions occur in the brain, kidneys, heart,

liver, lungs, and skin and result in seizures and epilepsy, mental retardation, autism, and renal and pulmonary organ system dysfunction. Somatic mutations of these genes have been identified in patients suffering LAM. An often co-morbidity associated with LAM is the presence of renal angiomyolipoma. In this review, the therapeutic response to everolimus and the clinical trials that led to its approval for the treatment of TSC-associated sub-ependymal giant cell astrocytoma and renal angiomyolipoma is summarized.

What is the relevance of the study?

Angiomyolipoma is one of the leading causes of death in TSC patients. Renal failure resulting in end-stage renal disease is largely due to encroachment of angiomyolipomas on normal renal parenchyma. Therefore, a therapeutic approach to treat this condition is desperately needed. A Phase III, randomized, double-blind, placebo-controlled (A Randomized, Double-blind, Placebo-controlled Study of RAD0001 in the Treatment of Angiomyolipoma in Patients With Sporadic Lymphangioleiomysmatosis (LAM) (EXIST 2)) studied the efficacy of everolimus in treating angiomyolipoma associated with sporadic LAM . The results are encouraging since 42 % of the treated patients showed a reduction (greater than 50 % volume). The median time to angiomyolipoma response with everolimus was nearly three months.

Is there a public health implication of the research described in this paper?

Although the everolimus treated patients had a significantly higher skin lesion response rate compared with placebo, the result showed that time of angiomyolipoma progression was significantly longer with everolimus versus placebo. This should facilitate the clinical assessment of the benefits/risk ratio of treatment for implementation of this therapy in LAM patients.

Newsworthy:

http://www.stourbridgenews.co.uk/news/local/10773581.Stourbridge_runner_completes_charity_challenge/

The story published in this article (Stourbridge runner completes charity challenge) describes the efforts of a runner to aid in the search for a cure for LAM. James Sutton, aged 31, was determined to do something after his partner Leanne Lillywhite, aged 30, was diagnosed with LAM. He has completed eight half-marathons and raised £3,335 to fund research for LAM.

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