TSC2/TSC1 Field:

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**Loss of TSC2 Confers Resistance to Ceramide and Nutrient Deprivation**
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Main Points covered in the paper

The results presented in this paper makes the connection between nutrient stress and activation of the mTORC1 by deleting its negative regulator tuberous sclerosis complex 2 (TSC2).

What is the relevance of the study?

The authors made an important observation that was opposite to the initial hypothesis. They had shown previously that ceramide kills cells in part by triggering nutrient transporter loss and restricting access to extracellular amino acids and glucose, suggesting that TSC2-deficient cells would be hypersensitive to ceramide. However, murine embryonic fibroblasts (MEFs) lacking TSC2 were highly resistant to ceramide-induced death. Consistent with the observation that ceramide limits access to both amino acids and glucose, TSC2−/− MEFs also had a survival advantage when extracellular amino acids and glucose were both reduced. These results suggest that mTORC1-dependent translation facilitates the adaptive cellular response to nutrient stress.

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

Not at this moment. The hypothesis that nutrient stress is overcome by activation of mTOR could be tested in in vivo using mTOR inhibitors but those studies have not been carried out yet.

**LAM or TSC Disease Models:**

Main Points covered in the paper

An important area of studies in pathology is epigenetics. The authors investigated whether microRNA (miRNA, miR) signaling is involved in the response of LAM to mTORC1 inhibition. They used LAM patients angiomyolipoma derived cells to identify Rapamycin-dependent miRNA expression.

What is the relevance of the study?

The authors focused their attention on 132 miRNA of known significance to tumor biology to identify those that were influenced by Rapamycin. They identified miRs 29b, 21, 24, 221, 106a and 199a as microRNA regulated by Rapamycin. Since Rapamycin response in patients is not observed in all individuals, it would be of interest to establish whether these miRNA are regulated at all in Rapamycin treated patients.

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

In principle yes. However just knowing that, in an experimental setting Rapamycin up-regulates multiple miRs, including pro-survival miRs, is not sufficient to connect the induction of miRs by Rapamycin to the response of LAM and TSC patients to Rapamycin therapy.

Other:

A commercially available cell line has been established (http://www.atcc.org/products/all/CRL-2620.aspx).

tsc2 ang1 (ATCC® CRL-2620™)

The tsc2 ang1 cell line was derived in 1998 from a cutaneous sarcoma taken from a Tsc2+/- mouse heterozygous for tuberin. It can be used for drug testing and for angiogenesis studies. The cell line is a useful model of TSC. It is the only genetically defined tuberous sclerosis cell line available that forms tumors.

Clinical Studies: