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LAM in the News
July 2013

TSC2/TSC1 Field:

Mol Endocrinol. 2013 Jul 2. [Epub ahead of print]

Uterine-Specific loss of Tsc2 leads to myometrial tumors in both the uterus and lungs.

Prizant H, Sen A, Light A, Cho SN, Demayo FJ, Lydon JP, Hammes SR.

Source
**Division of Endocrinology and Metabolism, Department of Medicine, University of Rochester Medical Center, Rochester, NY 14642, USA.*

Main points covered in the paper

As we know, Lymphangioleiomyomatosis (LAM) is a rare disease found almost exclusively in women. Since LAM shares features with uterine leiomyomas, benign tumors of myometrial cells prompted the authors to investigate whether LAM cells might originate from uterine leiomyomas containing Tsc mutations. To test the hypothesis, the authors deleted Tsc2 primarily in uterine cells and created a mice strain of Tsc2 knockout mice.

What is the relevance of the study?

The authors describe nearly 100% of uteri from uterine-specific Tsc2 knockout mice developed myometrial proliferation and uterine leiomyomas by 12 and 24 weeks, respectively. Myometrial proliferation and mTORC1/S6 activity were abrogated by the mTORC1 inhibitor rapamycin or by elimination of sex steroid production through ovariectomy or aromatase inhibition. More importantly, they found Tsc2 null myometrial tumors in lungs of older Tsc2 uterine-specific knockout females, suggesting that lung LAM-like myometrial lesions may indeed originate from the uterus. This mouse model may improve our understanding of LAM and leiomyomas, and might lead to novel therapeutic strategies for both diseases.

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

Although it would have been a nice development to have shown that the lung lesions also responded to treatment with mTOR inhibitors, the mouse model described here may improve our understanding of LAM and be an important research tool to develop novel therapeutic and drug discovery strategies.

LAM or TSC Disease Models:

Am J Pathol. 2013 Jul 15. pii: S0002-9440(13)00414-8. doi: 10.1016/j.ajpath.2013.05.024. [Epub ahead of print]

Osteoprotegerin Contributes to the Metastatic Potential of Cells with a Dysfunctional TSC2 Tumor-Suppressor Gene.

Steagall WK, Pacheco-Rodriguez G, Glasgow CG, Ikeda Y, Lin JP, Zheng G, Moss J.

Main points covered in the paper

Osteoprotegerin (OPG), a known modulator of smooth muscle proliferation was investigated to establish a possible link between its activity and the growth and proliferation of lymphangioleiomyomatosis (LAM) cells, because these cells have abnormal smooth muscle-like phenotype. The authors demonstrated that OPG stimulated the proliferation of cells cultured from explanted LAM lungs, and selectively induced migration of LAM cells.

What is the relevance of the study?

Since LAM has been associated with dysfunctional TSC2 gene it is a noteworthy fact that LAM cells expressed the OPG receptors. Moreover LAM lung nodules showed expression of OPG mRNA. Given the fact that Serum OPG was significantly higher in LAM patients than in normal volunteers, it suggests OPG may have tumor-promoting roles in the pathogenesis of lymphangioleiomyomatosis, perhaps acting as both autocrine and paracrine factor.

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

Not at this moment but a possible follow study to verify OPG levels in LAM patients is warranted.

Clinical Trials/Clinical Studies:

Med J Aust 2013; 199 (2): 121-123.

Everolimus treatment of abdominal lymphangioleiomyoma in five women with sporadic lymphangioleiomyomatosis.

Anna M Mohammadieh, Simon D Bowler, Elizabeth J Silverstone, Allan R Glanville and Deborah H Yates.

Main points covered in the paper

The MILES clinical trial demonstrated that an mTOR inhibitor (Sirolimus, a Rapamycin analog) was effective in a significant number of LAM patients showing a reduction in the decline of lung function in the treated patients. In addition, Sirolimus has also been associated with shrinkage of lymphangioleiomyomas as well as with shrinkage of renal AMLs. The study reported in this article describes the response of LAM patients to another mTOR inhibitor; everolimus. The aim was to examine the efficacy of everolimus on lymphatic abnormalities in LAM.

This analog has recently been accepted by the United States Food and Drug Administration (FDA) for treatment of renal AMLs in TSC.

What is the relevance of the study?

Although new information is always welcome on any clinical response of LAM patients to mTOR inhibitors, this open-label treatment of five patients with sporadic LAM (sLAM) just does not have the power to provide further understanding of the relationship between mTOR inhibition and LAM. Nevertheless, the data showed that the five patients experienced significant shrinkage or complete resolution of the lymphangioleiomyomas during treatment. Adverse events were compatible with the known side-effect profile of everolimus.

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

The data provides the first evidence that everolimus has efficacy in the treatment of lymphangioleiomyoma and chylous ascites in sLAM. Given the fact that there are important differences in the pharmacokinetics and safety profile of the available mTOR inhibitors, this study provides the initial suggestion that a comprehensive comparison among them should be initiated in order to improve the clinical response of these kinds of drugs in the treatment of LAM.

Newsworthy:

A resource page containing medical reports of LAM patients is available at the following link: http://radiopaedia.org/cases/lymphangioleiomyomatosis-1