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LAM in the News
September 2013

LAM or TSC Disease Models:

Eur Respir Rev. 2013 Sep 1;22(129):302-11. doi: 10.1183/09059180.00002813.
Sex-specific lung diseases: effect of oestrogen on cultured cells and in animal models.
Shim B, Pacheco-Rodriguez G, Kato J, Darling TN, Vaughan M, Moss J.

Main points covered in the paper

This is a good review on some of the experimental findings associated with the role of estrogen in lung diseases, in general, and LAM in particular.

What is the relevance of the study?

The review summarizes both the cellular and the animal models to establish a connection between the estrogen levels, estrogen receptor expression and specific signaling cascades involved in the potential progression of LAM.

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

Not directly, but the possibility of devising treatment options based on combinatorial use of drugs might be an outcome for the future.

Clinical Trials/Clinical Studies:

Chest. 2013 Sep 19. doi: 10.1378/chest.13-1071. [Epub ahead of print]
Sirolimus decreases circulating LAM cells in patients with lymphangioleiomyomatosis.
Cai X, Pacheco-Rodriguez G, Haughey M, Samsel L, Xu S, Wu HP, McCoy JP, Stylianou M, Darling TN, Moss J.

Main points covered in the paper

A leading theory that might explain the multi-system manifestations of LAM is the one that proposes that it is due to metastatic dissemination of LAM cells. These cells would have the genetic mutations that have impact on the control of the mTOR pathway. Since Sirolimus has been shown to slow the decline of lung function, the authors tested the hypothesis of whether treatment with Sirolimus would also induce a reduction of circulating LAM cells.

What is the relevance of the study?

The authors isolated cells from blood , urine and chylous effusions and determined the status of the TSC2 gene. LAM cells with TSC2 alterations were identified in 100% of blood specimens and 75% of urine samples from patients before therapy. After two years of treatment duration with Sirolimus, a marked reduction in the detection rates of LAM cells was observed (to 25% in blood and 8% in urine). Noteworthy was the fact that greater loss of circulating LAM cells was seen in post-menopausal patients.

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

The data supports the suggestion that a treatment biomarker might be established using the detection of these cells in bio-fluids. This would have an important positive impact in the management of the disease when patients are under treatment with Sirolimus.

www.ashg.org/2013meeting/abstracts/fulltext/f130120719.htm

A frameshift mutation of TBC1D7, a subunit of the TSC1-TSC2 complex upstream of mTORC1, causes a new distinct clinical phenotype with intellectual disabilities.

L. Micale[1], A. Abdullah Alfaiz[2,3], B. Mandriani[1], C. Fusco[1], B. Augello[1], M. T. Pellico[1], J. Chrast[2], L. Zelante[1], A. Reymond[2], G. Merla[1].

Main points covered in the paper

The genes implicated in LAM are known to be involved in the pathology known as tuberous sclerosis complex (TSC), a multi systems disorder characterized by the development of hamartomas (benign tumors) in various organs as well as a high incidence of epilepsy, intellectual disability, and autism. In addition to TSC1 and TSC2, a recently identified gene, TBC1D7, form a complex that controls the activity of mTORC1. Therefore, identification of gene alterations in TBC1D7 will expand our understanding of LAM. In this report, the authors describe such an alteration in TBC1D7. Using cell lines derived from the affected subjects, they determined that the genetic alterations are indeed connected to regulation upstream of mTORC1.

What is the relevance of the study?

Using a genomic approach (exome sequencing) the researchers identified two sisters with a novel homozygous truncating mutation in TBC1D7: c.18-21delGAGA; p.R7TfsX21. Both siblings share similar clinical phenotypes with medium intellectual disabilities. They present myopia, astigmatism, prognathism, osteo-articular defects, behavior abnormalities, learning difficulties and celiac disease.

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

This study reinforces the involvement of TBC1D7 as an independent contributor to dis-regulated mTOR1 activity and provides an additional tool to screen LAM patients that are not known to have defects in either TSC2 or TSC1. Although at this stage it does not provide

an additional therapeutic option, the findings might be important in the assessment of prognosis and/or treatment response.

Respir Med. 2013 Sep 8. pii: S0954-6111(13)00365-X. doi: 10.1016/j.rmed.2013.08.045. [Epub ahead of print]
A pilot study assessing the effect of bronchodilator on dynamic hyperinflation in LAM.
Baldi BG, de Albuquerque AL, Pimenta SP, Salge JM, Kairalla RA, Carvalho CR.

Main points covered in the paper

Although it is know that a significant positive response (30 %) to bronchodilators (BDs) on spirometry can be found in LAM patients, the effect of these medications on exercise outcomes, including dynamic hyperinflation (DH) has not been documented.

The authors report the results of a randomized, double-blind, placebo-controlled, crossover trial on 38 LAM patients, comparing inhaled placebo versus salbutamol, a bronchodilator.

What is the relevance of the study?

Pulmonary function tests during an endurance test (stationary bicycle) were performed after each intervention. The results showed that just a minor fraction of the patients met the criteria for a positive response to BD. During sub-maximal exercise, BD did not reduce DH or dyspnoea nor did it improve exercise tolerance in the entire population.

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

Although salbutamol produced a slight improvement in airway obstruction, it is very disappointing to see that the approach did not lead to a reduction in DH or increase in exercise tolerance in patients with LAM.

