LAM Health Project
Patient Insights. Patient Perspectives.

LAM in the News
May 2013

TSC2/TSC1 Field:

J Med Genet doi:10.1136/jmedgenet-2013-101680

Disruption of TBC1D7, a subunit of the TSC1-TSC2 protein complex, in intellectual disability and megalencephaly

José-Mario Capo-Chichi[1], Joseph Tcherkezian[2], Fadi F Hamdan[1], Jean Claude Décarie[3], Sylvia Dobrzeniecka[4], Lysanne Patry[1], Marc-Antoine Nadon[1], Bettina E Mucha[1], Philippe Major[1], Michael Shevell[5], Bouchra Ouled Amar Bencheikh[4,6], Ridha Joober[7], Mark E Samuels[1], Guy A Rouleau[6], Philippe P Roux[2,8], Jacques L Michaud[1]

Main points covered in the paper

As it has been known for sometime now, mutations in TSC1 or TSC2 genes are linked to the tuberous sclerosis complex (TSC). This disease is known to lead to the development of hamartomas (or benign tumors) in various organs as well as neurological disorders such as epilepsy, intellectual disability and autism. In this report, the authors identified another gene product (TBC1D7) a protein described as a component of the TSC1/TSC2 complex involved in the regulation of mTORC signaling.

What is the relevance of the study?

There is a wealth of information linking alterations of the TSC1/TSC2 complex to the TSC disorder. In addition, significant support for alterations in theTSC2 gene causing LAM has been disclosed. However, it is reasonable to expect that additional genes might be involved in both TSC and LAM. Thus, mutations in TBC1D7 might also cause TSC although loss of its function has not yet been documented in humans.

In this particular study, homozygosity mapping and exome sequencing was used to study a consanguineous family with intellectual deficiency and megalencephaly but without any specific features of TSC. A rare coding variant (c.538delT:p.Y180fsX1) in TBC1D7 was identified in the regions of homozygosity shared by the affected siblings. The authors showed that this mutation abolished TBC1D7 expression and cells from the affected individuals had increased mTORC1 signaling.

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

Indirectly. The results suggest that disruption of TBC1D7 causes intellectual deficiency but without the other typical features found in TSC. Thus, it is possible that mutations of this gene might also be involved in LAM, specially in those patients that are shown not to have defects on TSC2. However, as shown in this study, alterations in TBC1D7 should result in

activation of the mTORC pathway, a target of the rapamycin based therapy for LAM.

Cell. 2013 May 9;153(4):840-54. doi: 10.1016/j.cell.2013.04.023.
The mTORC1 Pathway Stimulates Glutamine Metabolism and Cell Proliferation by Repressing SIRT4.

Csibi A, Fendt SM, Li C, Poulogiannis G, Choo AY, Chapski DJ, Jeong SM, Dempsey JM, Parkhitko A, Morrison T, Henske EP, Haigis MC, Cantley LC, Stephanopoulos G, Yu J, Blenis J

Main points covered in the paper

The regulation of key metabolic and survival cellular pathways is mediated by the activity of the mTORC1 complex through an increased nutrient uptake and metabolism. The study reported in this paper provides a molecular mechanism of how mTORC accomplishes this event. The role of mTORC1 in metabolic control appears to be mediated in part by controlling the metabolic conversion of glutamine, as first suggested by the data showing that mTORC1 pathway was linked to glutamine addiction of cancer cells. The authors propose a complex mechanism that involves epigenetic and post-translational regulation of the key enzymes controlling glutamine metabolism involving glutamate dehydrogenase (GDH), SIRT4, the mitochondrial-localized sirtuin that inhibits GDH. The authors propose that mTORC1 represses SIRT4 expression by promoting the proteasome-mediated destabilization of cAMP-responsive element binding 2 (CREB2), a key transcription factor regulating SIRT4 expression.

What is the relevance of the study?

This study involved an experimental system that indirectly assessed the activity of mTORC and appears to illustrate a relationship between mTORC1, SIRT4, and cancer. The authors suggest that cells that are energy-addicted, with high mTORC1 signaling as is the case in LAM, can be therapeutically targeted by using the information obtained from this study. However, in the case of LAM, the growth characteristic of the lesions is very different from the one depicted in the experimental system thus making the direct connection to LAM treatment options is not clear at this time.

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

Although the study increases our understanding of how mTORC, and by inference, TSC2 and others genes that regulate mTORC activity, contribute to the defects seen in LAM, the study is only at the research stage and further evaluation in disease relevant models are

required.

LAM or TSC Disease Models:

Am J Pathol. 2013 May 10. pii: S0002-9440(13)00277-0. doi: 10.1016/j.ajpath.2013.04.002. [Epub ahead of print]
Positioning Ganglioside D3 as an Immunotherapeutic Target in Lymphangioleiomyomatosis

Gilbert ER, Eby JM, Hammer AM, Klarquist J, Christensen DG, Barfuss AJ, Boissy RE, Picken MM, Love RB, Dilling DF, Le Poole IC.
Department of Medicine, Loyola University Stritch School of Medicine, Maywood, Illinois.

Main points covered in the paper

In the quest for therapies for LAM, there has been discussion around the use of immunotherapies by targeting disease specific antigens expressed in the LAM cells. In this report, the authors show over-expression of ganglioside D3 (GD3) in LAM. They also discuss the sensitivity of cultured LAM cells to complement mediated cytotoxicity via GD3 antibodies.

What is the relevance of the study?

GD3 normal expression is largely restricted to neuronal cells in the brain. However, its over-expression in LAM cells might provide a potential target for therapy.

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

At this moment there is no program devoted to the development of an immune-therapy for LAM.

J Histochem Cytochem. 2013 May 28. [Epub ahead of print]
Lymphatic Endothelial Differentiation in Pulmonary Lymphangioleiomyomatosis Cells

Davis JM, Hyjek E, Husain AN, Shen L, Jones J, Schuger LA.
Department of Pathology, Biological Sciences Division, University of Chicago, Chicago, Illinois (JEH, ANH, LS, JJ, LAS).

Main points covered in the paper

Although the exact nature of LAM cells is still undergoing discussion, a school of thoughts proposes that LAM belongs to the family of perivascular epithelioid cell tumors (PECOMAs), characterized by spindle and epithelioid cells with phenotypes that includes both smooth muscle and melanocytic cell lineage. The study described in this paper used antibodies against four lymphatic endothelial markers: podoplanin ; prospero homeobox 1 (PROX1), vascular endothelial growth factor receptor 3 (VEGFR-3), and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1)-to determine whether LAM cells show lymphatic differentiation. The study showed that lymphatic endothelial differentiation is a feature of LAM.

What is the relevance of the study?

The results contribute to the characterization of LAM by providing evidence of a previously unidentified third lineage of differentiation in this disease. Moreover, the finding might have an impact in the histological diagnosis of LAM.

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

Not an immediate implication but it suggests that potential future treatment might involve targeting the process of lymphangiogenesis, akin to the treatment of solid tumors by targeting angiogenesis.

Newsworthy:

URMC Opens Clinic, Initiates Research on Rare Lung Disease in Women
http://www.urmc.rochester.edu/news/story/index.cfm?id=3826