Results of trial testing Rapamycin as a treatment for fibrofolliculomas announced

Earlier this month, the results of a trial testing Rapamycin as a treatment for facial fibrofolliculomas were published. 19 patients completed the 6 month double-blind, randomised, facial left-right controlled trial. The number of patients who reported cosmetic improvement with Rapamycin was not significantly more than those patients who reported no improvement at all or improvement with the placebo drug. Additionally, 13 out of 19 patients reported one or more side effects, burning, redness, dryness and itching. Overall, these results suggest that Rapamycin is not an effective treatment for fibrofolliculomas.

This study was performed by Professor Dr Maurice can Steensel and his team at Maastricht University Medical Centre, and funded by the Myrolytis Trust.

To read more about the trial, please read our news item or blog post.

Getting to know you

This quarter, meet Tim from the USA who was diagnosed with BHD in 2012, and Davide Bondavalli. Dr Bondavalli is an Honorary Research Associate at the Cancer Council of Victoria, Melbourne Australia, and a member of the steering committee for the International Consortium for the Investigation of Renal Malignancies (I-ConFIRM). He has just completed his medical training, specialising in medical genetics and performed his dissertation research on Birt-Hogg-Dubé syndrome. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

BASIC:

Goncharova et al. Folliculin controls lung alveolar enlargement and epithelial cell survival through E-cadherin, LKB1, and AMPK. Cell Rep. 2014; 7 (2) : 412-23

• Goncharova et al. show that loss of FLCN in type II alveolar epithelial cells (AECs) led to increased apoptosis and cell permeability due to loss of E-cadherin expression, subsequent LKB1 dysregulation and consequent AMPK downregulation. FLCN loss also led to an increased inflammatory response in vivo, as measured by increased MMP3 and MMP9 expression. This study suggests that FLCN promotes cell survival and the assembly of epithelial cell junctions via the E-cadherin-LKB1-AMPK signalling axis, and suppresses inflammation, and is required for correct lung physiology and function.


• Yan et al. report that AMPK is constitutively activated, leading to increased PGC1a activity and a consequent increase in mitochondrial biogenesis and ROS production in FLCN-null mouse embryonic fibroblasts (MEFs). This ultimately activates HIF signalling and leads to metabolic changes consistent with the Warburg Effect. A nonphosphorylatable FLCN S62A mutant was unable to bind and inhibit AMPK, meaning that FLCN binding is required to inhibit AMPK.

- Possik et al. report that FLCN deletion leads to constitutive activation of AMPK and a subsequent increase in autophagic flux and intracellular ATP levels. This leads to increased stress resistance and protection from apoptosis in C. elegans nematodes, mouse embryonic fibroblasts, and the FLCN-null FTC-133 thyroid carcinoma cell line. Furthermore, inhibiting autophagy in FTC-133 lead to a reduction of colony formation in soft agar assays, suggesting that AMPK hyperactivity in response to FLCN-loss provides cells with a tumorigenic advantage.


- Park et al. show that FNIP1 is crucial for the development of invariant Natural Killer T (iNKT) cells in mice. Dysregulated mTOR signalling in these cells lead to higher energy consumption, cells did not have the required energy reserves for proliferation and maturation to stage 3, and died somewhere between stage 2 and 3 of iNKT cell development. However, mTOR dysregulation is not fully responsible for this phenotype, as in vivo treatment of pups, did not rescue the iNKT cell phenotype.

**CLINICAL:**


- Gijezen et al. report that Rapamycin may not be an effective treatment for BHD facial fibrofolliculomas.


- Murakami et al., 2014 report the cases of two patients who showed all three symptoms of BHD. Retrospective analyses of 62 Asian cases of BHD reported in the literature revealed that there are only four reported cases of Asian patients developing all three symptoms of BHD.


- Kuroda et al. report the pathology of kidney tumours from a series of 6 Japanese BHD patients. All tumours had intertumoral peripheral small papillary tufts (ITPSTs) at the interface between the tumour and normal kidney tissue, suggesting that ITPSTs might be a diagnostic hallmark of BHD.


- Lopez-Garcia et al. describe the histological subtypes of trichodiscomas in a series of 42 American patients diagnosed between 1987 and 2013. They describe 11 subtypes, including some that are previously unreported. They urge dermatologists to become familiar with these subtypes as some are associated with genetic syndromes, such as BHD and TSC.

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