Birt-Hogg-Dubé Newsletter

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You are receiving this email because you have expressed an interest in BHD. We hope you will enjoy this and future editions. If you do not wish to receive this newsletter, please see the end of the newsletter for instructions.

BHDSyndrome.org updates

The BHD Literature Database has been updated to incorporate additional subcategories. It is now possible to sort the list of papers according to the type of paper (basic, clinical or case study), the organ or symptom of interest and/or if the paper includes animal work. More about this update can be found here.

The BHD Article Library of open access papers has been tidied up to make it easier to find older papers. Both the "Basic Research" and "Clinical Research" pages are now split into years of publication, and the papers in each year are listed alphabetically.

The BHD Signalling Diagram has been removed from our "What is BHD?" review for researchers, and is now a stand alone resource, which can now be accessed from both the "Featured" section on our home page and the "Resources" page in our "For Researchers" section.

Getting to know you

This quarter, meet Anna from the UK who was diagnosed with BHD last year, and Angela Pacitto, a PhD student in Professor Sir Tom Blundell's lab, who is investigating the crystal structure of Lst7, the yeast orthologue of Folliculin, to find out more about how it functions. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

BASIC:

Laviolette *et al*. Human folliculin delays cell cycle progression through late S and G2/M-phases: effect of phosphorylation and tumor associated mutations. PLoS One. 2013 Jul 11;8(7):e66775. (Free full text)

- Laviolette *et al*. show that FLCN expressing cells show a 2-4 hour delay in progression through S-phase of the cell cycle, which increased to a 2 – 6 hour delay in the G2/M phase, indicating that FLCN delays cell cycle progression. Three BHD-associated mutant versions of FLCN showed cell cycle profiles similar to FLCN-null UOK-257 suggesting that all three ablate FLCN function. The authors also show that S62 and S73 become phosphorylated as the cell cycle progresses, and that when FLCN is phosphorylated at these residues, it is less stable and is no longer able to slow cell cycle progression.

Bastola *et al*. Folliculin Contributes to VHL Tumor Suppressing Activity in Renal Cancer through Regulation of Autophagy. PLoS One. 2013 Jul 29;8(7):e70030. (Free full text)

- Bastola *et al*. show that VHL activates the expression of FLCN both at the mRNA and protein level. Knockdown of FLCN in 786-O cells carrying a reconstituted VHL allele enhanced the tumorigenic potential of these cells when they were xenografted in to nude mice. This enhanced tumorigenesis seemed to be independent of the mTOR pathway as mTORC1 signalling was reduced in FLCN knockdown cells, as shown by reduced phosphorylation of S6, S6K and 4EBP. Similarly to VHL, FLCN was found to inhibit the onset of autophagy by inhibiting and promoting the accumulation of LC3B and LC3C respectively, suggesting that FLCN is at least partially responsible for the tumour suppressor action of VHL.

Wong and Harbottle. Genetic modification of dividing cells using episomally maintained S/MAR DNA vectors. Mol Ther Nucleic Acids. 2013 Aug 13;2:e115. (Free full text)

- Wong and Harbottle report the successful use of a Scaffold/Matrix Attachment Region (S/MAR) DNA vector to reintroduce a functional copy of the *FLCN* gene in to FLCN-null cells. Characterisation of the UOK257 cells carrying the S/MAR plasmid (UOK257-FS) showed that FLCN expression had been successfully reconstituted in these cells. UOK257-FS cells displayed reduced cell-cell contact, increased TGF-β signalling, reduced cell proliferation rates, and reduced mTOR signalling under serum-starved conditions, compared to the parental UOK257 cell line, indicating that FLCN function had also been reinstated in these cells. Xenograft experiments also showed that UOK257-FS cells had not formed tumours at 150 days post injection, unlike UOK257 cells, although cell spheroids between 0.2 – 0.5 cm^2 were isolated from one animal. Subsequent RT-PCR analysis of the UOK257-FS spheroids showed that FLCN expression had been retained and that TGF-β signalling also remained elevated over at least 50 cell divisions.

Venables *et al*. MBNL1 and RBFOX2 cooperate to establish a splicing programme involved in pluripotent stem cell differentiation. Nat Commun. 2013 Sep 18;4:2480.

- Venables *et al*. used a high throughput RT-PCR screen to find genes that are alternatively spliced during fibroblast reprogramming and differentiation and found that *MBNL1* controls the alternative splicing of *FNIP1* during late mesoderm differentiation. In primary fibroblasts, a shorter isoform of FNIP1 – lacking the final 84 bp of exon 6, corresponding to amino acids 208-235 – predominated. Reprogramming of these fibroblasts to induced pluripotent stem cells (iPSCs) caused the longer, canonical, isoform of FNIP1 to predominate. This splicing pattern was fully reversed upon *in vitro* differentiation of iPSCs into fibroblasts. Sequence analysis across species shows that two thirds of the alternatively spliced exons found in this study (including FNIP1) arose during the emergence of jawed vertebrates, indicating that alternative splicing of these genes may play an important role in the evolution and physiology of jawed vertebrates.

CLINICAL:

Raymond *et al*. An oncocytic adrenal tumour in a patient with Birt-Hogg-Dubé syndrome. Clin Endocrinol (Oxf). 2013 Jul 15. doi: 10.1111/cen.12292.

- Raymond *et al*. describe the case of a 62 year old woman with histologically confirmed trichodiscomas indicative of BHD. Further screening revealed the presence of two lung cysts and an adrenal mass. Resection of the adrenal mass confirmed it to be an oncocytic adrenal tumour, which was likely to be malignant. Genetic testing confirmed a diagnosis of BHD. The authors analysed the prevalence of adrenal masses in a cohort of 14 BHD patients; one patient was found to have an adrenal nodule. Retrospective analysis of the literature yielded three additional reports of adrenal tumours in BHD patients. However, no patients in a cohort of 359 cases of sporadic adrenocortical carcinoma fulfilled the diagnostic criteria for BHD.

The ISUP Renal Tumor Panel, The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol. 2013 Oct;37(10):1469-1489. [Epub ahead of print]

- The ISUP Renal Tumor Panel reports recommended additions and updates to the World Health Organisation classification of renal tumours. The Panel recommends that as hybrid oncocytic/chromophobe tumour only occurs in three settings, a diagnosis of BHD should be considered when this tumour is observed. They also recommend that HLRCC-associated RCC should be considered as a distinct epithelial subtype within the classification system, due to its aggressive behaviour.

To participate in an interview feature, submit information or suggest a topic for the next newsletter, please contact us at contact@BHDSyndrome.org.

BHD foundation