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Benign anomaly to malign dysplasia: Variable expression of lamin B receptor mutations in humans

Ten years ago, K G Papavinasasundaram, then a post-doc in my lab, discovered that the Neurospora sterol biosynthetic enzyme C-14 sterol reductase, had a sequence that was very similar to that of the C-terminal ~ 450 residues of the lamin B receptor (LBR), a ~ 630 residue integral protein of the vertebrate inner nuclear membrane (Papavinasasundaram and Kasbekar 1994). The N-terminal ~ 180 residues of LBR are nucleoplasmic, associate with the nuclear lamina and heterochromatin, and are believed to play an important role in maintaining nuclear architecture. My student Prakash Arumugam showed subsequently that the human LBR C-terminal domain could complement a Neurospora C-14 sterol reductase mutant and thus established its C-14 sterol reductase function (Prakash *et al* 1999). Subsequent studies by Prakash focused on a paralog of the LBR C-terminal domain encoded by the *TM7SF2* gene. The TM7SF2 protein was assumed to be the 'housekeeping' C-14 sterol reductase because it was localized to the endoplasmic reticulum and lacked residues corresponding to the LBR N-terminal domain. To our surprise, Prakash was unable to demonstrate complementation of either the Neurospora or yeast C-14 sterol reductase mutants with human TM7SF2 (Prakash and Kasbekar 2002), although Roberti *et al* (2002) demonstrated that bovine TM7SF2 did have C-14 sterol reductase function.

Subsequently, Hoffmann *et al* (2002) reported that LBR mutations are responsible for Pelger-Huet anomaly (PHA), a benign human autosomal dominant trait in which blood granulocyte nuclei are hypolobulated and have an abnormal chromatin structure. One homozygous mutant individual had ovoid granulocyte nuclei and mild skeletal abnormalities. Another paper by Waterham *et al* (2003) reported that homozygosity for a LBR mutation is responsible for the autosomal recessive *in utero* lethal disorder called hydrops-ectopic calcification-'moth eaten' (HEM) or Greenberg skeletal dysplasia. The healthy mother of the affected fetus had hypolobulated granulocyte nuclei and abnormal chromatin structure thus confirming her PHA status. In a third paper, Shultz *et al* (2003) reported that the mouse *ichthyosis* locus is in fact the *Lbr* gene and that homozygosity for mutations in it (Lbr^{ic}/Lbr^{ic}) can cause phenotypes ranging from one similar to PHA, to alopecia, variable expression of syndactyly, hydrocephalus and skeletal abnormalities. Thus PHA and Greenberg/HEM dysplasia may represent the extremes of a single clinical spectrum and the phenotypic differences among the mutant homozygotes may be attributed to differences in mutation sites (Oosterwijk *et al* 2003).

Intriguingly, cells cultured from the HEM fetus were deficient in C-14 sterol reductase activity although no mutation was found in *TM7SF2* (Waterham *et al* 2003). Moreover this deficiency could be complemented by transfection with control LBR cDNA. This meant that at least in these cells TM7SF2 is not the primary C-14 sterol reductase confirming our previous data in Neurospora and yeast and implying that, as concluded by Waterham *et al*, 'the physiological function (of human TM7SF2) remains to be discovered'.

To sum up: (i) The phenotype of human and mouse LBR mutants can range from the benign Pelger-Huet anomaly to the lethal Greenberg skeletal dysplasia and include the phenotypes of the ichthyosis mouse mutant. (ii) The results of Prakash; and, more importantly, Waterham *et al*, are inconsistent with a function for human TM7SF2 as a major sterol C-14 reductase. Bovine TM7SF2, however, was shown to be a sterol C-14 reductase. A knock-in mouse deleted for TM7SF2's sterol C-14 reductase function (if any) might provide clues to its physiological function. RNAi in cultured human cells may provide another way to understand human TM7SF2 function.

References

Hoffmann K, Dreger C K, Olins A L, *et al* 2002 Mutations in the gene encoding the lamin B receptor produce an altered nuclear morphology in granulocytes (Pelger-Huet anomaly); *Nature Genet.* **31** 410–414

Oosterwijk J C, Mansour S, van Noort G, *et al* 2003 Congenital abnormalities reported in Pelger-Huet homozygosity as compared to Greenberg/HEM dysplasia: highly variable expression of allelic phenotypes; *J. Med. Genet*. **40** 937–941

Papavinasasundaram K G and Kasbekar D P 1994 The *Neurospora crassa erg-3* gene encodes a protein with sequence homology to both yeast sterol C-14 reductase and chicken lamin B receptor; *J. Genet*. **73** 33–41

Prakash A, Sengupta S, Aparna K and Kasbekar D P 1999 The *erg-3* (sterol $\Delta^{14,15}$-reductase) gene of *Neurospora crassa*: generation of null mutants by repeat-induced point mutation and complementation by proteins chimeric for human lamin B receptor sequences; *Microbiology* **145** 1443–1451

Prakash A and Kasbekar D P 2002 Genes encoding chimeras of *Neurospora crassa erg-3* and human TM7SF2 proteins fail to complement Neurospora and yeast sterol C-14 reductase mutants; *J. Biosci*. **27** 105–112

Roberti R, Bennati A M, Galli G, Caruso D, *et al* 2002 Cloning and expression of sterol Δ^{14}-reductase from bovine liver; *Eur. J. Biochem.* **269** 283–290

Shultz L D, Lyons B L, Burzenski L M, *et al* 2003 Mutations in the mouse *ichthyosis* locus are within the lamin B receptor gene: a single-gene model for human Pelger-Huet anomaly; *Hum. Mol. Genet.* **12** 61–69

Waterham H R, Koster J, Mooyer P, *et al* 2003 Autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3*b*-hydroxysterol Δ^{14}-reductase deficiency due to mutations in the lamin B receptor gene; *Am. J. Hum. Genet*. **72** 1013–1017

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