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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

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