

Blood, Sweat and Tears—or Is It Teeth, Sweat Glands, and Hair?

A very interesting story has unfolded over the past few years regarding the pathogenesis of hypohidrotic ectodermal dysplasia (HED). The gene harboring mutations responsible for the X-linked form of this disorder, which is characterized by abnormal formation of teeth, hair, and eccrine sweat glands, was identified by positional cloning about 3 years ago. Designated *ED1*, it encodes a transmembrane protein, called ectodysplasin (Eda), that contains a collagen-like region in its extracellular domain. This region is thought to mediate formation of trimers as the extracellular portions of the molecules extend from the cell surface.

Mutations in the mouse homologue of human *ED1* have been found in a mouse mutant called tabby (*ta*), which has a murine phenotype equivalent to HED. Since Eda appears to be involved in the induction of ectodermal placodes, which give rise to structures that fail to form in both HED and *ta*, Eda was proposed to function as a membrane-bound ligand, although the mechanism of signal transduction was not known. This speculation led to a search for an Eda receptor. The receptor was predicted to be encoded by an autosomal gene based on the existence of autosomal forms of HED that are clinically indistinguishable from the X-linked form. The search has now ended with the identification of a receptor for Eda.

The latest chapter of the story begins with a mouse mutant named downless (*dl*). The close similarity between the *dl* and *ta* phenotypes suggested the possibility that *dl* encoded the Eda receptor. Positional cloning of *dl* by Headon and Overbeek revealed it to be a novel member of the tumor necrosis factor (TNF) receptor. This argues for its being the Eda receptor since TNF receptors typically bind trimeric ligands, the form proposed for Eda. Moreover, its expression pattern corresponds well to sites in developing skin, where ectodermal placodes form.

Armed with the mouse *dl* cDNA as a probe, Monreal et al quickly cloned the human *DL* gene. They next searched for *DL* mutations in HED patients with suspected autosomal inheritance. They identified *DL* mutations in 3 families with autosomal recessive HED and in 2 families with autosomal dominant HED. Two of the recessive families displayed consanguinity. As expected, the affected members were homozygous for the putative mutations and their parents were heterozygous for the mutations. Affected members in the third recessive family were compound heterozygotes. Mutations in the recessive families probably act through haploinsufficiency.

The mutation in one of the dominant families predicts a truncated protein lacking a key functional domain, the so-called death domain, which lies at the carboxyl terminal of the molecule. Trimerization of the cytoplasmic death domain is required for signal transduction, typically to transmit signals that bring about cell death. Such mutant proteins could participate in interactions of trimeric ligands with trimeric receptor molecules, but they would not transmit signals downstream. Thus, the mutation would act in a dominant negative manner, which would explain why this type of mutation is inherited as a dominant, while the other loss of function mutations are inherited as recessives.

Monreal et al noted that some families with HED do not map to either the *ED1* or the *DL* locus, implying the existence of at least a third HED locus. A mouse mutant named crinkled (*cr*) displays a phenotype very similar to that of tabby and downless. The crinkled gene has not yet been cloned, but it represents a good candidate for the third HED locus.

Another interesting aspect of this story is that although the Eda ligand is membrane bound, it contains an extracellular cleavage site for the secreted metalloprotease, furin. Thus, it is possible that the trimerized ectodomain of Eda is cleaved to produce a ligand that diffuses at least locally in search of its receptor. Such cleavage is characteristic of TNF ligands.

Headon DJ, Overbeek PA. *Nat Genet* 1999;22:370-374.

Monreal AW, et al. *Nat Genet* 1999;22:366-369.

Barsh G. *Nat Genet* 1999;22:315-316.

Editor's comment: *The evidence to date strongly supports the view that DL in humans (and dl in mice) is a receptor for Eda and that signal transduction involves trimerization of Eda and its receptor as occurs with other TNF:TNF receptor interactions. Membrane-bound Eda may be cleaved from the cell of origin to diffuse to the cells it influences. The evidence further suggests that the downstream signals are required for induction of ectodermal placodes, which give rise to teeth, hair follicles, and sweat glands.*

The unfolding of this story provides another good example of how human and mouse genetics are interrelated and how analysis of mutant phenotypes yields insight into normal biology. Also, given the fact that, even in adults, cells in hair follicles recapitulate the developmental program that produces hair in early life, it seems quite possible that this work will lead to advances in the treatment of hair loss and in hair removal.

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