<Further Development 18_09>

The Ectodysplasin Pathway and Mutations of Hair Development

Vertebrates are classified by their cutaneous appendages. Hair and mammary glands are the basis for classifying organisms as mammals, and birds are the only extant lineage with feathers. Fish are recognized by their variety of scales. Amazingly, hair, feathers, mammary glands, fish scales, and teeth all form through reciprocal interactions of the epidermis and its underlying mesenchymal cells. (As described in Chapter 12, the mesenchyme beneath the tooth placodes is derived from neural crest, not mesoderm.) One pathway that connects all cutaneous appendages is the ectodysplasin (EDA) cascade (Figure 1). This pathway seems to be specific for cutaneous appendage formation, and mutations involving the components of the EDA pathway often cause syndromes involving two or more of these appendage types. When EDA binds to one of its receptors (EDAR or EDARADD), it separates the NF-kB transcription factor from its inhibitor and allows it to activate or repress particular genes.

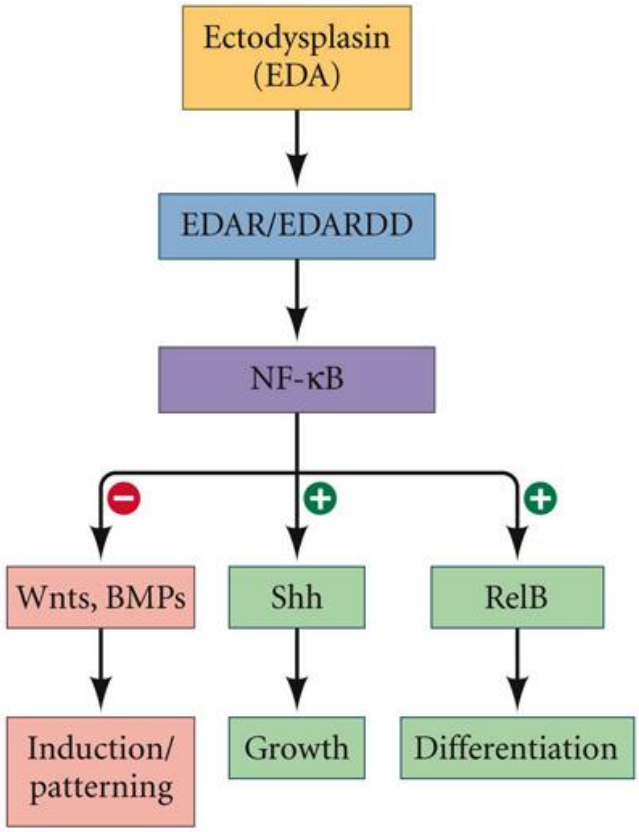

Figure 1 Outline of the ectodysplasin (EDA) pathway and some of the genes regulated by it.

EDA signaling directly or indirectly regulates the Wnt, BMP, and Shh signaling pathways and is thought to regulate both the patterning of hair follicles and the differentiation of the follicles. People lacking *EDA* have a syndrome that includes sparse hair, absent eyelashes and eyebrows, the lack of

most teeth, and the inability to sweat. Often they also lack mammary glands (which are modified sweat glands; see Gritli-Linde et al. 2007). The syndromes caused by mutations in the *EDA*, *EDAR*, and *EDARADD* genes are essentially identical and are referred to as anhidrotic ectodermal dysplasia (Mikkola 2007).

One of the functions of the EDA pathway is to activate fibroblast growth factor-20 (Fgf20) in the hair epithelial placodes. The Fgf20 appears to initiate the formation of the underlying dermal condensation. Fgf20 governs the formation of the primary and secondary dermal condensations in developing hair follicles and subsequent formation of hair (Huh et al. 2013).

Another function of the EDA pathway is to induce the expression of Foxi3 in the epithelial cells (Shirokova et al. 2013). Heterozyosity of Foxi3 has been selected in certain breeds of dogs (Mexican hairless, Chinese crested, and Peruvian dogs; the homozygous recessive embryos die in utero). These breeds of dogs are characterized by their sparse hair and missing teeth

Ectodermal dysplasia also occurs in other vertebrates. In zebrafish, the EDA pathway is critical in forming the placodes that generate the body scales and the pharyngeal teeth (Harris et al. 2007), and the chick feather placodes are similarly regulated by the EDA pathway (Houghton et al. 2005; Drew et al. 2007). In stickleback fish, the armorless phenotype seen in many freshwater lakes is the result of independent mutations of the *EDA* gene (Colosimo et al. 2005). Thus, the ectodysplasin pathway appears to regulate many types of cutaneous appendages in many species.

In humans, the thick hair associated with Asian populations has been found to be associated with a variant of the *EDAR* gene that predominates in Japan and China and is essentially absent in native European populations (Fujimoto et al. 2008). Furthermore, a causal connection between this allele ("370A") of *EDAR* and the thickened hair is suggested by experimental evidence (Kamerov et al. 2013) that mice with this allele also have thicker hair. Mice with the 370A variant of EDAR also have more eccrine sweat glands than mice with the wild-type allele of EDAR*. Similarly, the 370A version of the human *EDAR* gene is associated with a greater number of eccrine sweat glands.

(*Eccrine sweat glands are the major sweat gland of human skin. Most other mammals have apocrine sweat glands, which in humans, are confined to the human armpits, groin, and external ear. Eccrine sweat glands are much better at producing sweat than apocrine glands (which produce an oily secretion), and most non-human mammals have to use other means than sweating (such as panting) to cool their bodies in heat or after strenuous activity.)

Literature Cited

Colosimo, P. F. and 9 others. 2005. Widespread parallel evolution in sticklebacks by repeated fixation of Ectodysplasin alleles. *Science* 307: 1928–1933.

Drew, D. F., C. M. Lin, T.-X. Jiang, G. Blunt, C. Mou, C.-M. Chuong and D. J. Headon. 2007. The Edar subfamily in feather placode formation. *Dev. Bio*. 305: 232–245.

Gritli-Linde, A. and 9 others. 2007. Abnormal hair development and apparent follicular transformation to mammary gland in the absence of hedgehog signaling. *Dev. Cell* 12: 99–112.

Harris, M. P., N. Rohner, H. Schwarz, S. Perathoner, P. Konstantinidis and C. Nüsslein-Volhard. 2008. Zebrafish *EDA* and *EDAR* mutants reveal conserved and ancestral roles of ectodysplasin signaling in vertebrates. *PLOS Genet*. 4: e1000206.

Houghton, L., C. Lindon, and B. A. Morgan. 2005. The ectodysplasin pathway in feather tract development. *Development* 132: 863–872.

Huh S. and H. K. Närhi, P. H. Lindfors, O. Häärä, L. Yang, D. M. Ornitz, M. L. Mikkola. 2013. Fgf20 governs formation of primary and secondary dermal condensations in developing hair follicles. *Genes Dev*. 27: 450–458.

Kamberov Y. G., and 27 others. 2013. Modeling recent human evolution in mice by expression of a selected EDAR variant. *Cell* 152: 691–702.

Mikkola, M. L. 2007. Genetic basis of skin appendage development. 2007. *Semin. Cell Dev. Biol*. 18:225–236.

Shirokova V., and M. Jussila, M. K. Hytönen, N. Perälä, C. Drögemüller, T. Leeb, H. Lohi, K. Sainio, I. Thesleff, and M. L. Mikkola. 2013. Expression of Foxi3 is regulated by ectodysplasin in skin appendage placodes. *Dev Dy*. 242: 593–603.

Tan J., and Y. Yang, K. Tang, P. C. Sabeti, L. Jin, and S. Wang. 2013. The adaptive variant EDARV370A is associated with straight hair in East Asians. *Hum Genet*. 132(10): 1187–1191.