Edar Signaling in the Control of Hair Follicle Development

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Ectodysplasin receptor Edar and its ligand Eda A1, as well as their related receptor Xedar and ligand Eda A2, are recently discovered members of the tumor necrosis factor superfamily that signal predominantly through the nuclear factor-κB and c-jun N-terminal kinases pathways. Mutations in genes that encode proteins involved in Edar signaling pathway cause hypohidrotic ectodermal displasias in humans and mice and characterized by severe defects in development of ectodermal appendages including hairs, teeth, and exocrine glands. Here, we summarize the current knowledge of molecular mechanisms underlying the involvement of Edar signaling pathway in controlling hair follicle (HF) development and cycling. Genetic and experimental studies suggest that Edar signaling is involved in the control of cell fate decision in embryonic epidermis, as well as in the regulation of cell differentiation programs in the HF. Loss or gain of Edar signaling affects the initiation of several HF types (guard and zig-zag HF), hair shaft formation, as well as sebaceous gland morphology. We also review data on the cross-talk between Edar and Wnt, transforming growth factor-β/bone morphogenic protein/activin, and Shh signaling pathways in the control of HF development and cycling.

Key words: hair follicle/Edar/NF-κB
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Hair follicle (HF) is an ectodermal appendage that shows in postnatal life a dynamic cycling activity with periods of active growth and hair fiber formation (anagen), apoptosis-driven involution (catagen), relative resting, and hair shedding (telogen–exogen) (Paus and Cotsarelis, 1999; Fuchs *et al*, 2001; Stenn and Paus, 2001; Millar, 2002; Botchkarev and Paus, 2003). HF morphogenesis and cycling are controlled by similar signaling networks within and between the follicular epithelium and mesenchyme employing molecules that belong to the Wnt, transforming growth factor-β (TGF-β)/bone morphogenic proteins (BMP), Hedgehog, fibroblast growth factor, Notch, epidermal growth factor, tumor necrosis factor, and neurotrophin families (Cotsarelis and Millar, 2001; Fuchs *et al*, 2001; Millar, 2002; Botchkarev and Kishimoto, 2003; Schmidt-Ullrich and Paus, 2005).

Ectodysplasin receptor Edar is a recently discovered member of the tumor necrosis factor (TNF) receptor superfamily that signals predominantly through nuclear factor-κB (NF-κB) transcription factors (Mikkola and Thesleff, 2003). Defects in genes that encode proteins of the Edar signaling pathway cause hypohidrotic ectodermal dysplasias (HED) in humans and similar conditions in mice (Drogemuller *et al*, 2003). HED is characterized by severe defects in ectodermal appendage development, including hairs, teeth, and exocrine glands. The rapidly accumulating information proves a critical role for Edar signaling in molecular signaling network that regulate the development of ectodermal appendages (reviewed by Mikkola and Thesleff, 2003). Here we summarize current knowledge about the role of Edar signaling in HF development and growth. We also focus on interplay between Edar signaling pathway and other key molecular pathways that are involved in the control of HF development and cycling.

Abbreviations: BMP, bone morphogenic proteins; HF, hair follicle; JNK, c-jun N-terminal kinases; NF-κB, nuclear factor-κB; TNF, tumor necrosis factor

Molecular Components of the Edar Signaling Pathway

The Ectodysplasin family of ligands includes two trimeric type II membrane proteins (Eda A1 and Eda A2; Fig 1) both containing a short intracellular domain, transmembrane region, and extracellular portion with collagenous domain and a TNF-ligand motif in the C-terminal region (reviewed by Mikkola and Thesleff, 2003). Eda A1 differs from the Eda A2 by presence of only two additional amino acids in the TNF motif (Yan *et al*, 2000; Hymowitz *et al*, 2003). Despite these minor structural differences, Eda A1 and Eda A2 show very high specificity to the corresponding receptors Edar and Xedar (Bayes *et al*, 1998; Yan *et al*, 2000; Hymowitz *et al*, 2003). Cleavage of Eda A1/2 by the furin-like enzyme leads to formation of soluble extracellular molecule which is able to interact with corresponding receptors and mediate the signals (Chen *et al*, 2001; Elomaa *et al*, 2001).

Similar to the most TNF receptors, Edar contains extracellular ligand binding N-terminal domain, single transmembrane region and intracellular region containing death domain (Headon and Overbeek, 1999). Eda A1 binding to Edar leads to recruitment of auxiliary death domain containing protein Edaradd, which binds selected TRAF proteins (TRAF1–3 and possibly 5 and 6, but not TRAF4,

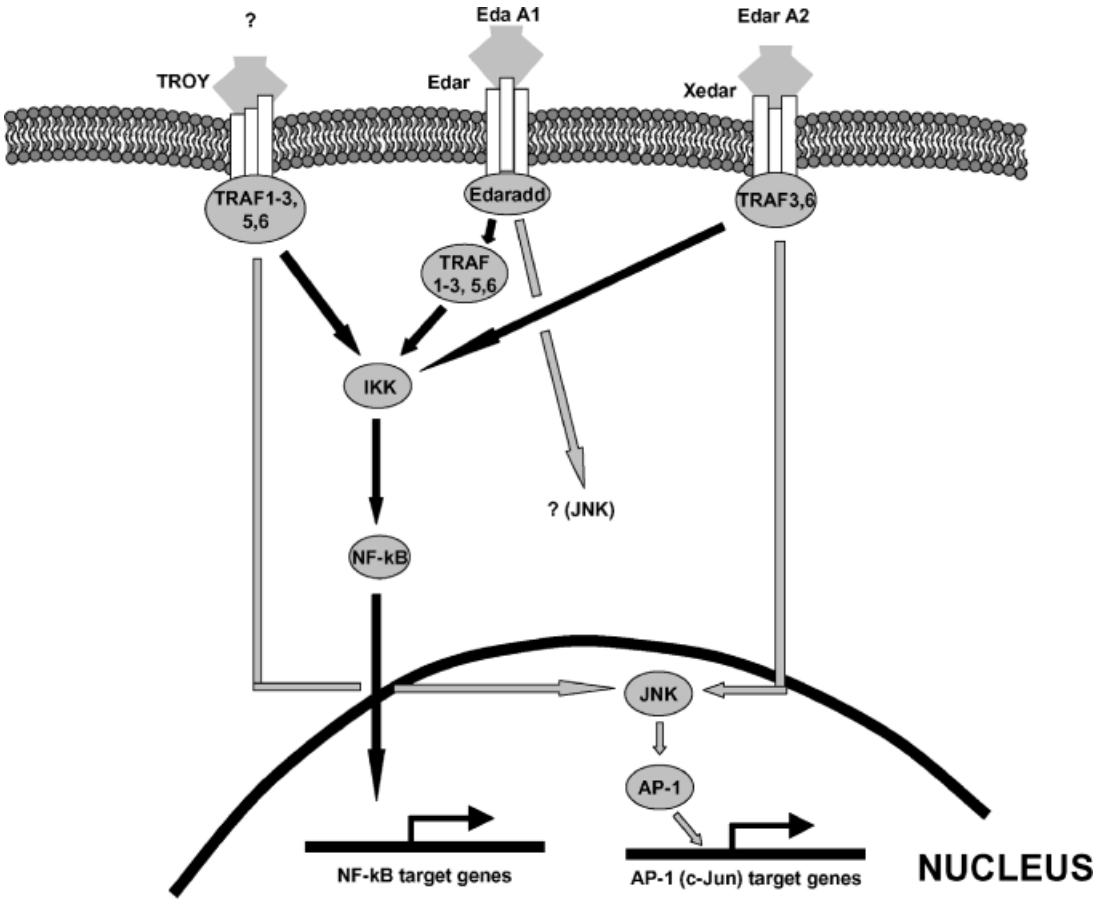

Figure 1
Molecular components of the Edar, Xedar, and Troy signaling pathways. Scheme illustrating the molecular composition (ligands, receptors intracellular adaptor proteins, downstream effectors) of the Edar, Xedar, and Troy signaling pathways.

Headon *et al*, 2001; Yan *et al*, 2002; Fig 1). Edar signal leads to activation of NF-κB transcripton factors, their translocation to nucleus and modulation of the activity of the corresponding target genes (Smahi *et al*, 2002). Although some TNF family receptors activate c-jun N-terminal kinases (JNK) pathway in addition to NF-κB pathway, Edar showed only weak activation of JNK pathway (Kumar *et al*, 2001; Mikkola and Thesleff, 2003).

In contrast to Eda A1/Edar signaling, Eda A2 binding to Xedar leads to interaction of its intracellular domain with TRAF3 and TRAF6 and activation of both NF-κB and JNK pathways (Sinha *et al*, 2002; Fig 1). Eda A1 and Eda A2 do not interact with recently discovered TNF family receptor TROY that shows high structural similarity to Edar (Kojima *et al*, 2000). TROY signaling involves recruitment of the TRAF2, TRAF5, TRAF6 and possibly TRAF1 and TRAF3 and leads to strong JNK and weak NF-κB activation (Kojima *et al*, 2000; Kumar *et al*, 2001; Fig 1).

Deficiency in Edar Signaling Affects HF Morphogenesis

In normal mouse fur, HF morphogenesis results in the formation of four hair types (Sundberg and Hogan, 1994; Vielkind and Hardy, 1996): (1) Guard (tylotrich) hairs are thick, straight and represent about 5%–10% of the hairs in mouse fur; (2) Awl hairs are also straight and thick but significantly shorter than guard hairs; (3) Auchene hairs are similar to the awl hairs in length except that they have a single contraction; (4) Zig-zag hairs comprise about 70% of the normal hairs in mouse fur and show two contractions. Guard or primary HF are induced between E14.5 and E16.5, whereas non-tylotrich or secondary HF producing the awl, auchene and zig-zag hairs are induced in murine back skin from E16.5 to P0.5 (Sundberg and Hogan, 1994; Vielkind and Hardy, 1996). Microscopically, guard HF may be distinguished from the other HF types by the enlarged size of proximal hair bulb and two-lobular sebaceous glands.

The crucial role of the components of Edar signaling pathway (Eda A1, Edar, Edaradd) in HF development is evident from the fact that mice with spontaneous mutations in the corresponding genes (Tabby [*Ta*], Downless [*Dl*], and Crinkled [*Cr*]) show lack of guard and zig-zag hairs (Ferguson *et al*, 1997; Headon and Overbeek, 1999; Headon *et al*, 2001). Coat of these mice consists of two intermediate types of hairs which resemble the awl and auchene hairs in length but lack of normal arrangements of pigment granules in hair medulla; (Kindred, 1967; Sundberg, 1994; Table I). Also, these mice show absence of hairs behind the ears and on the tail, as well as lack of the sweat and Meibomian glands (Gruneberg, 1971a, b). In contrast to Edar deficiency, genetic Xedar ablation is not accompanied by any visible skin or HF abnormalities (Newton *et al*, 2004).

TRAF6 and NF-κB serve as important downstream components of Edar signaling (reviewed in Mikkola and Thesleff, 2003; Fig 1). The genetic ablation of TRAF6 in mice also results in hair defects similar to Tabby, however, TRAF6 null

Table I. Hair phenotype of mice with genetic loss or gain of Edar and Xedar signaling

Gene	Hair phenotype when gene is mutated or deleted	Hair phenotype when gene is overexpressed	References
Eda (Tabby)	Guard and zig-zag hairs are missing. Awl hairs are present, whereas auchene hairs are either absent (majority of the animals) or reduced in number. Total number of pelage hairs is normal. Absence of hairs behind the ears and on the tail		Kindred (1967) Gruneberg (1971a) Sundberg (1994) Ferguson *et al* (1997) Drogemuller *et al* (2003)
Eda A1		CMV-Eda A1 mice on Tabby background: Guard and tail hairs are present, but zigzags are missing. Hyperplasia of sebaceous glands	Srivastava *et al* (2001)Cui *et al* (2003) Mustonen *et al* (2003) Zhang *et al* (2003)
		K14-Eda A1 mice on FVB/N background: Curly or straight hairs that resemble guard and awl hairs of WT mice. Zigzag and auchene hairs are missing. Formation of "fused" follicles during morphogenesis. Retardation of catagen	
		Inv-Eda A1 mice on C57BL/6 background: Guard, awl and auchene hairs are normal, zig-zag hairs are missing. Formation of curly hairs instead of zig-zag hairs. Some follicles are fused	
Eda A2		Apparently normal hair development	Cui *et al* (2003) Mustonen *et al* (2003)
Edar (Downless)	Phenotype identical to Tabby and Crinkled	Not determined	Headon and Overbeek (1999)
Edaradd (Crinkled)	Phenotype identical to Tabby and Downless	Not determined	Headon *et al* (2001) Yan *et al* (2002)
Xedar	Apparently normal hair development	Not determined	Newton *et al* (2004) Naito *et al* (2002)
TRAF6	Guard and zig-zag hairs are missing, awl hairs are abnormal. Sebaceous glands are hypoplastic	Not determined	

mice also show hypoplastic sebaceous glands (Naito *et al*, 2002). Prevention of NF-κB activation by transgenic expression in skin of its repressor IκBα also leads to hair defects similar to that of seen in *Ta*, *Dl*, and *Cr* mice (Schmidt-Ullrich *et al*, 2001). These observations suggest critical roles for TRAF6 and NF-κB in Edar signaling and their possible involvement in regulating the expression of Edar targets in the HF keratinocytes.

Discovery of the molecular basis of the *Ta*, *Dl*, and *Cr* mutations led to detailed morphological characterization of the Eda A1, Edar, and Edaradd expression during HF morphogenesis. At E14.5–E15.5, Eda mRNA is expressed in the interfollicular epidermis, Edar, and Edaradd transcripts are seen in the hair placodes, whereas Eda A1 and Edar proteins are seen in both hair placodes and interfollicular epidermis (Yan *et al*, 2000; Laurikkala *et al*, 2002; Mikkola and Thesleff, 2003). During later steps of HF development, Eda and Edar transcripts are expressed in hair bulb keratinocytes, whereas Eda A1 and Edar proteins are seen in differentiating cells of the hair matrix (Yan *et al*, 2000; Mikkola and Thesleff, 2003). In contrast to Eda A1, Eda A2 protein is not expressed in the epidermis and hair placodes at E14.5–E18.5 and is seen in the hair bulb epithelium only at P1.5, whereas Xedar protein is expressed in differentiating hair matrix keratinocytes starting from E17.5 (Yan *et al*, 2000). At E14.5, Xedar and TROY transcripts are seen in the interfollicular epidermis and hair placodes, whereas later their expression becomes more localized in hair bulb keratinocytes (Kojima *et al*, 2000; Yan *et al*, 2000).

Thus, these expression patterns together with HF phenotypes seen in *Ta*, *Dl*, and *Cr* mice suggest an important role for Edar signaling in the HF initiation and in hair shaft formation. Also, strictly epithelial expression of the components of Edar pathway suggest their role in the intra-epithelial signaling exchange between keratinocytes of developing HF, as well in modulating the responsiveness of HF epithelium to mesenchymal signals.

Gain of the Edar Function Leads to Partial Restoration of the Tabby Phenotype and Alters Cell Fate Decision in the Epidermis

Recent pharmacological and genetic studies confirmed distinct roles for Edar and Xedar signaling in the control of HF development. In particular, it was shown that pharmacological administration of soluble Eda A1-Fc chimeric protein to pregnant Tabby mice between E11.5 and E15.5 lead to appearance of the guard HF, tail hairs, and exocrine glands (Gaide and Schneider, 2003). But treatment with Eda A2-Fc does not rescue the Tabby phenotype. Interestingly, HF morphogenesis in the tail of Tabby mice could be induced even when Eda A1-Fc treatment starts within few days after birth. But Eda A1-Fc treatment is not resulted in the appearance of zig-zag hairs (Gaide and Schneider, 2003). This work shows the importance of proper intensity and timing of Edar signaling during skin morphogenesis and suggests that genetic defects in Edar signaling may be ef-

fectively corrected by administration of the ligand at appropriate time window during embryogenesis.

Genetic studies also suggest a possibility for partial rescuing the Tabby phenotype by transgenic expression of Eda A1 under control of the CMV promoter (Srivastava *et al*, 2001). Eda A1 overexpression leads to restoration of the guard HF, tail hairs, and sweat glands in Tabby mice (Srivastava *et al*, 2001; Cui *et al*, 2003). In contrast to Eda A1 transgenic mice, Eda A2 overexpression is not capable of rescuing Tabby phenotype (Cui *et al*, 2003). Interestingly, transgenic increase of Eda A1 expression also results in hyperplasia of the sebaceous glands suggesting the role for Edar signaling in regulation of the sebocyte activity (Cui *et al*, 2003). But Eda A1 overexpression is not able to restore zig-zag hairs in Tabby mice and even result in suppression of their formation in wild-type mice suggesting the importance of proper intensity of Edar signaling for the formation of zig-zag hairs.

Further insights into the role of Edar signaling in the control of hair shaft formation were obtained by generating transgenic mice overexpressing Eda A1 under control of the K14 or involucrin promoters that target transgene expression either to basal epidermal and outer root sheath keratinocytes or to differentiating keratinocytes of the epidermis and HF inner root sheath, respectively (Mustonen *et al*, 2003; Zhang *et al*, 2003). Both K14-EdaA1 and Inv-EdaA1 mice show quite similar hair phenotypes. Some of the K14-Eda A1 mice show formation of only curly hairs, whereas the others have only straight hairs that resemble guard and awl hairs seen in wild-type mice (Mustonen *et al*, 2003). In Inv-Eda A1 transgenic mice, guard, awl and auchene hairs look normal, whereas zig-zag hairs are replaced by curly hairs that show single column of air cells in the medulla (Zhang *et al*, 2003).

Gain of the Eda A1 levels in the epidermis of K14-EdaA1 and Inv-EdaA1 transgenic mice also results in alterations of the HF patterning and formation of the "fused" HF because of the loss of proper spacing between neighboring hair placodes (Mustonen *et al*, 2003, 2004; Zhang *et al*, 2003). "Fused" HF were joined together in their permanent portions by the outer epithelial layers, and within a fusion, each HF possessed its own hair bulb, dermal papilla, hair shaft, and sebaceous gland (Mustonen *et al*, 2003, 2004; Zhang *et al*, 2003). Interestingly, the "fused" HF show unchanged patterns of cyclic activity and proceed through all hair cycle stages together with other HF that show normal morphology (Zhang *et al*, 2003).

Taken together, these data suggests that Edar signaling is involved in the control of cell fate decision in embryonic epidermis, as well as in the regulation of cell differentiation programs in the HF. The effects of Edar signaling on HF development show stringent spatio-temporal dependence, and are also strikingly dependent on the amount of biologically active ligand in close vicinity of target cells. But additional efforts are required to fully understand the differences in molecular mechanisms of Edar involvement and Edar targets in controlling two distinct steps of HF morphogenesis (HF initiation *vs* hair shaft formation). Also, cross-talk between Edar signaling and other molecular pathways involved in the formation of distinct hair types remain to be further clarified.

Cross-Talk Between Edar and Other Signaling Pathways that Control HF Development

Several lines of evidence suggest the involvement of Wnt and TGF-β/activin/BMP signaling pathways in controlling the expression of Eda and Edar: in embryonic explants of murine skin Eda is induced by Wnt6, whereas Edar expression was induced by activin (Laurikkala *et al*, 2002). Interestingly, Edar induction by activin requires presence of mesenchyme, whereas Eda induction seems to be mesenchyme independent (Laurikkala *et al*, 2002). Importance of Wnt signaling in regulation of the Eda expression was confirmed by analysis of Lef-1 knockout embryos (Laurikkala *et al*, 2002) and by transient transfection experiments with Eda promoter *in vitro* (Durmowicz *et al*, 2002). In chicken skin, Edar is positively regulated by β-catenin, whereas BMP signaling inhibits Edar expression (Houghton *et al*, 2005).

The molecular analysis of embryonic HF in Tabby mice shows that at E14.5 (i.e., when the placodes of guard HF become visible in wild-type mice) the expression of placode markers, such as β-catenin, Lef-1, Shh, Ptch, BMP-4, and activin A is absent in Tabby skin (Laurikkala *et al*, 2002). As Edar expression is seen in hair placodes of β-catenin conditional knockout mice (Huelsken *et al*, 2001), these data suggest Edar signaling as up-stream regulator of the Wnt, Shh, and BMP pathways during the initiation of guard HF.

But the mechanism underlying the interaction between Edar and Wnt/Shh/BMP signaling pathways during induction of other HF types remains to be further clarified. Initiation of the awl, auchene, and zig-zag HF is absent in noggin knockout mice (Botchkarev *et al*, 1999, 2002), whereas Shh overexpressing mice (promoter—human keratin 1) show lack of guard, awl, and auchene HF (Ellis *et al*, 2003). Also, BMP4 administration into postnatal telogen skin selectively blocks telogen–anagen transition in non-guard HF, whereas guard HF show normal anagen development (Botchkarev *et al*, 2001). It appears to be very intriguing to define whether Edar signaling is involved in the controlling the expression of the components of BMP and Shh pathways during initiation of zig-zag HF as well as during cell differentiation phase of the HF morphogenesis and cycling.

Conclusion

During the last decade, a substantial progress has been achieved in delineating the molecular structure and function of Edar signaling pathway, which is now recognized as powerful regulator of skin development and postnatal remodeling. Edar signaling is intimately involved in the control of cell fate decision and cell differentiation during HF development. But additional efforts are required to fully understand molecular mechanisms and cross-talk between Edar and other signaling pathways that control skin and HF development and growth. The progress in this area of research would hopefully bridge the gap between our current knowledge of Edar functions in skin and potential clinical

application of the components of Edar signaling pathway for correction of skin and hair growth disorders.

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