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Mini review

Ectodysplasin A (EDA) – EDA receptor signalling and its pharmacological modulation

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ABSTRACT

The TNF family ligand ectodysplasin A (EDA) regulates the induction, morphogenesis and/or maintenance of skin-derived structures such as teeth, hair, sweat glands and several other glands. Deficiencies in the EDA – EDA receptor (EDAR) signalling pathway cause hypohidrotic ectodermal dysplasia (HED). This syndrome is characterized by the absence or malformation of several skin-derived appendages resulting in hypotrychosis, hypodontia, heat-intolerance, dry skin and dry eyes, susceptibility to airways infections and crusting of various secretions. The EDA–EDAR system is an important effector of canonical Wnt signalling in developing skin appendages. It functions by stimulating NF-κB-mediated transcription of effectors or inhibitors of the Wnt, Sonic hedgehog (SHH), fibroblast growth factor (FGF) and transforming growth factor beta (TGFβ) pathways that regulate interactions within or between epithelial and mesenchymal cells and tissues. In animal models of *Eda*-deficiency, soluble EDAR agonists can precisely correct clinically relevant symptoms with low side effects even at high agonist doses, indicating that efficient negative feedback signals occur in treated tissues. Hijacking of the placental antibody transport system can help deliver active molecules to developing foetuses in a timely manner. EDAR agonists may serve to treat certain forms of ectodermal dysplasia.

1. Ectodysplasin A and ectodermal dysplasias

Ectodermal dysplasias comprise more than 180 different heritable syndromes affecting at least two ectodermal structures such as hair, teeth, nails or exocrine glands [1]. The most common ectodermal dysplasia, X-linked hypohidrotic ectodermal dysplasia (XLHED), is characterized by missing or sparse hair (hypotrychosis), abnormal or missing teeth (hypodontia or anodontia), reduced sweating ability (hypohidrosis), and defects of various lipid- or mucus-secreting glands. XLHED is caused by mutations of the ectodysplasin A (*EDA*) gene [2]. *EDA* mutations are also associated with selective tooth agenesis (STA), an inherited condition in which teeth only are affected, with no pathologic involvement of other ectodermal appendages [3]. EDA is a TNF family ligand that binds to EDA receptor (EDAR). EDAR signals *via* an adaptor protein, EDAR-associated protein with a death domain (EDARADD). Mutations in the *EDAR* or *EDARADD* genes cause hypohidrotic ectodermal dysplasias identical to XLHED, except for their autosomal dominant or recessive modes of transmission [4,5].

2. Ectodysplasin A

The human *EDA* gene was first identified by positional cloning in XLHED patients and is located on the long arm of the X chromosome [2]. EDA is a 391 amino acid residues-long membrane protein with a short intracellular domain, a transmembrane domain, a stalk region of uncharacterized function, a consensus furin cleavage sequence responsible for proteolytic processing of EDA, a short positively-charged sequence required for interactions with heparan-sulfate proteoglycans, a bi-partite collagen-like domain and a 150 amino acid residues-long C-terminal TNF homology domain (THD) responsible for receptor binding (Fig. 1A). *EDA* transcripts undergo complicated splicing events giving rise to numerous EDA isoforms (up to nine in mouse keratinocytes), of which only the longest two, EDA1 and EDA2, contain the THD, interact with receptors and are known to be biologically active [6,7]. EDA1 and EDA2 differ by two amino acid residues in the THD (Glu308 and Val309) as a result of differential usage of a splice donor site at the end of exon 7 (Fig. 1A) [8]. EDA1 binds to EDAR, while the 2 amino acid residues shorter EDA2 specifically interacts with another TNF receptor family member, XEDAR [8]. EDA1, EDA2

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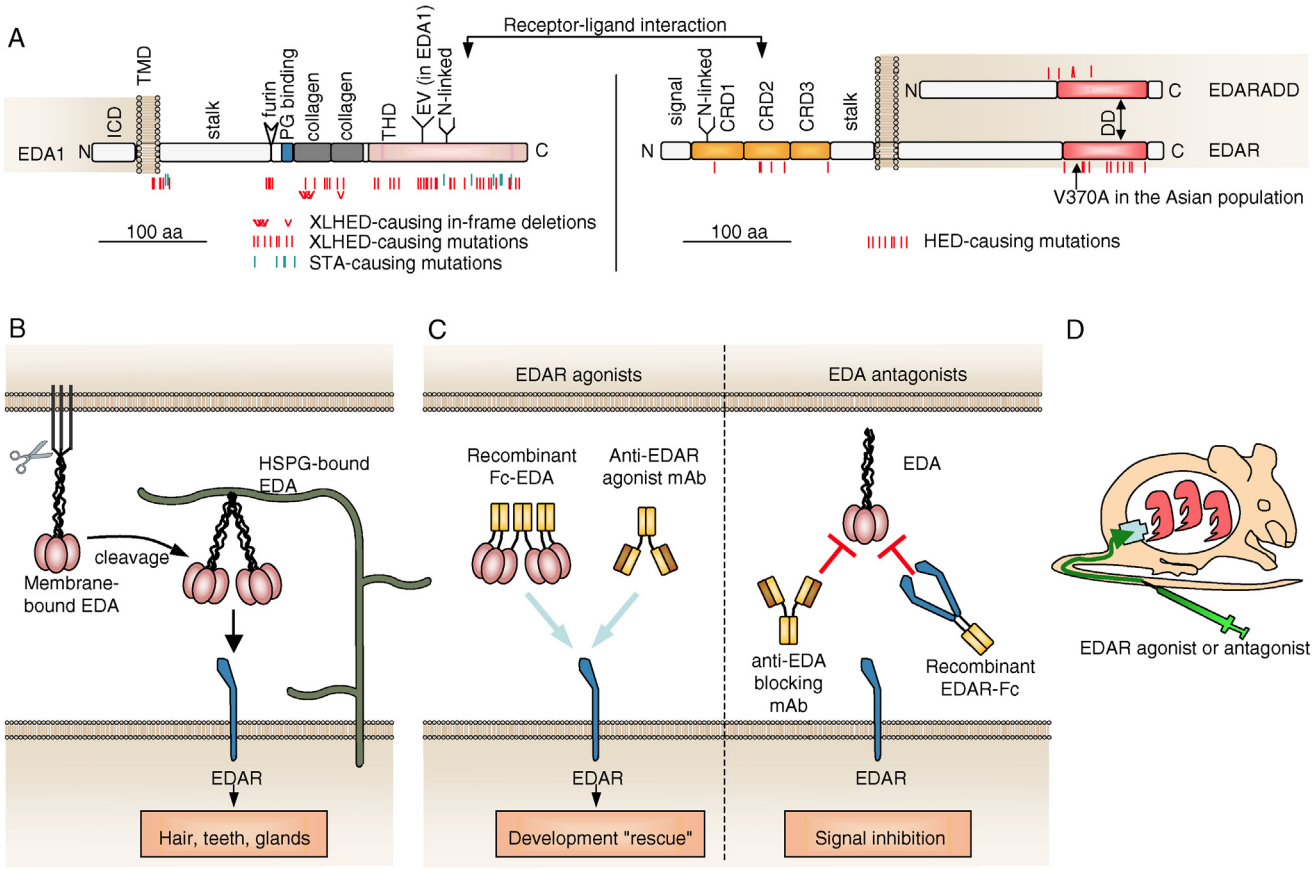

Fig. 1. Protein organization and mode of action of the ligand and receptor pair EDA1-EDAR and some of their agonists and antagonists. (A) Structural organization of EDA1, EDAR and EDARADD. HED- and STA-causing mutations are those listed in UniProt. DD: death domain. (B) Principle of EDAR activation by endogenous EDA1. (C) Principle of action of soluble agonists and antagonists of the EDA–EDAR pathway. (D) Principle of *in utero* delivery of agonists and antagonists of EDAR signalling *via* transplacental antibody transport.

and their receptor binding specificity are conserved in mammals and birds [9]. *XEDAR* is a p53-induced gene with no obvious implications in ectodermal appendage development [10,11]. *EDA* mutations identified in XLHED patients touch several distinct regions of the protein that are therefore believed to be of functional importance [12] (Fig. 1A). The first one lies at the beginning of the stalk region, but why this region is important for EDA expression or function is unknown. Interestingly, fishes that have evolved in fresh water display a dramatic reduction in their bony armour compared to ocean fishes of the same species, which is due to the selection of a low-abundance allele of *Eda* that includes, among other polymorphisms, a Leu79Pro transition at the beginning of the stalk region [13]. The second region is the furin consensus cleavage site, indicating that EDA1 must be released to a soluble form to display activity (Fig. 1A and B). The third region is the THD. The THD forms homotrimers that can bind three individual receptors at each monomer–monomer interface [14]. XLHED- and STA-causing mutations in this domain interfere either with trimer formation, or with receptor binding [3,12]. The fourth region is the collagen domain that serves to keep two or more EDA1 trimers in close proximity within the same molecule and therefore potentiate its ability to stimulate EDAR signalling [12,15] (Fig. 1A and B). Finally, the proteoglycan-binding domain of EDA, which is mostly coded by the very short exon 3, may restrict EDA diffusion in tissues once it is released in a soluble form [15] (Fig. 1B). Mutations in the proteoglycan-binding region have not been reported in XLHED patients, either because this interaction is not essential for the function of EDA, or because disruption of the interaction can be achieved neither with a single point mutation nor with exon 3 deletion, which would induce a frame shift.

3. EDAR

EDAR is a typical TNF receptor family member with a signal peptide, three cystein-rich domains (CRDs), a transmembrane domain and an intracellular region comprising a so-called "death domain" [5] (Fig. 1A). Most mutations in patients with autosomal HED are located within CRD2, which is involved in ligand binding, or within the death domain, which is involved in signal transmission (Fig. 1A). A function activating polymorphism (Val370Ala) found in the death domain of EDAR in East Asian and Native American populations is associated with a thicker hair phenotype [16,17]. In the death receptors Fas and TRAILR2, the death domain recruits Fas-associated protein with a death domain (FADD), that itself recruits and activates cystein proteases of the caspase family to execute apoptotic cell death. EDAR does not interact with FADD, but instead recruits EDARADD, another adaptor protein with a death domain [4] (Fig. 1A).

4. EDAR activates canonical NF-κB

Deficiencies for EDA, EDAR or for the adaptor protein EDARADD all induce HED with similar if not identical manifestations. EDARADD, unlike FADD, does not recruit caspases, but possesses consensus binding sites for TNF receptor associated factors (TRAFs), and in particular TRAF6 [4,18]. TRAF6 mediates the activation of the transcription factor NF-κB downstream of several TNF receptor family members (*e.g.* EDAR, RANK and CD40) or other receptors (IL1R, TLRs). Thus, *Traf6*-deficient mice do not only develop ectodermal dysplasia similar to *Edar*- or *Edaradd*-deficient mice, but also osteopetrosis, alymphoplasia-RANK signalling is