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Interplay between EDA-EDAR and WNT signalling pathways in the development of skin appendages in hypohidrotic ectodermal dysplasia

Współzależność między ścieżkami sygnałowymi EDA-EDAR oraz WNT w rozwoju przydatków skóry w hipohydrotycznej dysplazji ektodermalnej

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Abstract

Ectodermal dysplasia comprises a group of hereditary disorders affecting the development of the skin and its appendages. Among the more than 150 characterised forms of ectodermal dysplasia, hypohidrotic ectodermal dysplasia is the most prevalent in children. Hypohidrotic ectodermal dysplasia is marked by reduced sweating, sparse hair, a limited number of conical-shaped teeth, and brittle nails. The condition results from mutations in genes involved in the EDA-EDAR-EDARADD-NF-κB signalling pathway, which is crucial for early epithelial-mesenchymal communication during the formation of skin appendages. The Wnt/β-catenin pathway also plays a vital role in the development of hair follicles, teeth, and other ectodermal structures. In this article, publicly available single-cell gene expression data from a mouse model were re-analysed to investigate the expression profiles of genes from both the EDA-EDAR and WNT pathways. *Wnt10b*, *Dkk4* and *Edar* were confirmed to be expressed in epidermal keratinocytes, particularly in Fgf20-positive early placode-forming cells. Furthermore, correlated expression of *Edaradd* and *NF-κB* was observed during early appendage formation, while Eda ligand expression was detected in Dkk1-positive mesenchymal progenitor cells, transiently amplifying to become the first dermal condensate and subsequently dermal papilla cells. These findings further support previous observations that EDA-A1 signalling through EDAR-EDARADD and NF-κB enhances WNT pathway activity, creating a mutually reinforcing network. Disruption of this feedback loop between the EDA-EDAR and WNT pathways give rise to the characteristic phenotypes of hypohidrotic ectodermal dysplasia observed in children. Early restoration of the EDA-EDAR and WNT signalling pathways may offer a promising therapeutic strategy for rescuing skin appendage development and thus reducing the effects of ectodermal dysplasias in the future.

Keywords: hypohidrotic ectodermal dysplasia, EDA-EDAR signalling, WNT pathway, skin appendages, hair follicle development

Streszczenie

Dysplazja ektodermalna to grupa dziedzicznych zaburzeń rozwoju skóry i jej przydatków. Spośród ponad 150 scharakteryzowanych postaci dysplazji ektodermalnej najpowszechniej występującą u dzieci jest hipohydrotyczna dysplazja ektodermalna, manifestująca się ograniczoną potliwością, rzadkim owłosieniem, obecnością zaledwie kilku stożkowatych zębów oraz łamliwymi paznokciami. Ten fenotyp jest wynikiem mutacji w genach należących do szlaku sygnałowego EDA-EDAR-

EDARADD-NF-κB, który jest kluczowy dla wczesnej komunikacji naskórkowo-mezenchymalnej podczas formowania się przydatków skóry. Podczas rozwoju zębów, włosów i innych struktur ektodermalnych niezbędne jest także uczestnictwo szlaku WNT z β-kateniną. W artykule ponownie przeanalizowano publicznie dostępne dane z transkryptomiki pojedynczych komórek w modelu mysim i zbadano profile ekspresji genów należących do szlaków sygnałowych EDA-EDAR oraz WNT. Na tej podstawie potwierdzono ekspresję genów *Wnt10b*, *Dkk4* oraz *Edar* w keratynocytach naskórka, szczególnie wśród tych Fgf20-dodatnich, tworzących wczesne plakody. Ponadto zaobserwowano, że korelowało to z ekspresją genów *Edaradd* i *NF-κB*. Ekspresja ligandu Eda była natomiast obecna w Dkk1-dodatnich, mezenchymalnych komórkach progenitorowych, przejściowo aktywowanych w celu stworzenia początkowego skupiska komórek dermalnych dla przyszłej brodawki włosa. Wymienione odkrycia potwierdzają zaobserwowany wcześniej wpływ sygnalizacji EDA-A1 przez EDAR-EDARADD i NF-κB na wzmocnienie aktywności szlaku WNT, tworzący wzajemnie wspierający się system regulacyjny. Zaburzenia w sprzężeniu zwrotnym pomiędzy tymi ścieżkami manifestują się typowym fenotypem dla dzieci z hipohydrotyczną dysplazją ektodermalną. W związku z tym wczesne przywrócenie działania szlaków EDA i WNT może wyznaczyć drogę do skutecznych terapii przywracających rozwój przydatków skóry i redukujących objawy dysplazji ektodermalnej w przyszłości.

Słowa kluczowe: hipohydrotyczna dysplazja ektodermalna, sygnalizacja EDA-EDAR, szlak WNT, przydatki skóry, rozwój mieszków włosowych

INTRODUCTION

Ectodermal dysplasias (ED) comprise a group of inherited disorders that affect the development and maintenance of two or more structures derived from the ectoderm, including hair, nail, skin, and sweat glands. Hypohidrotic (or anhidrotic) ectodermal dysplasia (HED), also known as Christ–Siemens–Touraine syndrome, is the most common form of ED. It may be inherited in an X-linked (XL), autosomal recessive (AR), or autosomal dominant (AD) manner[1–3]. HED is characterised by sparse hair, abnormal or missing teeth (hypodontia or anodontia), reduced sweating, and slow-growing or absent nails. The condition affects approximately 1/15,000 to 1/100,000 individuals worldwide[4–6]. The clinical manifestations of HED are diverse and can significantly impact the quality of life, as shown in Fig. 1.

Skin abnormalities

Sweat gland deficiency is one of the hallmark features of HED, manifesting as a reduced ability to sweat

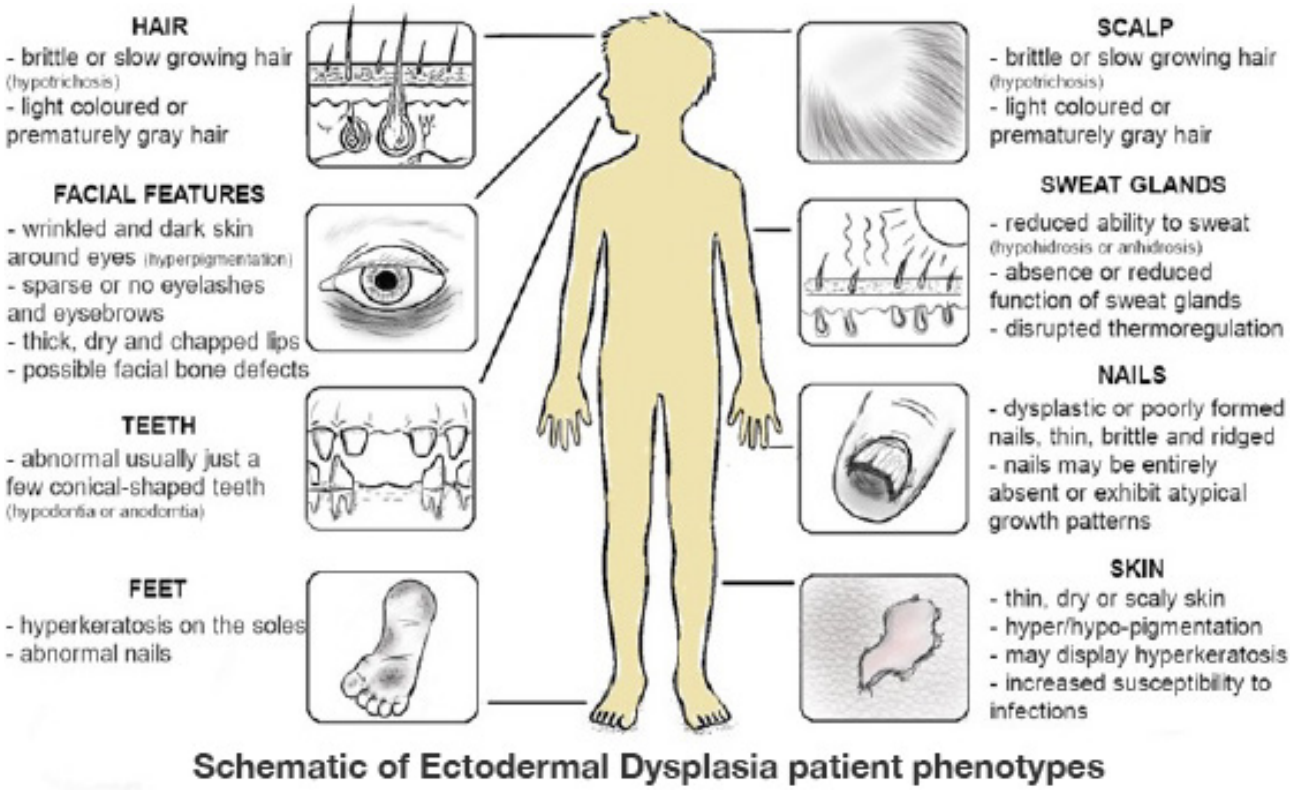

Fig. 1. Schematic of ED patient phenotypes. The clinical manifestations of ED vary depending on the specific type, but they generally affect structures derived from the ectoderm, including the skin, hair, nails, teeth, and sweat glands

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(hypohidrosis or anhidrosis) due to underdeveloped or absent eccrine glands. This leads to heat intolerance and recurrent episodes of hyperthermia. The skin is typically thin, dry, and eczematous, with regional hyperkeratosis. Characteristic periorbital hyperpigmentation and fine wrinkles around the eyes give an appearance of premature aging[4] (Fig. 1).

Hair abnormalities

Affected individuals have sparse scalp hair (hypotrichosis), which is often light-coloured, brittle, and slow-growing. Eyebrows and eyelashes are also sparse or absent[5] (Fig. 1).

Dental abnormalities

Tooth development abnormalities, including hypodontia (missing teeth) or malformed teeth, are common. Usually, just a few conical-shaped teeth are present, often smaller and pointed in appearance[4,7]. Other clinical manifestations include dysmorphic facial features, respiratory issues, and immune system implications (Fig. 1).

Nail abnormalities

Nails, derived from the ectodermal layer, can be affected by ED, though not all individuals with the condition experience nail abnormalities. Common manifestations include small, brittle, discoloured, or misshapen nails, which may grow slowly or shed periodically, and are prone to splitting and breaking[8–10].

At the cellular and molecular levels, the development of the skin and its appendages is a complex process. However, EDA-EDAR and WNT are the two major pathways playing a critical role in this process. Mutations or impairment in any of the components of these two pathways lead to abnormalities in the development of ectodermal derivatives[4,5].

EDA-EDAR-EDARADD PATHWAY AND ITS FUNCTION IN DEVELOPMENT OF SKIN APPENDAGES

The *EDA* (ectodysplasin A) gene encodes the ligand EDA, which belongs to the tumour necrosis factor (TNF) ligand superfamily. EDA has 8 isoforms due to alternative splicing, of which only EDA-A1 (a 391-amino acid protein) and EDA-A2 (a 389-amino acid protein) have receptor-binding domains. EDA-A1 is a type II transmembrane protein with 4 functional domains; an N-terminal intracellular domain, a furin protease recognition sequence, a collagen-like repeat domain, and a C-terminal TNF homology domain (THD). EDA-A1 contains a unique 2-amino acid motif (Val-Glu) in comparison to EDA-A2 in THD, required for EDAR (ectodysplasin A receptor) selective binding. In EDA-A1, the C-terminal portion comprising the collagen and TNF homology domains is cleaved at the furin consensus site, releasing homotrimers that can bind to its receptor EDAR, which is encoded on chromosome 2. While EDA-A2 shares much of its structure with EDA-A1, it lacks the Val-Glu motif in the TNF homology domain, which defines its binding to XEDAR (X-linked EDA receptor), also known as EDA2R (ectodysplasin A2 receptor) instead of EDAR[11,12] (Fig. 2). In general, the EDA protein plays a crucial role in the development of ectodermal tissues.

It is involved in epithelial-mesenchymal signalling during the morphogenesis of ectodermal organs[13]. It promotes cell adhesion to the extracellular matrix, which is consistent with its role in regulating epithelial-mesenchymal interaction during the development of ectodermal appendages[13,14]. EDA also participates in multiple signalling pathways, such as Wnt/β-catenin, JNK, BMP/Smad, and FGF signalling[15]. In relation to the skin and its appendages, EDA defines structure in several ways. In hair follicles (HF), it enables the development of HF types prior to birth and then modulates hair thickness and influences hair fibre shape in adults[16,17]. A mouse model study suggests that transgenic expression of the EDA-A1 isoform can rescue the development of several skin appendages[18,19]. In teeth, EDA deficiency can reduce the size of the region where Sonic hedgehog (*Shh*) is expressed in the primary enamel knot, leading to the formation of an abnormal enamel organ and a hypoplastic function incisor[14,20]. Mutant mice lacking EDA exhibit taurodontism, characterised by enlarged pulp chambers with absent or delayed tooth root bifurcation (tooth root branching)[13,21].

EDAR encodes the receptor EDAR, which belongs to the TNF receptor family. EDAR is a type I transmembrane protein containing 448 amino acids. It is a receptor for the soluble ligand EDA isoform A1, but not for the EDA isoform A2[11,12]. It has 3 cysteine-rich domains (CRDs) in the extracellular region, a transmembrane region, and an intracellular signalling domain known as the death domain.

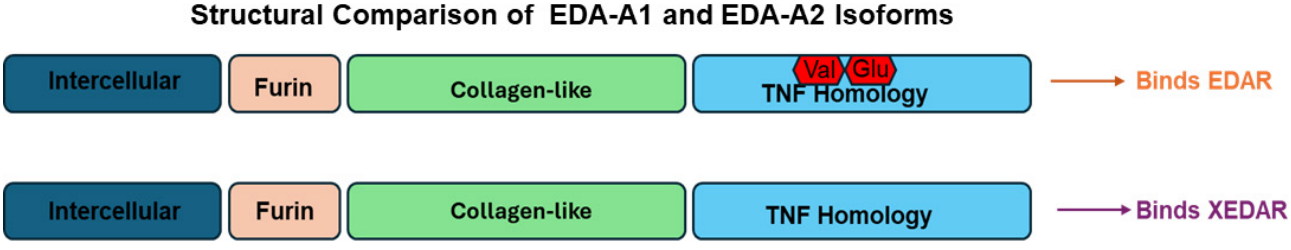

Fig. 2. Structural comparison of EDA-A1 and EDA-A2 isoforms and their selective binding to specific receptors: EDAR and XEDAR

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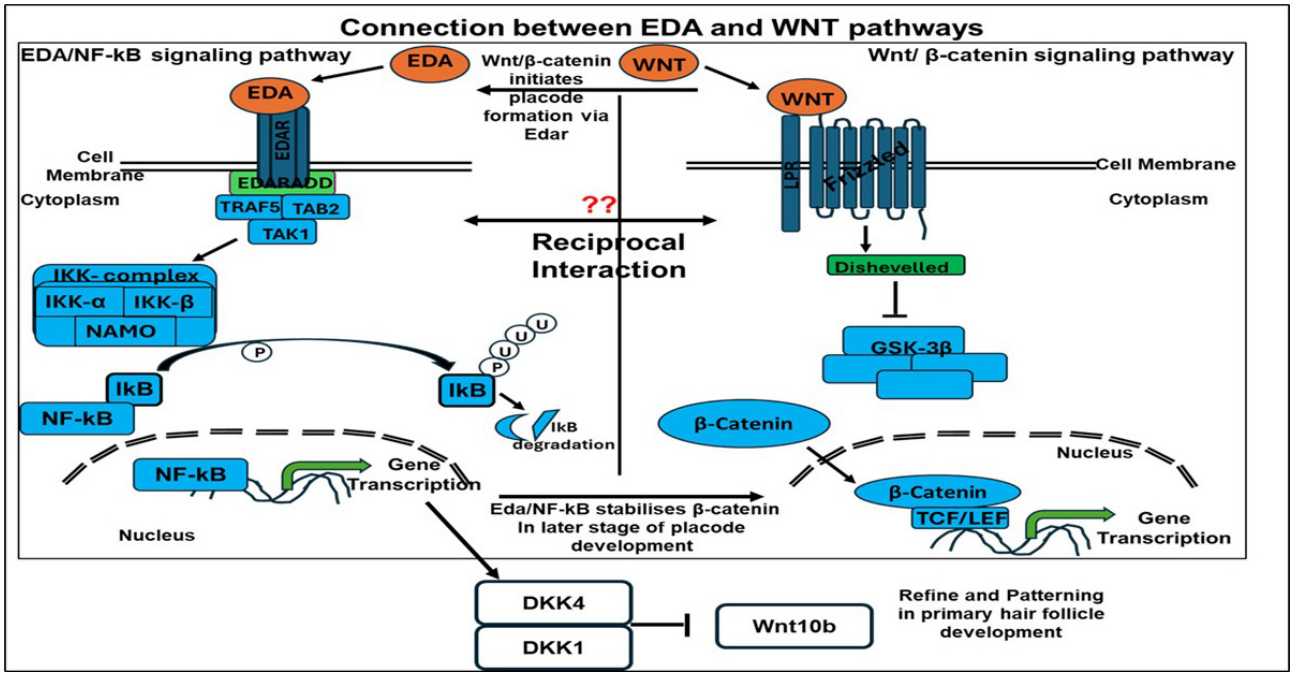

Fig. 3. Summary schematic presentation of the EDA and WNT pathways and their connections in skin appendage development. The mutual coordination of the EDA and WNT pathways is necessary for refining and patterning primary hair follicle development, where Wnt/β-catenin initiates placode formation via the activation of Edar, and the Eda-Edar-NF-κB pathway reinforces the stabilisation of β-catenin in the later stage of placode development. Further reciprocal interactions between these two pathways remain to be discovered

The CRDs in EDAR are characteristic of the TNF receptor superfamily and are essential for ligand binding – in this case, to EDA-A1, and are therefore also referred to as the ligand-binding domain (LBD).

The homotrimers released from EDA-A1 binds specifically to the LBD region of EDAR, which then recruits to its intracellular death domain the adaptor protein EDARADD (EDAR-associated death domain), a 208-amino acid protein. EDARADD consists of a C-terminal death domain and a Traf-binding consensus sequence[11,12]. The death domain interacts with EDAR, and the Traf-binding consensus sequence combines with the TRAF6/TAK1/TAB2 complex. TRAF6 acts as a scaffold molecule to recruit the IKK complex, and activated IKK then phosphorylates IkB proteins, leading to their degradation[11,13]. The degradation of IkB releases NF-κB (nuclear factor-kappaB), which then translocates to the nucleus to initiate the transcription of downstream genes[22]. Thus, the death domain of EDARADD interacts with the death domain of EDAR, forming the EDA-EDAR-EDARADD complex, which initiates a signalling cascade leading to the activation of NF-κB[23]. NF-κB translocates to the nucleus (Fig. 3) and activates the transcription of target genes required for epidermal patterning and appendage formation. The EDA-A1-EDAR signalling pathway is required for the development of ectodermal derivatives such as hair, teeth, nails, and sweat glands[24].

Thus, impairment in any of these components can disrupt the signalling cascade, leading to the manifestation of HED, characterised by defects in the structure of the appendages mentioned previously. On the other hand, EDA-A2/XEDAR signalling pathways is more specific to mammary gland development and less critical in the development of appendages. It may possess a redundant or compensatory role and is rarely linked to human disease[24].

EDA-EDAR IN HAIR MORPHOGENESIS

HF morphogenesis is a complex biological process mediated by communication between epithelial and mesenchymal cells. HF induction begins with a signal from the mesenchyme, known as the "first dermal message", promoting the formation of thickenings in the epithelium called HF placodes[25]. The identity of this signal is still unclear, though its transduction has been associated with the Wnt signalling pathway. Impairment of this pathway, whether through ablation of the Wnt transducer, i.e. β-catenin, in the dermis, or through abrogation of epidermal Wnt secretion, prevents the formation of placodes[26,27]. The formed placode acts as a signalling centre. Reanalysis of single-cell gene expression data in mice revealed activation of EDA-EDAR signalling in the formed placodes (Fig. 4), alongside the expression of many downstream genes, including *Fgf20*[28], *Shh*[29], *Wnt10b*, and *Dkk4*[17]. *Fgf20* is necessary for the clustering of underlying dermal fibroblasts, leading to the formation of the dermal condensate (DC), which subsequently matures into hair follicle dermal papillae[17,28]. Shh is essential for the formation of proper DC and, consequently, for HF development; its absence results in arrest of this process[29–31]. Similarly, *Wnt10b*, among other Wnt ligands constituting the placode signal, is crucial for hair development

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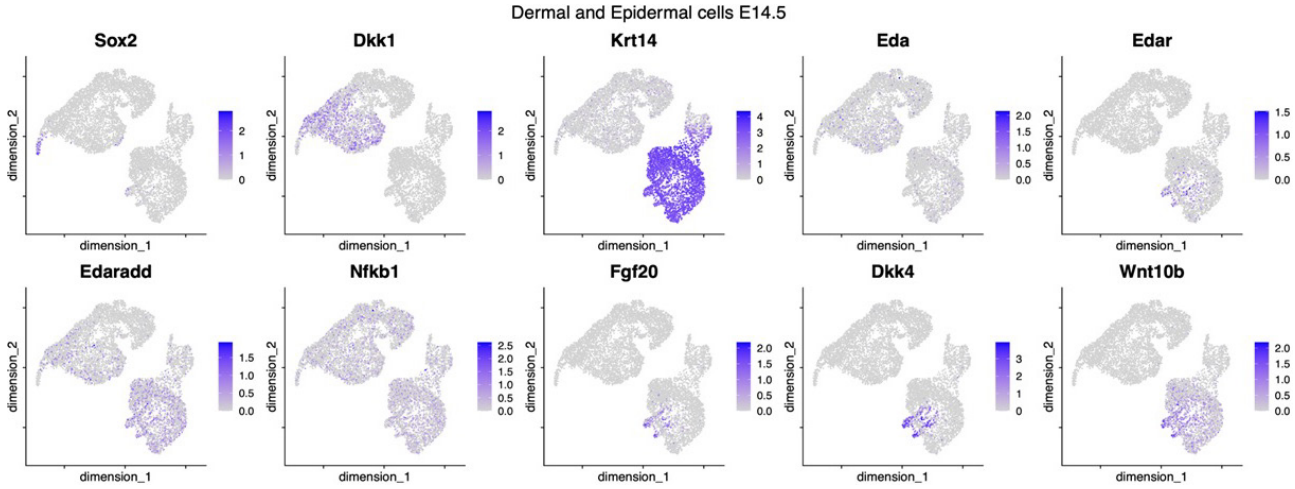

Fig. 4. UMAP plots depicting the expression of EDA/EDAR-related genes in dermal (left) and epidermal (right) cells during hair morphogenesis on day E14.5. Sox2 is a marker of dermal condensate (DC), Dkk1 marks DC progenitors, and Eda, Edar, Edaradd and Nfkb1 belong to the Eda-Edar pathway. Krt14, Fgf20, Dkk4, Wnt10b are epidermal placode markers

and growth[27], while *Dkk4* expression can potentially control placode size and spacing[32].

WNT PATHWAY AND ITS FUNCTION IN DEVELOPMENT OF SKIN APPENDAGES

WNTs (Wingless and Int-1) are typically 350–400 amino-acid long, and are secreted, lipid-modified signalling glycoprotein[33]. They have a two-domain structure: the amino-terminal is composed of a cluster of alpha-helices with 10 conserved cysteine residues forming 5 disulphide bridges, while the carboxy-terminal domain is dominated by two beta-sheets and maintained by 6 disulphide bridges. These disulphide bridges are thought to maintain a globular secondary structure. WNTs undergo lipid modification and glycosylation to ensure proper secretion and binding to their receptors[34]. They act as ligands to activate different Wnt pathways via paracrine and autocrine routes, binding to frizzled receptors on the cell membrane. Sequences of WNT proteins are conserved across species, and the orthologs are easy to identify[35]. WNT proteins control a wide range of processes, such as cell fate, embryonic development, stem cell proliferation, maintenance and differentiation, tissue homeostasis, and regulation of gene expression[36]. They play pivotal roles in the development of skin and its appendages, such as placode formation, epithelial cell fate decisions, and inductive signalling to dermal condensation. Some of the Wnt genes, such as *Wnt3*, *Wnt7b*, *Wnt7a*, *Wnt10a* and *Wnt10b*, play well-known roles in hair follicle development. For example, overexpression of *Wnt3a* activates β-catenin and promotes hair growth. Macrophage-derived extracellular vesicles containing Wnt3a enhance hair follicle regeneration[37]. *Wnt10b* promotes hair growth by enhancing the switch from telogen to anagen. In *in-vitro* culture, *Wnt10b* enhances the differentiation of cultured skin epithelial cells into the hair shaft and inner root sheath by stabilising β-catenin. *Wnt7a* and *Wnt7b* are important regulators of hair follicle stem cell (HFSC) homeostasis and the hair follicle cycle[38,39]. *Wnt5a*, a non-canonical Wnt, is expressed in bulge and secondary hair germ cells during the telogen stage, antagonises the function of canonical Wnts, and inhibits dermal cell proliferation[40] Meanwhile, Wnt1a-enriched conditioned media accelerates hair follicle progression from telogen to anagen[41]. Wnt modulators, such as R-spondins, which enhance Wnt signalling during development, regulate hair follicle development and HFSC homeostasis, affecting hair regeneration[42]. *Wls* (also known as Wntless, Evi, and GPR177) encodes a multipass transmembrane protein that transports lipid-modified Wnts to the cell surface. Genetic ablation of epithelial *Wls* inhibits hair placode formation and diminishes the expression of placode markers[41]. At the cell surface, WNT protein binds to the N-terminal extracellular cysteine-rich domain of a frizzled family receptor (FZD). To facilitate Wnt signalling, the co-receptor LRP5/6 may be required alongside the interaction between the WNT and FZD proteins. Upon activation of the receptor, a signal is sent to the cytoplasm through the phosphoprotein Dishevelled (DSH), which, along with other components, inactivates GSK-3 β and induces β-catenin stability[33,36]. Epithelial deletion of β-catenin results in the absence of hair and mammary placode formation[43]. Stabilised β-catenin binds to the T-cell factor (TCF)/lymphoid enhancer factor (LEF) complex and translocates to the nucleus (Fig. 3). DKK1 (Dickkopf) inhibits Wnt action by binding with the LRP co-receptor, and skin-specific overexpression of Dkk1-leads to a complete block in the development of skin appendages. Overexpression of Dkk1 also halts tooth development at the placode stage[41]. In the nucleus, β-catenin facilitates the expression of genes involved in epithelial tissue development. Activation of the Wnt/β-catenin pathway directs epithelial cells towards appendage formation, and overexpression of stabilised β-catenin in mouse skin results in more hair formation and faster hair regeneration[44]. The Wnt/ β-catenin signalling pathway is considered the central signalling pathway for the transformation of hair follicles

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from the resting phase to the growth phase. It participates in all stages of hair follicle development and determines the differentiation fate of cells during development[45].

CONNECTION BETWEEN EDA AND WNT PATHWAYS

The Wnt signalling pathway and the EDA-EDAR-NF-κB pathway are deeply interconnected in the development of ectodermal appendages – such as hair follicles, teeth, and sweat glands – and their dysregulation contributes to the phenotypes observed in EDA pathway-deficient patients, such as in HED. These pathways interact in complex ways to ensure proper patterning and maintenance of these structures[17]. However, their reciprocal recruitment at different stages of skin appendage development is still unexplored (Fig. 3). Both pathways regulate the expression of overlapping target genes involved in ectoderm development. For instance, genes like *Shh* and *Dkk4* are regulated by both pathways and play roles in hair follicle and tooth development[46]. The EDA-EDAR pathway influences Wnt signalling by modulating the activity of β-catenin. EDAR signalling has been shown to stabilise β-catenin, enhancing Wnt-mediated gene transcription. In the same way, activated Wnt/β-catenin can upregulate the expression of EDAR, creating a positive feedback loop during hair follicle formation[15,17]. Studies have shown that elevated EDAR signalling can lead to increased expression of Wnt10b and Dkk4, demonstrating amplified signal transduction through these pathways[47]. Dkk4, a Wnt inhibitor, is regulated by EDAR signalling and can modulate Wnt activity to fine-tune it during developmental processes such as tooth development. EDA-EDAR-NF-κB signalling is required to refine and maintain the pattern of Wnt/β-catenin activity in the later stage of placode development[48]. Specifically, Wnt10b has been identified as a direct NF-κB target gene, necessary for maintaining the localised expression pattern critical for appendages[17]. Thus, in conclusion, several studies have shown that activation of the EDA-EDAR-NF-κB pathway influences Wnt signalling genes and vice versa during the earlier embryonic development of skin and its appendages, shaping and refining their structure[17,49].

In EDA-deficient patients with EDA mutations, this upregulation fails, leading to reduced or absent Wnt expression and impaired or delayed initiation of appendage formation. Wnt and EDA cooperate in positive feedback loops. Canonical Wnt/β-catenin signalling initiates placode formation, which triggers EDA expression and then reinforces Wnt signalling via NF-κB activation. This loop is essential for amplifying and stabilising epithelial patterning signals. Indeed, without EDA, this loop is disrupted, resulting in abortive placode development and sparse or absent hair, conical or missing teeth, and hypoplastic glands. During development, Wnt10a/b and EDA are co-expressed in epidermal placodes, hair germs, and dental lamina. This spatial co-localisation suggests they act in coordinated modules during morphogenesis. In Eda-null (Tabby) mice, expression of Wnt10a is dramatically reduced in placodes during budding morphogenesis[50].

Rescue of EDA signalling restores Wnt expression and partially rescues hair and tooth development. WNT10A mutations in humans also cause syndromes with overlapping phenotypes, such as odontohypophosphatasia and HED.

CONCLUDING REMARKS

The most prevalent form of ED in children is HED, in which impaired development of skin appendages results from mutations in genes related to the EDA-EDAR-EDARADD signalling pathway. Independently, the canonical WNT signalling pathway was previously identified as a key regulator in the development of hair and teeth. In this study, mouse single-cell gene expression data were re-analysed, confirming the expression of *Edaradd* and *NF*-κB alongside canonical WNT pathway genes in epidermal placodes. Expression of the Eda ligand was found in Dkk1+ dermal cells, thus providing additional convergent evidence supporting previous findings that EDA-A1 signalling enhances WNT pathway activity, forming a mutually reinforcing regulatory network during the early stages of skin appendage primordial formation. These findings highlight the potential for early therapeutic restoration of EDA and WNT pathway activity, offering a promising avenue for treating patients with ED and restoring proper development of skin appendages in the future.

MATERIALS AND METHODS

- Raw 10X sequencing data from control E14.5 mouse skin samples were processed using the standard 10X CellRanger pipeline. The resulting nUMI count matrices were deposited at GEO: GSE198487 by Qu et al.[30]. They were filtered, centred, and normalised in Seurat[51,52].
- Image analysis scRNA-seq data was visualised using the ggplot2 and cowplot R libraries.
- Software R (https://www.r-project.org/) and Seurat (http://satijalab.org/seurat/).

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study; final approval of manuscript: KK. Collection, recording and/or compilation of data; writing of manuscript: AJ, KŁ, APC, KK. Analysis and interpretation of data; critical review of manuscript: AJ, KŁ, KK.

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