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Review Article

Collagen XVIIα1 in skin and hair aging: Mechanisms, stem cell niche regulation, and translational strategies

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ABSTRACT

Collagen XVIIα1, encoded by *COL17A1* and historically known as BP180/BPAG2, is a type II transmembrane collagen enriched in hemidesmosomes of basal keratinocytes. Through interactions with integrin α6β4, laminin-332 and other dermal–epidermal junction (DEJ) components, collagen XVIIα1 links the keratin cytoskeleton to the basement membrane. Recent studies indicate that this junctional anchorage supports epidermal homeostasis by preserving stem cell adhesion, polarity and regenerative capacity. During aging, collagen XVIIα1 levels decline and proteolytic processing increases, including ADAM9/ADAM10-dependent ectodomain shedding and cleavage by inflammatory proteases. These changes weaken DEJ integrity and are associated with photoaging and impaired repair. In hair follicles, collagen XVIIα1 is also required for hair follicle stem cell (HFSC) maintenance, and its reduction is linked to HFSC exhaustion, hair aging phenotypes and altered niche signals that may influence melanocyte stem cell–dependent pigmentation. This review summarizes translational approaches targeting collagen XVIIα1 and proposes practical in vivo readouts for target engagement. Key gaps include mechanism attribution, durable functional restoration at the DEJ, persistence within the epidermal–follicular niche and a shortage of rigorous human studies.

1. Introduction

Aging affects all organs and is most conspicuous in skin. Intrinsic (chronological) and extrinsic (exposome-related) drivers together cause thinning, dryness, wrinkling, dyspigmentation, and loss of elasticity [1,2]. Cellular senescence, often triggered by DNA damage and oxidative stress, erodes regenerative capacity and disturbs extracellular-matrix homeostasis, providing a rationale for emerging senotherapeutic approaches in skin [3].

Stem-cell maintenance in human skin relies on a niche that integrates extracellular-matrix cues with paracrine, vascular, and immune inputs to coordinate polarity, quiescence, and renewal [2,4]. With aging, the DEJ flattens and hemidesmosomes become less abundant, weakening basal-cell anchorage. In hair follicles, aging can push HFSCs out of quiescence toward epidermal commitment and follicle miniaturization [4,5].

Collagen XVIIα1, encoded by *COL17A1*, is concentrated at the DEJ, stabilizing hemidesmosomes and shaping stem-cell dynamics and polarity. Historically, it was described as BP180/BPAG2 in the bullous pemphigoid literature, where it serves as a major autoantigen [6,7], and was later cloned and reclassified as type XVII collagen, linking DEJ integrity to polarity-dependent regeneration at a molecular level [6,8].

Here, we synthesize how collagen XVIIα1 shapes skin and hair-follicle stem cell niches during aging and summarize translational strategies aimed at enhancing endogenous collagen XVIIα1, limiting proteolytic loss, or providing exogenous support. We focus on three themes: junctional anchorage, regulated proteolysis, and niche crosstalk.

2. Molecular and biological properties of collagen XVIIα1

2.1. Domain architecture and structural organization of collagen XVIIα1

Collagen XVIIα1 is a type II transmembrane collagen with a short, basic intracellular domain (ICD) and a large extracellular ectodomain (ECD) composed of alternating collagenous and non-collagenous segments [8,9]. The ICD can adopt partial structure near anionic

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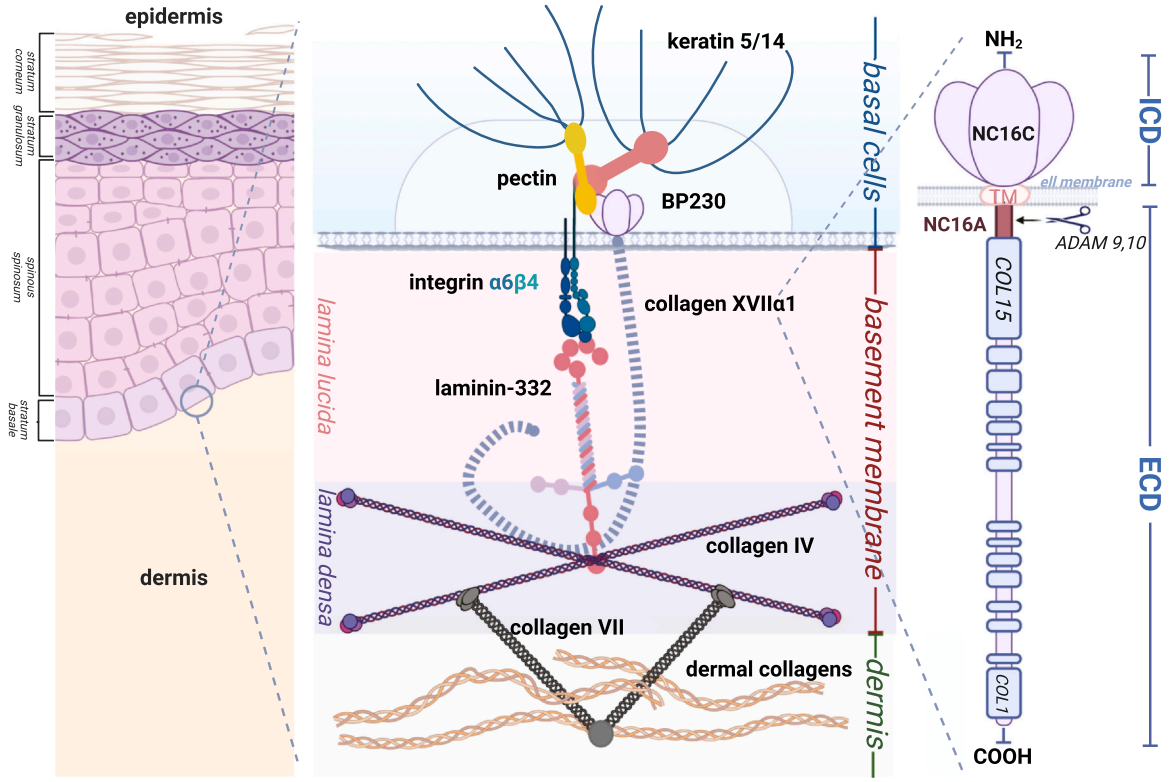

Fig. 1. Structural organization and molecular interactions of collagen XVIIα1 at the DEJ. Schematic overview of collagen XVIIα1 in basal keratinocytes. Collagen XVIIα1 is a type II transmembrane collagen with a short ICD and a large ECD composed of alternating collagenous and non-collagenous regions. The ICD binds BP230 and plectin, linking keratin 5/14 filaments to the plasma membrane. The ECD extends across the lamina lucida and associates with integrin α6β4, laminin-332, and collagen IV, linking the keratin cytoskeleton to the basement membrane and, indirectly, to collagen VII anchoring fibrils in the lamina densa. Cleavage within NC16A by ADAM9/ADAM10 mediates ectodomain shedding and may weaken junctional adhesion during epidermal homeostasis.

membranes, whereas the ECD forms a trimeric coiled-coil triple helix. Notably, the NC16A region harbors ADAM9/10 cleavage sites that mediate constitutive and inducible ectodomain shedding, providing a direct link between domain architecture and regulation [7,10].

2.2. Tissue distribution and expression patterns

In skin, collagen XVIIα1 localizes to hemidesmosomes of basal keratinocytes, securing attachment to the basement membrane [11]. It is also expressed in other stratified epithelia and contributes to specialized differentiation, including tooth enamel formation [12]. Non-hemidesmosomal pools have been proposed to participate in adhesion-coupled signaling and polarity regulation [13,14]. Although aberrant expression has been reported in epithelial malignancies and low-abundance expression in selected non-epithelial tissues [7], this Review focuses on skin and hair follicle biology, where collagen XVIIα1 is most directly linked to junctional integrity and stem cell–niche regulation.

2.3. Molecular interactions and functional roles

Key molecular interactions of collagen XVIIα1 are summarized in Fig. 1. In basal keratinocytes, the ICD of collagen XVIIα1 binds hemidesmosomal plaque proteins, including plectin and BP230, and connects keratin intermediate filaments to stable cell–matrix adhesion. Disruption of this linkage contributes to epidermolysis bullosa simplex-like phenotypes [15]. The ECD mediates extracellular coupling through laminin-332-associated interactions within the α6β4 integrin-containing adhesion complex, thereby strengthening keratinocyte attachment to the basement membrane [16,17]. Ectodomain shedding is dynamically regulated during repair, facilitates keratinocyte migration and re-epithelialization, and has been linked to downstream signaling pathways including mTOR [18]. These properties are directly relevant to regeneration and aging. Collagen XVIIα1 proteolysis promotes hair follicle stem cell loss and follicle miniaturization, and collagen XVIIα1 also influences proliferative control in the interfollicular epidermis, linking junctional integrity to long-term tissue maintenance [5,19].

3. Skin aging: collagen XVIIα1-dependent mechanisms in the interfollicular epidermis

As a core hemidesmosomal component at the DEJ, collagen XVIIα1 anchors basal keratinocytes to the basement membrane and helps maintain the stem cell–niche interface. This junctional adhesion supports epidermal homeostasis by stabilizing cell polarity and providing a permissive microenvironment for appropriate fate decisions. With aging, reduced collagen XVIIα1 abundance and increased proteolytic destabilization can loosen niche attachment and disrupt polarity cues. Over time, these changes compromise epidermal stem cell fitness and renewal capacity, contributing to impaired regeneration, epidermal thinning and tissue fragility in the interfollicular epidermis.

3.1. Collagen XVIIα1 in epidermal stem cell aging

Epidermal homeostasis relies on coordinated communication between ESCs and their niche, which combines adhesion, mechanical inputs and signaling to support long-term tissue renewal [20]. In the interfollicular epidermis, the basement membrane (BM)

provides structural support and positional cues that guide stem cell polarity and fate decisions. Collagen XVIIα1 is a transmembrane hemidesmosomal protein that helps maintain this interface by anchoring basal keratinocytes at the DEJ and stabilizing junctional architecture.

Functional studies indicate that collagen XVIIα1 is a critical determinant of ESC fitness and niche retention. Genetic depletion or age-associated reduction of collagen XVIIα1 weakens hemidesmosomes and loosens basal keratinocyte attachment to the BM, which over time contributes to epidermal thinning and reduced regenerative capacity [5,14]. In human skin, collagen XVIIα1 is enriched in epidermal stem cell niches, and its reduction in aged, photoaged and UV-irradiated epidermis impairs keratinocyte regeneration, flattens the DEJ and thins the epidermis [21]. At the tissue level, collagen XVIIα1 loss limits stem cell retention and accelerates epidermal aging [22].

Regulated proteolysis drives collagen XVIIα1 loss at the DEJ, loosening junctional adhesion during aging and stress. In aged and photoaged skin, collagen XVIIα1 levels are reduced and correlate with DEJ deterioration [21]. Mechanistically, collagen XVIIα1 undergoes ectodomain shedding mediated by ADAM metalloproteinases, particularly ADAM9 and ADAM10, which destabilizes hemidesmosomes and weakens keratinocyte adhesion. Notably, oxidative stress can further enhance collagen XVIIα1 shedding, with hydrogen peroxide-induced ectodomain release showing a particular dependence on ADAM9 [23]. In inflammatory injury settings, neutrophil elastase can further accelerate collagen XVIIα1 degradation and exacerbate junctional instability during tissue injury [24]. Biomechanical stress has emerged as an upstream trigger. Emerging evidence suggests that, in a mechanical stretch model, MMP2-dependent extracellular matrix remodeling promotes collagen XVIIα1 proteolysis and accelerates regenerative exhaustion, which links age-related changes in tissue mechanics to erosion of the epidermal stem cell niche [25].

Beyond adhesion, collagen XVIIα1 also shapes stem cell behavior by influencing polarity and division orientation. Maintaining an appropriate balance between symmetric and asymmetric divisions is required to preserve epidermal stem cell pools, and collagen XVIIα1 loss is associated with a shift from basement membrane-parallel symmetric divisions toward asymmetric, differentiation-linked divisions, contributing to gradual stem cell depletion [13,23,26]. In addition, physiological fluctuation in collagen XVIIα1 levels appears to create a fitness gradient among basal stem cells, such that stem cells with high collagen XVII preferentially expand as “winner” clones, whereas stressed cells with low collagen XVIIα1 are eliminated through competition-associated delamination. At the mechanistic level, collagen XVIIα1 interacts with the aPKC–PAR polarity complex. Disruption of this interaction leads to abnormal spindle orientation, destabilized PAR3 localization and expansion of suprabasal differentiated cells, resulting in an earlier loss of stemness in basal keratinocytes [13,26].

Recent work also places collagen XVIIα1 within regulatory programs supporting epidermal homeostasis. METTL14-mediated m6A modification enhances translation of *Col17a1* and other hemidesmosomal transcripts, strengthening adhesion and improving tissue stability [27]. Rather than acting solely as a structural anchor, collagen XVIIα1 therefore connects junctional organization to polarity control and upstream stress pathways within the epidermal stem cell niche.

Taken together, age-associated collagen XVIIα1 loss and proteolysis weaken hemidesmosomes and alter division programs toward asymmetric, differentiation-biased outputs. Over time, this can promote delamination and stem cell exhaustion. Fig. 2 summarizes these shared but compartment-specific principles across the interfollicular epidermis and hair follicle.

3.2. Therapeutic strategies targeting collagen XVIIα1 in skin aging

Given its role in epidermal adhesion and polarity control, collagen XVIIα1 has been explored as a target for interventions aimed at mitigating cutaneous aging. As outlined in Fig. 3, current strategies can be organized along an indirect-to-direct continuum, including indirect niche and DEJ modulation, preservation of endogenous collagen XVIIα1, collagen XVIIα1-related supplementation strategies, and targeted delivery. Available studies suggest that preserving collagen XVIIα1 or compensating for its loss can improve DEJ-associated features in preclinical models, although collagen XVIIα1-specific effects remain difficult to separate from broader repair responses. Fig. 3 further summarizes representative strategies, target engagement or efficacy readouts, and major translational hurdles for each intervention class.

Indirect niche and DEJ modulation is supported by studies of peptides, extracts, and physical interventions. Topical or synthetic peptides such as palmitoyl-RGD have been reported to increase basement membrane-associated proteins, including collagen XVIIα1, and to improve DEJ organization in experimental systems [28,29]. Complex extracts may also help preserve collagen XVIIα1 by reducing inflammatory and proteolytic stress. For example, caviar extract mitigated UV-associated damage through a proposed NF-κB–MMP pathway associated with preservation of collagen XVIIα1 [30]. However, for multi-component extracts, compositional heterogeneity and attribution remain major limitations, and the observed benefits may reflect broad anti-inflammatory or matrix-stabilizing effects rather than collagen XVIIα1-directed restoration. Energy-based interventions have likewise been implicated in collagen XVIIα1 regulation. Experimental and large-animal studies suggest that radiofrequency and ultrasound can increase basement membrane components, including collagen XVIIα1, and improve DEJ architecture [31], although direct evidence in human skin remains limited.

Direct supplementation provides a more collagen XVIIα1-proximal strategy. Recombinant human collagen XVIIα1 (rhCOL17) has also gained attention as a biomimetic scaffold. Preclinical work suggests that exogenous supplementation can attenuate UV-induced epidermal damage and partially restore basement membrane-associated architecture in photo-damaged skin [32]. More recent studies further reported that topical rhCOL17 improves repair in UVB-induced photoaging and laser-injury mouse models, accompanied by enhanced DEJ integrity and activation of $Lgr6^{+}$ epidermal stem cells [33].

Targeted delivery has emerged as an enabling strategy to improve local retention and tissue access; for example, rhCOL17 has recently been formulated as a transdermal nanocomplex to enhance cutaneous penetration and retention in preclinical photo-damage settings [34]. Together, these findings support the feasibility of collagen XVIIα1-oriented supplementation in preclinical settings, while underscoring the need for mechanism-anchored readouts and attribution controls to define how much of the benefit is directly attributable to collagen XVIIα1.

Rather than pointing to a single modality, the emerging literature suggests that collagen XVIIα1 can be supported through multiple, mechanistically distinct routes. Most evidence remains preclinical or exploratory, but these approaches highlight collagen XVIIα1 as a useful organizing principle for interventions aimed at preserving epidermal integrity during aging. A recurring challenge is attribution. Because energy-based procedures and topical biomaterials, and delivery platforms can remodel the DEJ and trigger repair programs on their own, future studies should incorporate collagen XVIIα1-specific readouts to define target engagement and quantify the incremental benefit of collagen XVIIα1 stabilization or supplementation.

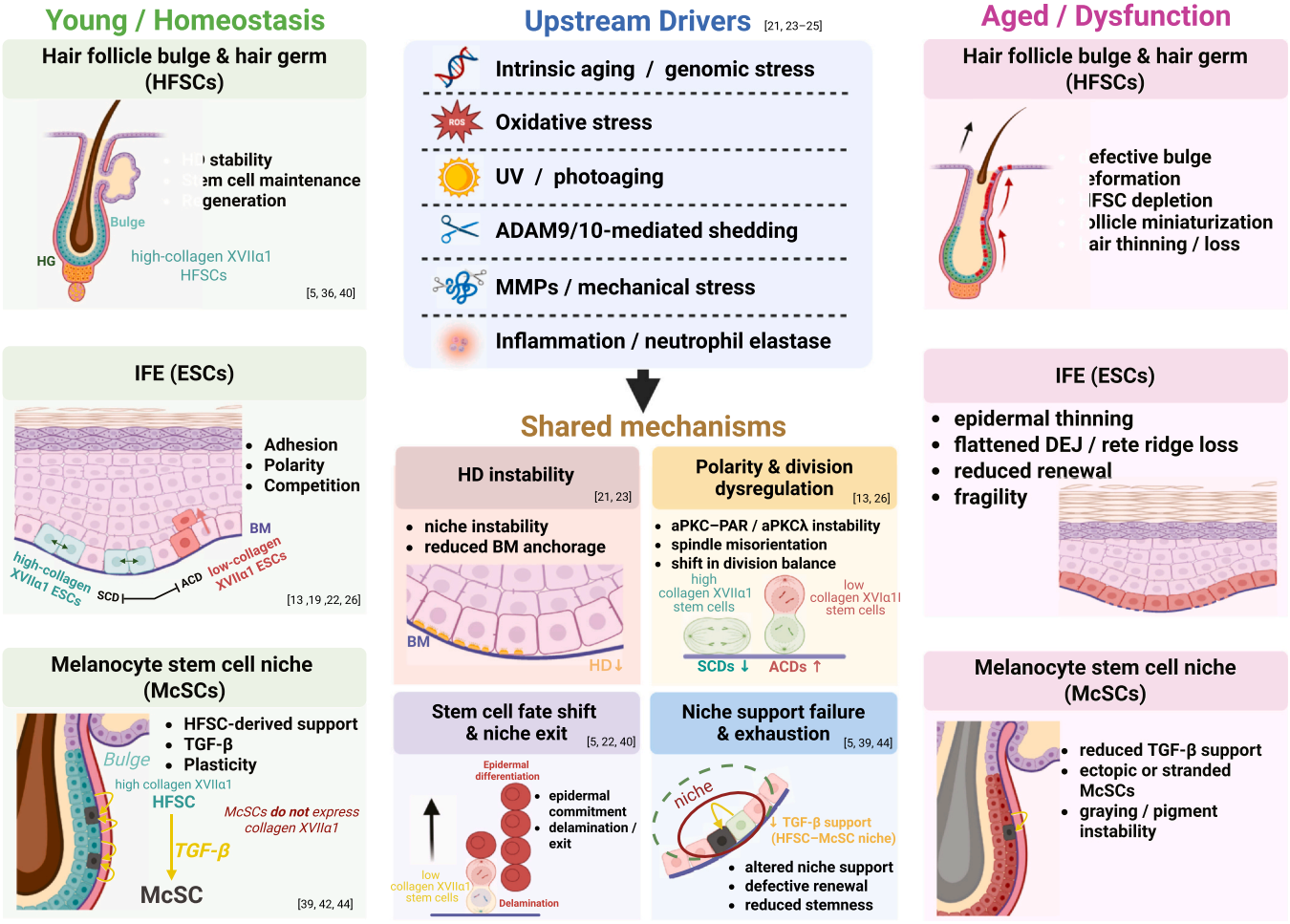

Fig. 2. Collagen XVIIα1 as a niche integrator in epidermal and hair follicle stem cell aging. Left, collagen XVIIα1 supports niche integrity in young/homeostatic epithelial stem cell compartments, including the interfollicular epidermis and hair follicle bulge/hair germ, by maintaining hemidesmosome stability, basement membrane anchorage, stem cell maintenance, polarity-associated programs, and regenerative competence. In the melanocyte stem cell niche, collagen XVIIα1 acts indirectly through HFSC-supported epithelial integrity and paracrine support, including TGF-β. Middle, intrinsic/genomic stress, oxidative stress, UV/photoaging, ADAM9/10-mediated shedding, MMP-associated mechanical stress, and inflammation/neutrophil elastase promote collagen XVIIα1 decline and destabilization, converging on hemidesmosome instability, polarity and division dysregulation, stem cell fate shift with niche exit, and niche support failure/exhaustion. Right, these changes contribute to defective bulge reformation, HFSC depletion, follicle miniaturization and hair thinning/loss; epidermal thinning, flattened DEJ/rete ridge loss, reduced renewal, and fragility in the IFE; and reduced TGF-β support, ectopic or stranded McSCs, pigment instability, and hair graying. McSCs do not express collagen XVIIα1 directly; pigmentation-related effects are therefore niche-mediated. Reference numbers indicate representative supporting studies. **Abbreviations:** ESCs, epidermal stem cells; HFSCs, hair follicle stem cells; McSCs, melanocyte stem cells; BM, basement membrane; HD, hemidesmosome; DEJ, dermal–epidermal junction; UV, ultraviolet; TGF-β, transforming growth factor-β.

4. Collagen XVIIα1 in hair aging: regulation of hair follicle and melanocyte stem cell niches

Beyond the interfollicular epidermis, collagen XVIIα1 also contributes to the maintenance of stem cell populations in hair follicles, where epithelial and melanocyte stem cells occupy a closely coupled niche system. Hair follicle aging involves stem cell attrition and follicle miniaturization, and is often accompanied by impaired coordination between epithelial and melanocyte lineages, leading to hair thinning and pigmentary change. In this context, collagen XVIIα1 serves as a junctional organizer of the epithelial niche, linking adhesion, polarity and fate regulation in HFSCs, while indirectly influencing McSC maintenance through niche integrity and paracrine support.

4.1. Collagen XVIIα1 in HFSCs aging

Hair follicles are dynamic skin appendages that cycle through telogen, anagen and catagen throughout life [35]. Continuous hair regeneration relies on HFSCs in the bulge and hair germ (HG), where close contact with an extracellular matrix (ECM)-rich niche helps preserve quiescence, activation potential and long-term regenerative capacity [36]. Within this compartment, the bulge is generally more quiescent, whereas the HG is more primed for activation at the onset of a new hair cycle.

Multiple studies identify collagen XVIIα1 as a key requirement for HFSC maintenance during aging. In humans, biallelic pathogenic variants in *COL17A1* cause junctional epidermolysis bullosa (JEB) [37]. *Col17a1* knockout mice represent an established model of skin fragility caused by collagen XVIIα1 deficiency [38]. Across both settings, collagen XVIIα1 deficiency is associated with premature hair graying and progressive hair loss, supporting an essential role for collagen XVIIα1 in sustaining HFSC integrity [5,39]. At the molecular level, collagen XVIIα1 deficiency destabilizes hemidesmosomes, weakens HFSC anchorage to the basement membrane and may facilitate premature niche exit.

Aging-associated genotoxic and oxidative stress can further accelerate collagen XVIIα1 proteolysis in hair follicles. Neutrophil elastase has been implicated in this process, and its activity is associated with progressive loss of collagen XVIIα1 in HFSCs [5]. Reduced collagen XVIIα1 weakens stem cell–niche adhesion and can shift HFSCs toward an epidermal keratinocyte fate, contributing to follicle exhaustion and miniaturization.

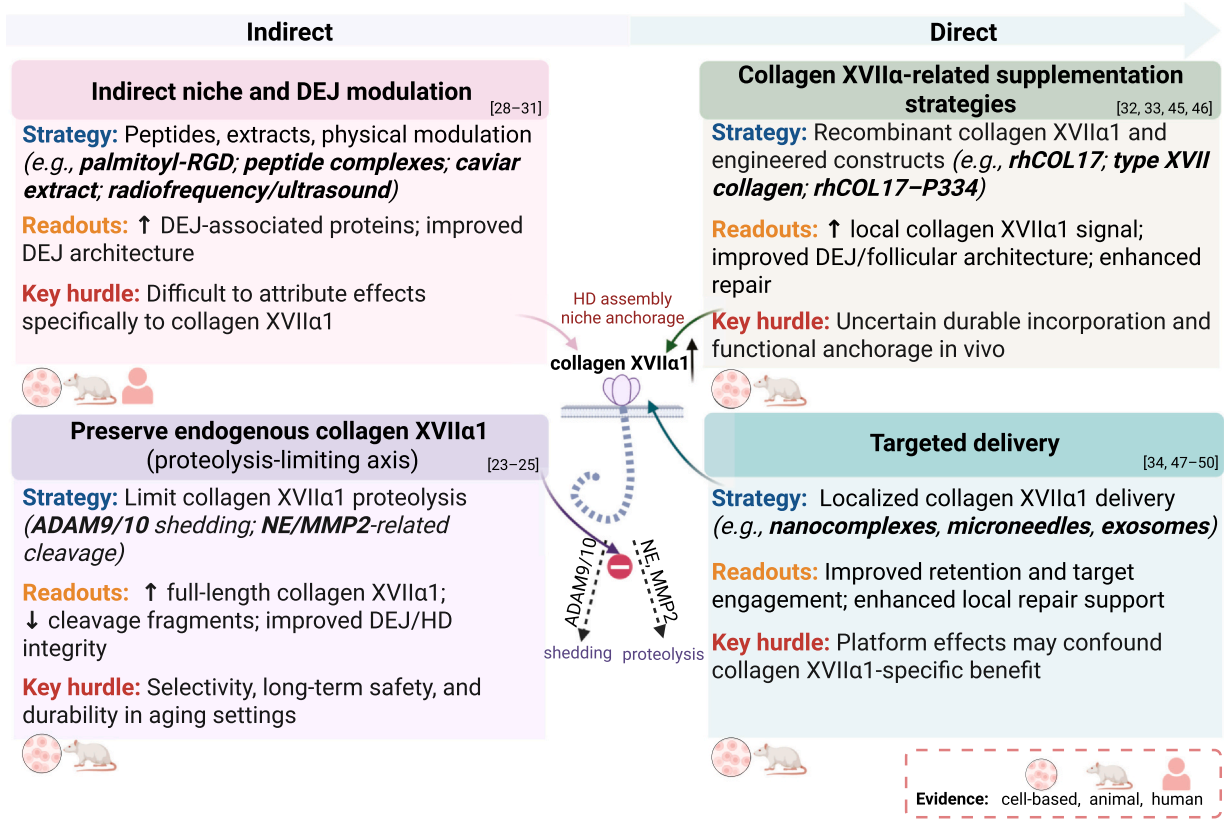

Fig. 3. Translational strategies targeting collagen XVIIα1 in skin and hair aging. Strategies are arranged along an indirect-to-direct continuum and grouped into indirect niche/DEJ modulation, preservation of endogenous collagen XVIIα1, collagen XVIIα1-related supplementation, and targeted delivery. The central hub summarizes key collagen XVIIα1-related processes, including HD assembly, niche anchorage, shedding, and proteolysis. For each category, representative strategies, readouts, and translational hurdles are shown. Reference numbers within each module indicate representative supporting studies. Evidence icons denote cell-based, animal, and human studies. **Abbreviations:** DEJ, dermal–epidermal junction; HD, hemidesmosome; ADAM, a disintegrin and metalloproteinase; NE, neutrophil elastase; MMP2, matrix metalloproteinase 2.

Beyond a structural role, collagen XVIIα1 also influences HFSC polarity and division behavior. In young hair follicles, collagen XVIIα1 has been reported to cooperate with aPKCλ to maintain a balanced output of symmetric and asymmetric divisions and to preserve the stem cell pool [13,40]. By contrast, in aged or stressed follicles, reduced collagen XVIIα1 and impaired polarity control favor stress-responsive asymmetric divisions, which generate differentiation-biased progeny rather than regenerating stem cells. With aging, reduced collagen XVIIα1 promotes stress-associated activation and a shift toward epidermal differentiation, which is linked to gradual HFSC depletion, follicle miniaturization and hair thinning [5]. In parallel, activation of c-MYC and NOTCH1 signaling in aged HFSCs can reinforce premature differentiation and loss of stemness [5].

Non-hemidesmosomal pools of collagen XVIIα1 may be particularly susceptible to age-related proteolysis, mirroring observations in interfollicular epidermal stem cells [19]. Overall, DNA damage, protease-driven collagen XVIIα1 loss and impaired polarity control converge to erode the HFSC niche and promote hair follicle aging and progressive hair loss.

4.2. Collagen XVIIα1 and melanocyte stem cells (McSCs): pigmentation aging

Melanocyte stem cells (McSCs) sustain hair and skin pigmentation and contribute to ultraviolet (UV) protection. They reside in the bulge and HG, where niche-derived cues tightly regulate their behavior [41,42]. Although McSCs were long considered largely quiescent, recent work supports substantial plasticity, including reversible transitions between stem-like and activated states that help maintain pigmentation over time [41,42]. This dynamic behavior is spatially organized within the niche: the HG is relatively permissive for activation and differentiation, whereas the bulge and upper outer root sheath provide a more protective environment that can support reversion toward a stem-like state. Signaling programs such as BMP act as important gatekeepers during activation and differentiation decisions within this niche [43].

McSCs do not express collagen XVIIα1, but their maintenance depends on an intact epithelial niche shaped by HFSCs [39]. Perturbations in this niche can therefore influence McSC quiescence and survival. Transforming growth factor-β (TGF-β) signaling is one candidate mediator. HFSC-derived TGF-β helps maintain McSC immaturity and quiescence and restrains premature differentiation [44]. When collagen XVIIα1-dependent hemidesmosomal stability in HFSCs is compromised, the niche microenvironment and paracrine support are likely altered. This effect is indirect and niche-mediated rather than cell-autonomous in McSCs. This may reduce effective TGF-β signaling and increase susceptibility of McSCs to activation and depletion during aging.

Overall, collagen XVIIα1 is most plausibly linked to pigmentation aging through its role in maintaining the structural and signaling competence of the epithelial niche, with TGF-β representing a key pathway connecting niche integrity to McSC preservation [44]. In this framework, collagen XVIIα1 loss in HFSCs is expected to impair epithelial support for McSC plasticity and quiescence, thereby promoting hair graying and pigmentary instability.

4.3. Therapeutic strategies targeting collagen XVIIα1 in hair and pigmentation aging

Within the follicular niche, therapeutic development is currently centered on direct supplementation and targeted delivery. In androgenetic alopecia (AGA)–relevant mouse models, local supplementation

with recombinant type XVII collagen has been reported to promote hair regrowth and improve follicular morphology [45]. These studies suggest that reinforcing collagen XVIIα1-related junctional support may be beneficial, although direct evidence for durable incorporation and target engagement in vivo remains limited.

Beyond direct protein replacement, collagen XVIIα1-derived constructs are being engineered to improve stability and retention within the niche. For example, a biomimetic recombinant human collagen XVIIα1–P334 conjugate (rhCOL17–P334) has been reported to enhance tissue repair and support hair follicle regeneration in vivo [46]. These studies support collagen XVIIα1-based scaffolding as a feasible niche-reinforcement concept in preclinical models.

To overcome the practical challenge of follicular delivery, dissolving microneedle platforms have been explored for localized administration. In an AGA-relevant setting, a collagen XVIIα1-loaded dissolving microneedle patch was reported to improve hair regrowth, illustrating how spatial targeting and controlled release can be incorporated into collagen XVIIα1-based delivery [47]. Subsequent designs have introduced microenvironment-responsive features intended to match payload behavior to local niche states, and recombinant collagen XVIIα1-based composite microneedles have shown benefit in androgenetic alopecia models [48]. Further refinements include borate-modified recombinant type XVII collagen microneedles loaded with IGF-1, which combine niche reinforcement with a growth factor cue to support follicular recovery [49].

Cell-free biologic delivery is also under exploration. Exosomes enriched with collagen XVIIα1-related collagenous sequences have been reported to enhance HFSC activity, with candidate regulatory links proposed (for example, an hsa-novel-238a–CASP9 axis) [50].

Attribution remains a central translational challenge. Delivery platforms and extracellular vesicles can trigger repair responses on their own, so collagen XVIIα1-specific controls are needed to distinguish platform-driven effects from collagen XVIIα1-dependent mechanisms. Practical options include collagen XVIIα1-depleted payloads, neutralization approaches, and collagen XVIIα1-deficient recipient models.

Overall, emerging data suggest a pragmatic path. Strategies preserving collagen XVIIα1-related junctional support and niche integrity may benefit from delivery systems, such as microneedles or extracellular vesicles, that access the follicular compartment and maintain local exposure. Establishing target engagement and durability within the follicular microenvironment will be critical for translating collagen XVIIα1-oriented interventions for hair aging and hair loss.

For a concise overview, Fig. 3 schematically summarizes the collagen XVIIα1-targeted modalities discussed above and relates each strategy class to its mechanistic rationale, representative evidence level, and major translational hurdles.

5. Challenges and future directions

Collagen XVIIα1 links stem cell–niche integrity to skin and hair aging, but several hurdles need to be addressed before collagen XVIIα1-oriented strategies can be translated to clinical practice. A central issue is the biology of collagen XVIIα1 itself. Unlike fibrillar collagens such as type I or III, which function as extracellular structural proteins in the dermis, collagen XVIIα1 is a transmembrane protein whose activity depends on keratinocyte-intrinsic synthesis, membrane insertion and assembly into hemidesmosomes. It therefore remains uncertain whether exogenous collagen XVIIα1 or collagen XVIIα1-derived biomaterials can achieve functional incorporation into hemidesmosomal complexes in vivo. Alternatively, these interventions may act indirectly by reinforcing the extracellular niche, modulating adhesion-dependent signaling, or stabilizing endogenous collagen XVIIα1. Distinguishing direct incorporation from indirect support is a key mechanistic priority.

From a translational standpoint, evidence for collagen XVIIα1-based interventions is still largely preclinical. Cell and animal models have been essential for demonstrating biological relevance and testing delivery concepts, but they offer limited guidance on durability, dosing and inter-individual variability in humans. A related challenge is attribution: benefits observed in preclinical systems may reflect general responses to biomaterials, micro-injury, or co-delivered growth factor cues rather than restoration of collagen XVIIα1-dependent anchorage per se. This gap highlights the need for early-phase human studies that incorporate objective target engagement measures together with clinically meaningful endpoints.

Progress will likely come from combining mechanistic rigor with delivery and assay development. Approaches that improve access to the epidermal–follicular niche, reduce proteolytic loss of collagen XVIIα1, or selectively boost endogenous collagen XVIIα1 function may prove more practical than protein supplementation alone. Addressing these issues will be critical for defining the therapeutic potential of collagen XVIIα1 in skin rejuvenation and hair regeneration.

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CRediT authorship contribution statement

Zixuan He: Conceptualization, Literature search, Writing (original draft), Visualization. **Fenglin Zhuo:** Conceptualization, Supervision, Writing (review and editing), Funding acquisition.

Declaration of Competing Interest

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