Review

Hair regeneration: Mechano-activation and related therapeutic approaches

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Abstract

Hair regrowth through mechano-stimulation and other therapeutic approaches has emerged as a significant area of research in regenerative medicine. This review examines recent advances in hair regeneration strategies, with a particular focus on mechanical stimulation and complementary treatments. Studies have demonstrated that skin stretching can activate hair follicle stem cells and promote hair growth under specific conditions and durations. This process involves intricate signaling interactions, particularly through the WNT and BMP pathways, and follows a two-stage mechanism that recruits and modulates the function of macrophages. Mechanical stimulation induces the release of growth factors such as HGF and IGF-1, which activate stem cells and support hair follicle regeneration. Beyond mechanical activation, emerging hair restoration therapies, including MSC transplantation, MSC secretome therapy, and platelet-rich plasma treatments, have shown promising results. These innovative strategies overcome the limitations of conventional therapies, offering effective solutions for various types of hair loss. Additionally, here we discuss the molecular mechanisms underlying hair follicle growth and repair, the influence of external factors, and novel hair follicle formation processes, such as chimeric follicle development and follicular neogenesis. Special attention is given to the roles of dermal papilla cells and their interactions with mesenchymal cells in promoting hair regrowth. The key strategies and underlying mechanisms discussed in this review will drive future research and potential clinical applications.

Keywords

hair regeneration, mechano-activation, molecular signaling, cellular interactions

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Introduction

Hair loss affects individuals worldwide, impacting both appearance and mental well-being. Conditions like alopecia disrupt the natural hair growth cycle or damage follicles, leading to hair loss.[1] Current treatments, including medications, surgery, and therapies with platelet-rich plasma (PRP), offer varying success rates and often require ongoing commitment.[2] Despite these advances, a lasting solution for all patients remains elusive.

Recent advances in mechanobiology provide new insights into hair regrowth by exploring how mechanical forces regulate the behavior of hair follicle stem cells (HFSCs).[3] Understanding the biomechanical cues that influence HFSC activity and differentiation becomes important for innovative regenerative therapies.[4] Mechanobiology, which examines how physical forces like matrix stiffness and stretching impact cellular and

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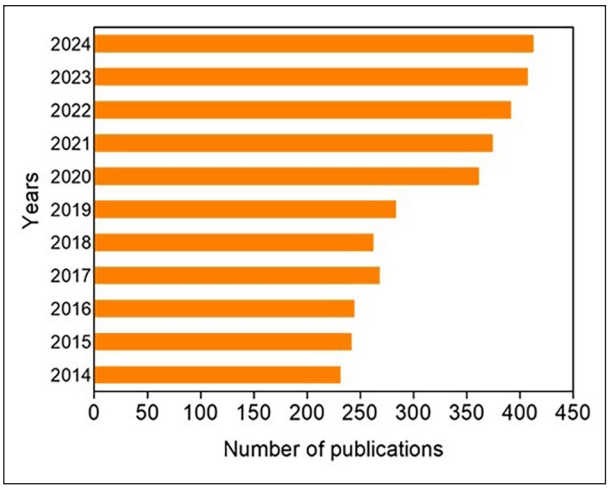

Figure 1. Number of articles published on "Hair regeneration" in the last 10 years according to PubMed, demonstrating consistent growth over the years and indicating an expanding research scope.

tissue processes, is rapidly gaining attention.[3,5] Cells detect these forces through receptors such as integrins and ion channels, which activate key signaling pathways like YAP/TAZ and Wnt/β-catenin.[6] While mechanobiology has long been explored in areas like bone repair and wound healing, its role in hair regrowth is beginning to show promise, particularly in modulating regenerating cellular activity.[7,8]

Hair follicles go through distinct growth (anagen), transition (catagen), and rest (telogen) phases.[9] Specialized cells in the bulge region regulate this cycle by responding to environmental cues such as matrix stiffness and interactions with dermal papilla cells.[10] Mechanobiology-based therapies thus aim to harness these cues to activate or enhance the regenerative capacity of the regenerating cells.[11] For instance, modifying the stiffness of the extracellular matrix (ECM) has been shown to influence HFSC activation, thereby promoting hair growth.[12,13] Furthermore, stimulation devices have demonstrated promise in improving blood flow and activating growth mechanisms that enhance hair follicle function.[14] Targeting mechanotransduction pathways, which mediate how cells respond to mechanical signals, could offer novel solutions for managing hair loss.[15]

Moreover, studies have underscored the critical role of the hair follicle microenvironment in promoting hair growth.[13,16] Specific T cells have been shown to protect HFSCs from systemic damage, highlighting the complex interplay between immune factors and follicle health.[17,18] By integrating engineering principles with these biological insights, new solutions for hair loss can be developed. In particular, viewing hair follicle regulation from a mechanobiological perspective can enhance therapeutic treatments for alopecia. Future therapies will likely need to address both immune and mechanical factors to effectively promote hair regrowth, which can offer a more comprehensive approach to hair restoration. Figure 1 illustrates the steady increase in the number of articles published on hair regeneration over the past decade, highlighting the growing interest and the need for further expansion in this research field.

While previous works have primarily emphasized biochemical therapies or stem cell transplantation strategies, here we uniquely highlight the mechanical regulation of HFSCs and their surrounding microenvironment, proposing a comprehensive mechanobiological framework for hair regeneration. For this, we begins with an overview of the structure and mechanisms underlying hair loss and regeneration, followed by a discussion of the key mechanotransduction pathways involved in hair follicle renewal. We then explore the therapeutic potential of mechanobiological approaches in hair restoration and conclude with an outlook on future directions, clinical implications, and potential advancements in the field.

Hair structure, loss, and regeneration

Anatomy of the hair follicle: A brief overview

The hair follicle is a complex, dynamic structure responsible for the production and growth of hair. It is located within the skin, specifically in the dermis layer, and extends into the subcutaneous tissue (as shown in Figure 2) is crucial for uncovering hair growth mechanisms and developing effective treatments for hair loss. This section explores the essential layers and components of the hair follicle, highlighting their roles in maintaining follicle health and regulating the hair growth cycle.

Outer root sheath (ORS). The outer root sheath (ORS) forms the outermost layer of the hair follicle, extending from the skin surface to the follicle base, where it connects with the epidermis and consists of stratified epithelium.[20] It provides structural support, houses blood vessels that supply essential nutrients for hair growth, and plays a key role in immune privilege, shielding the follicle from autoimmune attacks.[21,22] The ORS bulge region serves as a niche for HFSCs, which are critical for hair regeneration.

Recent studies have expanded our understanding of the ORS, identifying the follicular trochanter, an epithelial protrusion near the bulge, as a potential marker for HFSCs, expressing CD200 and keratin 15.[23] This structure may reflect distinct stages of ORS remodeling during the hair cycle. Furthermore, the ORS has been implicated in mechanotransduction. ORS cells respond to mechanical stimuli by releasing ATP, serotonin, and histamine, which activate surrounding sensory neurons, suggesting a role in tactile sensation.[24] These finding suggests a novel mechanism by which the hair follicle contributes to tactile sensation. Although direct confirmation study on melanocyte stem cells in the ORS is lacking, previous research has shown that follicular melanocytes can migrate along the ORS in response to specific stimuli, highlighting a

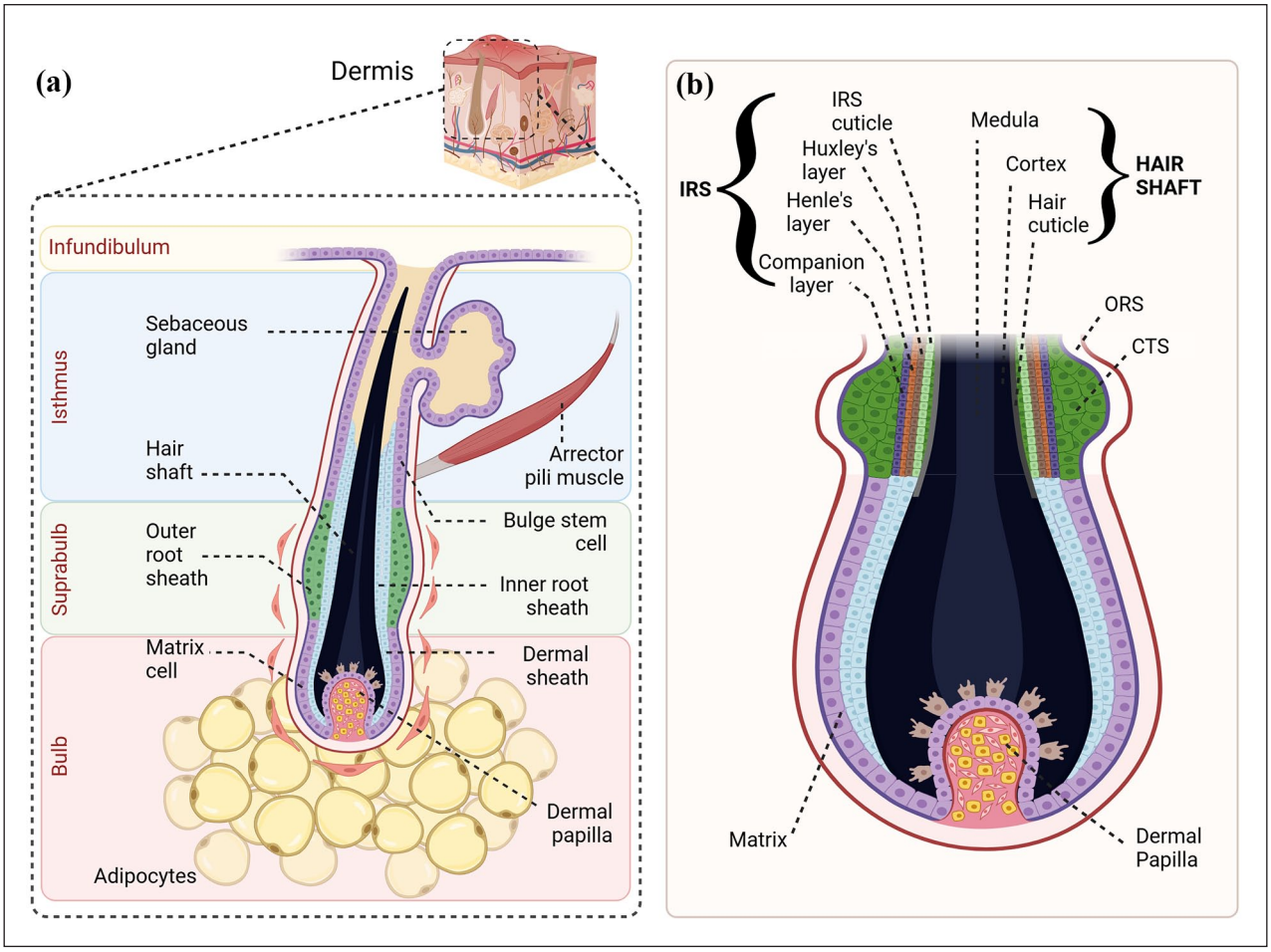

Figure 2. The structure of hair follicle. (a) The hair follicle is composed of four primary sections: the bulb, suprabulb, isthmus, and infundibulum. (b) When viewed in a cross-section, the hair follicle presents as a cylindrical structure comprising eight concentric layers. These layers form three main components: the outer root sheath (ORS), the inner root sheath (IRS), and the hair shaft. The IRS consists of four distinct layers: the companion layer, Henle's layer, Huxley's layer, and the IRS cuticle. The hair shaft itself is made up of three parts: the medulla, cortex, and hair cuticle. The connective tissue sheath (CTS) surrounds the entire hair follicle, providing mechanical support and helping maintain its shape and integrity, especially during hair growth and mechanical stress (modified from Cuevas-Dias Duran et al.[19]).

potential role for the ORS in hair pigmentation, warranting further investigation.[25]

Inner root sheath (IRS). The inner root sheath (IRS) lies between the outer root sheath and the hair shaft, comprising three distinct layers: Henle's layer, Huxley's layer, and the IRS cuticle.[26] It plays a crucial role in hair development by serving as a structural barrier that separates the growing hair from the outer root sheath, ensuring the proper environment for follicular maturation.

Recent works have elucidated the critical function of IRS in hair formation. An et al., identified keratin 71 (KRT71) as essential for optimal hair shaft formation, offering potential targets for hair regeneration therapies.[27] This aligns with earlier findings demonstrating the importance of KRT71 in maintaining hair follicle integrity.[28] Additionally, the IRS expresses key proteins that contribute to its specialized function. Trichohyalin, a structural protein, is retained within IRS cells and plays a pivotal role in forming the rigid framework of the follicle.[29] Furthermore, the expression of certain S100 proteins in the innermost IRS layers suggests their involvement in normal follicular physiology.[30]

Dermal papilla. The dermal papilla (DP), located at the base of the hair follicle, is composed of specialized fibroblasts that regulate hair growth by functioning as a key signaling center.[31,32] It secretes various growth factors and morphogens that orchestrate the hair cycle, activating hair follicle stem cells to initiate new growth phases.[31,32] Notably, dermal papilla cells also possess the ability to induce new follicle formation during embryonic development and wound healing.[32]

Molecular studies have identified at least four distinct subpopulations, each contributing to different layers of the hair shaft and sheaths.[32] Additionally, Kang et al.

demonstrated that 5-bromo-3,4-dihydroxybenzaldehyde (a marine-derived Wnt activator shown to enhance DP cell proliferation) promotes hair growth by activating the Wnt/β-catenin and autophagy pathways while inhibiting TGF-β signaling in DP cells.[33] Under substate mechanical cues (>2 kPa stiffness), DP cells upregulate Wnt10b and FGF7 secretion, initiating epithelial-mesenchymal interactions that drive neo-folliculogenesis in vivo.

Further insights into dermal papilla function continue to emerge. Zhang et al. revealed that the Shh gene regulates DP cell proliferation and apoptosis, influencing its differential expression during the secondary hair follicle cycle in cashmere goats.[34] These findings provide a deeper understanding of hair growth regulation and offer new potential targets for therapeutic hair regeneration.

Bulge region and HFSCs. The bulge region of the hair follicle serves as a critical niche for HFSCs, which possess multipotent capabilities and play a fundamental role in hair follicle regeneration.[34,35] Acting as a stem cell reservoir, HFSCs contribute to the hair growth cycle by responding to signals from the dermal papilla and surrounding microenvironment, thereby initiating new growth phases.[35] Beyond their role in hair regeneration, these stem cells also participate in wound healing by aiding in skin repair following injury.[36]

HFSCs exhibit remarkable plasticity, with studies demonstrating that nestin-expressing HFSCs can differentiate into neurons, glial cells, keratinocytes, and smooth muscle cells in vitro.[37] These cells have also shown promise in nerve regeneration and functional recovery in spinal cord injury models, highlighting their potential for broader regenerative applications.[38] Furthermore, the bulge region has been identified as a source of nestin-expressing stem cells that can migrate to the DP and surrounding skin tissues during wound healing, further emphasizing their role in tissue repair and regeneration.[39]

HFSCs are highly heterogeneous, with recent studies offering deeper insights into their diverse functional subpopulations. For example, K19-expressing cells within the bulge region have been identified as label-retaining cells, suggesting K19 as a potential marker for skin stem cells.[40] This discovery highlights the complexity of hair follicle cycling regulation and opens new avenues for investigating HFSC behavior, with implications for future therapeutic strategies in hair restoration and regenerative medicine.

Hair shaft. The hair shaft, the visible portion of the hair above the skin, is composed of three distinct layers, each contributing to the structural and functional integrity of the hair. The innermost layer, the medulla, is present only in thick hairs and is absent in finer hair types.[41] Surrounding the medulla is the cortex, which provides the hair with its mechanical strength and determines its pigmentation.[41]

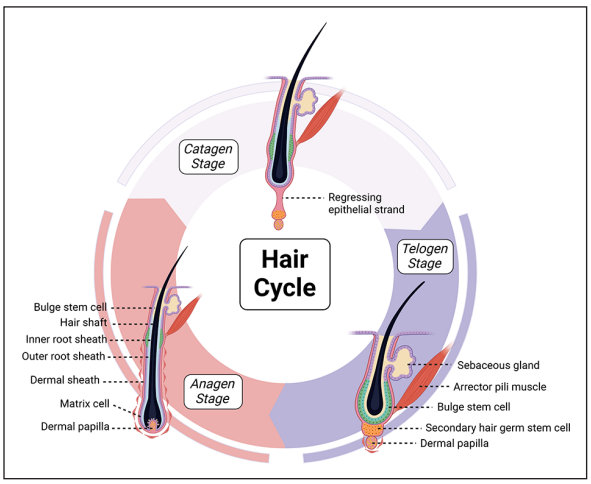

Figure 3. The hair growth cycle consists of three distinct phases. Anagen: the active growth phase, driven by matrix cell proliferation and dermal papilla nourishment. Catagen: a regression phase in which the follicle detaches from the dermal papilla, ceasing growth and beginning regression. Telogen: a dormant phase that persists until the hair sheds and the cycle restarts (modified from Chen et al.[45]).

The outermost layer, the cuticle, consists of overlapping keratinized cells that form a protective barrier, shielding the inner structures from environmental damage and mechanical stress.[41]

Advances in microscopy and modeling have deepened our understanding of the molecular and structural properties of hair shaft. Using advanced light microscopy, Fellows et al. analyzed the cellular composition of human hair, revealing distinct fluorescence lifetimes across cuticle cell layers.[42] These findings suggest variations in chemical environments within different cuticle layers, improving our knowledge of hair structure and the impact of chemical treatments. Additionally, James et al. developed a physically accurate reflectance model for fur fibers, incorporating key structural components of the hair shaft, such as the cortex, cuticle, and medulla.[43] This model provides valuable information on the optical properties of hair and fur, which are influenced by internal structural variations.

While direct evidence linking mTOR signaling to hair shaft thickness is not yet confirmed, related research continues to uncover the intricate biological mechanisms governing hair formation.[41] These studies contribute to a deeper understanding of hair biology and may inform the development of novel therapeutic strategies for hair growth disorders and structural hair damage.

Hair growth cycle

The hair growth cycle consists of three main phases—anagen, catagen, and telogen—that regulate hair development and renewal (as illustrated in Figure 3). The anagen phase,

lasting 2–8 years, is the active growth stage where hair follicles proliferate and elongate.[44] With aging, this phase shortens, leading to hair thinning and reduced follicle count. Premature anagen termination can accelerate hair loss. The catagen phase is a brief transitional stage (~2 weeks) where hair detaches from the DP, and epithelial cells undergo apoptosis, initiating follicle regression.[15,44] Disruptions in dermal papilla relocation can lead to premature follicle termination and shedding. The telogen phase (~2–3 months) is the resting stage, during which 9% of scalp hair remains dormant before new growth begins.[44] If hair enters telogen prematurely, it can result in telogen effluvium, causing excessive shedding. The exogen phase marks the final stage, where new hair growth pushes out the old strand, completing the cycle.

Role of HFSCs in hair cycling

HFSCs, located in the bulge area near the sebaceous gland, are critical for the regeneration of hair follicles.[46] During the telogen (resting) phase, these cells remain quiescent, preserving their regenerative potential for future cycles.[47] Upon the transition to the anagen (growth) phase, HFSCs activate, proliferate, and differentiate into various cell types required for hair growth, including keratinocytes and melanocytes, which are essential for hair formation and pigmentation, respectively.[48]

A defining characteristic of HFSCs is their remarkable plasticity, enabling them to adapt and differentiate into distinct cell types over time.[49] Additionally, HFSCs are self-renewing, maintaining a constant pool of stem cells that supports both the structural integrity and esthetic appearance of hair.[47] This regenerative capacity ensures continuous hair follicle turnover throughout an individual's lifespan.[48]

HFSCs divide asymmetrically, generating both specialized progeny and new stem cells, thus preserving the stem cell population while contributing to hair follicle regeneration.[47] Furthermore, HFSCs are highly responsive to environmental signals, particularly chemical cues like Wnt proteins, which trigger the activation of HFSCs and initiate the anagen phase.[50–52]

Importantly, they exhibit mechanosensitivity, responding to changes in the ECM stiffness, which influences their behavior and function.[13] This ability to sense and adapt to mechanical forces highlights the importance of the stem cell niche in regulating stem cell fate.[13,53] Mechanosensitive HFSCs can detect alterations in their microenvironment, allowing them to adjust their regenerative potential accordingly.[12,50] This feature is crucial for maintaining hair follicle homeostasis, ensuring proper tissue organization and function during the cycling process.[13,53]

The unique combination of dormancy during telogen and rapid activation during anagen allows HFSCs to drive the cyclical regeneration of hair follicles throughout adulthood.[12,13,53] Understanding and potentially harnessing the mechanisms governing HFSC behavior presents promising avenues for developing therapies for hair loss and other hair growth-related disorders.

Microenvironmental factors influencing HFSCs

The activity of HFSCs is intricately regulated by their surrounding microenvironment, often referred to as the niche.[53] Within this niche, a dynamic interplay of biochemical signals and mechanical forces interacts with cell-to-cell communication, controlling HFSC behavior, such as their transition from dormancy to activation and differentiation.[53] These interactions ultimately regulate the phases of hair growth and shedding.

Biochemical signals are crucial in influencing HFSC activity. For example, bone morphogenetic proteins (BMPs) play a key role in maintaining HFSC quiescence during the telogen phase of the hair growth cycle. BMPs achieve this by inhibiting cell cycle progression and suppressing pathways that promote HFSC activation.[52] In contrast, Wnt proteins stimulate HFSC activity. When Wnt signaling is increased, it encourages HFSC proliferation and differentiation, facilitating the transition from telogen to the anagen phase.[52,54,55] The coordinated action of Wnt proteins, fibroblast growth factors (FGFs), and transforming growth factor-beta (TGF-β) creates a finely tuned signaling environment that governs HFSC behavior.[52,54,55]

Conversely, the ECM factors are increasingly recognized as critical regulators of HFSC function. The stiffness of the ECM surrounding HFSCs can significantly influence their behavior by modulating cellular tension and activating specific signaling pathways.[12,13,53] For instance, a softer ECM tends to maintain HFSC quiescence by reducing cellular tension and inhibiting the activation of transcription factors like YAP and TAZ.[13] Conversely, a stiffer ECM increases cellular tension, triggering pathways that promote HFSC activation and differentiation.[13] These mechanical cues are transduced through integrins, which connect the ECM to the cytoskeleton, mediating the response to mechanical signals.[13]

Another significant factor is the interaction between HFSCs and DP cells, which reside at the base of the hair follicle. The DP cells act as a central signaling hub, releasing factors such as Wnts and FGFs that directly influence HFSC activation and development.[55] The close proximity of DP cells to HFSCs facilitates rapid, targeted regulation of HFSC activity, ensuring efficient communication for hair follicle cycling.

The regulation of HFSCs by their microenvironment underscores the critical need to consider these biochemical signals and mechanical cues when developing targeted therapies for hair regrowth. By elucidating the interactions between these factors, we can design treatments that optimize the regenerative capacity of HFSCs, resulting in

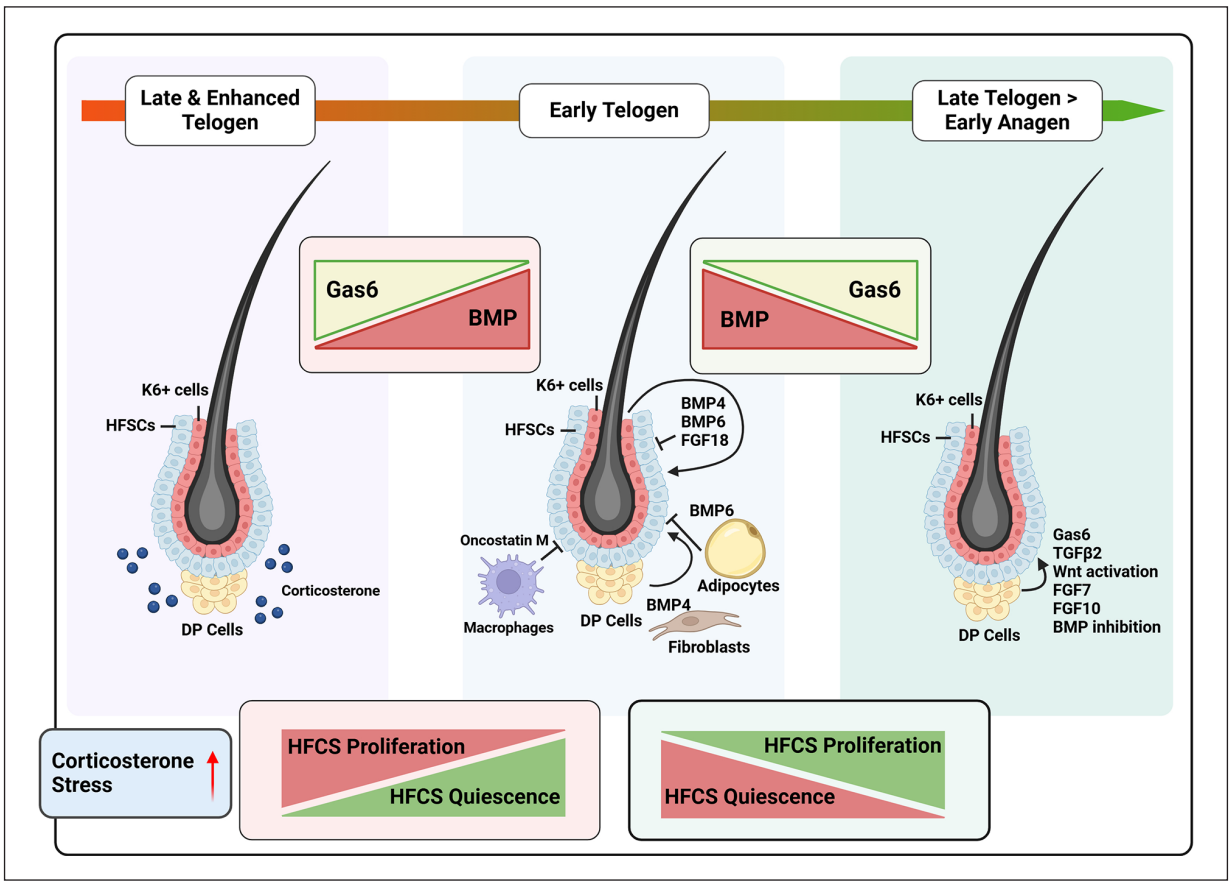

Figure 4. Microenvironmental factors regulating hair follicle stem cells (HFSCs) during the telogen-to-anagen transition. (Left) Late & Enhanced Telogen: High BMP (Bone Morphogenetic Protein) signaling and low Gas6 expression maintain HFSC quiescence. Elevated corticosterone levels, linked to stress, prolong telogen. (Middle) Early Telogen: BMP4, BMP6, and FGF18 from fibroblasts, adipocytes, and DP (dermal papilla) cells sustain quiescence, while macrophages secrete Oncostatin M, modulating HFSC activity. (Right) Late Telogen to Early Anagen: Gas6 increases while BMP signaling decreases, promoting HFSC activation. Additional factors such as TGFβ2, Wnt activation, FGF7, and FGF10 contribute to BMP inhibition and hair cycle re-entry. This figure highlights the systemic (corticosterone) and local (BMP, Gas6, FGF, Wnt) factors governing HFSC fate and hair follicle regeneration (modified from Quist et al.[56]).

more effective hair regeneration strategies. In the following, we further detail the molecular pathways associated with microenvironmental influences on hair loss and regeneration (Figure 4).

Molecular pathways involved in hair growth

Multiple canonical pathways sense and transduce mechanical cues into HFSC responses (as summarized in Table 1). The Wnt/β-catenin pathway, activated by substrate strain or shear, leads to nuclear accumulation of β-catenin and transcription of proliferation genes such as *cyclin D1*, mediated by Lef-1, thereby promoting anagen entry[3] Conversely, BMP2/4 signaling through Smad1/5 maintains HFSC quiescence by upregulating cell-cycle inhibitors (e.g. *p21*),[57] while TGF-β1/3 acting via Smad2/3 triggers catagen initiation and apoptosis in the lower follicle.[58] The Notch pathway (Jagged1-Notch1) regulates cell fate decisions: Notch intracellular domain interacting with RBP-Jκ downstream drives differentiation, particularly in the matrix and inner root sheath.[59] Finally, PI3K/Akt activation, often downstream of integrin engagement, phosphorylates Akt, which in turn activates mTOR to support HFSC survival and differentiation under mechanical stretch.[60]

Wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway plays a key role in regulating hair follicle development and hair growth. Specifically, the canonical Wnt/β-catenin pathway is crucial for the regulation of HFSCs[55] Sustained β-catenin expression in HFSCs at the hair germ and bulge activates the LEF/TCF complex, promoting the transcription of downstream target genes such as c-Myc and cyclin D1. This enhances HFSC activation, proliferation, and regulated differentiation during hair regeneration.[63] The Wnt/β-catenin pathway is thought to

Table 1. Mechanotransduction pathways involved in HFSC functions.

Mechanotransduction pathway	Key downstream regulators	HFSC functions	Ref.
Wnt/β-catenin	β-catenin → TCF/Lef-1 → *cyclin D1*	Proliferation (anagen entry)	Chu et al.[3], Myung et al.[61]
BMP2/4	Smad1/5/Smad4 → *p21, p27*	Quiescence (telogen maintenance)	Hu et al.[62], Kandyba et al.[57]
TGF-β1/3	Smad2/3/Smad4 → pro-apoptotic genes	Catagen initiation & apoptosis	Botchkarev et al.[58]
Notch (Jagged1–Notch1)	NICD → RBP-Jκ → differentiation genes	Differentiation (matrix & IRS layers)	Turkoz et al.[59]
PI3K/Akt	Akt → mTORC1/2 → translation factors	Survival & differentiation under stretch	Chen et al.[60], Hu et al.[62]

be the key driver for transitioning hair follicles from the resting phase to the growing phase and is involved in all stages of hair follicle development.[63,64] Despite being evolutionarily ancient, many components of the Wnt signaling pathway are essential for cellular growth, proliferation, and normal tissue repair.[65,66]

TGF-β/BMP signaling pathway. The TGF-β and BMP signaling pathways are integral regulators of hair follicle development and the hair growth cycle. These pathways play opposing roles in the regulation of hair follicle dynamics, particularly in the transition between different phases of the hair growth cycle. BMPs are a large subgroup of the TGF-β family.[67,68] Vertebrates express more than 10 types of BMPs, which share a conserved structure with other TGF-β family members. BMP-2 and BMP-4, in particular, have been widely studied in the context of hair follicles and show periodic expression changes throughout the hair follicle cycle.[67–69] Hair follicle growth progresses through two phases: the early growth phase (I–IV) and the late growth phase (V–VI). BMP-2 expression is minimal during the early growth phase (I–IV) and progressively increases during the late growth phase (V–VI). In the quiescent phase, BMP-2 expression peaks, then declines as the follicle enters the late quiescent period.[68,69]

BMP signaling, particularly through BMP2 and BMP4, maintains HFSC quiescence by activating Smad1/5 pathways. This signaling suppresses proliferation, antagonizes Wnt activation, and preserves the resting state of HFSCs during the telogen phase. BMPs also promote terminal differentiation and help regulate chromatin states that reinforce stem cell dormancy. Disruption of BMP signaling leads to premature activation of HFSCs, impaired hair follicle maintenance, and cycling defects.[70,71]

In contrast, TGF-β signaling, primarily TGF-β1 and TGF-β3 through Smad2/3, promotes the transition of hair follicles from growth (anagen) to regression (catagen) by inducing apoptosis and suppressing epithelial proliferation. While BMP signaling preserves stemness and supports the resting and differentiation phases, TGF-β signaling facilitates follicle regression and stem cell clearance. Together, these opposing pathways tightly regulate hair follicle cycling and homeostasis by balancing quiescence and activation.[58,72]

Notch signaling pathway. The Notch signaling pathway is another essential regulator of hair follicle development and hair growth. The mammalian Notch receptor family consists of four receptors (Notch1-4) and five ligands, which engage in cell-to-cell interactions: Delta-like 1 (Dll-1, Dll-3, Dll-4), Jagged-1, and Jagged-2.[73] Ligand binding triggers three cleavages of the Notch extracellular domain, releasing the Notch intracellular domain, which translocates to the nucleus to activate the transcription of target genes such as hairy and enhancer of split, runt-related transcription factor, and Notch inhibitory membrane protein. This signaling cascade subsequently activates the Wnt/β-catenin pathway, influencing a variety of biological processes. Notch signaling plays a pivotal role in maintaining hair follicle shape during morphogenesis but has minimal effect on cell fate.[74,75] In embryonic development, Notch signaling influences the final stages of hair follicle formation. Mice lacking Notch signaling exhibit short, fine, and curly hair. Notch1 is expressed in cortical precursor cells, while Notch2 and Notch3 are activated in mitotic progeny during the hair follicle growth phase.[75]

PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway is a critical regulator of various cellular processes, including cell survival, proliferation, differentiation, and metabolism. It plays an essential role in the regulation of hair follicle development and hair growth, particularly in promoting hair follicle stem cell activation, survival, and the progression of the hair growth cycle. The PI3K/AKT pathway is integral to hair follicle growth and regeneration in in vitro models. Following injury to the hair follicle or epidermis, AKT phosphorylation increases, which upregulates the hair cycle.[60,76] In studies investigating the role of PI3K in hair growth, Chen et al. used the PI3K inhibitors perifosine (krx-0401) and LY294002, finding that PI3K inhibition blocked the transition from telogen to anagen.[60] Conversely, PTEN inhibitors, which activate PI3K, promoted this transition. Furthermore, PI3K/AKT signaling has been shown to enhance the function of interfollicular

epidermal stem cells and HFSCs, while also stimulating the release of growth factors and cytokines that accelerate wound healing and hair regeneration.[76] These findings highlight the multifaceted role of PI3K/AKT signaling in hair cycle regulation and growth.[77]

Factors contributing to hair loss

Hormones. Hormones such as thyroid hormones, dihydrotestosterone (DHT), estrogen, and testosterone are critical regulators of hair growth and the hair cycle. Both hypothyroidism and hyperthyroidism can promote the transition from anagen to telogen, leading to telogen effluvium (TE) and diffuse hair loss. As noted by Vincent and Yogiraj, diffuse hair loss is a common sign of thyroid dysfunction, particularly in individuals aged 0–40 years, while alopecia areata (AA) and androgenic alopecia (AnA) are more prevalent in those over 40 years old.[78] The relationship between thyroid dysfunction and alopecia becomes more pronounced with age.[79]

DHT, an androgen produced by the metabolism of testosterone through the enzyme 5-alpha-reductase type 2, plays a key role in androgen-dependent hair follicles. While androgens stimulate hair growth in certain regions, DHT contributes to follicular miniaturization in androgenic alopecia. By binding to androgen receptors in the hair follicle, DHT shortens the anagen phase, lengthens the telogen phase, and induces apoptosis in hair follicle cells.[80]

Estrogen is thought to have a protective effect against hair loss, despite testosterone's conversion to DHT accelerating hair loss. This is supported by observed changes in hair parameters during pregnancy, postpartum, and menopause, periods marked by fluctuations in estrogen levels. During pregnancy, elevated estrogen levels increase hair growth and diameter, while reducing shedding. However, other pregnancy-related changes, such as increased levels of progesterone, prolactin, and growth factors, may also contribute.[81] In contrast, postpartum TE is associated with a drop in estrogen and progesterone. Similarly, menopause-related estrogen deficiency contributes to decreased hair density, shorter anagen phases, and conditions like female-pattern androgenic alopecia (FPAnA).[81] Evidence suggesting that the frontal hairline is often spared in FPAnA, due to elevated aromatase activity (which converts androgens to estrogen), further supports estrogen's protective role in hair loss.[82–85] However, further research is needed to clarify the pathophysiological mechanisms by which estrogen influences hair loss.

Stress. Stress can contribute to hair loss through several mechanisms, but it is just one of many potential causes. The relationship between stress and hair loss has been widely studied. Substance-P dependent inflammatory pathways are implicated in stress-induced alopecia, and stress can also mediate the transition from anagen to telogen, contributing to TE.[82] Cortisol, the primary stress hormone, regulates the hair cycle and proteoglycan synthesis.[82] Elevated cortisol levels have been associated with both male and female androgenic alopecia, compared to healthy individuals. Proteoglycans, such as versican, decorin, and glycosaminoglycans, play critical roles in the hair cycle.[86,87] Versican helps protect cells from oxidative stress-induced apoptosis, while decorin promotes anagen and stimulates hair growth. Excessive cortisol levels, however, impair proteoglycan synthesis and promote their breakdown, which negatively impacts hair follicle function.[84,86,87] Inhibiting cortisol could therefore support anagen phase promotion and hair growth by maintaining proteoglycan levels.[84,86,87]

Inflammation. Inflammation is closely associated with the progression of alopecia by promoting the transition from anagen to telogen, which is implicated in several subtypes of hair loss, including stress-induced alopecia, AnA, and AA. Chronic and systemic inflammatory disorders disrupt the balance between the anagen and telogen phases, contributing to conditions like telogen effluvium (TE).[88] In various non-stressed in vivo mouse models, inflammatory mechanisms such as excessive mast cell activation, perifollicular macrophage accumulation, and the involvement of Substance P, known for its pro-inflammatory effects on immune and epithelial cells, have been shown to exacerbate stress-induced hair loss.[89,90] Furthermore, a murine study found an increase in Substance P-immunoreactive nerve fibers in the skin during the early stages of AA. Subcutaneous administration of substance P induces mast cell degranulation and promotes the transition to the catagen phase.[90] These findings underscore the role of inflammation and substance P in regulating both stress-induced alopecia and AA.

Mechanical cues and mechanotransduction pathways in hair regeneration

ECM mechanics and remodeling

The ECM surrounding HFSCs plays a pivotal role in regulating their behavior and controlling hair follicle cycling.[13] Far more than a mere structural scaffold, the ECM serves as an active communication hub, dynamically influencing the quiescence, activation, and differentiation of HFSCs.[12,13] Understanding the composition and mechanical properties of the ECM is essential for unraveling the complex mechanisms governing hair regeneration and identifying potential therapeutic strategies for hair loss conditions.[12,13]

The ECM of the hair follicle is composed of various macromolecules, each contributing to its structural integrity and functional properties.[12,13] Collagen types I, III, and IV form the backbone of the ECM, providing tensile

strength and serving as a scaffold for cell adhesion and migration. This collagen network supports cellular interactions within the follicular niche, enabling the maintenance of stem cell functions.[87,91] Fibronectin, a critical glycoprotein in the ECM, facilitates cell-ECM interactions by binding to integrins on the cell surface, thereby mediating cell adhesion and migration. These processes are integral for HFSC function and the progression of the hair cycle.[92] Furthermore, laminin, a key component of the basement membrane, is indispensable for the structural organization of the hair follicle. It interacts with cell surface receptors on HFSCs, regulating their behavior, including self-renewal, adhesion, and differentiation.[92] Elastin fibers, although less abundant than collagen, contribute to the elasticity and resilience of the ECM, enabling the hair follicle to withstand repeated growth and regression cycles without compromising structural integrity.[93] Tenascin-C, an ECM glycoprotein, plays a key role in hair follicle morphogenesis and cycling. Its spatiotemporally regulated expression supports cell adhesion, migration, and proliferation during the anagen phase.[94]

Alternatively, proteoglycans, including heparan sulfate proteoglycans, are another crucial component.[78,95] These complex molecules enhance matrix hydration and viscoelasticity, creating a dynamic environment that can respond to mechanical stresses.[78,95] Additionally, proteoglycans serve as reservoirs for growth factors, sequestering and presenting key signaling molecules to HFSCs and other cells within the niche.[78,95] Hyaluronic acid, a non-sulfated glycosaminoglycan, further supports the ECM promoting tissue hydration, facilitating cell migration and signaling through interactions with cell surface receptors.[95]

Together, these diverse ECM components work together to create a complex and dynamic microenvironment that supports HFSC function and regulates hair follicle cycling. The interplay between these molecules and their interactions with cells are essential for maintaining the balance between HFSC quiescence and activation throughout the different phases of the hair growth cycle.

Beyond composition, ECM mechanics are crucial for hair follicle maintenance and regeneration. In particular, stiffness plays a pivotal role in modulating HFSC behavior and is dynamically regulated during the hair follicle cycle.[13] During the resting telogen phase, the ECM is relatively soft, which helps maintain HFSC quiescence by stabilizing BMP signaling.[96–101] Conversely, during the anagen phase, increased ECM stiffness activates mechanosensitive receptors, including integrins, which initiate signaling pathways such as YAP/TAZ and Wnt/β-catenin.[89–91] These pathways are essential for HFSC activation, proliferation, and hair growth, as discussed also in the following sections.[96–101] Given its pivotal role, the modulation of ECM stiffness represents a promising therapeutic strategy for hair loss. By altering ECM mechanical properties using biomaterials or pharmacological agents, it may be possible to regulate HFSC activity and stimulate hair growth, offering new treatment avenues for conditions such as alopecia, as further discussed in the following sections. BMP2/4 act as telogen quiescence factors, while collagen I and III deposition peaks during anagen, reinforcing HFSC anchorage to the basement membrane.

One important aspect is that ECM is dynamically remodeling, an essential process in hair follicle cycling, which involves the continual adaptation of both the composition and mechanical properties of the ECM. This remodeling occurs in response to the changing needs of HFSCs and the surrounding cells throughout the hair follicle cycle.[96–101] Proper regulation of ECM remodeling is thus crucial for maintaining a functional niche for HFSCs and ensuring the correct progression of the hair cycle.[97] As discussed, during the telogen phase, the ECM remains not only soft but also relatively stable, providing an environment that supports HFSC quiescence and stem cell maintenance through reducing mechanical stresses.[96–101] This unique ECM environment prevents premature activation of HFSCs, allowing them to remain in a dormant state until they receive the appropriate signals to enter the anagen phase.

The balance between ECM production and degradation is thus critical for maintaining ECM stability. Fibroblasts, which produce ECM components, work in concert with ECM-degrading enzymes, such as matrix metalloproteinases, to maintain this equilibrium. This careful regulation ensures that the ECM structure remains intact during telogen, providing a stable niche for the quiescent HFSCs.[85] Additionally, the ECM during telogen serves as a reservoir for quiescence-promoting factors, such as BMPs. These factors are sequestered within the ECM, allowing for their controlled release during the resting phase. This retention mechanism ensures that signaling molecules necessary for HFSC maintenance are available when needed, thereby supporting the quiescent state of HFSCs.[12,52,98]

As the hair follicle transitions from telogen to anagen, ECM remodeling occurs to facilitate the activation and proliferation of HFSCs. Changes in ECM composition, such as increased collagen deposition and fibronectin reorganization, help create a stiffer matrix, which triggers mechanosensitive pathways involved in HFSC activation and hair growth. This remodeling process ensures that the ECM adapts to the mechanical and biochemical demands of the growing hair follicle.[10,99–103]

Integrin-mediated FAK signaling: Linking ECM mechanics to cells

Integrin-mediated FAK signaling plays an important role in linking the mechanical properties of the ECM to cellular responses. Integrins, which connect the ECM to the cytoskeleton, are essential for detecting and transmitting mechanical signals within HFSCs.[6] When ECM stiffness

increases or mechanical pressure is applied, integrins aggregate into focal adhesions, activating of FAK.[104] These focal adhesions are complex protein assemblies that include adaptor proteins like talin and vinculin, which connect integrins to the actin cytoskeleton. These structures act as mechanosensors, with their size and composition changing in response to mechanical forces, thereby modulating downstream signaling cascades.[105,106] These series of events in focal adhesion activation reinforces mechanotransduction signaling that influences HFSC behaviors.

At the core of integrin and focal adhesion signaling is FAK, which activates two primary signaling pathways: MAPK/ERK and PI3K/Akt.[106–109] In response to mechanical stress, the MAPK/ERK pathway promotes cell growth and survival, stimulating transcription factors that regulate HFSC activation and hair follicle regeneration.[109] Concurrently, the PI3K/Akt pathway supports HFSC survival and metabolism, ensuring energy availability during the anagen phase.[110,111] Akt signaling also governs cell cycle progression and prevents cell death, facilitating the expansion of HFSCs for hair follicle development.[76] Moreover, FAK signaling is crucial for reshaping the cellular architecture, enabling HFSC activation and movement during hair follicle regrowth.[76,112,113] FAK regulates Rho GTPases and other cytoskeletal regulators to orchestrate the cellular changes required for HFSCs to respond to mechanical signals.[114–116]

Cytoskeletal mechano-players: Transmitting mechanosignals to the nucleus

The cytoskeleton plays an essential role in mechanotransduction within HFSCs, acting as both a sensor and transmitter of mechanical signals to intracellular pathways. Comprising three key components, actin filaments, microtubules, and intermediate filaments, the cytoskeleton is fundamental for translating extracellular mechanical cues into cellular responses. These structural elements work together to modulate cellular behavior in response to mechanical stimuli, directly influencing HFSC function and hair follicle cycling.[116–118]

Among other elements, actin filaments are central to generating intracellular tension, operated through actomyosin contractility.[119–121] This process is regulated by RhoA GTPase, which activates actin polymerization and promotes the formation of stress fibers.[122–124] The myosin motor proteins interact with actin filaments, generating tension that transmits mechanical signals to the nucleus.[123–130] These forces regulate the nuclear translocation of YAP/TAZ, critical effectors in mechanotransduction.[118] The activation of YAP/TAZ in turn modulates gene expression, driving HFSC proliferation during the anagen phase, while lower tension conditions in telogen help maintain HFSC quiescence.[131,132] This dynamic modulation of actin-mediated tension is crucial for controlling hair follicle growth and regeneration (Figure 5).

On the other hand, microtubules, which provide structural support under compressive forces, also serve as tracks for intracellular transport, facilitating the proper positioning of cellular components during mechanical stress.[119–121] These tubules interact with focal adhesions, key sites for mechanosensitive signaling, thereby influencing pathways like FAK-MAPK/ERK that govern HFSC proliferation and differentiation (Figure 5).[121–123] Furthermore, the dynamic reorganization of microtubules is crucial during cell migration, particularly in the anagen phase, when hair follicle cells need to reposition to support hair growth.

Lastly, intermediate filaments, such as keratins in epithelial cells and vimentin in mesenchymal cells, play a pivotal role in protecting HFSCs from shear stress and deformation.[126] These filaments distribute mechanical forces across the cytoplasm and interact with the nuclear lamina to directly transmit forces to the chromatin, influencing gene expression.[116–119] Intermediate filaments are particularly important during the catagen phase, when the hair follicle undergoes structural regression and the cytoskeleton must withstand significant mechanical stress.[9]

Recent studies have further elucidated the role of cytoskeletal dynamics in HFSC behaviors.[4,129] For example, Ruan et al. has highlighted the role of ZO-1, a tight junction protein, in enhancing the self-renewal of prehematopoietic stem cells derived from OCT4-reprogramed human HFSCs.[130] This process is mediated through cytoskeletal remodeling, demonstrating the critical involvement of the cytoskeleton in regulating stem cell behavior. These findings underscore the potential for therapeutic interventions targeting cytoskeletal components to promote hair regeneration and improve hair loss treatments.

YAP/TAZ signaling: A central mediator of mechanotransduction

The Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are critical in the mechanotransduction process in HFSCs.[118] These proteins serve as key mediators, responding to mechanical stimuli and regulating HFSC behavior.[131] When exposed to mechanical stress or increased ECM rigidity, YAP and TAZ translocate from the cytoplasm to the nucleus, where they interact with TEAD transcription factors (Figure 5).[132]

In the nucleus, the YAP/TAZ-TEAD complex binds to specific genomic regions, activating genes involved in cell growth, survival, and development.[132] During the telogen phase, low mechanical tension in the scalp during telogen could indeed contribute to cytoplasmic retention of YAP/TAZ through phosphorylation-dependent mechanisms.[101] This sequestration is crucial for maintaining HFSC quiescence during telogen, preventing premature activation.[101]

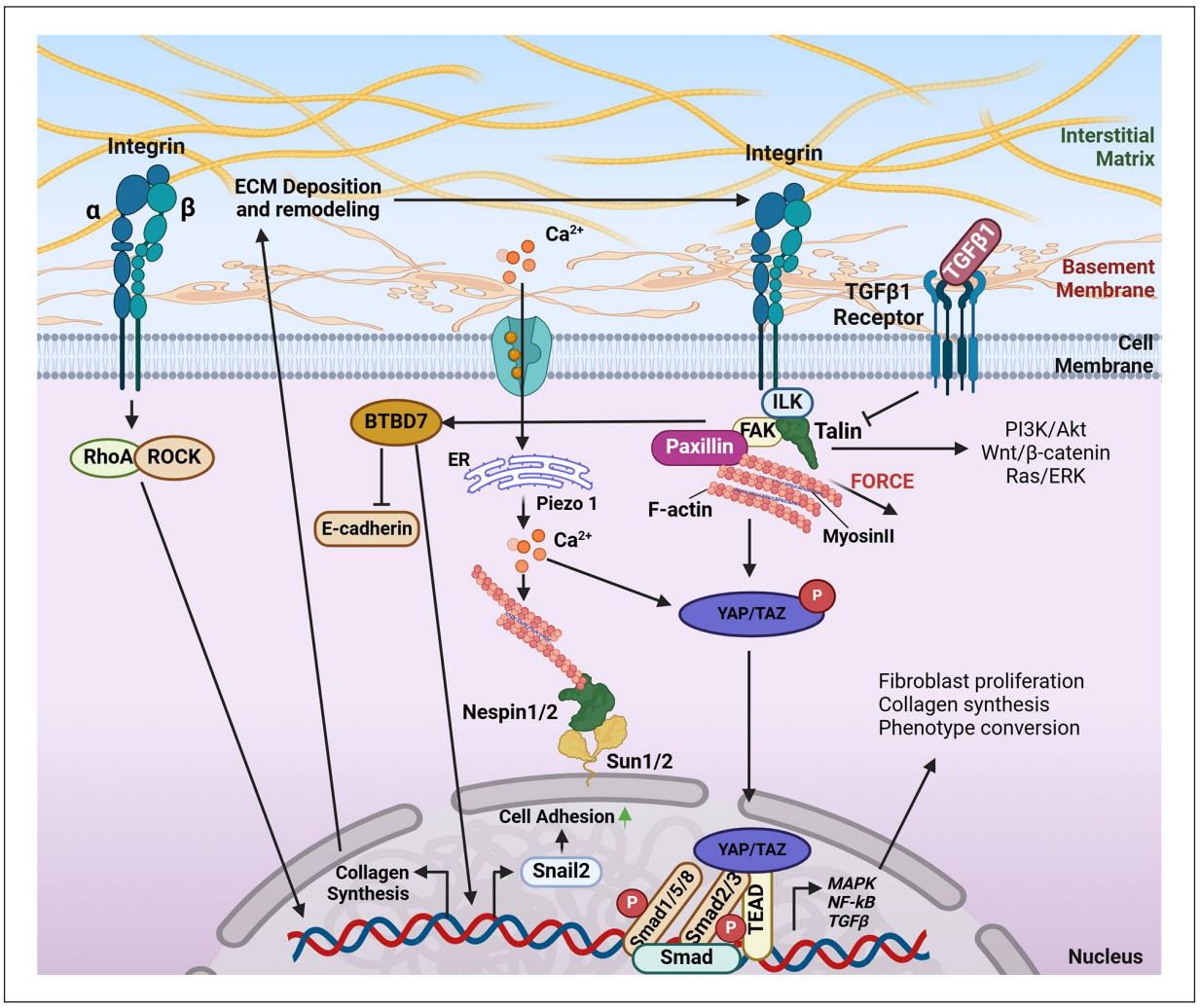

Figure 5. Significance of ECM mechanics in HFSC mechanotransduction process. The integrins convey mechanical and biochemical signals from ECM into cells and facilitate cell proliferation, differentiation, migration, and invasion. Activation of the RhoA/ROCK pathway enhances collagen and fibronectin accumulation, while Talin/FAK promotes F-actin assembly along with myosin II, conveying the mechanical cues to the nucleus. Meanwhile, YAP/TAZ is translocated into the nucleus to promote the transcription of downstream genes, collagen synthesis, and cell differentiation. ECM: extracellular matrix, ER: endoplasmic reticulum, ERK: extracellular signal-related kinase, FAK: focal adhesion kinase, ILK: integrin-linked kinase, P: phosphate, TGFβ: transforming growth factor β (modified from Di et al.[6]).

Recent findings indicate that modulating YAP and TAZ activity can significantly affect HFSC behavior and hair follicle cycling; promoting YAP activity can drive the progression to anagen, while suppressing YAP and TAZ extends the telogen phase.[118,133] These studies suggest that targeting YAP/TAZ signaling may offer therapeutic potential for treating hair loss disorders.

Wnt/β-catenin pathway: Synergy with YAP/TAZ in anagen promotion

As previously discussed, the Wnt/β-catenin pathway is integral to hair follicle development, and its signaling is modulated by mechanical forces during the anagen phase.[134,135] When exposed to mechanical stress, β-catenin is less likely to undergo degradation, leading to its accumulation in the cytoplasm. This stabilization occurs through the disruption of the catenin destruction complex and activation of mechanosensitive proteins that bind to β-catenin.[136,137] As β-catenin levels rise, it translocates to the nucleus, where it interacts with TCF/LEF transcription factors to activate genes involved in cell cycle progression and HFSC activation.[63]

Recently, the interplay between Wnt/β-catenin and YAP/TAZ pathways during the anagen phase has become particularly significant. Both pathways are modulated by mechanical signals and converge to regulate genes that promote stem cell activation and proliferation.[134–138] This

synergy ensures a coordinated response to signals that drive the transition from telogen to anagen and support continuous hair growth.[137–142]

Calcium signaling via piezo1 channels: Rapid Mechanotransduction Pathway

Piezo1 channels are pivotal the rapid sensing of mechanical forces in various cell types, including HFSCs.[143] These specialized ion channels are capable of detecting changes in membrane tension, allowing calcium ions to enter the cell and initiate a cascade of intracellular signaling events.[143] In HFSCs, mechanical stress activates Piezo1 channels, causing a rapid influx of calcium ions, which triggers the activation of calcium-dependent enzymes, particularly calcium/calmodulin-dependent protein kinase II (CaMKII).[143–145] CaMKII activation has wide-ranging effects on cellular function, including the regulation of cytoskeletal dynamics through its influence on Rho GTPases, such as RhoA, Rac1, and Cdc42.[146–148]

The calcium-dependent modulation of Rho GTPases is essential for the adaptability of HFSCs, particularly during early stages and the onset of the hair growth cycle.[149] The rapid respond to mechanical changes enables HFSCs to integrate mechanical cues with other signaling stimuli, fine-tuning their activation and proliferation. Importantly, calcium signaling via Piezo1 channels does not operate in isolation but interacts with other mechanotransduction pathways, particularly integrin-mediated signaling.[150] The rapid calcium influx through Piezo1 channels modulates focal adhesion dynamics and integrin clustering, affecting downstream signaling cascades such as FAK and MAPK/ERK pathways.[145–148] This crosstalk between calcium and integrin signaling creates a complex network of mechanotransduction that allows for both rapid and sustained responses to mechanical stimuli.[145–149]

Furthermore, calcium signaling influences the activity of mechanosensitive transcription factors such as YAP/TAZ, where calcium-dependent activation of kinases modulates their phosphorylation state and nuclear translocation, thus transcriptional activity.[150] This interaction adds another layer of regulation to mechanotransduction, linking rapid calcium signaling to longer-term transcriptional changes.[150,151] Recent study, such as the work by Deng et al., have demonstrated the critical role of Piezo1-mediated mechanotransduction in HFSC homeostasis and hair regeneration, highlighting its potential as a therapeutic target for hair loss disorders.[152] The study showed that in a murine AGA model, cyclic strain (10%) induced strain-mediated overactivation of YAP/TAZ in the connective tissue sheath, depleting progenitors via increased apoptosis assays and premature catagen morphology.

In summary, calcium signaling via Piezo1 channels represents a rapid and dynamic mechanotransduction pathway in HFSCs. Its interaction with other signaling cascades, including integrin-mediated pathways and transcriptional regulators like YAP/TAZ, creates a sophisticated system for sensing and responding to mechanical forces. This intricate signaling network is crucial for regulating HFSC behavior and hair follicle cycling, offering potential avenues for therapeutic interventions in hair regeneration and related fields.

Mechano-therapeutic targets and mechano-stimulation approaches for hair regeneration

Therapeutic targets of mechanosensitive molecules

The mechanotransduction pathways governing HFSC behaviors present a wealth of potential therapeutic targets for hair regeneration. As discussed in Part 3, HFSCs respond to mechanical cues through a complex network of mechanosensitive molecules, including integrins, focal adhesion complexes, cytoskeletal elements, ion channels, and downstream signaling effectors. Furthermore, the mechanical properties and composition of ECM are critical regulators of HFSC fate. Therefore, targeting these extracellular and intracellular molecules involved in mechanotransduction offers innovative strategies to modulate HFSC activity and promote hair growth.

First, therapeutic strategies aimed at modulating ECM stiffness and composition can be used to promote HFSC activation and proliferation.[13] For instance, ECM-derived biomaterials or small molecules that promote collagen synthesis and crosslinking increased ECM stiffness, thereby stimulating integrin activation and downstream signaling pathways such as YAP/TAZ and Wnt/β-catenin.[91,153,154] Conversely, interventions that soften the ECM during telogen phase, such as inhibition of collagen crosslinking via LOX inhibitors, may help maintain HFSC quiescence and prevent premature activation.[155–157] Other ECM components, such as hyaluronic acid, proteoglycans, fibronectin, and laminin, can also be targeted to modulate ECM mechanics and the resulting cellular mechanosignaling.

In terms of intracellular molecules, integrins represent key targets to reinforce or attenuate the ECM cues to the cytoskeleton and nucleus. Small molecules or antibodies that selectively activate or inhibit specific integrin subtypes can modulate HFSC behaviors. For example, agonists that enhance integrin clustering and focal adhesion formation can promote FAK activation and downstream signaling cascades, driving HFSC activation and hair growth. Inhibiting integrin signaling, on the other hand, may be beneficial in conditions where excessive HFSC activation leads to premature depletion of the stem cell pool.

As a central hub in integrin-mediated signaling, FAK presents a compelling therapeutic target.[103–107] FAK inhibitors

Table 2. Key mechanosensitive therapeutic targets in hair regeneration.

Therapeutic target	Mechanism of action	Therapeutic implications
Integrins (e.g. β1, α6)	Mediate cell-ECM adhesion and transmit mechanical signals to activate FAK and downstream pathways; regulate cytoskeletal remodeling and HFSC activation	Targeting integrin signaling can enhance HFSC activation and hair follicle regeneration, and improve the efficacy of mechanical stimulation therapies
YAP/TAZ	Act as mechanosensitive transcriptional co-activators; translocate to the nucleus in response to ECM stiffness or stretch; promote proliferation and stemness of HFSCs	Modulating YAP/TAZ activity may boost hair growth and follicle regeneration, and synergize with other regenerative signals
Piezo1	Mechanosensitive ion channel that rapidly responds to membrane tension; mediates Ca2+ influx and activates downstream signaling cascades	Pharmacological or mechanical activation of Piezo1 can stimulate HFSC proliferation and hair growth
Wnt/β-catenin	Canonical pathway activated by mechanical cues and cross-talk with YAP/TAZ; regulates HFSC fate and anagen initiation	Enhancing Wnt/β-catenin signaling via mechanical or pharmacological means can promote robust hair regeneration

can modulate the activity of downstream pathways such as MAPK/ERK and PI3K/Akt, thereby controlling HFSC proliferation, survival, and differentiation.[103–106,108–110] However, the careful selection of FAK inhibitors with specificity for HFSCs and minimal off-target effects is essential to avoid potential side effects.

The role of cytoskeletons in transmitting mechanical forces makes them a valuable therapeutic target. Drugs that modulate actin polymerization, microtubule dynamics, or intermediate filament assembly could influence HFSC behavior. For instance, promoting actin polymerization and stress fiber formation can enhance actomyosin contractility and YAP/TAZ nuclear translocation, driving HFSC activation and proliferation. Conversely, disrupting cytoskeletal tension can maintain HFSC quiescence during telogen.[118–120]

Piezo1 channels, which serve as rapid sensors of mechanical forces, offer another potential therapeutic target. Agonists that activate Piezo1 channels triggers a rapid influx of calcium ions, stimulating CaMKII activation and downstream signaling pathways involved in HFSC activation.[142–144] However, precise regulation of Piezo1 activity is necessary to prevent excessive calcium influx and potential cytotoxicity.

Given the central role of YAP/TAZ in mechanotransduction, targeting these transcription factors represents a promising therapeutic strategy for hair regeneration. Small molecules that promote YAP/TAZ nuclear translocation and TEAD binding stimulate HFSC proliferation and hair growth. Conversely, inhibitors that prevent YAP/TAZ nuclear entry or disrupt YAP/TAZ-TEAD interaction can suppress HFSC activation and extend the telogen phase (Figure 5).[131]

The synergistic activation of Wnt/β-catenin pathway with YAP/TAZ during the anagen phase presents an attractive target for hair regeneration.[134–138] Small molecules that stabilize β-catenin promote its nuclear translocation or enhance its interaction with TCF/LEF transcription factors, stimulating HFSC activation and hair growth.[63] However, careful regulation of Wnt signaling is essential to avoid potential side effects, such as the formation of skin tumors.[55,63–65]

In summary, the intricate mechanotransduction pathways governing HFSC behaviors offer a diverse array of therapeutic targets for hair regeneration. By selectively modulating the activity of ECM components, integrins, cytoskeletal elements, ion channels, and downstream signaling effectors, it may be possible to precisely control HFSC fate and promote hair growth in a variety of hair loss conditions. Further research is needed to identify and validate these therapeutic targets and develop safe and effective mechanotherapeutic strategies for hair regeneration. The following section highlights several exemplary studies related to these approaches (Table 2).

Mechano-stimulation approaches

Mechanobiology offers innovative approaches for treating hair loss disorders by targeting the mechanical cues that regulate HFSC behaviors. This emerging field has led to the development of various therapeutic strategies, including non-invasive mechanical stimulation devices and biomaterials designed to modulate the ECM and intracellular mechanosignaling.

In fact, many conventional devices that employ the mechanical stimulation concept have been developed for hair regeneration, each employing different approaches to deliver mechanical forces to the scalp (Figure 6). Scalp massage tools are handheld devices designed to provide gentle, consistent mechanical stimulation to the scalp, often featuring textured surfaces or vibrating elements to enhance their effects.[158] These tools stimulate blood flow, relax scalp muscles, and activate mechanosensitive pathways in HFSCs.[158] Studies have shown that regular scalp massage can increase hair thickness and reduce hair shedding.[158]

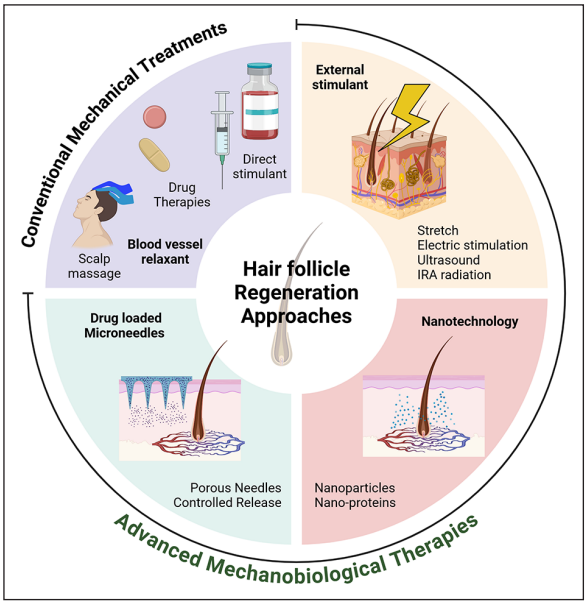

Figure 6. Strategies for hair regeneration through application of mechanical stimuli or mechanobiological activation of cells. The figure categorizes the strategies into conventional mechanical treatments and advanced mechanobiological therapies. In particular, the latter includes external stimulation (e.g. stretching, electric stimulation, ultrasound, and infrared-A (IRA) radiation), mechanical-tuned hydrogels and scaffolds, nanoparticles for targeted drug or protein delivery, and microneedles with delivery capacity (created with BioRender.com).

Similarly, Low-Level Light Therapy (LLLT) devices with mechanical vibration (20–60 Hz) and mild pressure (10–30 kPa) applied for 10–30 min daily have demonstrated synergistic effects on hair growth. While LLLT promotes cellular energy production, mechanical vibration activates Piezo1 channels and other mechanosensitive pathways.[151,152] Clinical trials have demonstrated that LLLT devices with mechanical vibration can significantly improve hair density and thickness.[159,160]

Alternatively, vacuum therapy devices, which create negative pressure on the scalp, are also used for hair growth. This method increases blood flow, stimulates collagen production, and activates HFSCs.[161] While research on vacuum therapy for hair growth is limited, earlier studies suggest potential benefits, though clear mechanisms require further elucidation.

From another angle, acupuncture and acupressure involve stimulating specific points on the body, including the scalp, using needles or manual pressure.[162] These techniques are believed to promote blood flow, reduce inflammation, and activate HFSCs.[162] Some studies have shown that acupuncture can improve hair growth in individuals with alopecia areata.[162]

More recently, microneedle devices often employ needle lengths of 0.5–1.5 mm and treatment durations of 5–10 min per session, two to three times per week to induce mechanical micro-injury and stimulate regenerative pathways have been used for applying mechanical forces to scalp and help hair growth.[163,164] For instance, derma-rollers create micro-injuries in the scalp, and studies revealed the system can stimulate collagen production and growth factor release.[163,164] While technically creating micro-injuries, the procedure is minimally invasive, and the primary effect is mechanical stimulation. The micro-injuries trigger the wound healing response, which involves the release of growth factors and the activation of HFSCs. Studies have shown that microneedling can improve hair growth, particularly when combined with topical treatments like minoxidil, which opens K^+ channels on DP cells, increasing VEGF secretion and microvascular growth to support the anagen phase.[163–165]

While these approaches of applying mechanical forces have been used clinically and have often demonstrated the efficacy, the exact mechanisms of improving the hair growth such as the mechanotransduction molecules involved and the signaling pathways are largely undiscovered, warranting further research areas to advance the clinical applications of those apparatus for targeted and more effective therapeutic effectiveness.

On the other stream, advanced biomaterials with controlled mechanical properties or delivery capabilities have emerged as promising platforms to modulate HFSC behaviors and promote hair regeneration (Figure 6). Designed to mimic the natural ECM conditions with specific mechanical properties found in different phases of the hair follicle cycle, these biomaterials provide a controlled microenvironment that can influence HFSC functions and fate. Furthermore, nano- and microscale biomaterials are engineered to encapsulate and deliver therapeutic molecules, such as drugs, proteins, and genes, targeting key mechanobiological pathways to restore hair follicle functions.

As highlighted, the stiffness of the ECM plays a crucial role in regulating HFSC behaviors throughout the hair follicle cycle.[12,13,41,53] During the telogen phase, the ECM surrounding HFSCs is relatively soft, which can help maintain stem cell quiescence; in contrast, the anagen phase is characterized by a stiffer ECM, which can promote HFSC activation and proliferation.[12,13,41,53] By engineering biomaterials with specific stiffness properties tuning to the hair cycle, it would be possible to recreate these mechanical cues in vivo and to control HFSC functions in hair regeneration process (Figure 7(a)). For this purpose, soft hydrogels, among other biomaterials, can be developed to mimic the mechanical properties of the telogen-like environment.[12,13,41,53,100] These materials typically have a low elastic modulus, similar to that of the natural ECM during the resting phase of the hair follicle cycle.[13] Koester et al. investigated how matrix stiffness influences HFSC potency and gene activation. They modified HFSC organoid cultures using hydrogels with tunable stiffness mimicking

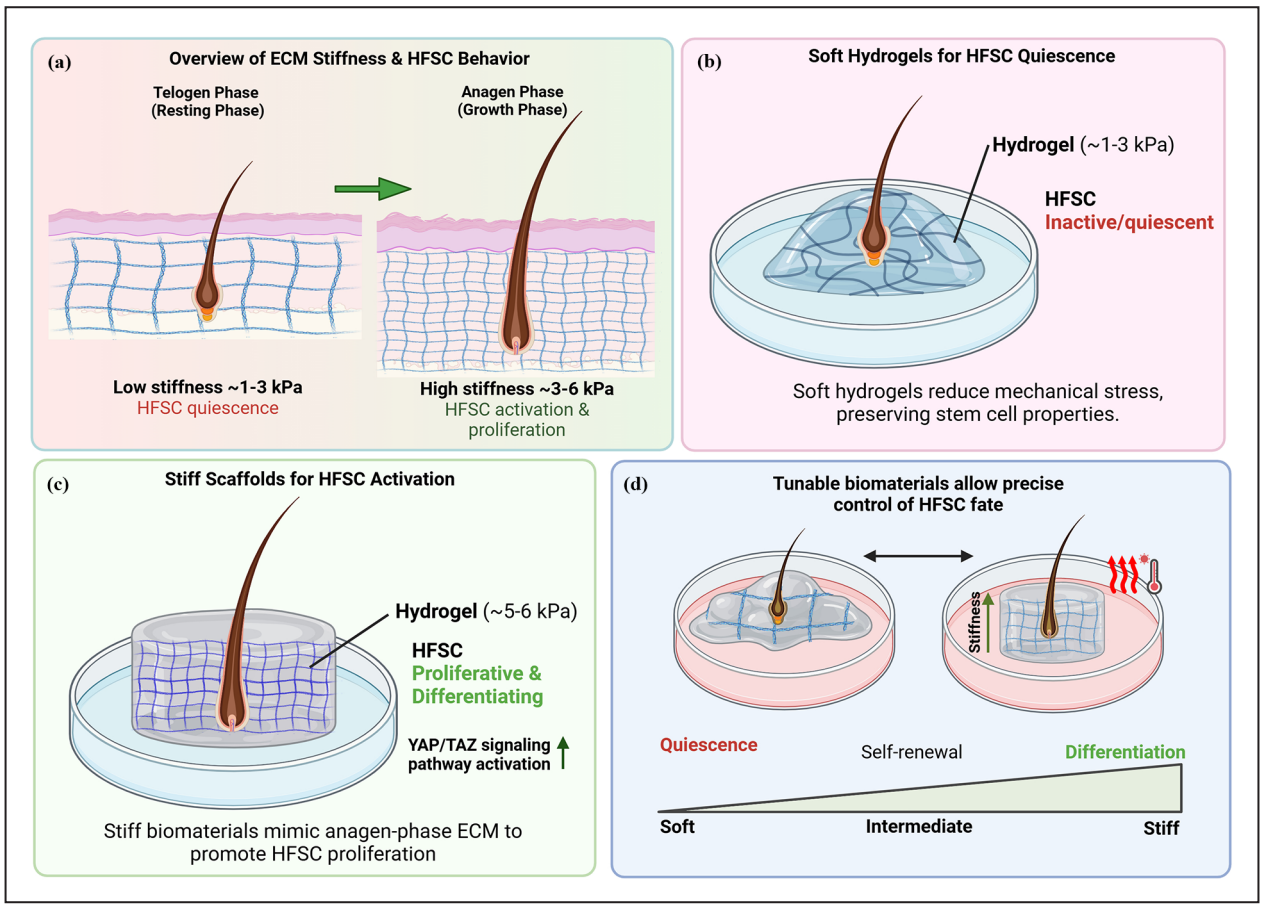

Figure 7. ECM stiffness modulated by biomaterials to mimic in vivo niche and enhance hair regeneration. (a) An overview of effect of ECM stiffness on HFSC behaviors. (b) Soft ECM conditions, mimicked by hydrogels (~0.5 kPa), maintain HFSC quiescence during the telogen phase, whereas (c) stiff ECM conditions (2–10 kPa), recreated using collagen-based scaffolds, promote HFSC activation and proliferation during the anagen phase.[154] (d) Biomaterials, such as PEG hydrogels, with tunable ECM stiffness can be used to study HFSC self-renewal and differentiation.

young (1–3 kPa) and aged (5–6 kPa) basement membranes (BMs). In soft hydrogels mimicking young BMs, both young and aged HFSCs demonstrate comparable activation of bivalent self-renewal and differentiation genes. This environment maintained chromatin accessibility and reduced mechanical stress on HFSCs, effectively restoring their regenerative potential. The softer matrix allowed for greater nuclear deformability, facilitating the expression of key genes such as SOX9 and LHX2, essential for HFSC function (Figure 7(b)).[13,166,167]

Conversely, stiffer hydrogels (5–6 kPa) that simulate aged BMs exhibited a detrimental effect on HFSC function. This increased stiffness attenuates gene activation in young HFSCs, mirroring the impaired functionality observed in aged stem cells. The stiffer environment led to decreased chromatin accessibility at bivalent promoters, effectively silencing critical genes necessary for stem cell activation and self-renewal.[12] The aging process induced significant changes in the ECM composition, notably through increased collagen accumulation. This remodeling further resulted in a stiffer BM, typically around 5–6 kPa. The stiffer niche exerted mechanical stress on HFSCs, compressing chromatin and repressing the transcription of genes vital for self-renewal and differentiation.[13,166]

Interestingly, studies suggest that moderately stiff scaffolds (around 5 kPa) may enhance HFSC proliferation and differentiation in certain contexts. This apparent contradiction highlights the complex relationship between matrix stiffness and stem cell behavior. The mechanosensitive YAP/TAZ signaling pathway has emerged as a key player in mediating the effects of ECM stiffness on HFSCs.[118] This pathway is known to promote cell proliferation and is crucial for epidermal stem cell self-renewal and differentiation. Activation of YAP/TAZ signaling in response to increased matrix stiffness may contribute to enhanced HFSC proliferation and hair follicle regeneration under certain conditions.[118] However, it is important to note that YAP/TAZ activity tends to decrease with age, correlating with reduced proliferative potential of epidermal progenitors. This age-related decline in YAP/TAZ signaling may

partially explain the impaired regenerative capacity of HFSCs in older individuals. These findings collectively suggest that optimizing scaffold stiffness and targeting mechanosensitive pathways like YAP/TAZ can offer promising strategies for enhancing HFSC function and promoting hair follicle regeneration. Further research is needed to fully elucidate the complex interplay between ECM properties, mechanotransduction pathways, and HFSC behavior in the context of hair follicle biology and regenerative medicine (Figure 7(c)).[13,118]

As noted, one of the key advantages of using engineered biomaterials is the ability to provide a controlled microenvironment for HFSCs. This level of control allows for isolating the effects of mechanical cues on HFSC behaviors, which is challenging to achieve in vivo due to the complex interplay of various factors in the hair follicle niche (Figure 7(d)). By systematically varying the stiffness of the hydrogel, they were able to identify optimal mechanical conditions for maintaining HFSC stemness and promoting their differentiation into hair follicle lineages.

In parallel, these biomaterials can be combined with growth factors or drugs to further enhance their efficacy in promoting hair growth (Figure 8(a)). For example, the gelatin-based hydrogels, when incorporated with bFGF and VEGF (50 ng/mL each), showed synergistic effects in promoting HFSC proliferation and hair follicle formation in comparison to either the scaffold or growth factor alone (Figure 8(b)).[168,169] Similarly, Wu et al. created hybrid hydrogel system that combined mechanical cues with controlled release of minoxidil, a widely used hair growth-promoting drug (Figure 8(c)).[170] This approach allowed for sustained delivery of the drug while providing appropriate mechanical stimulation to HFSCs, resulting in enhanced hair growth in a mouse model of alopecia. Other bioactive molecules have also been incorporated to modulate HFSC behavior. Abu et al. developed a chitosan-based scaffold functionalized with laminin-derived peptides, which enhanced HFSC adhesion and promoted their maintenance in a 3D culture system (Figure 8(d)).[171]

Lastly, these biomaterials offer exciting possibilities for engineering hair follicle constructs utilizing advanced technologies such as 3D bioprinting and organoid systems. These innovative platforms can recapitulate the intricate in vivo cell-cell and cell-matrix interactions, thereby applicable for in vivo implantation or drug testing in ex vivo culture systems (Figure 9). Recently, Yao et al. explored 3D bioprinted scaffolds with gradient stiffness properties to recreate the complex mechanical microenvironment of the hair follicle.[172] This approach allowed for the spatial organization of key cell populations involved in hair follicle formation, including HFSCs, dermal papilla cells, and epithelial progenitors, enabling controlled differentiation and promoting hair follicle morphogenesis. Mechanistically, the stiffness gradient guided HFSC migration and proliferation while regulating Wnt/β-catenin and BMP signaling pathways, both critical for follicular fate determination and cycling.

While research on hair regeneration remains in its early stages, insights from 3D bioprinting, organ-on-chip platforms, and organoid technologies in other biomedical fields can be leveraged for hair tissue engineering in the near future.

However, despite the promise of biomaterials in modulating HFSC behaviors, several challenges must be addressed before clinical translation. These include fine-tuning mechanics of biomaterials to dynamically mimic the in vivo niche, optimizing degradation profiles to align with the hair growth cycle, ensuring adequate vascularization of engineered constructs, and developing methods for large-scale production and quality control of these advanced materials. Recent research on hair-on-a-chip models aims to address limitations in current hair follicle research by replicating the hair follicle microenvironment more accurately. These models offer potential for studying hair follicle morphogenesis, regeneration, and the hair follicle cycle.[173,174] Optimization of hair follicle spheroids, including co-culture with various cell types and growth factor transfection, has shown promise in creating full-thickness skin equivalents containing hair in vitro. Additionally, hair-on-chip technologies are being explored for noninvasive biomarker detection and drug delivery applications, offering advantages over conventional sampling methods.[175]

As discussed, biomaterials engineered with specific physicochemical properties offer a powerful strategy for modulating HFSC behaviors and promoting hair regeneration. By mimicking the natural mechanical cues found in different phases of the hair follicle cycle, these materials may provide a controlled microenvironment that can influence HFSC functions and fate. Furthermore, integrating these materials with growth factors, drugs, and other bioactive molecules enhances their potential as versatile platforms for next-generation hair loss treatments. As research in this field continues to progress, these biomaterial-based approaches may lead to more effective and personalized therapies for various forms of alopecia and other hair loss disorders.

Future perspectives and conclusions

In this review, we have explored the critical role of mechanical cues and mechanotransduction pathways in regulating HFSC behaviors and hair regeneration. We highlighted the importance of the ECM and mechanical stimuli, intracellular mechanosensitive elements, and the mechanosignaling processes in mediating the HFSC responses. By dissecting their intricate interactions, we sought to provide a framework for understanding the mechanobiology of hair regeneration and identifying potential therapeutic targets for hair loss disorders.

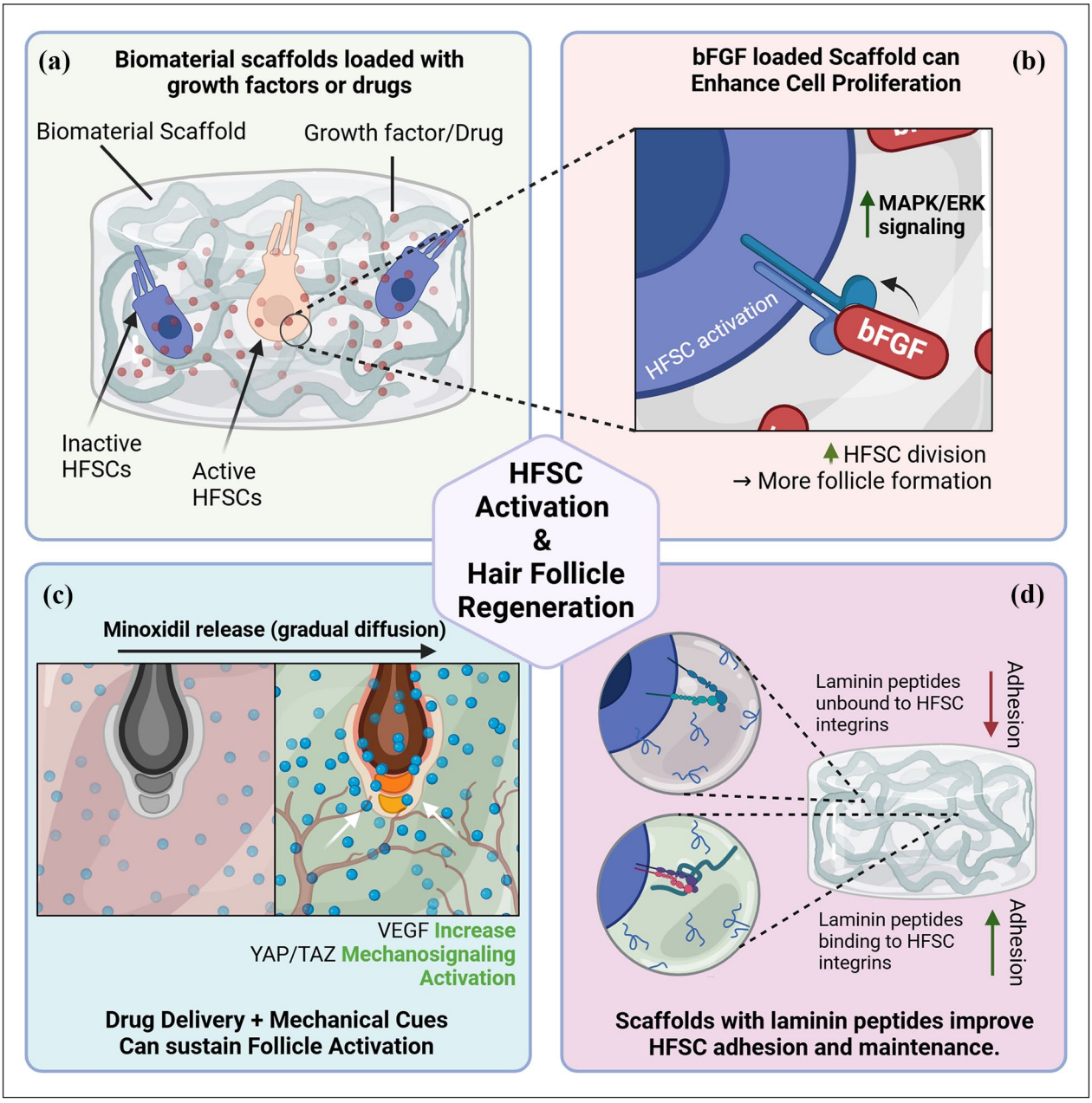

Figure 8. Biomaterial-based strategies for enhancing HFSC function and hair follicle regeneration. (a) Hydrogels and porous scaffolds combined with growth factors or drugs stimulate HFSC activation. (b) Gelatin-based scaffolds incorporating basic fibroblast growth factor (bFGF) promote HFSC proliferation via MAPK/ERK signaling, enhancing hair follicle formation. (c) A hybrid hydrogel system delivers mechanical cues and sustained minoxidil release, activating VEGF-mediated vascularization and YAP/TAZ signaling to drive HFSC proliferation. (d) Chitosan scaffolds functionalized with laminin-derived peptides enhance HFSC adhesion through integrin binding, supporting long-term HFSC maintenance in 3D culture.

While multiple signaling pathways influence hair regeneration, mechanosignaling is particularly crucial, given the exquisite sensitivity of HFSCs to mechanical forces and their microenvironment. Harnessing this process can offer a promising avenue for developing novel hair loss treatments. For this purpose, an array of molecular targets within the mechanosignaling network can be proposed; ECM components, integrins, FAK, cytoskeletal proteins, Piezo1 channels, and transcription factors like YAP/TAZ and β-catenin, which can be strategically modulated to regulate HFSC fate and promote hair growth.

In this mechano-modulation scenario, some non-invasive devices have been developed and are currently in clinical use, such as scalp massage tools, LLLT devices with vibration, microneedling devices, and vacuum therapy devices. However, these devices face limitations,

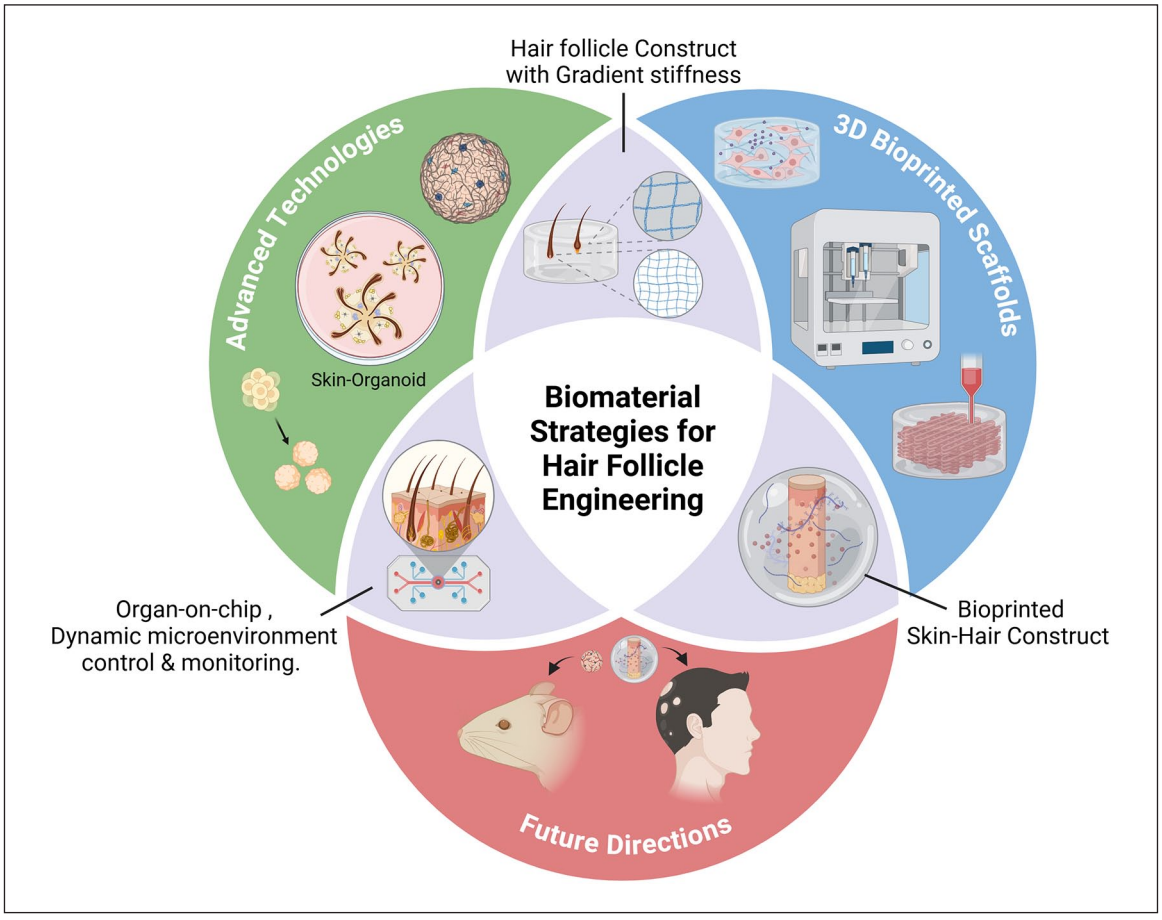

Figure 9. Advanced approaches for engineering hair follicle constructs, such as 3D bioprinting, organoid culture systems, and organ-on-chip platforms. (a) 3D bioprinting enables precise spatial organization of key cell populations, including HFSCs, dermal papilla cells, and epithelial progenitors, while gradient stiffness scaffolds regulate HFSC migration and proliferation via mechanotransduction pathways such as Wnt/β-catenin and BMP signaling. (b) Organoid culture systems recapitulate in vivo-like cell-cell and cell-matrix interactions, promoting follicular morphogenesis and functional hair follicle development. (c) Organ-on-chip platforms create dynamic microenvironments for real-time monitoring of HFSC behavior and drug screening. These cutting-edge technologies offer promising avenues for personalized regenerative therapies and in vitro hair growth models.

including variability in effectiveness, the need for consistent use, and limited long-term data. More importantly, the mechanistic studies of these devices are largely lacking, highlighting the need for future research to optimize device parameters, elucidate activated pathways, and develop controllable and targetable methods to enhance the therapeutic efficacy.

More precise designs of mechano-therapeutic approaches are thus under investigation, focusing on modulating ECM mechanics and targeting specific mechanobiological pathways. Notable approaches include ECM-based therapies utilizing biomaterial scaffolds and ECM-modifying enzymes, integrin-targeting strategies with peptides and antibodies, FAK modulation via small molecule inhibitors, and cytoskeletal remodeling agents. Furthermore, mechano-stimulation can be integrated with genetic modifications or advanced 3D tissue engineering techniques, such as bioprinting and organoid systems, to enhance therapeutic efficacy and expand applications, including ex vivo drug testing platforms.

A critical yet often overlooked aspect is cellular crosstalk, specifically HFSC-DP cell interactive mechanosignaling. These reciprocal interactions are essential for hair follicle development and cycling. Disruptions in this communication can contribute to hair loss disorders, suggesting that therapies enhancing HFSC-DP cell mechanosignaling may be more effective than those targeting HFSCs alone. In this context, mechano-active platforms that stimulate HFSC-DP feedback signaling ex vivo hold significant potential. Creating controlled mechanical environments may optimize HFSC and DP cell functions for transplantation, either by utilizing exosomes from mechanically stimulated cells or by directly culturing cells into organoids for transplantation.

For clinical translation, several challenges must be addressed. The materials and devices used in mechanotherapeutic approaches must meet stringent safety and efficacy standards for regulatory approval, such as those set by the FDA. For cell-based therapies, there are additional challenges related to cell sourcing, expansion, and delivery. It is also essential to develop robust methods for characterizing and standardizing the mechanical properties of biomaterials and devices to ensure consistent and reproducible results. The development of standardized protocols and regulatory guidelines will be essential for bringing mechanotherapeutic approaches to the clinic.

In conclusion, mechanobiology offers an exciting frontier for treating hair loss disorders. By harnessing the mechanical cues to regulate HFSC behaviors, we can develop innovative, effective therapies for hair regeneration. As research in this area continues to advance, emerging mechano-therapeutic strategies—integrating biomaterials, devices, and cell-based approaches—may offer new hope for individuals struggling with hair loss. A deeper understanding of the mechanotransduction pathways in HFSCs and the crosstalk with DP cells, combined with the development of biomaterial engineering and regulatory frameworks, will be pivotal in driving these therapies toward clinical translation.

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Ethical consideration

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