Getting under the skin of hair aging: the impact of the hair follicle environment

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Abstract
Like the skin, our hair shows striking changes with age, producing hairs with altered diameter, lustre and texture. The biology of hair aging has focused predominately on various aspects of the hair cycle, follicle size and the fibre produced, but surprisingly the impact of the aging scalp dermal environment on the hair follicle and fibre has been generally overlooked. Hair loss affects both sexes with incidence increasing with age. In men, male pattern-balding (androgenetic alopecia) is driven by androgens and follows a specific pattern of frontotemporal and vertex regression. Women also experience female pattern hair loss (FPHL), presenting as more general, diffuse hair thinning. Hair thinning in women is commonly associated with the menopause, corresponding with other age-related changes in skin. The rapidly growing hair follicle undergoes continued renewal throughout the life span of an individual, where it is exposed to a substantial number of extrinsic and intrinsic stressors. As the hair follicle sits deep within the dermis with its bulb residing in the hypodermis, detrimental age-related changes in the surrounding scalp skin may likely disrupt the hair follicle machinery. The impacts of these changes are unknown, but evidence suggests that scalp skin aging and hair follicle aging go hand-in-hand. Herein, we summarize the evidence that the age-related changes observed in sun-exposed human skin also occur in scalp skin and that these changes are likely to play a contributing role in the aging hair phenotype.

KEYWORDS
aging, dermal environment, dermal papilla, dermal sheath, hair follicle

1 | THE HUMAN HAIR FOLLICLE

The hair follicle environment encompasses the hair follicle, skin appendages and the surrounding tissue (Figure 1). The hair follicle, with its associated sebaceous gland, is an ectodermal-mesodermal tissue residing within a hair follicle unit, which normally contains two to five follicles. The exceptional capacity for regeneration shown by the hair follicle due to its ability to cycle throughout life allow for phenotypic changes to take place, for example size or colour of the hair. Each cycle encompasses the regression of the lower follicle.
WILLIAMS et al. (catagen), followed by a period of rest, now considered to be a maintenance stage (telogen),
shedding of the existing hair (exogen), followed by remodelling of the lower follicle and production of a new hair fibre (anagen). In a healthy human scalp, approximately 90% of hair follicles are in anagen, which normally lasts up to 8 years resulting in the generation of long hairs, with each one cycling independently. Approximately 100 club hairs are shed daily, and the average hair follicle goes through 10-30 growth cycles in a lifetime.

The time taken in each part of the hair cycle alters over this lifetime with an increased telogen and decreased anagen duration. Kenogen refers to an empty follicle when the fibre is shed before early anagen has been initiated. Although the incidence of kenogen in terms of age has not been investigated, a 2-year study on females with alopecia found for periods lasting 2-12 months, 22% of the hair follicles were in kenogen, which contributed to the overall hair loss.

While the main portion of the hair follicle is derived from the ectoderm, there are two significant mesenchymal components of the follicle, namely the dermal papilla (DP) and the dermal sheath (DS), which originate from the same cellular progenitors as the interfollicular dermal fibroblasts (DFs). The interfollicular fibroblasts are responsible for synthesising and maintaining the extracellular matrix (ECM) of the dermis, while the DP and DS have crucial roles in regulating hair growth; hence, they represent distinct fibroblasts populations, with unique gene expression profiles.

1.1 | The follicular dermal papilla

The DP in the hair follicle bulb co-ordinates hair follicle growth and cycling. The DP is composed of specialized fibroblasts acting as the control centre for the hair cycle. The volume of the DP correlates with follicle size and is attributed to the number of cells and cell volume and ECM. Cell volume is thought to be variably reliant on the amount of ECM produced, a theory supported by thicker terminal hair follicles having a higher abundance of ECM in contrast to finer vellus follicles.

While the bulb matrix epithelial cells undergo apoptosis during catagen, the DP remains intact and condenses, moving upwards with the epithelial peg to rest near the stem cell laden bulge region. Prior to anagen, epithelial-mesenchymal interactions between the bulge stem cells and the DP activate the proliferation of the secondary hair germ, leading to the remodelling of the hair follicle. The anagen DP instructs the surrounding matrix cells to proliferate and differentiate forming the different layers of the follicle and fibre thereby governing the thickness of the hair shaft produced. While DP cells are not thought to proliferate, increased cell number is believed to result from recruitment of neighbouring DS cells. As well as its role in hair follicle cycle signalling, the DP is also thought to be a reservoir of mesenchymal stem cells.

1.2 | The follicular dermal sheath

The DS is best described as a collagen fibre “sock” comprised of three collagen layers and specialized DS cells. It is continuous with the base of the DP and encapsulates the bulb and the follicle to just below the level of the sebaceous gland. In mice, DP and DS cells lost during telogen and catagen are thought to be replenished by a mesenchymal stem cell pool within the DS. Rat vibrissae DS cells can migrate into amputated follicles and replenish the DP cells; furthermore, DS cells from male scalp implanted into female forearm initiated hair growth.

**Figure 1** The anatomy of the hair follicle environment. Longitudinal section through human female scalp. The scalp comprises of the epidermis sitting above the dermis with the hypodermis below. The anagen hair follicle bulb resides in the hypodermis and extends up through the dermis to the epidermis. The hair follicle has a complex structure comprising of the mesenchymal dermal papilla, proliferating bulb matrix keratinocytes, which give rise to the hair fibre and the inner and outer root sheaths. The connective tissue dermal sheath encapsulates the whole follicle up to just below the sebaceous gland, at which level the arrector pili muscle is also attached.
with hair fibres thicker than the pre-existing vellus hairs suggesting DS have inductive capacities, or can be recruited into existing follicles to modulate hair growth.[14] Other studies have reported that upper DS cells can also regenerate the DP,[15] although some have reported a lower capacity to reform the DP[13] suggesting there are two populations of DS cells, upper and lower, the lower referring to the DS cup. The DS cup sits beneath the DP and histologically looks to be feeding into the papilla and vice versa.[16] DS cells have not only been suggested to migrate within the hair follicle but have been shown to migrate out of the hair follicle into the surrounding dermis during wound healing, repopulating, and coordinating at the wound site.[17]

2 | THE HUMAN HAIR FOLLICLE: FROM THE CRADLE TO THE GRAVE

Changes over the lifespan of the human hair follicle illustrate how it is impacted by aging. In utero, the foetus is covered in fine, unpigmented, downy lanugo hairs, which are replaced with vellus hairs after birth.[18] The advent of puberty due to elevated sex hormones sees the transformation of vellus to terminal hair follicles in specific regions of the body in both sexes.[19] In women, scalp hair density declines in early adulthood, while diameter increases up to the middle of the 3rd decade, after which it gradually decreases.[1] With increasing age, intrinsic and extrinsic factors lead to a more dominant telogen phase resulting in hair follicle miniaturization.[20] With age, the hairs are reduced in diameter with a reduction in hair density due to follicular miniaturization. There is also a loss of pigment resulting in grey or white hairs, a subject we shall only cover briefly since the focus of this review is on the dermal components. It is thought that dermal fibroblasts play a role in the regulation of melanogenesis in the skin[21] and the dermal papilla has a regulatory role in the follicle that modulates hair follicle pigmentation.[22] Grey and non-pigmented white hairs tend to have a greater diameter and growth rate. It is hypothesized this change in diameter is due to changes in the transfer of melanosomes from the melanocytes of the hair bulb matrix,[22,23] again this may be due to adaptations in the surrounding mesenchyme driving this hair aging phenotype. It is of note that these studies only investigated the correlation between hair diameter and pigmentation in men and women up to the age of 68 years; while other studies with older participants reported an overall decrease in hair diameter with age.[24]

2.1 | Influence of sex hormones on human hair growth

Androgens are the principle sex hormones driving the transformation of small vellus hair follicles into large terminal ones, for example the male beard. The requirement of androgen receptors is underlined by individuals with complete androgen insensitivity syndrome who lack functional androgen receptors and do not exhibit body hair.[25] Paradoxically, in genetically predisposed men, androgens can have the reverse effect on specific areas of the scalp, causing individual scalp terminal hair follicles to gradually regress to vellus follicles, resulting in androgenetic alopecia or male pattern balding.[19] That scalp hair follicles respond in a different way to the same circulating levels of androgens illustrates that they are individual organs with different levels of expression of the androgen receptor[26] and 5α-reductase activity.[27]

In contrast, regulation of the human hair cycle by oestrogens appears more complex.[28] Oestrogens significantly inhibit hair growth in several mammalian species, but in women elevated levels during pregnancy lead to thicker hair due to a longer anagen phase, by delaying their transition into telogen and exogen.[29] Postpartum this anagen longevity ceases and the hair follicles that were affected by an extended anagen phase enter telogen. Excessive shedding of hairs termed postpartum effluvium is often reported,[28] but this is predominately due to these additional hairs that were maintained in anagen during pregnancy re-synchronising and entering telogen.

The next dramatic change in oestrogen levels during a woman’s lifetime arises at the menopause. The menopause is an example of programmed reproductive aging, which occurs in women around the age of 50 years and is due to a switch from full ovarian function to complete termination of oestrogen biosynthesis in the ovaries. Many changes occur throughout the body due to this rapid transition to hypoestrogenism, one of which is an accelerated age-related deterioration of the skin.[29,30]

With the menopause, many women perceive a rapid decline in skin function, including dryness, increased number and depth of wrinkles, and loss of firmness and elasticity. These are all well-documented hallmarks of skin aging associated with atrophy of the epidermis, dermis, and hypodermis and are most apparent on the face and other sun-exposed areas,[31] although these presumably also take place in the scalp.

A study by Töz et al[32] compared a group of age-matched pre-menopausal women undergoing hysterectomy with, or without, bilateral salpingo-oophorectomy. Following oophorectomy, there was a significant increase in aging skin features, while those without an oophorectomy had no significant changes. This study highlights the rapid aging of skin following oestrogen deprivation since extensive changes were observed as early as 24 weeks.[31]

Many of the effects of oestrogen on aging female skin have stemmed from the comparison of postmenopausal women with or without the administration of oestrogen replacement.[29] Oestrogen replacement can reverse these changes by increased epidermal hydration and keratinocyte volume leading to more defined rete ridges. In addition, the content and quality of collagen, and the level of vascularisation are improved, boosting skin thickness and elasticity and reducing skin wrinkles.

These well-documented changes will no doubt also occur in scalp skin leading to significant changes in the hair follicle environment impacting on the maintenance of the terminal hair follicles. However, the effects of hypoestrogenism on FPHL are less well understood. In women, a gradual diffuse thinning of scalp hair has already started by the age of 50, accompanied by alterations in the growth, diameter and pigmentation of the hair fibre,[33] suggesting
a strong correlation with the menopause. There is some tricho-
gram evidence to suggest that in the treatment of female pattern
hair loss, oestrogens can prolong anagen and delay telogen.\[34\]
However, using the human hair follicle in vitro assay, responses
to oestrogens show specific donor differences in terms of both
gender and site.\[28\]

Two intracellular oestrogen receptors, ERα and ERβ exist that
are activated by the biologically active oestrogen, 17β-oestradiol
and both have been identified in human skin and the hair folli-
cles.\[34,35\] Immunohistochemical studies have shown that in situ, ERβ
is strongly expressed in human scalp anagen hair follicles in contrast
to ERα; furthermore, there is no difference in expression between
non-balding hair follicles derived men or women.\[35\] In vitro studies
have confirmed that in cultured human dermal papilla, dermal sheath
and dermal fibroblasts derived from female scalp, expression of ERβ
transcripts is significantly higher than the expression of ERα trans-
scripts.\[36\] Another study using cells cultured from occipital scalp
has reported that transcriptional and translational activities of the
androgen receptor and ERβ were highest in dermal papilla cells, fol-
lowed by dermal sheath cells and dermal fibroblasts, while ERα was
strongest in dermal sheath cells.\[37\]

However, while the menopause signals the cessation of ovarian
function, which in women of reproductive age provides the main
source of 17β-oestradiol, humans and some primates are unique in
that the adrenal cortex secretes large quantities of a precursor
androgen, dehydroepiandrosterone sulphate (DHEA-S). Therefore,
in tissues that contain the relevant enzymes, peripheral oestrogen
biosynthesis provides the main source of active oestrogens in post-
menopausal women.\[38\] It has been well established that human skin
and hair follicles express the full enzymatic machinery to synthe-
size oestrogen from adrenal precursors and thereby regulate the
bioavailability of oestrogens at the local level.\[39\] A key enzyme in
the terminal conversion of androgens to oestrogens is aromatase.
Interestingly, anatomical and gender differences in its activity in
human scalp have been reported. A comparison of men and women
suffering from hair loss revealed that while expression of aromatase
was higher in female hair follicles; in both, there was a striking dif-
ference between frontal or occipital follicles, with occipital follicles
exhibiting much higher levels.\[40\] Further evidence that the local
conversion of oestrogens in the hair follicle is important comes
from the use of aromatase inhibitors, used to treat breast cancer in
postmenopausal women. A common treatment-related side effect
of endocrine therapy to inhibit oestrogen activity is scalp hair thin-
ing.\[41\] Furthermore, a link between the risk of female pattern hair
loss and a polymorphism of the gene encoding aromatase has also
been described.\[42\]

Substantial biosynthesis of oestrogens has been reported in iso-
lated human anagen hair roots from the frontal, occipital and tempo-
ral scalp of men and women.\[43\] This study reported that synthesis
of oestrogen was significantly lower in men than women under
the age of 50 years; however, in women over the age of 50 years
there was a significantly lower production of oestrogen compared
with women under 50 years. Surprisingly, in men over 50 years the
reverse occurred, whereby oestrogen synthesis in scalp hair roots
was increased and was significantly higher than in women over
50 years. Therefore, it is highly likely that oestrogen bioavailabil-
ity in the postmenopausal scalp hair follicle is dependent on a local
intracrine source, subject to as yet, poorly understood regulation.
While DHEA-S is the most abundant circulating steroid in post-
menopausal women, this too declines with age, reduced to as little
10–20% of maximum concentrations in the elderly.\[38\] Therefore, it
follows that peripheral oestrogen biosynthesis will also significantly
reduce with age.

In addition to ERα and ERβ, oestrogens can also signal via
non-conventional pathways, including non-genomic, ligand-inde-
pendent or receptor independent mechanisms,\[44\] which in turn may
have independent, synergistic or opposing actions. Cell-specific
co-factors also have modulatory activity and ligands that display
oestrogenic activity in some cells paradoxically exhibit oestrogen
antagonism in others.\[30\] Oestrogens have been demonstrated to
have cytoprotective effects in a number of cells and tissues, al-
though their precise mechanism of action is unclear. Dermal fibro-
blasts derived from individuals with Friedreich's ataxia are extremely
sensitive to free radical damage and oxidative stress. However, while
oestrogens can protect against oxidative stress, the mechanism
seems to be independent of oestrogen receptors.\[45\] The antioxidant
properties of oestrogen appear to be due to the presence of the phe-
nolic A-ring that diminishes reactive oxygen species (ROS) using a
cyclic phenol-quinol mechanism.\[46\] Therefore, while oestrogen has
positive effects on the female human hair follicle, its mechanism of
action appears to be multifaceted due to the existence of diverse
and complex signalling pathways.

3 | HOW DOES AGING SKIN IMPACT THE
HAIR FOLLICLE ENVIRONMENT?

Structural and functional alterations in aging human skin are accel-
erated by extrinsic factors, of which the most well described is UV
induced photoaging.\[47\] The effect of photoaging on the structure
and function of the epidermis and dermis has best been described in
comparisons of non-sun-exposed and sun-exposed skin, for exam-
ple face.\[48\] We have recently described that in women aged 19 to 81
years, similar structural changes take place in scalp skin, including
loss of rete ridges, disorganisation of collagen and increased solar
elastosis.\[49\] The generation of solar elastosis in aging scalp skin will
have a detrimental effect on scalp dermis, which by association will
impact the hair follicles that reside there. Collagen crosslinking also
increases with age, resulting in tissue stiffening and changes in the
ECM biomechanical properties\[50\] which may impact remodelling
of the hair follicle during early anagen as it moves downwards in the
dermis.

Another hallmark associated with dermal aging is inflamma-
tory,\[51\] leading to elevated levels of pro-inflammatory cytokines,
proteolytic enzymes, and ROS, which increases oxidative stress and
damage to DNA, proteins and lipids in the hair follicle environment.
With time, the amount of ROS produced exceeds the antioxidant defence threshold and initiates matrix metalloproteinases (MMPs) to break down collagen.\(^{[52]}\)

### 3.1 The dermal hair follicle environment

The DFs are responsible for synthesising ECM giving the skin its structure and integrity.\(^{[53]}\) Major alterations in aged human skin are localized to the dermal ECM. Atomic force microscopy illustrates dermal collagen fibrils in young dermis are organized, intact, abundant and tightly packed, while in aged skin they are disorganized and fragmented, with abnormal elastin.\(^{[54]}\) Young adult skin has a ratio of 80% collagen I and 15% collagen III; however, with age this shifts increasing the percentage of collagen III to collagen I.\(^{[55]}\) The wrinkles that appear with age result from ECM atrophy, lower levels of collagen IV and VII and fewer DFs with a reduced ability to synthesize ECM components.\(^{[18]}\)

In the dermis, the two major subtypes of DFs are the upper papillary DFs and the lower reticular DFs. Murine skin lineage tracing has shown that they are derived from two different lineages; one gives rise to the papillary dermis and the DP while the second leads to the development of the reticular dermis and the hypodermis.\(^{[56]}\) The origin of the different mesenchymal cells in human scalp and how they are impacted by aging still needs to be elucidated.

An additional fibroblast population has recently been described in human skin, termed the inflammatory-associated fibroblast.\(^{[57]}\) Even in photo-protected skin, aging DFs lose their priming ability, with reduced proliferation and loss of their functional identity. Papillary populations become more reticular, while reticular populations also lose their identity. These inflammatory-associated fibroblasts in aged skin have increased expression of pro-inflammatory genes and a reduced ability for cell interaction. Reduced interaction with epidermal basal keratinocytes may explain the loss of rete ridges and reduced epidermal thickness associated with aging skin. Whether similar changes take place in hair follicle fibroblasts is unknown, but pro-inflammatory changes and reduced cell-cell interactions would also drive age-related structural and functional changes in the hair follicle. Inflammatory associated fibroblasts also display a senescence-associated secretory phenotype (SASP), with a distinct secretory profile associated with cellular senescence. The senescent fibroblast induces an irreversible arrest of proliferation, though the cell continues to be metabolically active releasing skin aging-associated secreted proteins\(^{[57]}\) that may have detrimental effects on neighbouring cells.\(^{[58]}\) A marker of senescence is P16 ink4a, which is up-regulated in male DP cells cultured from balding follicles. This is consistent with balding cells having a slower growth rate and correlates with balding DP cells undergoing premature senescence.\(^{[59]}\)

Aging is accompanied by increased mitochondrial dysfunction, associated with DNA damage and ROS generation.\(^{[60]}\) The presence of senescent cells in aging skin leads to increased ROS resulting in a decrease of the mitochondrial complex 2 of the electron transfer chain.\(^{[61]}\) Skin aging is mosaic, especially in terms of senescence, as the cells are not synchronized, entering senescence at different times dependent on their history and environmental conditions.\(^{[58]}\) ROS increases the expression of the secreted extracellular matrix-associated protein cysteine-rich protein 61 (CCN1), which is elevated in aged human skin. Raised expression of CCN1 in aged DFs inhibits the synthesis of type I and type III collagen, simultaneously increasing collagen degradation and fibril fragmentation by up-regulating MMP-1.\(^{[62]}\) A hallmark of skin aging is cleavage of collagen by MMPs that is not completely reconstituted by de novo collagen synthesis. Enhanced expression of MMP-1 along with decreased expression of its endogenous inhibitor tissue inhibitors of metalloproteinases type 1 (TIMP-1) is the main cause for the degeneration of the ECM in extrinsically aged skin.\(^{[63]}\) We have recently reported increased expression of mRNA MMP1 in DFs from aging female scalp.\(^{[69]}\) Furthermore, in cultured scalp DFs and hair follicle DS cells, we also saw an age-related increase in MMP-2 and MMP-3 protein expression, which also suggests increased collagen degradation.\(^{[49]}\)

Evidence supporting the role of the hair follicle dermal environment in hair follicle dermal environment comes from mouse transplant studies. Young and aged murine follicles transplanted into young host nude mice both started to establish blood vessel connections by week 2 and exhibited an increase in hair shaft growth by week 4, suggesting the young host dermal environment rejuvenated the aged follicles through efficient angiogenesis. However, when young and aged follicles were implanted in aged nude mice, neither regrew hair shafts.\(^{[64]}\)

Another mouse model has recently identified how mitochondrial dysfunction leads to skin wrinkling and hair loss.\(^{[65]}\) This study showed that transgene activation of mitochondrial DNA-depleted mice demonstrated hair loss and development of wrinkles in just four weeks. However, if mice were returned to a wild-type state, they regained their hair and lost their wrinkles.\(^{[65]}\) This study suggests that restoring mitochondrial function could provide an aging hair and skin therapy.

### 4 THE IMPACT OF THE HYPODERMIS ON THE AGING HAIR FOLLICLE

In aging human skin, there is a reduction in the thickness of the subcutaneous white adipose tissue (sWAT), due in part to a reduction in cell number, and the proliferative and differentiative capacities of the preadipocytes. A reduction in the thickness of sWAT is considered to be a typical hallmark of facial aging.\(^{[66]}\) The composition of sWAT also displays sexual dimorphism and exhibits significant variation between different ethnic groups, which may explain the gender and ethnic differences observed in skin aging.

In addition, the structure and mechanical properties of sWAT are influenced by inflammation. A recent study has suggested that in psoriasis the structure of the sWAT located underneath the lesional skin has an important role in its pathophysiology since it has
mechanical properties that are significantly different from that seen in non-lesional skin.\[^{67}\]

In contrast, dermal white adipose tissue (dWAT) is a fat depot containing adipocytes with phenotypical properties that differ from those located in sWAT. These properties include rapid reaction times and the capacity for trans-differentiation, which may explain their involvement in diverse physiological and pathological processes including wound healing, thermoregulation, skin aging and hair growth.\[^{68}\]

In scalp skin, the bulb of the terminal anagen hair follicle normally sits within the adipose rich dWAT of the hypodermis. In murine skin, this layer of dWAT is separated from the underlying sWAT by the panniculus carnosus, while in human skin it is arranged as "dermal cones" protruding up into the dermis connecting it with the underlying sWAT.\[^{69}\]

In terms of hair growth, the regeneration of murine dWAT has been shown to be synchronized to the hair cycle.\[^{69}\] Furthermore, functional analysis of adipocyte lineage cells in murine models with defects in adipogenesis demonstrated that intradermal adipocytes are required to activate hair follicle stem cells. Between telogen and anagen immature adipocyte, precursor cells become activated, increasing the size of the dermal adipose tissue resulting in the production of adipocytes that surround the anagen follicle, and then, with catagen the adipose tissue begins to decline.\[^{70,71}\]

There is also a significant correlation with the amount of dWAT in intrinsically and extrinsically aged skin. Several knock-out mouse models with accelerated aging phenotypes have significantly reduced dWAT layers.\[^{72}\] In mice subjected to chronic photo-damage, their skin is also characterized by a reduction in the volume of dWAT, where adipocytes have been replaced by fibrotic structures. Cell fate mapping studies in mice have confirmed that dermal fibrosis is concomitant with the recruitment of adipocyte-derived mesenchymal cells, accounting for the preponderance of myofibroblasts in dermal lesions.\[^{72}\] This process has been coined as "adipocyte-myofibroblast transition" or AMT. Interestingly, in murine skin, dWAT also demonstrates significant sexual dimorphism with dermal fibrosis more pronounced in the male.\[^{73}\]

Whether there are associated changes in the volume of dWAT with the asynchronous cycling of human scalp hair follicles is unknown, and it is possible each is surrounded by its own associated dWAT cone. However, the importance of adipocytes in hair growth has been highlighted by a recent report demonstrating that injection of autologous adipose-derived stromal vascular cells appears to be highly effective for the treatment of alopecia areata by increasing both hair density and diameter.\[^{74}\]

While quantitative changes in the volume and composition of dWAT in aging scalp skin have not been documented, our recent histological observations show structural changes revealing that the anagen follicle bulbs reside above the adipose and are no longer surrounded by the dWAT cones in aged scalp, suggesting a loss of contact (see Figure 2).\[^{75}\] Whether this age-related phenomenon of scalp skin drives hair aging has yet to be established.

5 | AGING SCALP SKIN

There are few studies that have investigated structural and functional changes occurring in the epidermis, dermis and hypodermis of human scalp skin with age. While terminal hair follicles will offer some protection against photoaging, similar detrimental changes are likely to occur in the dermis of the scalp comparable to that seen in the rest of the skin with age. A study in 1972 by Horii et al compared changes in male and female scalp with age. The dermis of female scalp was thicker, reaching maximum thickness at 35 years, before declining up to the age of 70 and rising again at 85. In males, maximum dermal thickness was reached at 55 years before declining up to 80 years. Total scalp thickness varied with sex and age, while epidermal thickness varied with age, but not gender. The hypodermis contributed to 50% of the scalp total thickness and was thicker in female scalp.\[^{76}\]

More recently, an immunohistochemical study compared pariatel scalp biopsies from 300 women and 350 men, divided into three age groups of 20–35, 50–60 and 60–70 years, and evaluated differences with regard to aging, gender and alopecia,\[^{77}\] although they did not compare the hair follicles. They observed a decrease in microvasculature (blood vessels, not lymphatics) with age, and in women a significant reduction in versican expression in the interfollicular dermis with age. Versican, together with decorin, account for the most abundant proteoglycans in postnatal human skin.\[^{77}\] Versican can co-localize with elastic fibres,\[^{78}\] but also binds with hyaluronic acid (HA) and is associated with skin viscoelasticity and hydration.\[^{79}\] Reduced scalp expression would lead to skin dryness and decreased elasticity due to inability to bind HA, resulting in a dry and rigid environment for resident hair follicles.

Changes in versican expression occur in the hair cycle; it is expressed in the DP of human anagen follicles, but is absent/low during telogen.\[^{80}\] Furthermore, DP versican expression is lost in the miniaaturized hair follicles of androgenetic alopecia.\[^{80}\] Whether an associated reduction in versican expression in female hair follicles with age or FPHL occurs has yet to be confirmed. Since versican appears to have a role in induction and maintenance of anagen hair follicles,\[^{77}\] decreased DP expression may lead to impaired hair follicle maintenance.

The study by Piérard-Franchimont\[^{76}\] evaluating interfollicular scalp skin with regard to aging, gender and alopecia also reported a higher expression of podoplanin, a marker for lymphatic vasculature and papillary DFs, in interfollicular female scalp compared with male scalp. They also observed that scalp lymphatic vasculature was significantly developed in older women, while young men with alopecia had enlarged lymphatic vessels that may be indicative of poor lymphatic drainage.

6 | THE RELATIONSHIP BETWEEN SCALP DERMAL AGING AND HAIR FOLLICLE AGING

Age-related structural and functional changes observed in human skin are likely to be paralleled in sun-exposed scalp skin, despite
Figure 2: Predicted changes within the aging scalp hair follicle environment. Annotated Herovici's stain of female scalp age 20 y vs 54 y annotated with predicted changes within the aging scalp hair follicle environment. Female aging is associated with changes in the organisation of collagen and deposition of elastin. Aging skin is also characterized by an increase in ROS. Increased levels of ROS induce chronic low-grade inflammation in the dermis and in scalp skin this may induce evacuation of DS cells from the follicle to help preserve the surrounding dermis. Aging will also lead to a reduction in number and size of sebaceous glands, and reduced production of sebum. There will be a diminished blood supply to the hair follicle which may impact on its size. Aging skin is characterized by a decrease in the hypodermis due to the differentiation of adipocytes to myofibroblasts leading to a fibrotic dermis which will impede the remodelling of the hair follicle during anagen and hinder its downgrowth into the hypodermis. This inhospitable environment may significantly contribute to an aging hair follicle phenotype with a reduction in the size of the dermal papilla size, ultimately leading to production of a thinner hair fibre.
the protection offered by the covering of terminal hair follicles. Structural changes, including thinning of the epidermis, flattening of the epidermal-dermal basement membrane and accompanying loss of the rete ridges, in addition to changes in the composition and architecture of the papillary and reticular dermis, will all impact on the integrity of the skin and the structural environment that the terminal hair follicles reside in. In particular, solar elastosis is reported to be a principal perpetrator leading to tissue stiffness and dysregulation of biomechanical skin function. Having a physically altered dermal environment that is much stiffer will ultimately impact on the ability of the hair follicle to move up and down during the remodelling phase with each hair cycle. This may result in new anagen hair follicles unable to penetrate as deeply in the dermis, impeding their growth, causing them to sit higher in the dermis, and subsequently becoming smaller with each cycle. It is also likely that age-associated changes in dWAT such as decreased thickness and increased AMT will also contribute to this phenomenon.

In addition to structural changes within the scalp dermal environment, a significant number of age-related biochemical changes also occur. A transcriptomic analysis of DFs derived from sun protected, inguinal iliac skin of young and old male Caucasians reported that expression profiles of DF subgroups undergo an age-related loss of functional and spatial identities. Chronic low-grade inflammation is a feature of aging skin and the study by Sole-Boldeo et al. found the most up-regulated genes in older fibroblasts are those involved with the immune response. An increase in the prevalence of inflammatory-associated fibroblasts in aging scalp skin with increased expression of pro-inflammatory genes and SASP will have a detrimental effect on the anagen hair follicle.

Single-cell RNA sequencing has shown that aged DFs experience a substantial decrease in their interactions with other skin cell types. This study used inguinal iliac skin and whether parallel changes take place in scalp and the follicular DP and DS cells has yet to be established. However, reduced interaction with undifferentiated bulb matrix keratinocytes will undoubtedly impact on maintenance of the anagen hair follicle. Since DS cells migrate into the dermis during wound healing, chronic unresolved inflammation associated with dermal scalp aging may induce evacuation of follicular DS cells into the surrounding dermal environment, leaving the hair follicle with an aged phenotype.

It is important to remember that hair aging is highly variable in terms of ethnicity, lifestyle, genetic predisposition and graphical location, which all impact on the hair type (e.g., diameter, density, colour, tensile strength and curl). These contributing factors means there are different starting parameters for each individual before hormonal changes and aging take their toll.

Some individuals experience early onset greying and some women experience hair thinning/loss earlier than others, again this could be a result of environmental or genetic factors. Even the hair care regime could be accelerating the hair aging process. Infrequent washing, repeated sun exposure, pollution and ozone exposure can increase oxidative stress in scalp skin due oxidation of lipids and squalene in the sebum. Sebum encompasses squalene, triglycerides, wax and cholesterol esters, and the products of fatty acid breakdown and coats the hair fibre and surface of the skin. These lipids play an essential role in the normal functioning of the skin barrier, but they are also vulnerable to external stressors since pollution and UV can cause peroxidation of lipids and squalene. Increased exposure to ground ozone increases lipid peroxidation and protein oxidation, depleting antioxidants in the stratum corneum. These lipids can become oxidized by pollution ozone and UV, causing oxidative stress and inflammation in the scalp. How this impacts on the hair follicle is unclear, but squalene monohydroperoxide (peroxidized squalene) induces hyperproliferation and inflammation in a keratinocyte cell line and co-localizes with the oxidative stress marker malondialdehyde in scalp prone to dandruff. In scalp skin of patients with alopecia areata lipid peroxidation is increased. This may be significant for the hair follicle, as murine studies found lipid peroxidation induced apoptosis in hair follicle cells resulting in early onset catagen.

There is still much to learn about scalp aging, and whether similar pro-inflammatory changes and reduced cell-cell interactions seen in non-haired skin also provide a hostile environment in scalp skin driving age-related structural and functional changes in the hair follicle remains to be fully elucidated. We hypothesize that the hair follicle environment is likely to have a significant impact on the homeostasis of the scalp anagen hair follicle and play an extensive role in hair aging, particularly in women.

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CONFLICT OF INTEREST
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