New Insight Into the Pathophysiology of Hair Loss Trigger a Paradigm Shift in the Treatment Approach

Neil S. Sadick MD,[a] Valerie D. Callender MD,[b] Leon H. Kircik MD,[c,d,e,f,g] Sophia Kogan MD[h]

[a]Cornell University, New York, NY
[b]Howard University, Washington, DC
[c]Icahn School of Medicine at Mount Sinai, NY;
[d]Indiana School of Medicine, Indianapolis, IN;
[e]Physicians Skin Care, PLLC, Louisville, KY;
[f]DermResearch, PLLC, Louisville, KY;
[g]Skin Sciences, PLLC, Louisville, KY
[h]Nutraceutical Wellness Inc, New York, NY

ABSTRACT

Hair loss affects millions of men and women of all ages and ethnicities, impacting appearance, social interactions, and psycho-emotional well-being. Although a number of options are available, they are limited, carry a potential risk of side effects, and none have proven to be comprehensive for treatment of hair loss. Across the spectrum of hair loss disorders, there has long been a segmentation into distinct mechanisms, driving the main trend in current therapeutics to focus on targeting single molecules or pathways. However, research points to similar dysregulation of intrinsic signaling pathways within follicle physiology that span the hair loss disorder spectrum – with a common inflammatory component identified in most hair loss pathogenesis, including that of androgenetic alopecia (AGA).

J Drugs Dermatol. 2017;16(11 Suppl):s135-140.

INTRODUCTION

Androgens, genetic susceptibility, chronic inflammation, oxidative stress, internal and external environmental triggers such as ultraviolet light, pollutants, aging, poor nutrition, as well as mediators of psycho-emotional stress (eg, cortisol and corticotropin releasing hormone) all contribute to dysregulation of complex follicle biology. Disruption of immune pathways affecting the follicle occurs through increased expression of pro-apoptotic and pro-inflammatory cytokines, perifollicular micro-inflammation, and release of reactive oxygen species (ROS). As we accept the multi-factorial nature driving hair loss, we can adopt new strategies to combat it, by aiming not at one, but at multiple targets. The rationale for this paradigm shift in hair loss therapy is the scope of this article. Herein is an update on our current understanding of hair physiology and the factors that have been scientifically demonstrated to influence hair follicle homeostasis and contribute to hair loss pathology.

Hair loss is chronic and progressive without treatment, affecting at least 50% of women by age 50 and 40% of men by age 35 (progressing to up to 70% in later life).[1-3] Hair is an important part of our appearance and social communication. It is therefore no surprise that its loss can cause significant psychological trauma in patients, which is further precipitated by the limited available treatment options that produce only variable results with chance for side effects.[2,4] Currently the only two FDA-approved drugs for hair loss are finasteride and minoxidil in men and only minoxidil in women.[5,6] The reason for lack of sustained, comprehensive, efficacious, and side effect-free therapies to date, may be the underappreciation of the impact and interplay of the multiple factors that influence the immunology and signaling pathways that regulate hair follicle biology.

As dermatologists we've traditionally segmented hair loss according to distinct causes and morphology, inflammatory vs. non-inflammatory, genetic vs. acquired, scarring vs. non-scarring, androgen-mediated vs. not.[7,8] This view has led to the design and development of drugs that target only single mechanisms, as exemplified by finasteride that inhibits production of dihydrotestosterone (DHT). However, recent research suggests that hair loss is multi-factorial and there may be more similarities than differences across the hair loss disorder spectrum. There is mounting evidence that just like most multigenic, chronic systemic and cutaneous disorders, hair loss is the result of an accumulation of multiple factors – genetic and environmental – that lead to the final molecular pathophysiology resulting in dysregulation of signaling pathways and inappropriate immune and inflammatory responses.[5,7-10] Chronic inflammation at the level of the follicle appears to be a common thread in all types of hair loss – a view supported by the wealth of research showing that even in traditionally 'non-inflammatory alopecias' like

androgenetic alopecia (AGA) there is a prominent micro-inflammatory and fibrotic component.[9,11] The observation that there are a plethora of mechanisms beyond androgens that contribute to hair loss lead many researchers to explore the role of inflammation and fibrosis in miniaturization of follicles,[12,13] and to identify their part in the pathogenesis of, and impediment to successful treatment of hair loss.[5]

Follicle immunology has thus become a topic of much hair research today as it is increasingly apparent that multiple immune driven pathways are involved in normal physiology of the follicle, as well as in the pathophysiology of hair loss when disrupted. Within the intrinsic follicular environment, multiple cytokines, growth and transcription factors signal the follicle to go into anagen vs. catagen phase and play a role in regeneration and renewal. In the event of micro-inflammation, overproduced cytokines like IL-1 and TNF-a are known to induce premature catagen, liberate ROS, cause apoptosis, and further propagate inflammation.[5,9] Likewise, factors like TGF-b are prominently overproduced by the dermal papilla cells in the presence of androgens and signal growth arrest, as well as play a role in perifollicular fibrosis and miniaturization.[14] These alterations in cytokine and protein expression – although not immediately destructive, over time chronically dysregulate physiological cycling dynamics and follicle stem cell homeostasis.[3,5,9,15-17] To this end, any therapy designed to comprehensively treat hair loss must address not only triggering factors but also their downstream signaling cascades, as well as mitigate inflammation.

Factors such as ultraviolet light, pollutants, toxins, stress, aging, smoking, antigenic exposure to bacteria, and fungi also generate ROS and promote a state of inflammation and oxidative stress in the follicle environment – contributing to hair loss.[18,19] Recent research has additionally elucidated the molecular mechanisms underlying the role of psycho-emotional stress in causing and exacerbating hair loss. Sustained and chronic stress can lead to perifollicular inflammation and disruption of follicle physiology via endocrine and neuroimmune mediators like corticotropin releasing hormone (CRH), cortisol, and substance P (SP), all of which have receptors on the follicle.[20,21,22]

As scientific research reveals more about hair follicle biology, we are compelled to look at the common thread within all hair disorders – the complex dysregulation of immune, inflammatory, and signaling cascades that regulate follicle homeostasis. Hence, any therapeutic that targets singular triggers such as androgens, without considering the pleiotropic downstream effects as well as the interplay of various signaling molecules, is destined to be incomplete. Further, the pathogenesis of hair loss is multi-factorial and requires a multimodal solution that can additionally address factors like stress, aging, environment and inflammation. In consequence, an updated look on hair loss therapeutics emerges, one that does not focus on singular targets (monotargeting), but comprehensively addresses the multiple factors that affect the follicle, the downstream deregulated follicle immunology and signaling, as well as inflammation. A thorough look at hair physiology and the triggers that deregulate it follows below, supporting the need for a paradigm shift in hair loss treatment towards multi-targeting therapeutic strategies.

The Regulation and Dysregulation of Hair Follicle Physiology – Consequences of Inflammation and Oxidative Stress

All phases of the hair cycle are subject to intrinsic controls that induce either anagen (growth) or catagen (regression and apoptosis), followed by telogen (rest), ensuring that under normal conditions shedding is followed by new growth. As hair loss is ultimately the result of premature entry into the catagen phase, identifying which signals control this is vital for considering therapeutics.[23] Growth in anagen is initiated by the dermal papilla cells (DPCs) which determine follicle and hair fiber characteristics, secrete mediators that regulate stem cells and influence growth of other follicular compartments.[24] Although the intricate machinery of the follicle hasn't been fully elucidated, a key signaling pathway regulating hair morphogenesis in anagen was identified to be the WNT pathway that mediates expression of a plethora of anagen-stimulating factors like IGF-1, bFGF, VEGF.[25-28] Conversely, catagen is believed to occur as a result of both decreases in expression of anagen-maintaining factors, as well as increase in expression of pro-apoptotic cytokines like TGF-b, IL-1, TNF-a.[29] Other controls intrinsically built into the follicle include its stem cell reservoirs and the hair follicle immune privilege (IP). The follicle being one of few sites in the body with IP, stresses the evolutionary importance of having it equipped with mechanisms for preventing the induction of both innate and adaptive immune responses. [30] The intrinsic mechanisms of the follicle are further subject to and integrated with signals from the macro-environment (eg, hormones, neurotransmitters) through endocrine, paracrine, and autocrine routes. As an example, androgens exert their effects via the DPCs, altering local immune balance by inducing DPC over-expression of catagen-promoting factors like TGF-b and other paracrine mediators that inhibit growth.[14,31,32] Aside from androgens, hair follicles express receptors for estrogens, cortisol, retinoids, insulin, thyroid hormones, vitamin D, and many other known and unknown factors – the full influence of which is still being investigated, but points to the fact that these affect intrinsic signaling pathways and that a balance of all is what ultimately determines hair growth.[14,31,32] Further, both follicles and other cells in the vicinity (eg, adipocytes, keratinocytes, fibroblasts, immune cells) also respond to systemic and environmental stimuli, generating mediators that shift local signaling, release ROS, and alter cycle control and growth.[5,8,33] In hair loss, whether it is sudden (anagen or telogen effluvium) where alteration in the cycles of numerous follicles happens concurrently, creating sudden diffuse shedding, or asynchronous and

gradual as with male pattern hair loss (MPHL)/female pattern hair loss (FPHL) where the duration of anagen is progressively shortened, while dormancy is increased - the compromise of intrinsic cycle controls and dysregulation of local follicle immune balance is inevitable.[5,8]

The immune system and inflammation are the body's primary defenses against noxious stimuli, as well as key mechanisms in healing. However, whereas acute inflammation can stimulate healing and in the case of follicles even lead to anagen induction, non-specific and chronic inflammation is a prolonged dysregulated cascade that suspends the body's normal responses, causing progressive damage. The prevalence of an inflammatory component in hair loss is underscored by the fact that it's observed in both traditionally 'inflammatory' and 'non-inflammatory' alopecias. Numerous histochemical, ultrastructural, and immunohistochemical studies have demonstrated perifollicular micro-inflammation in MPHL and FPHL presenting as lymphocytic infiltrates, mast cell degranulation, fibroblast activation, and immunoglobulin (IGM) deposits.[3,6,11,13,15,16] The term "micro-inflammation" was coined to allude to the indolent sub-clinical process of dysregulated chronic inflammation rather than the classic inflammatory attack seen on pathology in alopecia areata (AA), lupus, etc.[9] The basis for this phenomenon and its role in the pathogenesis of hair loss has been the subject of much research. In the instance of chronic processes like MPHL and FPHL, the micro-inflammatory component is localized to the vicinity of the bulge stem cell niche. The inflammatory processes, the release of ROS, and inflammatory mediators (eg, TNF-a, IL-1, histamine) alter the follicle immune milieu – and although not immediately destructive to the follicle, can over time dysregulate normal cycling dynamics and stem cell renewal.[5,9,11] In fact, studies show that biopsies from areas of clinically uninvolved scalp with high density scores in subjects with early AGA already demonstrate the presence of inflammatory infiltrates and fibrosis, indicating that micro-inflammation is not a secondary phenomenon but an active participant in pathogenesis.[3,8,15,16] A recent study also found a correlation between inflammatory infiltrates and apoptosis in miniaturized follicles, suggesting that inflammation can play a role in the pathogenesis of follicle miniaturization via activation of the extrinsic apoptotic pathway.[34] Further, sustained inflammatory processes also contribute to progressive perifollicular fibrosis.[9]

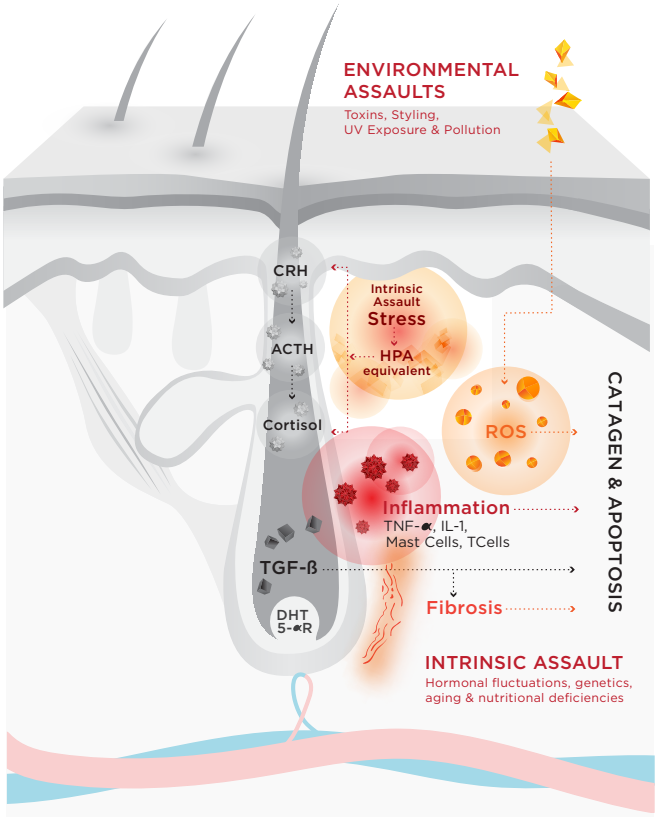
An important question is why the follicle becomes a target for an inflammatory reaction, whether it's micro-inflammation in AGA or an immune attack against self-antigens in AA. There are no definitive answers, but it is worth noting that inflammation is a multi-step process that may start from a primary event or a group of events, later perpetuated through a cyclic continuous cascade. In AGA for example, the localization of infiltrates to the upper follicle suggests the contribution of environmental factors in the inflammatory process. Colonization with normal microbial inhabitants or actual microbial toxins have been implicated.[8,9,11] Additionally keratinocytes have been shown to respond to irritants like UV irradiation, pollutants, and chemical or mechanical stresses by producing inflammatory cytokines and ROS.[5,9] Damage from free radicals triggers the release of inflammatory mediators, which thereby generate more ROS in a cyclic cascade. Oxidative stress overrides innate antioxidant defense mechanisms in aging cells and leads to apoptosis. In the case of the scalp, there is evidence it plays a pivotal role in hair greying and hair loss, where affected hair follicles were shown to be particularly vulnerable to ROS from environmental stressors.[23,35,36] Further, androgen signaling, TGF-b1, and mediators of stress have all been shown to be mediated via generation of ROS in the follicle – leading to growth arrest.[37,38] Aging hair exhibits up-regulation of oxidative stress and inflammatory response genes, predisposing follicles further.[35,36] And the compromise of regulatory mechanisms by psycho-emotional stress can also make follicles more susceptible to inflammatory attack, as in the case of AA.[8,20,22]

The presence and role of inflammation and oxidative stress cannot be ignored in the pathophysiology of hair loss and in the development of therapeutics. Adding anti-inflammatory therapies to treatment protocols of both AGA and trichotillomania with micro-inflammation lead to improved treatment outcomes.[11,39] Similarly, administration of anti-oxidants reversed the effects of oxidative stress on hair follicles in vitro and resulted in hair growth clinically.[37,38,40] This data supports the case for multi-targeted therapeutics for hair loss that can address the inflammatory and oxidative stress cascade, as well as the factors that precipitate it.

Consequences of Androgen Hormones

The fact that androgens influence hair growth has been known for ages. Androgen metabolism as well as androgen receptor (AR) levels and sensitivity are enhanced in balding scalp follicles in a spatial pattern in individuals with MPHL; and to a much lesser degree in FPHL, where the contribution of androgens is unclear, and stress, environment, and other hormones likely play a greater role.[34,41] Although the impact of androgens in the pathophysiology of hair disorders is the most elucidated of all hair loss triggers, ongoing research continuously reveals new molecular mechanisms behind androgen action. It is accepted now that the main target of androgens in hair follicles is the dermal papilla (DP), through which they induce secretion of autocrine and paracrine factors, dysregulating intrinsic signaling cascades that mediate hair growth.[17] Several factors induced from DP by androgens have been identified, with many more still to be discovered. It has been shown that androgens stimulate the DPCs to overproduce TGF-b, which is normally secreted to signal catagen and regression; and accordingly studies confirmed that androgen-induced TGF-b leads to catagen and suppression of follicular keratinocyte growth.[5,6,8,14,31] New research has

FIGURE 1. Multifactorial pathophysiology of hair loss.



identified that androgens also upregulate DPC production of WNT antagonist DKK-1, thus impairing hair follicle stem cell (HFSC) differentiation via dysregulation of WNT signaling, a pathway crucial for anagen entry.[17] Furthermore, once triggered, some other factors can maintain hair loss pathology without the presence of androgens, as seen in men castrated after puberty.[5,42] It is likely that the contribution of these downstream effectors to the dysregulation of follicle immune balance triggers a continuous cascade of immune and inflammatory processes that can progress even after androgens are removed. In fact, androgen-induced TGF-b was shown to induce oxidative stress in DPCs, as well as perifollicular fibrosis and inflammation via surrounding fibroblasts, thus playing a role in the chronic process of miniaturization.[38,43] Currently, pharmaceutical formulations only target one aspect of this signaling cascade – androgens. New insight into the mechanism however supports the use of multi-targeted therapeutics that can also target androgen receptors, gene expression, TGF-b, other downstream pro-apoptotic molecules, inflammatory cytokines, and oxidative stress.

Environmental vs. Genetic Triggers

Genetics play a role in all manifestations of hair loss and the genetic make-up of an individual can predispose them to any hair disorder (AGA, TE, AA).[8] AA clusters in families, and genetics also determine who will exhibit TE as a result of stress or another insult.[8] Although the genetics are far from being fully understood, it is now well accepted that, like most multifactorial chronic disorders with a variety of dysregulated signaling pathways, the mode of inheritance in hair loss is polygenic – dependent on multiple genes and interactions with the environment. In the case of FPHL and MPHL, although the androgen receptor was considered a main candidate gene in hair loss susceptibility, recent studies revealed several additional gene loci involving cell proliferation, perturbed neurological pathways, altered immune response, and WNT signaling – supporting androgen-independent mechanisms of predisposition, especially in FPHL.[5,44-46] The hair follicle is a conduit for intensive interactions with the internal and external environment. Although the effects of extrinsic and intrinsic factors are readily recognized in skin photoaging, their influence in hair loss is underappreciated.[47]

Large studies of identical twins with MPHL and FPHL showed that multiple non-genetic exogenous factors including smoking, absence of hat use, chronic stress, excessive alcohol consumption, and extreme exercise contributed significantly to the development and severity of hair loss.[10,48] Studies have shown that exposure to both extrinsic triggers (UV, pollutants, stress, tobacco, bacterial toxins, and antigens), as well as intrinsic factors (aging, poor nutrition) initiate perifollicular inflammatory signaling cascades that enhance pro-inflammatory gene expression and liberate ROS.[5,18,19,49] For example, exposure to UVR has been shown to trigger release of ROS and pro-inflammatory cytokines (eg, IL-1) in follicles and surrounding keratinocytes leading to apoptosis, cycle arrest, and injury of the putative site of follicular stem cells near the infundibulum.[5,9,49] It has been suggested that photoactivation of porphyrins from Propionibacterium spp. in the pilosebaceous duct can also contribute to oxidative tissue injury and follicular micro-inflammation.[9,50] Moreover, preclinical studies have illustrated that antioxidants provide photoprotection against oxidative damage.[1,35,47,51] While genetic predisposition is perhaps largely un-modifiable, genetic research has shown that epigenetic modification through environmental and endogenous factors can regulate gene expression, opening an opportunity to therapeutically intervene to rebalance the environment susceptible to hair loss by targeting inflammation, stress, and oxidative damage.[6]

Chronic Psycho-Emotional Stress (Cortisol and Other Stress Mediators)

Although clinical observations have provided anecdotal evidence into the brain-skin and brain-follicle axes, the molecular mechanisms underlying these connections have only recently been elucidated. Given the surrounding dense perifollicular meshwork of sensory nerve endings that are closely associated with mast cells and exhibit plasticity during chronic

stress, the follicles are a target of neuroimmunomodulatory and neuroinflammatory mediators like SP and nerve growth factor (NGF).[20,52-54] Studies have shown that psycho-emotional stress triggers systemic and local release of NGF (a catagen inducer) and SP from perifollicular nerve fibers, which leads to activation and degranulation of local mast cells that release a myriad of pro-inflammatory mediators like histamine and TNF-a – inducing neurogenic inflammation, release of ROS, early catagen, and hair growth arrest.[8,20,37,53-55] Moreover, SP was also found to up-regulate follicular expression of major histocompatibility complexes (MHC) that are normally down-regulated by hair follicles to maintain an immune privilege. Stress-mediated IP collapse renders the follicle open to activating inflammatory cascades and subsequent hair loss, a biologic imbalance that is implicated as the driving force in AA and scarring alopecias.[8,20,22]

As part of the neuroendocrine stress response, chronically elevated stress levels also lead to the production of excess systemic stress hormones, like cortisol, which are known to cause catagen, inhibit hair growth, and directly correlate with the development and exacerbation of hair loss disorders.[56,57] Furthermore, research has identified that the hair follicle is also uniquely equipped to produce its own stress hormones (ACTH, CRH, and cortisol) through an equivalent of the hypothalamic-pituitary-adrenal (HPA) axis, with established regulatory feedback loops.[21,22] At times of excess stress, systemic CRH binds to receptors on the follicle and stimulates the internal follicle hormone axis to produce ACTH, cortisol, and CRH locally - leading to further mast cell degranulation, inflammation, and apoptosis.[21,22]

Lending further evidence to the role of stress in dysregulation of follicle immune balance and perifollicular inflammation, a 2017 study of female medical students showed that prolonged life-stress exposure hampered hair growth, accompanied by significant fluctuations in TH1/TH2 cytokine balance compared to control group.[58] On a systemic level, chronically elevated cortisol levels (chronic stress) compromise the production and equilibrium of other hormones like TSH and thyroid hormones that are essential for proper hair follicle stem cell function and activation.[59] The sustained systemic endocrine disruption from elevated cortisol levels could provide further insight into poorly understood and complex processes like FPHL, and why these can be often precipitated by conditions that induce telogen effluvium. Stress is ubiquitous and the mechanisms through which the follicle is affected by it in one hair disorder apply to all hair disorders. Given the evidence above, managing and reducing stress levels, cortisol, SP, and the downstream mediators (inflammation, oxidative stress, destabilized mast cells, dysregulated immune signaling) should be a part of any hair loss treatment and prevention protocol. Since there are no pharmaceuticals that target stress, it would make sense to employ multi-targeting therapeutics with additional stress-adaptogenic properties.

CONCLUSION

The pathophysiology of hair loss is unequivocally multi-factorial and extremely complex, involving a plethora of factors and signaling pathways. Hormones, the brain-hair axis, and the environment-hair axis influence the hair follicle, chisel against its regulatory circuitry, and in the absence of strategies to counterbalance this attack, can ultimately override the hair follicle's internal controls. The result is a deleterious self-sustained inflammatory cascade as the new status quo (Figure 1). Restoring hair follicles to a state of homeostasis requires embracing a new outlook in terms of therapeutics. Current pharmaceutical interventions have limited success rate and possible side effects including sexual dysfunction and contact dermatitis. More importantly, these therapies focus on singular targets such as hair follicle testosterone metabolism, without considering the downstream effectors or the underlying pathophysiology of deregulated immune signaling and activated pro-inflammatory and pro-fibrotic cascades.

A paradigm shift in hair loss treatment is necessary, from monotargeting to multi-targeting therapeutic approaches that address not only androgens but also inflammation, oxidative stress, aging, elevated stress mediators like cortisol, their downstream signaling mediators, and also stimulate a nutrient-rich microenvironment in the hair follicle niche to promote repair and structural regeneration. Multi-targeted therapies such as platelet-rich plasma, low-level laser light and nutraceuticals are emerging and increasingly recognized for their efficacy as either standalone treatments or in combination with traditional hair loss protocols.[60-62] The common thread between these therapies is their multi-modal approach and focus on multiple signaling cascades, cytokines and growth factors that are altered in hair loss. In the next section we will review these novel therapy options, focusing on standardized nutraceuticals with their unique potential for synergistic, multi-targeted action of scientifically studied botanical phytochemicals.

DISCLOSURES

Dr. Sadick is the clinical investigator on the product. Dr. Kircik has received compensation from JDD for his editorial help. Dr. Callendar has no conflicts.

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AUTHOR CORRESPONDENCE

Sophia Kogan MD
E-mail:..... sophia@nutrafol.com