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The Inflammatory Aspect of Male and Female Pattern Hair Loss

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Abstract: Male and female pattern hair loss (MPHL and FPHL, respectively), is the most common cause of hair loss affecting nearly 80 million people in the US, yet treatment options remain limited and lacking. As the need for more effective therapeutics remains unmet, this perspective offers a unique angle by directing attention to the inflammatory aspect of MPHL and FPHL. Evidence and implications of inflammation as a characteristic feature of MPHL and FPHL are highlighted through evaluation of clinical and quantitative data. Comparable results suggest the presence of significant perifollicular inflammatory infiltrates, such as lymphocytes and histiocytes, as well as the involvement of inflammatory genes, such as *CASP7* and *TNF*, in the presentation of MPHL and FPHL. Resurfacing of the inflammatory aspect in MPHL and FPHL pathogenesis will advance future developments in MPHL and FPHL therapeutic options.

Keywords: hair loss, inflammation, male pattern baldness, female pattern baldness

Introduction

Male and female pattern hair loss (termed MPHL and FPHL, respectively, in this paper), affects approximately 50 million men and 30 million women in the US.[1,2] There is a 50% risk of development of MPHL in men over 50, and approximately 40% of women develop FPHL by the age of 50.[3,4] As the most common cause of hair loss in men and women, MPHL and FPHL impact the individual's self-esteem, self-image, and quality of life.[5] The fundamental pathophysiological hallmark of MPHL and FPHL is non-scarring alopecia (hair loss), stemming from a variation in the hair cycle and hair follicle miniaturization, resulting in the subsequent reduction of hair of the scalp.[6] Traditionally, the hair follicle cycle is divided into three main stages: anagen (active hair growth), catagen (cessation of hair growth), and telogen (follicular rest).[7] In MPHL and FPHL, however, the anagen phase of this cycle is diminished with every cycle while the telogen phase remains unchanged or even extended, yielding diminished hair growth and follicle miniaturization.[8] Eventually, the progressive decrease in the anagen phase, and the premature transition of the anagen to catagen phase, leads to hair thinning and inadequate hair growth length for successful projection through the surface of the scalp, leaving an uninhabited follicular pore.[1,6,9]

To date, treatment options are restricted to topical minoxidil and oral finasteride, as the only treatments recognized by the Food and Drug Administration (FDA) for MPHL and FPHL.[10] Other therapeutic options also include low-level laser therapy and platelet-rich plasma therapy.[11,12] The effectiveness of these treatments is

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limited to partial hair regrowth and the need for more effective treatments remains essential.[5,13] Resurfacing the inflammatory aspects of MPHL and FPHL will allow for a comprehensive understanding of MPHL and FPHL, as well as pave the way for efficacious and novel therapeutic options.

Inflammation and Hair Loss

While hair cycle variation and follicular miniaturization are regarded as key features of MPHL and FPHL, it is important to also underline the inflammatory aspect of MPHL and FPHL. For example, chronic inflammation signified by the presence of lymphocytes and histiocytes, was found in approximately half the tissue specimens of the over 300 tissue specimens collected from 23 patients with MPHL.[14] Significant perivascular infiltration of mast cells was observed in about 40% of the tissue specimens, suggesting a relationship between inflammation and MPHL.[14] In a similar study, 36% of biopsy specimens taken from 106 MPHL patients exhibited moderate to severe inflammation with predominantly lymphocyte and histiocyte inflammatory infiltrates.[15] In a related study, biopsy specimens obtained from over 400 patients with MPHL and FPHL were used to evaluate the presence of perifollicular inflammation with results indicating that approximately 71% of the MPHL and FPHL specimen samples exhibited inflammation.[16]

Inflammatory infiltrates have been characterized and suggested in the pathogenesis of MPHL and FPHL as observed by an increase in lymphocytes.[17] Immunohistochemical analysis of biopsies obtained from 3 males and 1 female with progressive alopecia revealed follicular infiltration of CD4$^+$ T-cells at the bulge of the hair follicle while control specimen showed a sparse number of T cells.[17] This study concluded that infiltration of inflammatory T-cells at the follicular bulge may be the culprit of the impaired hair cycle and successive hair loss in MPHL and FPHL. Similar evaluation of the role of the inflammatory process in the onset of MPHL was conducted using biopsy specimens from 19 MPHL patients and compared to 6 control subjects.[18] Histopathology of the specimens revealed significant lymphocytic infiltrates in the MPHL patients in comparison to the control subjects. More recently, the role of inflammation in FPHL was studied using scalp biopsies from 52 women with female pattern hair loss.[19] Lymphocytic folliculitis was observed in the obtained biopsies, indicating the presence of inflammation and suggesting lymphocytic infiltrations as a histological feature of MPHL and FPHL.[18,19]

In addition to clinical and histological evidence, the role of inflammation in MPHL pathology has been highlighted using Next-Generation Sequencing.[20] RNA was isolated from tissue samples of 5 MPHL patients that were classified according to the phenotypic severity of their MPHL using the Hamilton–Norwood scale. The samples were evaluated against a panel of 30 inflammatory and apoptosis genes using targeted RNA-Seq, revealing differential expression of *WNT7A, CASP7*, and *TNF* genes.[20] The overexpression of *WNT7A*, a hair growth gene, was observed in the moderate phenotypes of MPHL, while lower expression was exhibited in the severe late-stage phenotype of MPHL, suggesting hair growth cycle suppression in late stages of MPHL.[20] Both *CASP7* and *TNF*, genes central to cellular apoptosis and inflammation, were overexpressed in the moderate degrees of MPHL, indicating involvement of these genes in the early stages of MPHL.[20]

Therapeutic management of the inflammatory aspect of MPHL has also been shown to be beneficial.[21] In this study, 20 MPHL subjects with hair loss and pruritus, an inflammatory itching of the scalp, were given lotions consisting of antimicrobial and antifungal agents including triclosan and piroctone olamine, to use regularly for a period of 18 months.[21,22] The pruritus cleared up during the course of the treatment.[21] Biopsies taken every 6 months during the course of the study revealed a decrease in activated T cells, suggesting targeting inflammation as a potential approach for treating MPHL.[21]

Conclusion

The inflammatory role in the pathogenesis of MPHL and FPHL is supported by clinical, histological, and sequencing findings. Perifollicular infiltration of inflammatory cells such as lymphocytes, histocytes, and mast cells is exhibited in biopsy samples of MPHL and FPHL patients. Significant follicular infiltration of CD4$^+$ T-cells has also been observed as a source for impairment of the hair cycle and the consequential hair loss in MPHL and FPHL. RNA sequencing data signifies differential expression of inflammatory genes in MPHL pathogenesis. Conclusively, these findings suggest inflammation is elemental to MPHL and FPHL pathology and reinforce the need to address inflammation in prospective therapeutic developments. As the inflammatory aspect presents a promising therapeutic approach for slowing down hair loss, targeting

inflammation may be used to further the efficacy of existing treatments.[21,23] Future directions should include targeting inflammation for enhancing MPHL and FPHL management.

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Disclosure

The authors report no conflicts of interest in this work.

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