Fibrosis and stem cell epithelial-mesenchymal transition in primary cicatricial alopecias

To the Editor: We read with great interest the article by Aguh et al,[1] who present gene expression profiling of scalp biopsy specimens in central centrifugal cicatricial alopecia (CCCA). We commend the authors for their comprehensive appraisal of the wider fibrosis literature and its relation to CCCA pathogenesis. Yet, physicians and researchers interested in this disease may find it useful to be reminded of relevant work "closer to home" that appears to have been overlooked.

Epithelial hair follicle (HF) stem cell loss, bulge immune privilege collapse, and type 1 helper T-cell–biased inflammation are key pathogenic processes in the prototypic lymphocytic scarring alopecia, lichen planopilaris (LPP),[2] which is another form of primary cicatricial alopecia (PCA) that shares many features with CCCA, such as progressive permanent alopecia, replacement of HFs with scar-like fibrosis, and variable degrees of follicular inflammation.

Microarray analysis using laser capture microdissection for targeted extraction of messenger RNA from HF bulge cells revealed increased mesenchymal gene expression signatures in LPP.[2,3] We showed that bulge epithelial stem cells indeed attain a fibroblastoid phenotype in lesional LPP HF histologically, ultrastructurally, and by immunohistology. Moreover, the epithelial marker E-cadherin was greatly reduced, whereas key mesenchymal markers (eg, vimentin, smooth muscle actin, fibronectin) and transcription factors (snail family transcriptional repressor 1 and snail family zinc finger 2) were upregulated in the bulge compartment.[3] This suggests that epithelial-mesenchymal transition (EMT) of bulge HF stem cells is a central process in driving fibrosis in LPP and likely in other lymphocytic PCAs such as CCCA.

Next, we were able to show that stimulation with an EMT-promoting "cocktail" (comprising transforming growth factor beta 1, interferon gamma, epidermal growth factor, and the E-cadherin antagonist peptide A) was sufficient to rapidly induce an EMT gene and protein expression signature in the bulge of healthy, organ-cultured scalp HFs, thus identifying 4 key drivers of EMT induction. Moreover, these experimentally induced EMT changes could be prevented by the peroxisome proliferator activated receptor gamma agonist pioglitazone, which is already used in the clinic for managing LPP, and a topically applicable modulator, *N*-acetyl guanidinoethyl disulfide.[3] Arguably, these observations invite plausible working hypotheses on how a fibrotic signature may be induced in CCCA and how fibrosis can be pharmacologically counteracted.

Aguh et al[1] also discuss the lack of inflammation observed in CCCA relative to the prominent fibrosis seen. Again, evidence from another inflammatory scarring disorder, discoid lupus erythematosus, identifies significantly increased numbers of forkhead box p3–positive regulatory T cells in areas of fibrosis.[4] This raises the intriguing possibility that the counter-regulatory processes that suppress ongoing inflammation via regulatory T-cell–mediated transforming growth factor beta signaling[4] simultaneously drive fibrosis by promoting EMT in CCCA and other lymphocytic PCAs and may explain the coincidence of rather discrete inflammation with major fibrosis seen in these conditions.

Examining LPP and frontal fibrosing alopecia as model stem cell diseases, we argue that these disorders have both common and divergent pathogenic processes that ultimately determine the final hair loss phenotype.[5] It is likely that CCCA pathogenesis also shows commonality with that of other PCAs, such as EMT. Therefore, future studies should focus on identifying shared and divergent pathogenic processes, ultimately facilitating a pathobiology-based diagnosis of individual PCAs while aiding the development of well-targeted therapeutic interventions for these distressing conditions.

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