Transcriptomic analysis identifies regulators of the Wnt signalling and hypoxia-inducible factor pathways as possible mediators of androgenetic alopecia

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While our understanding of the genetics of androgenetic alopecia has advanced rapidly,[1] the molecular mechanisms are still poorly understood. This in part is due to samples of androgenetic alopecia scalp not being easy to obtain. Individuals with hair loss are not always keen to have scalp biopsies taken, and hair transplant technology has advanced such that punch biopsies are rarely taken from the balding site. This lack of material makes carrying out detailed investigation complicated. Moreover, the major mechanistic research focus over many years has been on the role of androgens.[2]

In this issue of the *BJD*, Liu *et al.*[3] have carried out whole-transcriptome analysis of hair follicles from individuals with androgenetic alopecia. Among their observations was the upregulation of genes associated with inhibition of Wnt signalling. While the inhibition of Wnt signalling and especially the role of the Wnt antagonist SFRP1 (secreted frizzled-related protein 1) have previously been reported,[4] the data presented in this paper further strengthen the role for Wnt inhibition in androgenetic alopecia. However, in addition to SFRP1 the authors also show upregulation of another Wnt pathway inhibitor, pigmentary epithelium-derived factor (PEDF). Using *ex vivo* cultured human hair follicles they further showed that PEDF promotes anagen-to-catagen transition and that siRNA to PEDF delays spontaneous *ex vivo* catagen.

PEDF is a member of the serine protease inhibitor superfamily and is a multifunctional, cell-type-dependent, pleiotropic protein with antiangiogenic, antioxidant and anti-inflammatory properties, as well as being a potent inhibitor of cell senescence.[5] PEDF activity in hair follicles is also likely to be multifunctional and may well depend on the status of the hair follicle.

PEDF is a potent inhibitor of hypoxia-inducible factor (HIF)-1α, as are EGLN1 and EGLN3, which drive HIF-1α degradation and were also shown to be upregulated in this study. These are very elegant data as a major role for HIF-1α is to promote glucose metabolism via aerobic glycolysis.[6] This is important because the primary metabolic strategy for the hair follicle is to engage in aerobic glycolysis, which is the preferential metabolism of glucose to lactate despite the presence of oxygen. This contrasts with the predominantly mitochondrial respiration of many tissues.[7] A consequence of increased degradation of HIF-1α in the hair follicle would be a switch from aerobic glycolysis to increased reliance on mitochondrial respiration.

This switch to increased mitochondrial respiration could have adverse effects on the hair follicle. Dermal papilla fibroblasts from balding scalps have been shown *in vitro* to be highly susceptible to oxidative stress and to undergo premature senescence.[8] The dermal papilla is an important hair growth regulatory centre, and a switch by the hair follicle to predominantly mitochondrial respiration as a result of increased HIF-1α degradation may be responsible for an increase in the production of reactive oxygen species and subsequent impairment of hair growth. Finally, HIF-1α also regulates angiogenesis, and upregulation of EGLN1 and EGLN3, as well as PEDF, would be postulated to decrease hair follicle blood vessel formation, impacting again on hair follicle function and possibly being a driver for follicle miniaturization.[9]

This paper therefore adds exciting new data to the hypothesis that changes in hair follicle metabolism may be associated with androgenetic alopecia.

Michael Philpott

Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts & The London School of Medicine and Dentistry, Queen Mary College University of London, London, UK
Email: m.p.philpott@qmul.ac.uk

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