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Still waters run deep: latent cytokine activity in nonlesional psoriasis skin

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Conflicts of interest

None declared.

Despite looking superficially unremarkable, the clinically uninvolved skin of patients with chronic plaque psoriasis has been shown to have a number of distinctions when compared with the skin of healthy control volunteers. The Koebner response,[1] first described in 1876, as well as other studies on the *abnormesverhalten* or the abnormal behaviour of uninvolved skin,[2] began to establish these differences but their underlying mechanisms could only be the subject of conjecture. Reports from the 1980s, making use of newly available monoclonal antibodies, found increased numbers of $CD4^+$ and $CD8^+$ T cells in the

uninvolved skin of patients with guttate psoriasis,[3] which gave an immunological basis to these discussions. Over the last 15 years, transcriptomic studies using microarrays, and later RNA-seq, have revealed a striking pattern of differential gene expression between lesional psoriasis skin and clinically uninvolved skin.[4–7] However, fewer studies have focused on the differences between clinically uninvolved skin and the normal skin of unaffected control subjects. The first direct treatment of such[6] revealed that while clinically uninvolved skin and healthy skin transcriptomes appeared to cluster together, setting a threshold to count all genes at least 1.3-fold altered in expression (with false discovery rate corrected *P*-value < 0.05) identified 58 genes upregulated and 121 genes downregulated in uninvolved psoriatic skin. These 179 differentially expressed genes encoded proteins involved in epidermal differentiation, antimicrobial defences, lipid metabolism and regulation of cutaneous vasculature. These results identified a 'prepsoriatic' gene expression signature within uninvolved skin and pointed to decreased lipid biosynthesis and increased innate immunity in clinically uninvolved psoriatic skin. In this issue of the *BJD*, Tian and colleagues (A. Chiricozzi *et al*.[8]) show that uninvolved psoriasis skin, distant from lesions, displays the molecular signature of interleukin (IL)-17 activity, in that there is elevated expression of genes downstream of IL-17, suggesting that the increased levels of IL-17 circulating in the blood of patients with psoriasis impacts nonlesional skin. Expanding on this, the authors use gene set enrichment analysis (GSEA),[9] a powerful statistical tool to identify significantly enriched or underrepresented groups of genes within large datasets (e.g. cDNA microarrays, RNA-seq or proteomics datasets). In this instance, the authors show that within the transcriptome of nonlesional psoriasis skin hides the gene set upregulated in psoriasis lesions, as well as keratinocyte gene sets induced by the action of IL-17A, IL17A+TNF (tumour necrosis factor)-α and IL-17A+IL-22, key cytokines in the pathogenesis of psoriasis. Interestingly, GSEA also detected the presence of T-helper (Th) 1, Th17, Th22 and Th2 T-cell signatures in the nonlesional skin. This was likely a result of circulating cytokines acting on the uninvolved skin, but also could suggest the presence of resting resident memory T cells, particularly in resolved lesions;[10] alternatively this 'residual disease genomic profile' could be the 'molecular scar' remaining in formerly lesional skin.[11] Given these most recent observations and the development of multiomics studies harnessing transcriptomics, lipidomics, proteomics, epigenetics and genetics, we are approaching an era where we will be able to provide a full mechanistic rationale for the 'abnormal behaviour' of clinically uninvolved skin.

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