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Supporting Information

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Novel interactions among ultraviolet B, skin and adipose tissue

DOI: 10.1111/bjd.16149

Linked Article: Kim *et al.* Br J Dermatol 2018; **178**:492–501.

A fascinating and unexpected link between ultraviolet (UV)B and adipose tissue has been proposed by the pioneering original article of Kim *et al.*,[1] published in the current issue of the *BJD*. It is well established that adipose tissue is not a mere inert fat-storage facility, but is an endocrine organ secreting multiple mediators, named 'adipokines'; furthermore, these adipokines are able to contribute to systemic inflammation.[2] These mediators are represented by conventional adipokines, such as adiponectin, leptin, visfatin and chemerin. Moreover, there is also a wide array of adipocytokines and adipochemokines secreted not all exclusively by adipocytes. Indeed, adipose tissue also contains endothelial cells, fibroblasts, macrophages, myeloid cells and T cells,[3] which contribute to their production. Adipokines are able to orchestrate the interaction between metabolic and immune systems. The mediators released either by adipocytes or by other cells resident in the adipose tissue may have a significant role in several autoimmune skin diseases, acting on immune cells and keratinocytes.[4] Subcutaneous (SC) and visceral fat are different in composition, metabolism and functions. Some studies have shown that a decrease in SC fat as well as an increase in visceral fat resulted in an augmented risk for metabolic syndrome.[5,6] These events are interrelated because the age-related impairment of the lipid storage capability of SC fat promotes excess visceral fat, leading to an altered metabolic homeostasis.[5,6] As UVB cannot cross the dermis, SC fat had been considered to be relatively unaffected by UVB exposure. However, the recent concept of bidirectional cross-talk between skin and adipose tissue highlights the possibility of a dynamic interplay.[7] The authors have previously reported that UVB-irradiated skin modulated SC fat metabolism via the release of pro-inflammatory factors.[8,9] However, how these factors could influence SC fat activity still remained unclear. In their current paper, Kim *et al.*[1] have shown for the first time that adipocytes treated with UVB-irradiated keratinocytes and fibroblasts produce specific adipochemokines, including C–X–C chemokines such as ENA-78, and C–C chemokines such as MIP-3α and RANTES, which impair triglyceride synthesis via downregulation of lipogenic enzymes. Moreover, they have confirmed the results *in vivo* comparing sun-exposed skin with sun-protected skin, exploring also the ability of UVB irradiation to induce macrophage infiltration into adipose tissue. Overall, the data from the article by Kim *et al.*[1] suggest that the bridge between UVB irradiation and SC fat is represented by the skin with a crucial role played by fibroblasts and keratinocytes. This manuscript has demonstrated that UVB exerts pro-inflammatory effects on SC adipose tissue. These results may help to explain why phototherapy does not reduce the risk of cardiovascular events in patients with psoriasis, in contrast to benefits described for systemic therapies.[10]

Additional studies are needed to investigate UVB effects on visceral fat tissue, as the latter is mainly associated with a higher risk of cardiovascular events.

Conflicts of interest

None to declare.

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Supporting Information

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Concurrent hidradenitis suppurativa and Dowling–Degos disease taken down a 'Notch'

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Linked Article: Pavlovsky *et al. Br J Dermatol* 2018; **178**:502–508.

The concept of 'collision tumours' is a well-accepted occurrence in dermatopathology.[1] In such scenarios, two different tumours are juxtaposed. Most cases are considered to have collided by chance but some may be more than coincidental, involving similar cell lineages or particular combinations of disease entities.[2] In clinical dermatology, the simultaneous overlap of two dermatoses is perhaps less appreciated and also may be attributed to randomness. But when such double entities become repeated phenomena, as is the case for hidradenitis suppurativa (HS) and Dowling–Degos disease (DDD), the questions change to why and how might this be happening?

The co-occurrence of HS and DDD was first mentioned in 1990,[3] and several further reports have followed. In this issue of the *BJD*, Pavlovsky *et al.*[4] describe four more individuals with HS–DDD. This study was also able to identify a founder mutation in *PSENEN*, which encodes a component of the γ-secretase complex. Mutations in *PSENEN* have previously been found in some other reports of HS–DDD as well as a small number of cases of HS. But how does *PSENEN* gene pathology tie in with the double clinical pathology? The answer appears to lie in the consequences of altered γ-secretase complex functioning.

The γ-secretase complex is a key regulator of the canonical Notch signalling pathway. Notably, intramembrane cleavage of Notch by γ-secretase releases its major intracellular signalling domain.[5] Notch signalling has been implicated in differentiation of both interfollicular and follicular epithelium, the hair growth cycle, follicular cyst development, sebaceous gland differentiation and melanocyte homeostasis – a combination of downstream effects that begins to link the clinicopathological anomalies of both HS and DDD. To address the possibility of aberrant Notch, Pavlovsky *et al.*[4] designed a Notch reporter assay and in the keratinocytes of their patient with HS–DDD they were able to show a reduction in Notch signalling (and in other associated Notch effector genes) that provides some rationale for the clinical collision of HS and DDD.

Nonetheless, some issues remain unresolved. It is unclear why mutations in *PSENEN* can cause either HS–DDD or isolated HS or, as also reported here as an original observation, isolated DDD. The particular clinical features do not appear to be the result of specific mutations as precisely the same genetic variant can have diverse phenotypic consequences. Perhaps modifier genes, currently unknown, may have some influence. What we do know, thanks to this study, is that the clinical and tissue impact of the observed pathology in HS–DDD is likely to reflect the direct consequences of aberrant Notch signalling. These data provide new insights into this particular 'clinical collision' and potentially offer new opportunities for improving patient management in the future, both preventative and therapeutic.

Conflicts of interest

None to declare.

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Survival of the fittest

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Linked Article: Egeberg *et al. Br J Dermatol* 2018; **178**:509–519.

Drug survival or persistence studies are best explained as 'the period of time during which a given drug continues to be an adequate treatment for a specific patient',[1] and provide clinically relevant information regarding biological treatments in the real-world setting.[2]

Efficacy and/or adverse events can affect the success or failure of a biologic. A second-line biologic could bias data with