Editorial

A specific molecular signature for psoriasis and eczema

Susana Coimbra[1,2]*, Alice Santos-Silva[1]*

[1]UCIBIO/REQUIMTE, Departamento de Ciências Biológicas, Laboratório de Bioquímica, Faculdade de Farmácia, Universidade do Porto (FFUP), Porto, Portugal; [2]CESPU, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, GRD-Paredes, Portugal

*These authors contributed equally to the work.

Correspondence to: Susana Coimbra. UCIBIO/REQUIMTE, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto R. Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal. Email: ssn.coimbra@gmail.com.

Abstract: Psoriasis and eczema seem to present a specific distinctive gene expression pattern. In the *Science Translation Medicine* (*Sci Transl Med*), Quaranta *et al*. reported a specific molecular signature of psoriasis and eczema. By using an intraindividual genome expression analysis in patients affected by both diseases, the authors identified genes and signaling pathways that are regulated in common and that are exclusive for each disease.

Keywords: Psoriasis; eczema; gene expression; *NOS2* gene; *CCL27* gene; disease classifier

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Eczema and psoriasis are two of the most common inflammatory cutaneous pathologies, and, although, clinical distinct, they share some similarities. Indeed, erythematous plaques and scales are characteristic of both diseases. Psoriasis is characterized by well delineated dry, reddish and silvery-white scaly plaques, typically on the elbows, knees and scalp. On the other hand, highly pruritic, eczematous erythematous plaques with excoriated papules, crusts, and serous exudate, most commonly on flexural areas and face, are associated with atopic dermatitis. However, a subset of psoriasis patients may present lesions that look like eczema, and oppositely, a subset of eczema patients may reveal plaque-type psoriasis lesions (1). Thus, in some cases it is difficult to differentiate these two diseases (2).

In the chronic state, both diseases present histologic similarities, namely increased epidermal hyperplasia, infiltrates of large numbers of T cells and dendritic cells and disrupted terminal differentiation of keratinocytes (2). In both cases, the genes that regulate proliferation of epidermal cells are up-regulated (2). However, in spite of the similarities in barrier abnormalities, it's believed that psoriasis and atopic dermatitis are mediated by different subsets of T-helper (Th) cells, Th1 and Th2, respectively. Th2 cells produce interleukin (IL)-4, IL5, and IL13, whereas Th1 cells produce interferon-γ. The etiopathology of eczema is not completely understood. According to some authors, genetic defects affect the cornification process resulting in abnormal skin cell proliferation and differentiation, which allows its penetration by immunogenic proteins and subsequent immune activation (3). However, other authors defend that activation of Th2 cells and of the Th22 pathway results in reactive epidermal hyperplasia (4). Concerning psoriasis, a chronic, recurrent, immune-mediated inflammatory disease, with a recognised genetic predisposition, it has been proposed that psoriasis development depends on skin infiltration of Th1 and Th17 cells that stimulate macrophages and dermal dendritic cells to release mediators that sustain inflammation and cause abnormal keratinocyte proliferation. Indeed, our team reported that besides Th1 response, Th17 pathway and the IL23/Th17 axis seem to be crucial in psoriasis pathogenesis (5). The discovery of new T cells subsets, namely Th17 and Th22 cells, opened new insights into the pathogenesis of these two inflammatory diseases.

Several options for psoriasis treatment are available, and based on what is known about psoriasis immune pathways, new therapeutics have been developed. Concerning eczema treatment, it is complex; therapies are limited, since little is known about potential therapeutic targets. Some therapies are used in both diseases treatment, but these two pathologies do not respond equally to therapy regimens (6).

The genes associated with eczema and psoriasis were

identified, and include genes that encode factors of the adaptive and innate immune system and of proteins that regulate terminal differentiation of keratinocytes (7,8). Eczema has been associated with genes related with Th2 response, such as *IL4*, *IL4RA*, *IL13*, and *RANTES/CCL5*, whereas psoriasis has been associated with Th1 and Th17 related genes, such as *IL12B* (*p40*), *IL23A* and *IL23R*. Concerning innate immune response, eczema seems to be associated with *NOD1*, *NOD2*, *TLR2*, *CD14*, and *DEFB1* genes, and psoriasis with *TNFAIP3* and *TNIP1*, which participate in tumor necrosis factor (TNF) signaling and regulation of the transcription nuclear factor kB (NF-kB). Regarding the genes of terminal differentiation, eczema has been linked to serine protease inhibitor (*SPINK5*), loricrin (*LOR*), involucrin (*IVL*) and filaggrin (*FLG*) (9). Deletion of the genes late cornified envelope 3B (*LCE3B*) and *LCE3C* in the epidermal differentiation complex (*EDC*) locus was shown to increase the risk for psoriasis (10).

It seems of particular interest to distinguish genes that are specific for eczema and psoriasis from those that are common to both diseases and commonly involved in general skin inflammatory diseases. By comparing lesional skin of psoriasis patients with lesional skin of atopic dermatitis patients, using microarray analysis, some authors reported a very distinctive gene expression pattern in eczema, as compared with psoriasis (11,12); the authors studied full thickness skin biopsies (11) or purified epidermal cells of chronic lesions (12) of patients with psoriasis or with atopic dermatitis. Gene expression analyses was also able to discriminate lichen planus (LP), eczema and psoriasis from each other, by studying lesional skin biopsies of patients with LP, eczema or psoriasis (13). Moreover, it was reported a low expression of the IL23/Th17 axis (14) and broad defects in epidermal cornification (15) in eczema comparatively to psoriasis. However, gene expression data was not always consistent.

Quaranta *et al*. (16) reported, in *Science Translation Medicine* (*Sci Transl Med*) [2014], the identification of genes that are common to eczema and psoriasis and genes that are specific for each disease; the great novelty of this study was that the interindividual variability, a limitation of other reported studies, was avoided, since the authors studied patients with both diseases.

Concerning epidermal integrity, the authors found that eczema associates with severe defects in cornification and barrier function (16), which is in accordance with previous data (15). Moreover, all chronic variants of eczema shared these defects. Psoriasis is related with disturbed epidermal development and differentiation. Indeed, multiple *EDC* genes of the small proline-rich protein family and the late cornified envelope family were overexpressed in psoriasis (16). The filaggrin gene was reported to be down-regulated in both psoriasis and eczema (16); others (17) reported previously that mutations in this gene predisposes to atopic eczema.

Concerning the immune system, in eczema, the genes involved were associated with reduced innate immunity, increased IL6 and Th2 pathway (16). Interestingly, as previously found (14), a lower expression of antimicrobial peptide lipocalin2 was observed for eczema (16). For psoriasis, the involved genes were related with immune mediators of Th17 response, IL10 family cytokines, and IL36 (16). Data confirms that psoriasis and eczema are modulated by different immune pathways; the Th17 response and the Th2 response seem to be crucial for psoriasis and eczema pathogenic course, respectively.

An emerging concern is the relationship between psoriasis and the risk for cardiovascular disease events. Psoriasis is known to be associated with several comorbidities that are accepted as risk factors for cardiovascular diseases, such as dyslipidemia, type 2 diabetes mellitus and obesity (18). In accordance, up-regulation of genes regulating glucose metabolism/insulin resistance and lipid metabolism/obesity, such as nitric oxide synthase 2 (*NOS2*), was found in psoriasis (16), confirming that besides an inflammatory cutaneous disease, psoriasis has significant systemic and metabolic implications.

Two genes, *NOS2* and *CCL27* presented a significant distinct regulation in psoriasis, eczema, and noninvolved skin (16). *NOS2*, which is associated with metabolic processes and with Th1 and Th17 responses, was up-regulated in psoriasis (16), which is in accordance with other findings (19). CCL27 is a T cell-attracting chemokine, important in skin inflammation; its gene was found to be up-regulated in eczema and down-regulated in psoriasis (16). A markedly decreased CCL27 mRNA and protein expression in psoriatic lesions was also reported by others (20). Based on these findings, the authors proposed this pair of genes, *NOS2* and *CCL27*, as a disease classifier. Although this classifier was tested successfully in 34 patients, further studies are warranted to test this hypothesis and to strength data. Nonetheless, the classifier proposed may contribute to establish diagnosis and to select the appropriate therapeutic regimen.

A classifier that is helpful to establish an accurate diagnosis, particularly when clinical and histological evaluations are unclear, will be an excellent tool to clinicians, and any attempt to identify disease classifiers

should be encouraged. Nowadays, thanks to development in genetic investigation, gene evaluation is no longer a complex and difficult process; thus, it is not surprising that it may be a perfect tool to diagnose eczema and psoriasis.

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