Acta Derm Venereol 2014; 94: 380–385

INVESTIGATIVE REPORT

Regulatory Networks Contributing to Psoriasis Susceptibility

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The non-involved, healthy-looking skin of psoriatic patients displays inherent characteristics that make it prone to develop typical psoriatic symptoms. Our primary aim was to identify genes and proteins that are differentially regulated in the non-involved psoriatic and the normal epidermis, and to discover regulatory networks responsible for these differences. A cDNA microarray experiment was performed to compare the gene expression profiles of 4 healthy and 4 psoriatic non-involved epidermis samples in response to T-cell lymphokine induction in organotypic cultures. We identified 61 annotated genes and another 11 expressed transcripts that were differentially regulated in the psoriatic tissues. Bioinformatics analysis suggested that the regulation of cell morphology, development and cell death is abnormal, and that the metabolism of small molecules and lipids is differentially regulated in psoriatic epidermis. Our results indicate that one of the early steps of psoriasis pathogenesis may be the abnormal regulation of IL-23A and IL-1B genes in psoriatic keratinocytes. ***Key words: non-involved psoriatic epidermis; T-cell lymphokines; gene expression analysis; regulatory networks; IL-23A.***

Accepted Jun 19, 2013; Epub ahead of print Jan 13, 2014

Acta Derm Venereol 2014; 94: 380–385.

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Psoriasis is a hyperproliferative, inflammatory skin disease that affects ~2–3% of the Caucasian population (OMIM 177900). It is a complex disease in which multiple genetic factors, together with not well-defined environmental factors, lead to the appearance of the disease phenotype: sharply demarcated, red, scaly lesions of varying extent. A number of genes and biological processes are involved in the development of the symptoms, and the disease is genetically heterogeneous (1).

The trigger of keratinocyte hyperproliferation in the initiation of the psoriatic lesion is thought to be the activation of the cellular immune system, with T cells, dendritic cells and various immune-related cytokines and chemokines implicated in the pathogenesis (2). Keratinocytes in the otherwise healthy-looking, non-involved skin areas of psoriatic patients already display an inherent sensitivity to proliferative signals, and this plays a crucial role in the development of psoriatic lesions (3, 4).

Large-scale gene expression profiling methods (differential display and microarray) have recently become very popular, and have been used to identify transcripts with altered gene expressions in psoriasis (5–7). These experiments have identified many genes and cellular processes playing important roles in the disease.

Besides the already known, marked differences in the global gene expression profiles of psoriatic and normal keratinocytes, the non-involved skin of psoriatic patients also differs considerably from the normal, healthy skin at the transcriptional level. This is clearly indicated by the above-mentioned functional differences in proliferative response of healthy and of psoriatic non-involved keratinocytes. Such differentially expressed transcripts and novel psoriasis susceptibility factors have been successfully identified (3, 5, 8).

In order to broaden our investigations of the differential responses of normal and of psoriatic non-involved skin samples, we have now performed a microarray analysis to compare gene expression changes in epidermis samples treated in organotypic skin cultures with a mixture of interferon (IFN)-γ, granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-3, a special combination that has been shown to mimic the effect of psoriatic T-cell lymphokines (3). Besides the identification of already known and novel susceptibility genes, our analysis of the possible connections between them led to the identification of cellular processes that can be inherently disregulated in the healthy-looking skin of patients in response to various external signals. Our results suggest the fine tuning of cell death regulation and the metabolism of lipids as the primary processes that are disregulated in the non-involved epidermis of psoriatic patients in response to external signals, and which may therefore play a key role in the early events of the disease mechanism.

One of the most interesting genes exhibiting altered gene expression changes in the psoriatic non-lesional epidermis following T-cell lymphokine treatment was IL-23A. A growing volume of evidence suggests that abnormal regulation of the IL-23 cytokine may be cru-

 doi: 10.2340/00015555-1708
Journal Compilation © 2014 Acta Dermato-Venereologica. ISSN 0001-5555

cial for the initiation of various organ-specific chronic inflammatory diseases, such as psoriasis and inflammatory bowel disease (IBD) (9, 10).

METHODS

Patients and samples

Shave biopsy samples were taken from the non-involved buttock area of 4 young male psoriasis patients and 4 age and gender-matched healthy controls. Tissue samples were obtained with the subjects' informed consent and the approval of the Ethics Committee of the University of Szeged. The study was performed in accordance with the Declaration of Helsinki guidelines and its later revision.

Organotypic skin cultures

All shave biopsies were cut into two pieces, and organotypic skin cultures were established from each piece (7). Briefly, skin specimens were placed on cellulose acetate/cellulose nitrate filters with 2.2-μm porosity (Millipore) and transferred to a stainless steel grid platform in a 6-well plate. Dulbecco's modified Eagle's medium (DMEM) supplemented with 12 mM glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin (all from Life Technologies, Carlsbad, CA) was used as a culture medium. In case of each donor one of the resulting organotypic cultures were left untreated and only incubated for 72h, while the other half was treated with 1 ng/ml IFNγ, 1 ng/ml GM-CSF and 0.3 ng/ml IL-3. Tissue samples were maintained at the air/liquid interface under standard culturing conditions (at 37°C in a 5% CO_2 atmosphere) for 72 h (3, 7). The tissue specimens were then incubated in Dispase solution (grade II, Roche Applied Science) overnight at 4°C, then the epidermis was separated from the dermis and placed in TRIreagent (Molecular Research Center Inc., Cincinnati, OH).

For the IL-23A and IL-1B real-time (RT)-PCR analysis, additional 4 control and 4 psoriatic non-involved epidermis samples were generated the same way as described above. They were also age- and gender-matched to the individuals whose samples were used for the original cDNA microarray experiments.

RNA preparation and microarray hybridization

RNA was isolated by using TRIreagent, according to the manufacturer's instructions. The quality of the resulting samples was analysed by using an Agilent Bioanalyzer 2100. Only samples containing sufficiently high quality RNA were used for further studies.

Labelled cDNA and the subsequent microarray experiments were performed by the Microarray Core Facility of the Department of Genetics, Cell- and Immunobiology, Semmelweis University, Hungary, using a Whole Human Genom Microarray, 4x44K (Agilent Technologies).

Data analysis and statistics

Array scanning and feature extraction was performed with default scenario by Agilent DNA Microarray Scanner and Feature Extraction Software 9.5.3. Total gene signal normalisation at the 75th percentile of raw signal values and baseline transformation at the median of each array was performed by GeneSpringGX software 10.1 (Agilent Technologies Inc.). After rejection of outlier features, the expressed genes showing a >2.0-fold differential expression were further analysed by statistical *t*-test using the GeneSpring software 10.1. Genes showing a fold change >2 and *p*-value <0.05 were exported from GeneSpring.

To analyse the IL-1B and IL-23A gene expression changes a non-parametric Wilcoxon test was applied using the SPSS software. Statistical significance was determined at $p<0.05$.

Literature search

A PubMed search was performed for each identified gene in order to identify keratinocyte and/or skin-specific functions, and to determine whether they have previously been implicated in the pathogenesis of psoriasis.

Gene ontology analysis

Gene ontology category enrichment analysis was performed, using the publicly available software tool DAVID (http://david.abcc.ncifcrf.gov/, Bethesda, MD) to identify cellular processes and molecular functions that were overrepresented in our dataset.

Ingenuity pathway analysis

The list of differentially expressed genes was analysed using the Ingenuity Pathway Analysis software system (www.ingenuity.com, Redwood City, CA). Each gene identifier was uploaded and mapped to the corresponding gene object in the Ingenuity Pathways Knowledge Database. These genes were then used as focus points, and possible connections were identified by the software. Networks of genes were built up algorithmically by using the identified connections.

Validation

The microarray results were validated by real-time RT-PCR. All the reactions were carried out to quantify the abundance of chosen transcripts, using custom primer sets and the Universal Probe Library (Roche, Basel, Schweiz) with an iQ Supermix (Bio-Rad, Hercules, CA). One microgram of total RNA from the organotypic culture samples was reverse transcribed, using the iScript TM cDNA Synthesis kit (Bio-Rad, Hercules, CA). Relative gene expression data were calculated by normalising the expression data for the 18S ribosomal RNA and using the $\triangle\triangle$Ct method.

RESULTS

Compared to healthy epidermis, non-involved psoriatic epidermis exhibits different gene expression changes in response to T-cell lymphokine treatment

We compared the gene expression changes of the psoriatic non-involved epidermis with those of the normal human epidermis by isolating RNA samples from the epidermal compartment of organotypic skin samples kept in the presence (referred to below as treated) or absence (referred to as untreated) of T-cell lymphokines. The generated labelled cDNA samples were analysed by microarray hybridisation. For all the control and psoriatic non-involved samples, we determined gene expression changes following T-cell lymphokine treatment by comparing treated samples with autologous untreated ones. First, common genes showing at least

2-fold up- or downregulation on average were chosen. Next, we selected all those transcripts that exhibited different mean expression changes between the control and psoriatic non-involved samples. Sixty-one known genes and 11 expressed transcripts met the above criterion (Table SI[1]).

Twelve differentially regulated genes with known functions have already been connected to the pathogenesis of psoriasis

PubMed search identified genes that had been already implicated in the pathogenesis of psoriasis. Among the 61 differentially regulated genes, we identified 12 that met this criterion (Table I), representing ~20.0% of the dataset.

Some of these genes (e.g. *IL-1A*, *IL-1B*, *IL-23A* and *TNC*) play important roles in the regulation of immune and inflammatory processes, while others (e.g. *KLK6*, *PRSS27* and *ARG1*) do so in the regulation of cell growth, proliferation and differentiation. The list included known members of the interleukin family (*IL-23A*, *IL-1A* and *IL-1B*), which serve a central role in the pathogenesis of psoriasis (11). MMP9 is an enzyme contributing to inflammatory responses and subsequent tissue remodeling especially in psoriatic arthritis (12). *TNC* was another gene with differential expression changes in response to T-cell lymphokines. This result is in agreement with earlier findings showing elevated TNC immunostaining in the superficial dermis and at the epidermal-dermal junction after scarification and induction of the Koebner reaction in non-involved skin of psoriatic patients (13).

Trypsine-like serine proteases (*KLK6*, *PRSS27* and *TMPRSS11D*) have been shown to exhibit a gradually increasing expression in normal, non-involved and lesional psoriatic skin samples (14–16). *ARG1*, an important player in nitric oxide (NO) metabolism has also been shown to be elevated in psoriatic tissues, resulting in low NO levels that may contribute to the hyperproliferation of epidermal keratinocytes in psoriatic patients (17). We additionally identified *FABP7* and *SPRR3*, close relatives of the well-known psoriatic markers FABP5 and SPRRs, respectively, involved in atypical cellular organisation and differentiation in psoriasis pathogenesis (18). We also picked out *IFI27* from our experiment, a gene that has been reported to display an elevated expression in most large-scale genetic investigations on psoriasis, independently of donor gender, age and ethnicity. It plays an important role in stress response and possibly in apoptosis regulation (19).

Gene ontology analysis

In order to identify biological processes that might be differentially regulated in psoriatic non-involved keratinocytes after lymphokine treatment, we performed gene ontology analysis, using the publicly available software tool DAVID, with the list of the identified 61 known genes. Cytokine-mediated signalling processes and the response to wounding were significantly represented by genes in our dataset ($p < 0.05$), while the regulation of apoptosis and apoptotic processes was also at the border of significance (Table II).

Ingenuity pathway analysis

Ingenuity pathway analysis suggested that many of the identified genes fell into two categories: pathways involving the regulation of cell morphology, cell development and cell death, and pathways involving the metabolism of small molecules and lipids.

In the former pathway, all the genes involved seem to be organised around three molecules; INFγ (11), tumour necrosis factor α (TNFα) (20) and signal transducer and activator of transcription 3 (STAT3) (21). None of them are present in our list of differentially expressed genes, but all of them are known important regulators of key processes in the pathogenesis of psoriasis.

Similarly, in pathways involving the metabolism of small molecules and lipids, the genes are organised around IFNγ and β-estradiol. Although these genes were not present in our list, the encoded proteins are known

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1708

Table I. *Twelve of the differentially expressed genes were previously implicated in the pathogenesis of psoriasis*

Genebank accession. no.	Gene name	Function	Reference
NM_018399	*VNN3* (vanin 3)	Inflammation, metabolism	Jansen, et al. 2009 (32)
NM_002160	*TNC* (tenascin C)	Immune regulation, inflammation, proliferation	Capuano, et al. 1999 (13)
NM_001012964	*KLK6* (kallikrein-related 6)	Tumour growth, proliferation, differentiation	Komatsou, et al. 2007 (15)
NM_031948	*PRSS27* (serine protease 27)	Proliferation, differentiation	Li, et al. 2009 (16)
NM_004262	*TMPRSS11D* (serine protease)	Cell growth, proliferation	Iwakiri, et al. 2004 (14)
NM_005416	*SPRR3* (small proline-rich protease 3)	Differentiation	Koizumi, et al. 1996 (33)
NM_000045	*ARG1* (arginase 1)	Proliferation, differentiation	Bruch-Gerharz, et al. 2003 (17)
NM_005532	*IFI27* (interferon, alpha-inducible protein 27)	Stress response, apoptosis	Suomela, et al. 2004 (19)
NM_004994	*MMP9* (matrix metallopeptidase 9)	Tissue reorganization	Cordiali-Fei, et al. 2007 (12)
NM_016584	*IL-23A* (interleukin-23A)	Immune regulation, inflammation	Pietrzak, 2008 (11)
NM_000575	*IL-1A* (interleukin 1A)	Immune regulation, inflammation	Pietrzak, 2008 (11)
NM_000576	IL-1B (interleukin 1B)	Immune regulation, inflammation	Pietrzak, 2008 (11)

Table II. *Gene ontology analysis identified biological processes that are significantly represented in the dataset*

Gene ontology term	*p*-value	Genes, *n*
Cytokine mediated signaling processes	0.0017	4
Response to wounding	0.0087	7
Apoptosis	0.052	6
Regulation of apoptosis	0.053	7

According to the gene ontology analysis, cytokine-mediated signaling processes and the response to wounding were significantly represented by genes in our dataset ($p<0.05$), while the regulation of apoptosis and apoptotic processes was at the border of significance.

to play major roles in the pathogenesis of psoriasis (Fig. S1[1]) (5).

Validation of the chip results by real-time-PCR

In order to validate the chip results, real-time RT-PCR analysis was performed on selected genes, using the original RNA samples that were applied in the cDNA microarray experiment. These results indicated a coordinated upregulation of gene expressions for many genes (e.g *IFI27*, *VNN3*, *AGPAT9* and *LAMC2*) in the healthy epidermal samples in response to T-cell lymphokines, whereas no such upregulation could be detected in the psoriatic non-involved samples in response to the same treatment (Fig. S2a[1]). The lack of upregulation could have been due to the fact that expressions of the different genes were already higher in the psoriatic non-involved untreated epidermis, and thus they were resistant to further stimuli (Fig. S2b[1]). All these results correlated well with the cDNA microarray data (data not shown).

Differential regulation of pro-inflammatory cytokine genes in healthy and in psoriatic non-involved epidermal samples in response to T-cell lymphokines

The gene expression changes of the pro-inflammatory cytokines IL-1β and IL-23 in response to lymphokine treatment were also analysed by real-time RT-PCR, using the original RNA samples together with additional 4 control and 4 psoriatic uninvolved epidermis samples. The mRNA expression of both genes was upregulated in response to T-cell lymphokines in the healthy epidermis samples (*IL-23A*: $p=0.043$; *IL-1B*: $p=0.063$), but no such changes were observed in the psoriatic non-involved epidermis compared to the untreated values (*IL-23A*: $p=0.208$; *IL-1B*: $p=0.865$; Fig. 1). There was a tendency for higher basal expression of both genes (*IL-23A*: 2.2 fold, *IL-1B*: 2.4 fold) in the untreated psoriatic non-involved epidermis samples compared to untreated healthy control skin (data not shown).

DISCUSSION

The trigger of keratinocyte proliferation during the initiation of psoriatic lesions is thought to be the activation of the cellular immune system, involving T cells, dendritic cells and various immune-related cytokines and chemokines (2). Psoriatic T cells have traditionally been regarded as the central players in the pathogenesis of the disease, but they only seem to acquire their pathogenic phenotype in a psoriatic environment (3). This suggests that dysfunctions of both the skin and the immune system are required for the development of the disease. Lesional CD4+ T cells produce a mixture of lymphokines that are growth stimulatory for psoriatic non-involved basal keratinocytes (3). *In vitro* recombinant IFNγ in the presence of GM-CSF and IL-3 can mimic this effect (3).

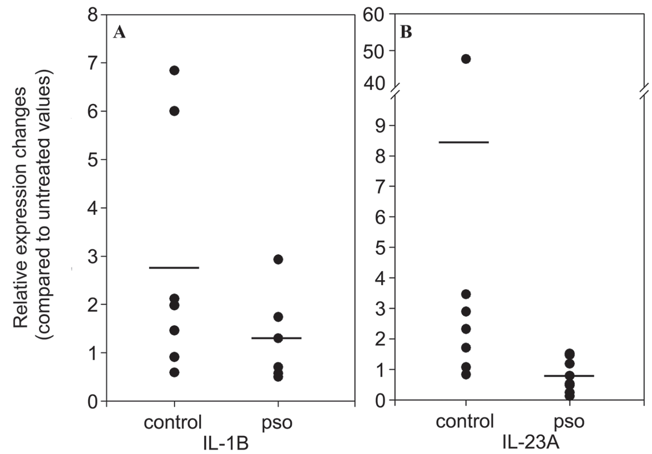

Fig. 1. RT-PCR experiments show differences in expression of *IL-1B* and *IL-23* in healthy and in psoriatic non-involved epidermis samples (pso) following T-cell lymphokine treatment *in vitro*. (A) A trend for elevated *IL-1B* expression levels are detected in the healthy epidermis samples ($p=0.063$), whereas no such changes are noted in the psoriatic non-involved samples. (B) Statistically significant *IL-23A* gene expression changes are detected in the control epidermis samples ($p=0.043$), whereas no such changes are noted in the psoriatic non-involved samples. (Statistical analysis was performed using the non-parametric Wilcoxon test), T-cell lymphokine treated samples were compared to the untreated ones. Horizontal lines represent mean values.

In order to gain deeper insight into this functional difference and the underlying regulatory networks that function differentially in healthy and in psoriatic non-lesional keratinocytes, we compared gene expression changes following T-cell lymphokine treatment *in vitro*, and selected all the genes that were differentially regulated. Our list of genes only partially overlapped with results of previous large- scale gene expression studies comparing the transcriptional profile of healthy and lesional psoriatic epidermis. The reason for that is currently not known. One explanation may be that our experimental setup allowed us to determine functional differences between the healthy and psoriatic epidermis. Alternatively, some differences may be explained by different gender, age, skin type, genetic background and ethnicity of the donors in the different studies. A large proportion of our identified genes were earlier described in connection with psoriasis pathomechanism suggesting that our experimental design was indeed capable to identify pathogenetically important genes (Table I).

Next, *in silico* analysis was used to organise the genes into networks using publicly available software tools. We found the deregulation of apoptosis and lipid metabolism as major factors responsible for the altered responsiveness to lymphokine treatment of psoriatic non-involved keratinocytes.

Together with hyperproliferation, decreased apoptosis plays an important role in the increased rate of cell production in the psoriatic epidermis (22), and this gene network was organised around *TNFA*, *IFNG* and *STAT3*. Another identified pathway was the metabolism of small molecules and lipids. These results are in accord with results of previous studies, showing that genes important in lipid and fatty acid metabolisms are abnormally regulated in the non-involved skin of psoriatic patients (5, 6). This network was organised around IFNγ and, interestingly, β-estradiol. Although IFNγ was not present in our actual dataset, it is known to be a central organiser of various pathogenic processes during psoriatic lesion formation. On the other hand, β-estradiol, may link these genes by possibly regulating them upon treatment.

Many of the identified genes were upregulated upon treatment of healthy tissue samples, whereas downregulation, or no changes were detected in the psoriatic non-involved samples. It is noteworthy that many genes were already upregulated in the untreated non-involved psoriatic epidermis samples compared to healthy ones, including the pro-inflammatory cytokine genes IL-23A and IL-1B, even before obvious inflammatory changes occur. Together with the fact that treatment of the patients with anti-p40 blocking antibodies targeting both IL-12 and IL-23 clearly results in an improvement of the patients' symptoms (24) our results reinforce the importance of the IL-23 axis in the pathogenesis of psoriasis. However, the development of the pathogenic T-helper 17 (TH17) cells relies on the presence of IL-1β. Furthermore, constitutive IL-1β activation in mice results in a TH17 cytokine profile, and the appearance of psoriasiform skin lesions, even in the absence of T cells (25). All these data, together with our results strongly argues that the improper regulation of early innate immune events to some unknown stimuli is a key factor in the pathogenesis of psoriasis.

In the non-lesional skin of psoriatic patients the microscopical structure of the skin seems normal, but the keratinocytes exhibit a special "wound" or "stress" phenotype, and in this state the major sources of the elevated IL-23A mRNA levels probably are the keratinocytes (26).

Later, in the formation of the lesions and in the stable plaque the adaptive immune system gets activated, and immune cells infiltrate the epidermis. In stable plaques the majority of expressed IL-23 is thought to be coming from the tissue resident and/or recruited dendritic cells, whereas the contribution of keratinocytes may be limited (23, 26).

Interestingly, this is true not only in the skin but also in the gut. In case of experimental colitis, for example, IL-23 may have a similar, dual role at the onset of disease and in its chronic phase, respectively (27). A link between the molecular pathogenesis of these two chronic inflammatory conditions is further strengthened by the fact that genetic polymorphisms of the *IL-23R* gene, encoding the receptor for IL-23, seem to play a role in the genetic predisposition of both conditions (28). Moreover, treatment modalities (e.g. biological therapies targeting TNFα and IL-23) are similar for psoriasis and inflammatory bowel disease.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Krisztina Vas and Dr. Róbert Kui for obtaining the biopsy samples, Andrea Tanácsné Bajkán for her excellent technical assistance, and Éva Viharosné Dósa Rácz for performing the statistical analysis. This work was supported by OTKA (K83277, K105985 and NK77437), TÁMOP (4.2.1/B-09/1/KONV-2010-0005 and TÁMOP-4.2.2.A-11/1/KONV-2012-0035. K. Sz. is supported by a János Bolyai Research Scholarship.

The authors declare no conflict of interest.

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