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Genetic support for the role of the NLRP3-inflammasome in psoriasis susceptibility

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ABSTRACT

Background: NACHT-leucine-rich repeat- and PYD-containing (NLRP)3 protein controls the inflammasome by regulating caspase-1 activity and interleukin (IL)-1 β processing. The contribution of IL-1 β in the pathogenesis of psoriasis is well recognised. Polymorphisms in *NLRP3* and caspase recruitment domain-containing protein (*CARD*)8, a negative regulator of caspase-1 activity, have been associated with susceptibility to common inflammatory diseases, such as Crohn's disease and rheumatoid arthritis.

Objective: To investigate the role for genetic variants in the NLRP3 inflammasome in psoriasis susceptibility.

Methods: In a patient sample comprising 1,988 individuals from 491 families and 1,002 healthy controls, genotypes for four selected single nucleotide polymorphisms (SNPs) in *NLRP3* (three SNPs) and *CARD8* (one SNP) were determined by TaqMan® Allelic Discrimination.

Results: Using the transmission disequilibrium test (TDT), a significant increase in the transmission of the *NLRP3* rs10733113G genotype to a subgroup of patients with more widespread psoriasis was demonstrated ($p=0.015$). Using logistic regression analysis in 741 psoriasis patients and 1,002 controls, the *CARD8* rs2043211 genotype was significantly different in cases and controls in overall terms (OR 1.3 (1.1-1.5), $p=0.004$) and for both genders.

Conclusions: Our data support the hypothesis that the inflammasome plays a role in psoriasis susceptibility.

KEY WORDS

psoriasis, NLRP3, CARD8

INTRODUCTION

Psoriasis is a common, chronic skin disease affecting about 3% of individuals in Northern Europe. Psoriasis is characterised by sharply demarcated erythematous plaques with adherent silvery scales. There is an intense hyperproliferation of keratinocytes which causes epidermal thickening and elongated rete ridges. Psoriasis is currently regarded as an inflammatory autoimmune disease involving both innate and adaptive immune mechanisms and skin barrier abnormalities (1-9).

NACHT-leucine-rich repeat- and PYD-containing (NLRP)3 protein, also known as cryopyrin, NLRP3, or CIAS1, is a fundamental component of the innate immune system (10). It is a multidomain protein that belongs to a large family of intracellular NOD-like receptors. It is stimulated by pathogen-associated molecular patterns (PAMPs), such as viral DNAs, toxins and peptidoglycans, as well as non-microbials, such as reactive oxygen species and ultraviolet (UV) irradiation (11). NLRP3 controls the inflammasome which regulates caspase-1-mediated interleukin (IL)-1 β processing. IL-1 β is produced as an inactive precursor (pro-IL-1 β) which is subsequently cleaved by caspase-1 to form biologically active IL-1 β . NLRP3 is most abundantly expressed in circulating macrophages and dendritic cells.

Caspase recruitment domain-containing protein (CARD)8, also known as TUCAN (tumour up-regulated CARD-containing antagonist of caspase nine), interacts physically with caspase-1 and negatively regulates caspase-1-dependent IL-1 β expression and nuclear factor (NF)- κ B activation (12). The *CARD8* rs2043211 single nucleotide polymorphism (SNP) introduces a premature stop codon, which results in the expression of a severely truncated protein. The variant CARD8 is unable to suppress NF- κ B activity, which leads to high constitutive levels of pro-IL-1 β (13).

Gain-of-function mutations in the *NLRP3* gene lead to hereditary periodic fever syndromes, such as the Muckle-Wells syndrome, characterised by excessive IL-1 production (14-16). It was further revealed that *NLRP3* and *CARD8* polymorphisms were significantly associated with susceptibility to common inflammatory diseases, such as Crohn's disease (17-19), rheumatoid arthritis (20), psoriatic juvenile idiopathic arthritis (21), diabetes type-1 (22) and celiac disease (23). These findings raise the hypothesis of the universal importance of the inflammasome in the pathogenesis of common auto-inflammatory disorders, which suggests that the inflammasome also may play a role in inflammatory skin diseases like psoriasis. In support of this, IL-1 β has been shown to play an important role in the pathogenesis of psoriasis (24). IL-1 β and its activating enzyme caspase-1 are both elevated in psoriatic skin lesions compared with healthy controls (25). IL-1 β secreted from epithelial cells promotes T-cell-dependent skin inflammation (26) and excessive IL-1 signaling leads to a Th17 cytokine profile and a psoriasis-like phenotype in mice (27).

The *NLRP3* polymorphisms rs10733113, rs35829419, rs4925663 and the *CARD8* polymorphism rs2043211 were chosen for study on the basis of their previously suggested association with auto-inflammatory disease (17, 20). As rs35829419 has been demonstrated to be associated with increased IL-1 levels (28) and rs2043211 with increased NF-kB expression (13), these SNPs are particularly of interest in an IL-1 β associated disease such as psoriasis.

In this manuscript, we provide genetic support of an association between polymorphisms in *NLRP3* and *CARD8* and psoriasis, suggesting a contribution by the inflammasome to psoriasis pathogenesis.

METHODS

Study population

The psoriasis families analysed in this report were sampled from a patient organisation (Swedish Psoriasis Association) and not from hospitals or outpatient clinics, which likely reduces ascertainment bias. The patient sample included 1,988 individuals from 491 different families, including 741 affected individuals (29). The occurrence and distribution of psoriasis and concomitant diseases was evaluated. Because the examination took place in the patients' homes, often with other family-members present, the classical assessment of PASI was not eligible. Instead, a one-point scale was used to assess the clinical severity of the disease (0 = no symptoms, 1 = symptoms). A total of nine predilection sites for psoriasis were assessed, which led to a score in a range from 0 (normal) to 9 (patients with the most widespread psoriasis). The assumption was made that a wide distribution reflects increased severity. This method for assessing clinical severity has been previously described (29). Patients with a severity score above 4 were considered to have more severe psoriasis, whereas patients with a severity score under 4 were considered to have milder psoriasis. The limit of 4 for classifying patients as having more severe or less severe psoriasis was determined by performing a dichotomous division of the sample, i.e. we split the patient sample into two equally large, non-overlapping, groups.

The controls were 1,002 healthy blood donors of Southern Swedish origin. Based on this patient sample, we have previously reported the identification of a novel psoriasis susceptibility locus on 3q21 (PSORS5; MIM 604316) (30). The patient material and ascertainment of families have previously been described (29). Informed consent was obtained from all patients. The study was approved by the Ethics Committee at Gothenburg University.

SNP selection and genotyping

Genomic DNA was prepared from venous blood samples using standard phenol-chloroform extraction procedures. HLA-Cw6 genotyping was performed using a sequence-specific primer approach (31).

The selection of all SNPs was based on their previous association with auto-inflammatory disorders. The *NLRP3* polymorphism rs35829419 is located in exon 3, rs10733113 and rs4925663 are located in a potential regulatory region downstream of *NLRP3* (17). The *CARD8* polymorphism rs2043211 is located in exon 6. Genotypes for the selected SNPs were determined by TaqMan® Allelic Discrimination. TaqMan SNP Genotyping Assays (ID c_30713847_10, c_25648615_10, c_26052022_10 and c_11708080_1) were used for genotype analysis according to the manufacturer's instructions (Applied Biosystems, Foster City, California, USA). The samples were analysed on a 7500 Fast Real-Time PCR System (Applied Biosystems). All cluster plots were manually inspected and ambiguous results were excluded. Likewise, families showing Mendelian errors were excluded.

Immunohistochemistry

Punch biopsies were obtained from lesional and uninvolved psoriasis skin from psoriasis patients and from healthy skin from 5 control subjects. The biopsies were fixed in 4% buffered formaldehyde and embedded in paraffin. Five-µm sections were stained according to a standard immunohistochemistry protocol using a primary mouse monoclonal antibody against human

NLRP3 (Nalpy-b Mab; Alexis Biochemicals, San Diego, CA, USA) at a dilution of 1:100. Bound antibodies were visualised using Shandon coverplates and Vectastain Elite ABC detection kit (Vector laboratories) for mouse-antibodies with DAB as substrate. Cell nuclei were counterstained with haematoxylin. Negative controls were obtained by omission of the primary antibody from the protocol.

Data analysis

Hardy-Weinberg equilibrium was calculated in accordance with standard procedures using chi2 analysis. Statistical analysis was performed using the R package (<http://www.r-project.org/>) and Haploview (www.broad.mit.edu/mpg/haploview). The transmission disequilibrium test (TDT) was used to test for a single allele and haplotype associations (32). The TDT is a family-based test that detects genetic linkage in the presence of genetic association. The outcome of the TDT is not affected by population structure due to the use of internal controls (i.e. the untransmitted allele). Transmission of alleles to each individual patient was evaluated. The TDT was analysed using the Haploview software package taking into account all affected individuals. Haplotypes were detected using Haploview.

For the analysis of cases and controls, we used a logistic model, which enables estimations of risk in terms of odds ratios (OR) with their corresponding 95% confidence intervals. The relationship between specific SNPs and severity/gender was analysed with logistic regression using an additive model ($dd = 0$, $Dd = 1$ and $DD = 2$, where D = major allele and d = minor allele). The dependencies between family members were handled by using the median statistic from a large number of independent samples. The relationship between age of onset and genotype was

examined using linear regression analysis with HLA-Cw6 status as covariate. None of the *NLRP3* SNPs were in linkage disequilibrium with each other ($r^2 < 0.1$).

The level of statistical significance was set at 0.05 and no adjustment for multiple testing was performed.

RESULTS

Association between genotypes/haplotypes and psoriasis

The selection of the *NLRP3* polymorphisms rs10733113, rs35829419, rs4925663 and the *CARD8* polymorphism rs2043211 was based on their previous association with auto-inflammatory diseases (17, 20). All genotypes were shown to be in Hardy-Weinberg equilibrium ($p > 0.05$, χ^2). Haplotype analysis was conducted to evaluate the combined effect of the SNPs on psoriasis susceptibility.

Using the family-based transmission disequilibrium test (TDT) taking into account all affected individuals, we found no overall statistically significant difference in the transmission of genotypes or combinations of genotypes. Transmission ratios close to 0.5 suggest random transmission (Table 1). We performed a subgroup analysis by dividing the patients based on the distribution of psoriasis in nine predilection sites, making the assumption that a wide distribution reflects increased severity. In this subgroup analysis, the *NLRP3* rs10733113G genotype was significantly overtransmitted to patients with more widespread psoriasis (>4 sites; $p = 0.015$; Table 1). Furthermore, one haplotype in the *NLRP3* gene was more frequently transmitted to patients with more widespread psoriasis ($p = 0.047$) whereas the complementary haplotype was less frequently transmitted ($p = 0.006$; Table 1).

We next aimed to confirm our TDT data in a partly independent sample by using a different study design, e.g. logistic regression analysis. In this case, 741 psoriasis patients and 1,002 healthy controls were analysed. Genotype frequencies in controls were in close agreement with previously published studies for healthy Caucasian individuals. For *CARD8* rs2043211, there was a statistically significant difference in genotype between cases and controls in overall terms for both genders (OR 1.3 (1.1-1.5), $p = 0.004$; Table 2). In the subgroup analysis, no significant

association was found after stratification for gender and severity (Table 2). The relationship between age of onset and genotype was examined using linear regression analysis with HLA-Cw6 status as covariate. No significant associations were found.

Table 1. Family-based transmission disequilibrium test of genotype and haplotype distribution							
Cases: individuals with psoriasis.							
SNP	Transm.	T:U	Chi2	P-value	P prem	T/U	Transmission Ratios T/(U+T)
NLRP3 rs10733113	G	126:115	0.50	0.479	0.99	1.10	0.52
NLRP3 rs4925663	G	229:216	0.38	0.538	1.00	1.06	0.51
NLRP3 rs35829419	A	62:60	0.03	0.856	1.00	1.03	0.51
CARD8 rs2043211	T	210:195	0.56	0.456	0.99	1.08	0.52
Haplotype NLRP3	Freq	T:U	Chi2	P-value	P prem	T/U	T/(U+T)
GCA	0.39	209.9 : 224.2	0.47	0.493	1.00	0.94	0.48
GCG	0.39	234.6 : 213.2	1.02	0.312	0.98	1.10	0.52
ACG	0.14	102.2 : 109.6	0.26	0.611	1.00	0.93	0.48
GAG	0.06	49.9 : 49.6	0.00	0.979	1.00	1.01	0.50
ACA	0.02	11.8 : 13.5	0.12	0.732	1.00	0.87	0.47

Cases: individuals with severity > 4							
SNP	Transm.	T:U	Chi2	P-value	P prem	T/U	Transmission Ratios T/(U+T)
NLRP3 rs10733113	G	33:16	5.90	0.015*	0.14	2.06	0.67
NLRP3 rs4925663	G	50:48	0.04	0.840	1.00	1.04	0.51
NLRP3 rs35829419	-	15:15	0.00	1.000	1.00	1.00	0.50
CARD8 rs2043211	A	51:45	0.38	0.540	1.00	1.13	0.53
Haplotype NLRP3	Freq	T:U	Chi2	P-value	P prem	T/U	T/(U+T)
GCG	0.39	57.1 : 37.8	3.95	0.047*	0.38	1.51	0.60
GCA	0.39	45.9 : 49.2	0.12	0.733	1.00	0.93	0.48
ACG	0.14	13.0 : 31.3	7.55	0.006**	0.06	0.42	0.29
GAG	0.06	13.9 : 12.0	0.14	0.708	1.00	1.16	0.54
ACA	0.02	3.0 : 0.7	1.36	0.244	0.96	4.29	0.81

Transm.= Transmitted

T:U= Transmitted:Untransmitted ratio

*p<0.05

**p<0.01

Table 2. Genotype association results in cases and controls

Logistic regression overall and for severity						
SNP		P-value	N	No. affected	OR	95% CI
NLRP3 rs10733113	<i>psoriasis</i>	0.563	1743	741	0.94	0.75-1.17
MAF: 0.17	men	0.677	817	336	0.93	0.68-1.30
	women	0.745	831	405	0.95	0.70-1.30
	<i>severity >4</i>	0.196	1184	182	1.36	0.87-2.23
NLRP3 rs4925663	<i>psoriasis</i>	0.159	1705	741	1.12	0.96-1.32
MAF: 0.4	men	0.513	801	336	1.08	0.85-1.38
	women	0.337	807	405	1.12	0.89-1.41
	<i>severity >4</i>	0.590	1146	182	1.08	0.81-1.45
NLRP3 rs35829419	<i>psoriasis</i>	0.902	1743	741	0.98	0.73-1.33
MAF: 0.02	men	0.069	816	336	0.65	0.42-1.04
	women	0.169	831	405	1.36	0.89-2.12
	<i>severity >4</i>	0.969	1184	182	1.01	0.60-1.85
CARD8 rs2043211	<i>psoriasis</i>	0.004**	1739	741	1.28	1.08-1.52
MAF: 0.33	men	0.027*	817	336	1.34	1.04-1.74
	women	0.029*	831	405	1.29	1.03-1.62
	<i>severity >4</i>	0.338	1180	182	1.16	0.86-1.57

Linear regression for age of onset using Cw6 as covariate

SNP	β -coefficient	SE	t-value	P-value
rs10733113	0,337	1,419	0,237	0,813
rs35829419	-0,594	1,016	-0,585	0,559
rs2043211	0,893	1,889	0,473	0,637
rs4925663	-1,057	0,997	-1,061	0,290

CI= Confidence Interval

OR= Odds-ratio

MAF= Minor Allele Frequency among Controls

*p<0.05

**p<0.01

Immunohistochemical distribution of NLRP3 in psoriasis

To describe the expression pattern of NLRP3 in psoriatic skin, immunohistochemistry was performed. As expected, the protein was strongly expressed in leucocytes both in blood vessels and in the inflammatory infiltrates of the psoriatic dermal papilla. NLRP3 was also strongly expressed in keratinocytes in both the hyperplastic epithelium of psoriasis lesions and normal epithelium. Notably, however, the parakeratotic cells on the surface of psoriasis lesions entirely lacked NLRP3 expression (Fig. 1).

Fig. 1. Expression patterns of NLRP3 in normal and psoriatic skin.

Immunostaining with a monoclonal antibody and an ABC detection system yielding brown precipitates at antigen sites. Nuclear counterstaining with haematoxylin. *A* shows an active lesion exhibiting the classical psoriasis signs: acanthosis, hyperkeratosis, parakeratosis and micro abscesses as well as angiogenesis and exudation of white blood cells in a dermal papilla. Note strong expression of NLRP3 protein in keratinocytes of active psoriasis lesions (*A,B,D*) as well as in non-lesional skin (*C*) and in control skin (*E*) but lack of expression in the superficial parakeratotic cells in a psoriasis lesion (*D*). Numerous NLRP3-expressing white blood cells within the lumen of a microvessel (*B*, upper arrow) and free in the stroma of the dermal papilla (lower arrow). Negative control (*F*). Scale bar 50 μ m.

DISCUSSION

Psoriasis is a multifactorial disease with a strong genetic component and intensive efforts have been made with the aim of defining genetic variations linked with the disease. Linkage and association studies have identified a disease susceptibility locus within the major histocompatibility complex (MHC) (33) close to HLA-C and several groups have reported that HLA-Cw6 itself is the major susceptibility allele (34). In addition, genome-wide association studies (GWAS) have identified nine regions linked to three pathways of biological relevance to psoriasis; the NF- κ B signalling pathway, also implicated in IL-1 β and inflammasome activation, mechanisms of T-cell (particularly Th17) differentiation and the perturbation of the epidermal barrier (8, 35-36). GWAS have the disadvantage of incomplete coverage, which may lead to regions, “gaps” that are not satisfactorily analysed. The genomic region encoding the *NLRP3* gene on 1q44 represents such a region of incomplete coverage (17).

NLRP3 mutations have been strongly implicated in auto-inflammatory fever diseases where the acute symptoms arise from an overproduction of IL-1 β , and a dramatic improvement in symptoms is seen upon blockade of IL-1 in these patients. In recent years, several common polymorphisms in *NLRP3* and *CARD8* have been implicated in increased susceptibility to chronic inflammatory conditions. Moreover, a recent paper suggested the rs35829419 to be functional and associated with increased IL-1 levels. Similarly, *CARD8* rs2043211 has been demonstrated to result in increased NF- κ B expression.

There are established similarities between psoriasis and Crohn’s disease , and several susceptibility loci are shared by both diseases (37). The SNPs analysed in the present study have previously been shown to be associated with auto-inflammatory diseases. Notably, SNPs

including *NLRP3* rs107331113, located in a regulatory region downstream of *NLRP3*, have been shown to be strongly associated with Crohn's disease, as well as expression levels of *NLRP3* and *IL-1 β* (17). Two studies from Sweden and New Zealand found evidence of interaction between *NLRP3* rs35829419 and *CARD8* rs2043211 with Crohn's disease, most evident after stratification by gender (18-19). By contrast, two other European studies found no association between the *CARD8* rs2043211 and Crohn's disease (38-39). Similarly, a large study by Lewis et al. failed to replicate findings of an association between *NLRP3* and susceptibility for Crohn's disease (40).

Very recently, an association between *CARD8* rs2043211 and ulcerative colitis was demonstrated, as well as an association with higher serum levels of *IL-1 β* , but only in females (41). The combination of *NLRP3* rs35829419 and *CARD8* rs2043211 genotypes was also associated with rheumatoid arthritis susceptibility and severity (20). Furthermore, rs35829419 was shown to be associated with celiac disease (23). Overlaps between inflammatory bowel disease susceptibility and other auto-inflammatory conditions such as psoriasis are well recognised (42).

In the present study, we have demonstrated that certain polymorphisms in *NLRP3* (rs107331113) and *CARD8* (rs2043211) are associated with psoriasis susceptibility. Our findings support the role of innate immunity in the pathogenesis of psoriasis. The SNP rs2043211 results in a severely truncated protein and the functional role of *CARD8* as an inhibitor of NF- κ B is compromised (13). The resulting increased NF- κ B activity would subsequently lead to increased expression of its downstream genes *NLRP3* and *IL-1 β* (43).

The investigated SNPs were chosen on the basis of previous findings suggesting a role for them in inflammatory disease. While the association of rs107331113 with Crohn's disease has been previously demonstrated by Villani et al.(17), a number of GWAS studies do not report such an association (44-50). As pointed out by Villani et al. (17), the markers on commercially available genotyping chips fail to cover the NLRP3 region sufficiently. Because of this restriction, important regions might be overlooked in GWAS analysis, making it crucial not to rely solely on GWAS studies, but to also apply other strategies to identify susceptibility genes. The current findings are the first ones to demonstrate an association between these SNPs and psoriasis. To confirm the relevance of these findings, additional studies should be carried out in other cohorts.

The qualitative immunohistochemistry demonstrated NLRP3 staining in psoriatic skin, which is supported by findings of NLRP3 mRNA both in normal and psoriatic skin (51). However, while de Koning et al. found extremely low staining for NLRP3 protein, we found a widespread staining using an even more diluted antibody. As the presence of the NLRP3 inflammasome complex and the NLRP3 inflammasome protein components in keratinocytes have been described in both cultured and primary human keratinocytes (52-54), it may be speculated that differences in protocols or patient samples may account for the discrepancy in findings compared to de Koning et al.

The expression of NLRP3 not only in the inflammatory cellular infiltrate in the dermis but also in the epithelial cells of the psoriatic epidermis raises the hypothesis of additional involvement in psoriasis pathogenesis. Thus, the inflammasome may also be implicated in the apoptotic, disturbed terminal differentiation in psoriasis.

Family-based TDTs require significantly more patients to detect the same level of association as in case-control studies (55). The advantage of the TDT is the use of internal controls (the untransmitted allele from heterozygous parents) that reduces the risk of population stratification and false-positive association signals (56). The results may not have withstood correction for multiple testing. However, the selection of the SNPs was based on their high prior probability of involvement in the disease pathogenesis. A confirmation as well as a more precise estimation of the genetic contribution to the pathogenesis of psoriasis needs to be obtained in independent cohorts. There are methods for integrating results from case-control studies and TDT to provide a combined estimate of the disease-marker association. However, since this approach requires that the subjects used in the two studies are independent of each other, the approach was not applicable in the present study.

IL-1 β has been identified as an important cytokine for the development of psoriasis (57). IL-1 β is produced by keratinocytes and the expression levels are enhanced in lesional psoriatic skin by tumour necrosis factor- α (TNF- α) and NF- κ B activation (58-59). The high levels of IL-1 β that are found in the psoriasis plaque have been shown to have the potential to drive keratinocyte proliferation, but also block insulin-induced keratinocyte differentiation (60). As systemic levels are very low, measurements of IL-1 β expression are difficult to perform in blood or plasma. Still, previous reports show increased levels of IL-1 β in psoriasis patients (61) and benefits of IL-1 blockade have recently been suggested in clinical trials (62-64).

The role of Th17 responses in the pathogenesis of psoriasis is well established. Furthermore, there is a link between the Th17 and IL-1 β pathways. IL-1 β secreted from epithelial cells promotes T-cell-dependent skin inflammation (26). IL-1 β is important for the IL-23-dependent

development of Th17 cells and stimulates the maturation of and cytokine production by these cells (65-66). Mice carrying a mutation in the *NLRP3* gene, which leads to inflammasome activity and constitutive IL-1 β expression, spontaneously develop a psoriasis-like skin phenotype with typical histological features and a Th17 cytokine profile (27). Patients with mutations in the gene encoding the IL-1 receptor antagonist (*IL-1Ra*) also develop a psoriasis-like phenotype with the infiltration of neutrophils and an IL-17 cytokine profile (67-68). Interestingly, generalised pustular psoriasis was successfully treated with the IL-1-receptor antagonist Anakinra (63).

Keratinocytes have been shown to express mRNA of key components for inflammasome assembly, which supports their role as immunocompetent cells (52-53). In psoriasis, caspase-1 activity has been reported to be increased in lesional, compared with non-lesional, psoriatic skin (58). Moreover, Salskov-Iversen et al. reported the marked mRNA induction of caspase-5, a suggested upstream activator of caspase-1 (69). Very recently, the inflammasome was shown to be activated in lesional psoriasis by cytosolic DNA (25, 70). This activation of AIM2 inflammasomes in keratinocytes was neutralised by the antimicrobial cathelicidin peptide LL-37 (25). Since vitamin D controls cathelicidin production in human skin, this mechanism may contribute to the antipsoriatic effects of topical vitamin D treatment.

IL-1 β has been identified as an important cytokine for the development of psoriasis. Moreover, generalized pustular psoriasis has been successfully treated with the IL-1-receptor antagonist Anakinra. By determining the role for different components of the inflammasome in psoriasis susceptibility, it may be possible to identify patients that may benefit from IL-1 β inhibiting drugs. As IL-6 is regulated via the IL-1 receptor/NF- κ B signaling, another treatment option for individual therapy might be the use of the newly developed IL-6 inhibitors.

In conclusion, we present data that support the hypothesis that the inflammasome and its components NLRP3 and CARD8 play a role in the defective innate immune response and chronic inflammation in psoriasis.

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Carlström, Ekman and Petersson performed the research and analyzed the data. Söderkvist and Enerbäck designed the study and participated in data interpretation. All authors participated in writing, drafting and revising the paper and approved of the submitted and final version of the paper.

CONFLICT OF INTEREST

There are no conflicts of interest.

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