NOD2 signalling in hidradenitis suppurativa

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Summary

Background. Hidradenitis suppurativa (HS) is associated with dysregulated immune responses including altered expression of cytokines, chemokines, and antimicrobial peptides and proteins (AMPs).

Aims. To evaluate the expression of nucleotide-binding oligomerization domain-containing (NOD)2 and related factors in HS skin samples and keratinocyte cultures.

Methods. We performed real-time PCR for NOD2, receptor-interacting serine/threonine-protein kinase (RIP)2, cyclic amine resistance locus (CARL), skin-derived antileukoproteinase (SKALP)/elafin, human β-defensin (hBD)2, LL37, psoriasin and RNase7 in lesional and nonlesional skin of 19 patients with HS and in keratinocyte cultures [unstimulated, muramyl dipeptide (MDP)-stimulated or Pam2CSK4 (Pam2)-stimulated] from and nonlesional skin.

Results. We observed significantly elevated mRNA expression for NOD2 (P < 0.01), hBD2 (P = 0.02), RNase7 (P < 0.001), psoriasin (P < 0.01) and SKALP/elafin (P = 0.02) in lesional compared with nonlesional skin. We found a significant correlation between NOD2 mRNA and hBD2 (r = 46; P = 0.04), psoriasin (r = 0.67; P < 0.01) and SKALP/elafin (r = 0.65; P < 0.01). In unstimulated, Pam2-stimulated and MDP-stimulated normal keratinocytes, NOD2, RIP2, CARL and SKALP/elafin expression significantly (P < 0.05) increased from 6 to 48 h, whereas in unstimulated, Pam2-stimulated and MDP-stimulated HS keratinocytes, RIP2, CARL and SKALP/elafin expression significantly (P < 0.05) declined from 6 to 48 h. mRNA expression of NOD2 (unstimulated, Pam2-stimulated, MDP-stimulated), CARL (unstimulated, Pam2-stimulated, MDP-stimulated) and SKALP/elafin (unstimulated, Pam2-stimulated) at 6 h was significantly increased in HS compared with normal keratinocytes.

Conclusion. We have shown for the first time that NOD2 signalling is activated in HS and might contribute to the pathogenesis via induction of AMPs and activation of other pathways such as nuclear factor κB signalling.

Introduction

Hidradenitis suppurativa (HS) is a common chronic inflammatory condition of intertriginous skin. Hyperplasia of the hair follicle epithelium, follicular hyperkeratosis and interfollicular epidermal hyperplasia are considered to be the early events in HS. In addition to a dysregulated immune-mediated inflammatory response, genetic predisposition is frequently discussed as an important risk factor. Predominantly loss-
function mutations have been reported in genes of the γ-secretase complex, namely NCSTN, PSEN1, PSENEN and PSTPIP1. Nucleotide-binding, oligomerization domain (NOD)2 mutations have been described in familial HS and HS-associated autoimmune conditions, such as PASH (pyoderma gangrenosum, acne vulgaris and supplicative hidradenitis) syndrome. Moreover, polymorphisms within the NOD2 gene have often been reported in Crohn disease (CD), which is not infrequently associated with HS and shares similar pathophysiological mechanisms. Notably, genetic variation in NOD2 and cigarette smoking, a significantly associated factor in HS, are also well-established risk factors for the development of CD.5–8 We aimed to analyse the expression profiles of NOD2 and related factors in samples of patients with HS and in keratinocyte cultures.

Methods

The study was approved (no. 5076-14) by the ethics committee of Ruhr-University Bochum, and conducted according to the Declaration of Helsinki. Informed consent was obtained from all study subjects.

Patients

This prospective study was performed on skin tissues from 19 patients with HS. Skin samples were taken from representative inflammatory HS lesions and from neighbouring nonlesional skin (10 mm from the lesional skin border; Fig. 1). Patient characteristics are detailed in Table 1. None of the patients had systemic therapy with antibiotic or immunosuppressive agents within 4 weeks before inclusion. Skin samples were obtained by 5-mm punch biopsy and immediately stored in RNAlater solution (Qiagen, Hilden, Germany) at −80 °C.

Cell cultures

Skin biopsies from the lesional skin of three patients with HS were used for cell isolation. After an overnight incubation period with 1% Proteinase K at 4 °C, the epidermis was detached from the dermis. Following enzymatic digestion of the epidermis with 1% collagenase, a single cell suspension was prepared. Isolated keratinocytes were cultured (Dermal Cell Basal Medium and Keratinocyte Growth Additive; American Type Culture Collection, Manassas, VA, USA) at 37 °C, 5% CO2 and 97% humidity. When cells reached 80–90% confluency, they were passaged in six-well plates and used for further experiments. As a control group, a commercially available primary keratinocyte (foreskin) cell line (American Type Culture Collection) was used. Both cell lines were treated with 50 ng/mL Pam2CSK4 (Pam2) and 10 μg/mL mureinyl dipeptide (MDP) for 6 and 48 s. After treatment, cells were lysed and frozen at −20 °C (Fig. 1).

RNA isolation and real-time PCR

Total RNA was extracted from cell lysates and skin samples (RNasy Lipid Tissue Kit; Qiagen, Chatsworth, CA, USA). The mRNA expression levels were quantified by real-time PCR (PowerSYBR Green PCR Master Mix) (ThermoFisher, Waltham, MA, USA) on a PCR analyser (Cobas z480; Roche, Mannheim, Germany) in accordance with Minimum Information for Publication of Quantitative Real-Time PCR Experiments Guidelines. Three widely used reference genes (GAPDH, β2-microglobulin and RPL38) were also tested; RPL38 exhibited the most stable expression levels and was used as the housekeeping control. Target mRNA expression results were normalized to corresponding RPL38 mRNA transcript levels (2ΔΔCT method). The primer pairs for NOD2, receptor-interacting serine/threonine-protein kinase (RIP)2, cyclic amine resistance locus (CARL), skin-derived antileukoproteinase (SKALP)/elafin, human β-defensin (hBD)2, LL37, psoriasin and RNase7 were designed using Primer Express software (PE Applied Biosystems, Foster City, CA, USA).

Statistics

MedCalc software (V19.1.7; MedCalc, Ostende, Belgium) was used for statistical analysis. Analysis of distribution was performed by the D’Agostino–Pearson test. For non-normally distributed variables, the Wilcoxon test (dependent samples) and the Mann–Whitney U test (independent samples) were used. Correlations were calculated using Spearman rank correlation coefficient (ρ). P < 0.05 was considered significant.

Results

Patient data

Patient data (median and range) are detailed in Table 2.

mRNA expression

We observed significantly elevated mRNA expression for NOD2 (P < 0.01), hBD2 (P = 0.02), RNase7
Figure 1  (a) Representation of hidradenitis suppurativa (HS) tissue collection. Skin samples were obtained from representative inflammatory HS lesions (lesional skin) and from adjacent healthy-appearing (nonlesional) skin approximately 10 mm from the lesion border. (b) Activation of nucleotide-binding oligomerization domain-containing (NOD)2 signalling pathway and antimicrobial peptide and protein (AMP) expression in lesional vs. perilesional HS skin (significant direct correlation: p and red arrowheads; significant inverse correlation: p and blue arrowheads; upregulation: red arrowhead; no regulation: = sign).  (c) Experimental setup and response of unstimulated/Pam2/muramyl dipeptide (MDP)-stimulated primary (normal) keratinocytes vs. HS keratinocytes isolated for lesional HS tissue (upregulation: red arrowhead; downregulation: blue arrowhead). CARL, cyclic amine resistance locus; hBD, human β-defensin; iE-DAP, D-glutamyl-meso-diaminopimelic acid; IKK, IκB kinase; MAPK, mitogen-activated protein kinase; MDP, muramyl dipeptide; NEMO, nuclear factor κB essential modulator; RIP, receptor-interacting serine/threonine-protein kinase; SKALP, skin-derived antileukoproteinase; TAK, transforming growth factor-β-activated kinase; UB, ubiquitin.
Table 1 Characteristics of 19 patients with hidradenitis suppurativa.

| Parameter                        | (N = 19) |
|----------------------------------|----------|
| Age, years; mean ± SD            | 41.63 ± 9.34 |
| Sex, n (%)                       |          |
| Female                           | 12 (63.2) |
| Male                             | 7 (36.8)  |
| Current smoker, n (%)            | 13 (68.2) |
| BMI, kg/m²; mean ± SD            | 28.86 ± 6.09 |
| BMI categories, n (%)            |          |
| Normal weight (≤ 24.9)           | 4 (21.1)  |
| Overweight (≥ 25)                | 4 (21.1)  |
| Obesity (≥ 30)                   | 11 (57.8) |
| Hurley stage, n (%)              |          |
| I                                | 3 (15.8)  |
| II                               | 9 (47.4)  |
| III                              | 7 (36.8)  |
| Positive family history          | 6 (31.6)  |
| Biopsy site, n (%)               |          |
| Axilla                           | 9 (47.4)  |
| Groin                            | 7 (36.8)  |
| Genital                          | 3 (15.8)  |

Table 2 mRNA expression in lesional and nonlesional skin of patients with hidradenitis suppurativa (n = 19).

| Protein  | Nonlesional, median (range) | Lesional, median (range) | P* |
|----------|-----------------------------|--------------------------|----|
| NOD2     | 1.22 (0.55–3.1)             | 2.91 (0.6–4.13)          | <0.01 |
| RIP2     | 4.68 (3.1–9.62)             | 4.27 (2.6–10.1)          | 0.89 |
| CARL     | 2.9 (1.5–6)                 | 2.4 (0.88–4.1)           | 0.06 |
| hBD2     | 0.65 (0.16–10)              | 3 (0.08–161.5)           | 0.02 |
| RNase7   | 37.2 (0.12–96.1)            | 109.6 (4.8–291.2)        | <0.001 |
| Psoriasin| 84.2 (3.1–790)              | 624.2 (3.1–3226)         | <0.01 |
| SKALP/elafin | 1.6 (0.12–8.96) | 6.98 (0.32–47.6) | 0.02 |

CARL, cyclic amine resistance locus; hBD, human β-defensin; NOD, nucleotide-binding oligomerization domain-containing; RIP, receptor-interacting serine/threonine-protein kinase; SKALP, skin-derived antileukoprotease. *Wilcoxon test.

(P < 0.001), psoriasin (P < 0.01) and SKALP/elafin (P = 0.02) in lesional skin compared with nonlesional skin samples from patients with HS.

Correlation between proteins in lesional skin samples

We found a moderate to strong correlation between NOD2 mRNA and hBD2 (r = 0.76; P < 0.01) and SKALP/elafin (r = 0.65; P < 0.01) in lesional HS skin samples.

RIP2 mRNA expression inversely correlated with hBD2 (r = -0.48; P = 0.04), psoriasin (r = -0.55; P = 0.02) and SKALP/elafin (r = -0.48; P = 0.03) in lesional skin (Table 3).

Cell culture

In unstimulated, Pam2-stimulated and MDP-stimulated normal keratinocytes, NOD2, RIP2, CARL and SKALP/elafin expression significantly (P < 0.05) increased from 6 to 48 h, whereas in unstimulated, Pam2-stimulated and MDP-stimulated HS keratinocytes, RIP2, CARL and SKALP/elafin expression significantly (P < 0.05) declined from 6 to 48 h (Table 4).

At 6 h, mRNA expression of NOD2 (unstimulated, Pam2-stimulated, MDP-stimulated), CARL (unstimulated, Pam2-stimulated, MDP-stimulated) and SKALP/elafin (unstimulated, Pam2-stimulated) was significantly increased in HS compared with normal keratinocytes. By contrast, at 48 h, mRNA expression of NOD2 (unstimulated, Pam2-stimulated, MDP-stimulated), RIP2 (unstimulated, Pam2-stimulated, MDP-stimulated), CARL (unstimulated, Pam2-stimulated, MDP-stimulated) and SKALP/elafin (unstimulated, MDP-stimulated) was significantly decreased in HS keratinocytes compared with normal keratinocytes (Table 4).

Discussion

NOD2 is an intracellular sensor of intracellular and extracellular pathogens such as bacteria, and is expressed in barrier cells of the skin, where it plays a significant role in wound healing and defence against pathogens. NOD2 is a member of the Nod-like receptor family and recognizes MDP, which is part of the cell wall of almost all bacteria. In keratinocytes, NOD2 regulates the expression of antimicrobial peptides and proteins (AMPs) through the activation of an intracellular signalling cascade that requires RIP. Once

Table 3 Lesional nucleotide-binding oligomerization domain-containing 2 and receptor-interacting serine/threonine-protein kinase 2 gene expression correlating with antimicrobial factors in hidradenitis suppurativa (n = 19).

| Comparators       | ρ* | 95% CI        | P   |
|-------------------|----|---------------|-----|
| NOD2 and hBD2     | 0.46 | 0.03 to 0.77 | 0.04 |
| NOD2 and psoriasin | 0.67 | 0.31 to 0.86 | <0.01 |
| NOD2 and RNase7   | 0.44 | -0.02 to 0.74 | 0.06 |
| NOD2 and SKALP/elafin | 0.65 | 0.28 to 0.85 | <0.01 |
| RIP2 and hBD2     | -0.48 | -0.77 to -0.03 | 0.04 |
| RIP2 and psoriasin | -0.55 | -0.80 to -0.13 | 0.02 |
| RIP2 and RNase7   | -0.42 | -0.74 to 0.04 | 0.07 |
| RIP2 and SKALP/elafin | -0.48 | -0.77 to -0.03 | 0.03 |

hBD, human β-defensin; NOD, nucleotide-binding oligomerization domain-containing; RIP, receptor-interacting serine/threonine-protein kinase; SKALP, skin-derived antileukoprotease. *Spearman coefficient of rank correlation.
Table 4 Gene expression in unstimulated and stimulated cultures of normal and lesional keratinocytes of three patients with hidradenitis suppurativa.

| Parameters            | Keratinocytes |          |          |          |
|-----------------------|---------------|----------|----------|----------|
|                       | Normal        | HS       | P        |          |
| NOD2 (unstimulated)   |               |          |          |          |
| 6 h                   | 0.03 (0.01–0.1)| 0.16 (0.13–0.22)< 0.01  |          |          |
| 48 h                  | 0.17 (0.1–0.51)| 0.055 (0.03–0.24)< 0.04  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| NOD2 (Pam2)           |               |          |          |          |
| 6 h                   | 0.085 (0.04–0.14)| 0.23 (0.07–0.43)< 0.01  |          |          |
| 48 h                  | 0.26 (0.14–0.38)| 0.17 (0.1–0.21)< 0.05  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| NOD2 (MDP)            |               |          |          |          |
| 6 h                   | 0.09 (0.05–0.12)| 0.16 (0.08–0.53)0.01  |          |          |
| 48 h                  | 0.16 (0.06–0.34)| 0.11 (0.02–0.22)0.29  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| RIP2 (unstimulated)   |               |          |          |          |
| 6 h                   | 8.9 (6.6–13.2)| 10.9 (5.8–14.6)0.29  |          |          |
| 48 h                  | 22.3 (14.6–33.7)| 2.9 (2.1–3.6)0.001  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| RIP2 (Pam2)           |               |          |          |          |
| 6 h                   | 9.5 (7.1–12.2)| 13.1 (4.1–23.2)0.11  |          |          |
| 48 h                  | 20.7 (16.9–34.1)| 3.1 (1.7–4.2)0.002  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| RIP2 (MDP)            |               |          |          |          |
| 6 h                   | 10.4 (8.3–16.3)| 12.7 (5.3–16.8)0.76  |          |          |
| 48 h                  | 28.6 (15.3–38.2)| 3.2 (2.1–5.4)0.001  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| CARL (unstimulated)   |               |          |          |          |
| 6 h                   | 13.7 (7.3–19.6)| 37.7 (18.1–54.6)0.01  |          |          |
| 48 h                  | 19.1 (11.6–30.3)| 7.8 (4.9–12.9)0.01  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| CARL (Pam2)           |               |          |          |          |
| 6 h                   | 10.9 (7.5–21.3)| 31.3 (10.1–57.4)0.01  |          |          |
| 48 h                  | 32.4 (13.7–42.9)| 8.5 (4.6–20.3)0.01  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| CARL (MDP)            |               |          |          |          |
| 6 h                   | 13.1 (8.1–28.9)| 37.7 (15.1–45.3)0.01  |          |          |
| 48 h                  | 28.4 (12.8–44.1)| 8.5 (4.3–15)0.01  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| SKALP/elafin (unstimulated) | 1.9 (0.8–3.4)| 4.3 (2.3–5.4)0.02  |          |          |
| 48 h                  | 2.5 (0.6–5.4)| 0.5 (1.0–1.2)0.01  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| SKALP/elafin (Pam2)   |               |          |          |          |
| 6 h                   | 3.1 (0.7–4.1)| 5.7 (1.9–13)0.01  |          |          |
| 48 h                  | 2.9 (0.4–6.9)| 1.5 (0.9–1.8)0.25  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |
| SKALP/elafin (MDP)    |               |          |          |          |
| 6 h                   | 2.7 (0.65–5.7)| 3.8 (2.7–9.5)0.07  |          |          |
| 48 h                  | 3.6 (0.85–6.3)| 1.1 (0.37–2.2)0.02  |          |          |
| 6 h vs. 48 h          | P < 0.05      | P > 0.05 |          |          |

hBD, human β-defensin; HS, hidradenitis suppurativa; MDP, muramyl dipeptide; NOD, nucleotide-binding oligomerization domain-containing; Pam2, Pam2CSK4; RIP, receptor-interacting serine/threonine-protein kinase; SKALP, skin-derived antileukopo-
stimulated normal keratinocytes (Fig. 1c), expression of NOD2, RIP2, CARL and SKALP/elafin significantly increased from 6 to 48 h. By contrast, in unstimulated, Pam2-stimulated and MDP-stimulated HS keratinocytes, RIP2, CARL and SKALP/elafin expression significantly declined from 6 to 48 h. At 6 h, mRNA expression of NOD2 (unstimulated, Pam2-stimulated, MDP-stimulated), CARL (unstimulated, Pam2-stimulated, MDP-stimulated) and SKALP/elafin (unstimulated, Pam2-stimulated) was significantly increased in HS compared with normal keratinocytes. However, at 48 h, mRNA expression of NOD2 (unstimulated, Pam2-stimulated), RIP2 (unstimulated, Pam2-stimulated, MDP-stimulated), CARL (unstimulated, Pam2-stimulated, MDP-stimulated) and SKALP/elafin (unstimulated, MDP-stimulated) was significantly decreased in HS compared with normal keratinocytes. HS keratinocytes differed from normal keratinocytes with respect to expression behaviour and timing, independently of stimulation. Unlike normal keratinocytes, HS keratinocytes were characterized by early gene upregulation of NOD2, RIP2, CARL and SKALP/elafin (Fig. 1c).

Apart from NOD2 and associated factors, we also investigated SKALP/elafin in HS, which is the first such study, to our knowledge. SKALP/elafin is an inducible keratinocyte-derived proteinase inhibitor with specificity for polymorphonuclear leucocyte-derived elastase and proteinase-3. SKALP/elafin is virtually absent in normal human epidermis but is found in a number of inflammatory skin diseases, including psoriasis.19,20 It seems to act as a modulator of epidermal inflammation by interfering with polymorphonuclear leucocyte trafficking and could protect structural proteins against elastase-mediated damage. It has also been found to possess antimicrobial activity and is thus part of the cutaneous host defence system. Inflamed epidermis (psoriasis, wound healing, ultraviolet-irradiated skin) contains keratinocytes that are hyperproliferative and display an abnormal differentiation programme, resulting in expression of anti-inflammatory proteins such as SKALP/elafin. Similar to other inflammatory epidermal changes, inflammation in HS is associated with SKALP/elafin gene upregulation, indicating common compensatory mechanisms in these conditions.19,20

Conclusion

We have shown for the first time that the NOD2 signalling is activated in HS and might contribute to the pathogenesis via induction of AMPs and activation of pathways such as NFκB signalling.

What's already known about this topic?

- HS is associated with dysregulated immune responses including altered expression of cytokines, chemokines and antimicrobial proteins.
- NOD2 signalling has not been studied in HS.

What does this study add?

- NOD2 signalling is activated in HS and might contribute to the pathogenesis of HS via induction of AMPs and activation of pathways such as NFκB signalling.

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