

The Oncostatin M Receptor Beta Axis Identified in Prurigo Nodularis

Zamaneh Mikhak,¹ Sonja Ständer,² Emma Guttman,³ Dieter Metzger,² Ana Pavel,³ Gil Yosipovitch,⁴ Jonathan Silverberg,⁵ Rohan Gandhi,¹ Joe Pirrello,¹ Katalin Kis-Toth,¹ LOTUS-PN Study Group, and John F. Paolini¹

¹Kiniksa Pharmaceuticals Corp., Lexington, MA, USA; ²University of Münster, Münster, Germany; ³Mount Sinai Hospital, New York, NY, USA; ⁴University of Miami, Miami, FL, USA; ⁵Northwestern University, Evanston, IL, USA

BACKGROUND

- Prurigo nodularis (PN) is a chronic skin disease characterized by intensely pruritic hyperkeratotic nodules¹
- The pathogenesis of PN is unclear but is thought to involve neuronal sensitization, triggering a pruritus-scratch cycle that results in inflammation, hyperkeratosis, fibrosis, and ultimately nodule formation^{1,2}
- PN carries a high unmet medical need, as the intractable pruritus, intense itching, and ensuing lesions lead to sleep loss, embarrassment, anxiety, and depression^{3,4}
- Currently, there are no approved treatments for PN
- Oncostatin M receptor β (OSMR β) is the shared receptor subunit for interleukin 31 (IL-31) and oncostatin M (OSM) signaling, cytokines important in pruritus, inflammation, hyperkeratosis, and fibrosis (Figure 1), 4 pathways that characterize PN pathology^{1,5}
- IL-31 is a known pruritogen in atopic dermatitis (AD)^{5,6}; however, its role in PN pathophysiology has not been elucidated
- The contribution of OSM to PN pathology is also unknown

OBJECTIVE

- Longitudinal Trial to Understand Symptomatology in PN (LOTUS-PN) was a longitudinal/observational study conducted in the United States and Europe to investigate PN pathophysiology
 - One exploratory goal of this study was to correlate mechanistic biomarkers with clinical endpoints
 - IL-31, OSM, IL-31 receptor α (IL-31R α), and OSMR β mRNA and protein expression were investigated in skin biopsies of enrolled PN patients and compared with healthy and AD samples; IL-31 levels were investigated in PN and AD plasma samples

Figure 1. IL-31 and OSM Receptor Signaling

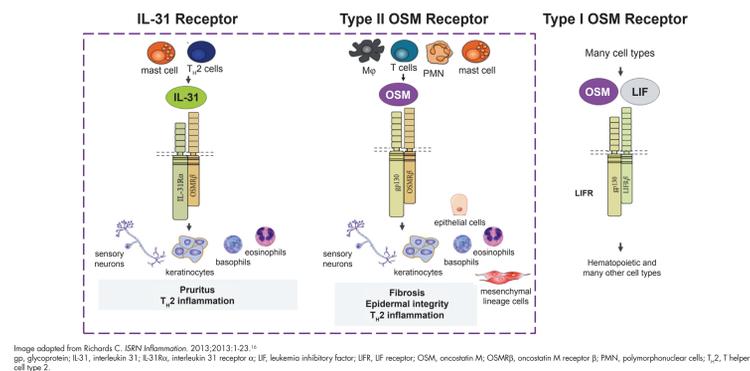


Image adapted from Richards C. *ISRN Inflammation*. 2013;2013:1-23.
 go, glycoprotein; IL-31, interleukin 31; IL-31R α , interleukin 31 receptor α ; IF, leukemia inhibitory factor; LIFR, LIF receptor; OSM, oncostatin M; OSMR β , oncostatin M receptor β ; OSMR α , oncostatin M receptor α ; T₂, T helper cell type 2.

METHODS

Design

- Eligible patients were adults ≥ 18 years of age with a diagnosis of PN (new or established)
 - Diverse etiologies were enrolled (eg, atopic, gastrointestinal, hematologic, infectious, renal disease)
- No investigational drug was administered
 - Patients received standard of care treatment deemed appropriate by their investigator physician
- This study assessed patients at baseline and at monthly scheduled intervals and during unscheduled visits for disease flare for a period of up to 12 months

Biopsy and Plasma Samples

- Lesional (LS) and non-lesional (NL) skin biopsies and plasma samples were collected from PN patients
 - Biopsy samples were split: half of the tissue was placed in RNA lysis buffer, and half was preserved for immunohistochemistry (IHC)
 - Analyses of baseline samples are presented in this work
 - Positive control biopsies (LS and NL) and plasma samples were collected from AD patients enrolled in the phase 1b KPL716 clinical study
 - Negative control biopsies from healthy volunteers (HC) were obtained independently from the tissue bank of the Guttman laboratory

Assessments

- Messenger RNA (mRNA) expression of IL-31, OSM, IL-31R α , and OSMR β was measured by quantitative real-time polymerase chain reaction (qRT-PCR) using a TaqMan Low-Density Array
 - The PN and AD experiments were run separately using the same set of HC samples
 - Samples were considered positive for target gene expression if the cycle threshold value was < 35
 - Ribosomal protein RPLP0 expression was used to normalize gene expression levels
- Protein expression of IL-31, OSM, IL-31R α , and OSMR β in tissues was analyzed using IHC
- IL-31 protein levels from plasma samples were measured using Single Molecule Array (Simoa)

Analyses

- Weekly average Worst Itch Numeric Rating Scale (W-NRS) values from PN and AD patients were calculated within the week the biopsy was taken
- RNA and protein expression levels were assessed based on W-NRS
 - PN subjects were grouped according to their baseline pruritus level as W-NRS < 7 or W-NRS ≥ 7
 - All AD patients recorded a W-NRS ≥ 5 at the time of biopsy
- The following measurements per target molecule were taken (labeled by figure panel)
 - A: qRT-PCR – qualitative presentation of percent positive biopsies for target gene expression
 - B: qRT-PCR – quantitative presentation of normalized gene expression
 - C: IHC of skin tissue (tissue staining for target molecules was scored as negative, questionable, positive, or strong positive)
 - D: Target molecule expression levels represented by IHC score
 - E: IL-31 plasma levels; single molecule array to measure plasma levels
- Statistical comparisons
 - Kruskal-Wallis test (quantitative presentation of normalized gene expression; *P* values adjusted for multiplicity)
 - Friedman test (target molecule expression levels represented by IHC score)

RESULTS

- Patient demographics are presented in Table 1

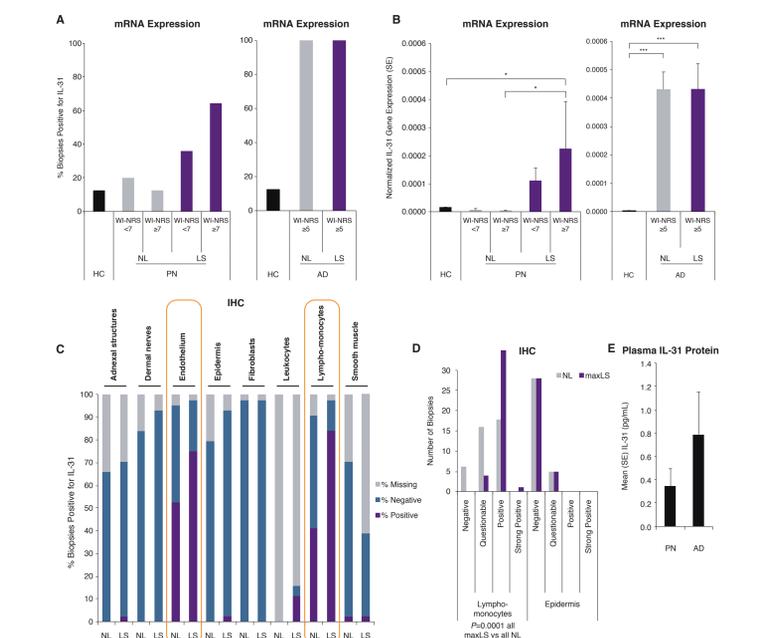
Table 1. Demographics

| | PN ^a N=54 | AD ^b N=32 |
|---|-------------------------|-------------------------|
| Age, mean (SD), years | 53.8 (12.9) | 35 (11.6) |
| Female, n (%) | 31 (57) | 15 (47) |
| Race, n (%) | | |
| White | 35 (65) | 18 (56) |
| Black or African American | 15 (28) | 9 (28) |
| Asian | 1 (2) | 3 (9) |
| American Indian or Alaska Native | 1 (2) | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 2 (6) |
| Multiple | 0 | 0 |
| Other | 2 (4) | 0 |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (4) | 7 (22) |
| Not Hispanic or Latino | 51 (94) | 25 (78) |
| Unknown | 1 (2) | 0 |
| Country of residence, n (%) | | |
| Germany | 15 (28) | NA |
| Poland | 5 (9) | NA |
| United States | 34 (63) | 30 (94) |
| Canada | NA | 2 (6) |

^a Patient demographics from LOTUS-PN; ^b patient demographics from phase 1b trial in patients with AD. AD, atopic dermatitis; NA, not applicable; PN, prurigo nodularis; SD, standard deviation.

- IL-31 mRNA was detectable in a higher percentage of LS PN biopsies than NL biopsies (1.8 times higher in patients with W-NRS < 7 and 5.1 times higher in patients with W-NRS ≥ 7 ; Figure 2A)
 - IL-31 mRNA was detectable in 100% of AD (LS and NL) biopsies
- IL-31 mRNA expression was higher in LS PN biopsies compared with NL PN biopsies in patients with W-NRS ≥ 7 (Figure 2B)
 - Numerically higher IL-31 mRNA expression levels were observed in LS PN samples with W-NRS < 7 compared with LS PN samples with W-NRS ≥ 7
 - LS samples from PN patients with W-NRS ≥ 7 as well as LS and NL samples from AD patients with W-NRS ≥ 5 expressed higher levels of IL-31 compared with HC samples
- Endothelial cells and lymphomonocytes were identified as primary sources of IL-31 production in PN biopsies (Figure 2C)
- Lymphomonocytes from LS PN biopsies expressed higher levels of IL-31 compared with lymphomonocytes from NL PN samples (*P* = 0.0001; Figure 2D)
- IL-31 protein was detected in both PN and AD plasma samples (Figure 2E)

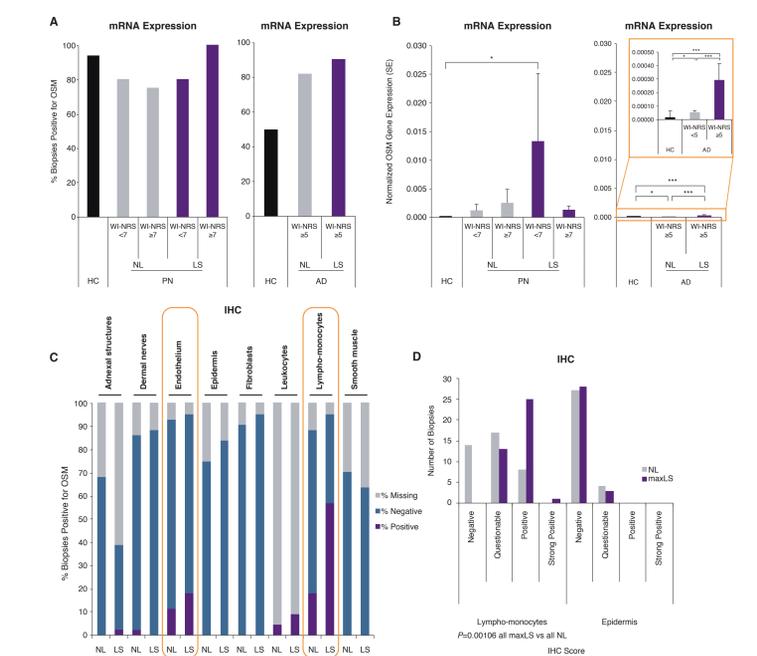
Figure 2. IL-31 Is Upregulated in Lesional PN Biopsies



W-NRS ranges from 0 ("no itch") to 10 ("worst imaginable itch").
 AD, atopic dermatitis; HC, healthy volunteers; IHC, immunohistochemistry; IL-31, interleukin 31; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis; SE, standard error; W-NRS, Worst Itch Numeric Rating Scale.
^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.005.

- OSM mRNA was detectable in 100% of LS biopsies from PN patients with W-NRS ≥ 7 and in 91% of LS biopsies from AD patients (Figure 3A)
- OSM mRNA expression was higher in LS PN biopsies from patients with W-NRS < 7 compared with HC samples (Figure 3B)
 - Numerically higher OSM mRNA expression levels were observed in LS PN biopsies with W-NRS < 7 compared with LS PN biopsies with W-NRS ≥ 7 , NL PN biopsies, and AD samples
- Endothelial cells and lymphomonocytes were identified as primary sources of OSM production in PN biopsies (Figure 3C)
- Lymphomonocytes from LS PN biopsies expressed higher levels of OSM compared with lymphomonocytes from NL PN samples (*P* = 0.00106; Figure 3D)

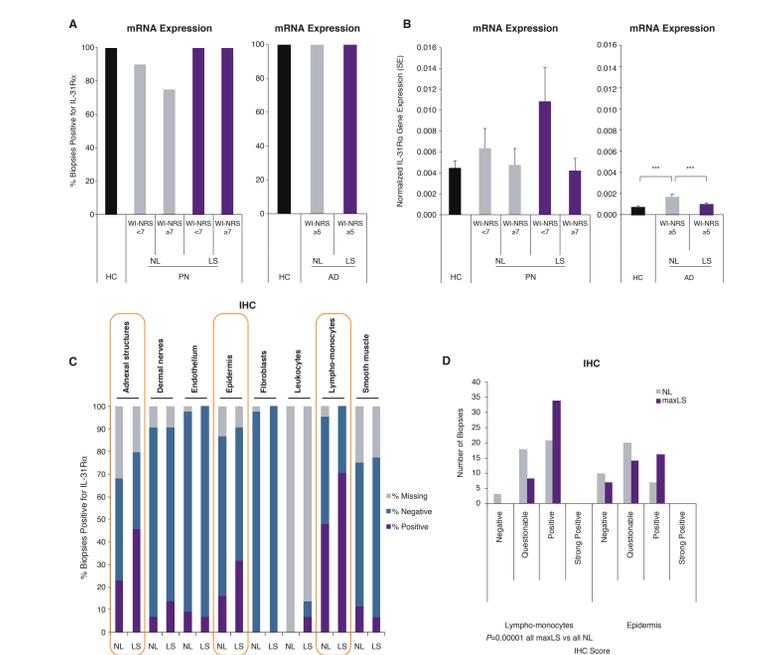
Figure 3. OSM Is Upregulated in Lesional PN Biopsies



W-NRS ranges from 0 ("no itch") to 10 ("worst imaginable itch").
 AD, atopic dermatitis; HC, healthy volunteers; IHC, immunohistochemistry; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; OSM, oncostatin M; PN, prurigo nodularis; SE, standard error; W-NRS, Worst Itch Numeric Rating Scale.
^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.005.

- IL-31R α mRNA was detectable in 75% to 100% of biopsies from healthy volunteers, PN patients, and AD patients (Figure 4A)
- Numerically higher IL-31R α mRNA expression levels were observed in LS PN biopsies with W-NRS < 7 compared with LS PN biopsies with W-NRS ≥ 7 , NL PN biopsies, AD, and HC samples (Figure 4B)
 - NL AD biopsies expressed higher levels of IL-31R α compared with LS AD and HC samples
- Adnexal structures, epidermis, and lymphomonocytes were common sources of IL-31R α in PN biopsies (Figure 4C)
- Lymphomonocytes from LS PN biopsies expressed higher levels of IL-31R α compared with lymphomonocytes from NL PN samples (*P* = 0.00001; Figure 4D)

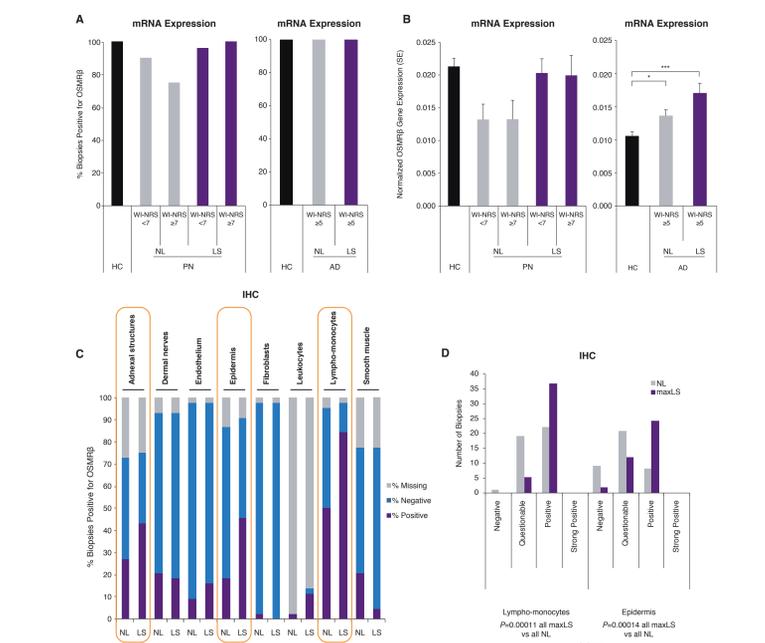
Figure 4. IL-31R α Is Upregulated in Lesional PN Biopsies



W-NRS ranges from 0 ("no itch") to 10 ("worst imaginable itch").
 AD, atopic dermatitis; HC, healthy volunteers; IHC, immunohistochemistry; IL-31R α , interleukin 31 receptor α ; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; PN, prurigo nodularis; SE, standard error; W-NRS, Worst Itch Numeric Rating Scale.
^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.005.

- OSMR β mRNA was detectable in 75% to 100% of healthy volunteers, PN patients, and AD patients (Figure 5A)
- Numerically higher OSMR β mRNA expression levels were observed in LS PN samples compared with NL PN samples (Figure 5B)
 - LS and NL AD samples showed higher levels of OSMR β expression compared with HC samples
- Adnexal structures, epidermis, and lymphomonocytes were common sources of OSMR β in PN biopsies (Figure 5C)
- Lymphomonocytes and epidermal cells from LS biopsies showed significantly higher expression levels of OSMR β than lymphomonocytes and epidermal cells from NL biopsies (*P* = 0.00011 and *P* = 0.00014, respectively; Figure 5D)

Figure 5. OSMR β Is Upregulated in Lesional PN Biopsies



W-NRS ranges from 0 ("no itch") to 10 ("worst imaginable itch").
 AD, atopic dermatitis; HC, healthy volunteers; IHC, immunohistochemistry; LS, lesional; maxLS, the maximum lesional value per subject if 2 LS biopsies were available; NL, non-lesional; OSMR β , oncostatin M receptor β ; PN, prurigo nodularis; SE, standard error; W-NRS, Worst Itch Numeric Rating Scale.
^a*P* < 0.05, ^b*P* < 0.01, ^c*P* < 0.005.

CONCLUSIONS

- The OSMR β axis molecules, IL-31, OSM, IL-31R α , and OSMR β , are upregulated in lesional PN biopsies versus non-lesional biopsies, based on gene and protein expression
- Increased IL-31 mRNA expression in PN biopsies is associated with increased pruritus severity
- IL-31 mRNA expression level in AD is increased in both LS and NL biopsies
- Endothelial cells and lymphomonocytes are the primary sources of IL-31 and OSM production, while adnexal structures, epidermis, and lymphomonocytes are common sources of IL-31R α and OSMR β in PN biopsies
- Lymphomonocytes in LS biopsies express higher levels of all OSMR β axis molecules compared with non-lesional samples

The OSMR β axis (IL-31, OSM, IL-31R α , and OSMR β) may play a role in the pathogenesis of PN given its prevalent expression in PN lesional skin and represents an attractive target for pharmacological intervention in PN

REFERENCES

- Ständer S, et al. *J Invest Dermatol*. 2018;128:1897-907.
- Yosipovitch G, et al. *J Invest Dermatol*. 2018;128:1897-907.
- Yosipovitch G, et al. *J Invest Dermatol*. 2018;128:1897-907.
- Yosipovitch G, et al. *J Invest Dermatol*. 2018;128:1897-907.
- Yosipovitch G, et al. *J Invest Dermatol*. 2018;128:1897-907.

DISCLOSURES

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