TITLE: The Oncostatin M receptor beta axis identified in prurigo nodularis

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ABSTRACT: Prurigo nodularis (PN) is characterized by intensely-pruritic hyperkeratotic nodules. The role of Oncostatin M receptor beta (OSMRβ), the shared receptor subunit for IL-31 and oncostatin M (OSM) signaling, involved in pruritus, inflammation and fibrosis, in PN pathogenesis is unknown. LOTUS-PN is a longitudinal/observational study conducted in the United States and Europe to investigate PN pathophysiology. Medical history, pruritus (eDiary), sleep, quality of life, disease severity, blood, and skin biopsies were collected from baseline to 12 months. Skin biomarker gene expression (RT-PCR; mRNA) and immunohistochemistry (IHC; protein) results were correlated with Worst Itch Numeric Rating Scale (WI-NRS). Gene expression results were benchmarked to atopic dermatitis (AD) and normal skin. IL-31 mRNA was expressed in 55% of lesional (LS) PN, 18% of non-lesional (NL) PN, 19% of healthy volunteer, and 100% of AD biopsies (LS and NL). IL-31 mRNA was expressed in 100% of LS biopsies from PN patients with WI-NRS ≥7. IL-31 protein (IHC) was expressed in mononuclear cells in the majority of LS PN biopsies (89%) vs 44% of NL PN biopsies. Polymorphonuclear cells (PMN), when present, and endothelial cells were other common sources of IL-31 in LS PN skin. Expression of OSM, IL-31Rα, and OSMRβ mRNA was ubiquitous (90-100%) in LS or NL PN, LS or NL AD or healthy volunteer biopsies. However, a higher proportion of LS PN biopsies contained mononuclear cells expressing IL-31Rα (1.7-fold), OSM (3.4-fold), and OSMRβ (1.8-fold) protein than NL PN biopsies. Epidermal cells, and when present, PMN, dermal nerves, and adnexal structures were other common sources of IL-31Rα and OSMRβ in LS PN skin. The OSMRβ axis (IL-31, OSM, IL-31Rα, and OSMRβ) may play a role in the pathogenesis of PN given its prevalent expression in PN LS skin and represents an attractive target for pharmacological intervention in PN.