SHORT COMMUNICATION

Absence of Full-length Neurokinin-1 Receptor Protein Expression by Cutaneous T Cells: Implications for Substance P-mediated Signaling in Mycosis Fungoides

Marina Tuzova1, Tara Conniff2, Clara Curiel-Lewandrowski3, Keri Chaney4, William Cruikshank1 and Deon Wolpowitz2*

1 The Pulmonary Center, 2 Department of Dermatology and Section of Dermatopathology, Boston University School of Medicine, Boston, MA 02118, 3 Arizona Cancer Center, Arizona State University, Tucson, and 4 Dana Farber Cancer Institute, Harvard Medical School, Boston, USA. *E-mail: dewolpow@bu.edu

Accepted Jan 25, 2015; Epub ahead of print Mar 18, 2015

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma composed of epidermotropic atypical effector memory T lymphocytes (1). MF patients can suffer from debilitating pruritus (1). Clinical and experimental observations implicate signaling by the neurokinin-1 receptor (NK1R) and its highest affinity ligand, substance P (SP), in the epidermotropism and pruritus of MF. In early-stage skin lesions of MF, malignant epidermotropic T cells line up at the dermal–epidermal junction (DEJ), the anatomic site of termination of SP-expressing nerves (2). SP induced chemotaxis and proliferation of normal T lymphocytes in vitro, and this effect utilized the NK1R (3, 4). The pruritus of MF remits with treatments that reduce or eradicate malignant T cells (5). The pruritus in some MF patients, based on case reports, can respond rapidly to aprepitant, an oral NK1R antagonist (6). NK1R expression and signaling has been demonstrated in T cells in vitro, and this effect utilized the NK1R (3, 5, 6). Fl-NK1R was not detected in CD3+ T lymphocytes from peripheral blood cytospins in normal donors and 4 of 4 MF subjects (both early and later stages of MF) (Fig. S2†), randomly selected from the ELISA samples (Table SII). Circulating versus organ-specific T cells can differ in their synthesis and cell surface expression of proteins, and NK1R-expression has been reported in circulating T lymphocytes (10, 11).

Given the presence of NK1R-expressing circulating T cells, we measured systemic SP levels in MF subjects whose demographics are presented in Table SII. These samples were divided into early stage (stages Ia, Ib) and later stages (IIa–III). Compared to healthy controls (median, 25–75%: 194, 102.5–212.8 pg/ml), early (499, 267.9–574 pg/ml; p = 0.0106) and later-stage MF groups (541.7, 395.1–582.7 pg/ml; p = 0.0032) showed a significant increase in serum SP levels (Fig. 1). Expansion or proliferation of SP nerves in the papillary dermis did not account for the elevated systemic SP in MF subjects. SP(+) nerves are a minority of the total percent of PGP9.5+ intra-epidermal and papillary dermal nerves in MF subjects (median; 25–75%: 4.8%, 1.7–6.6%), similar to NHS (8.1%, 4.4–12.8%) (2). SP-expressing nerves were located predominantly in the papillary dermis and rarely entered the epidermis in MF subjects (0%, 0–2.2% of PGP9.5+ intra-epidermal nerves) (Fig. 1). SP expression was not detectable in CD3+ T cells or in mast cells in NHS or MFS (2), Fig. 1 and Fig. S1†.

DISCUSSION

We postulated that putative SP/NK1R signaling in migration, proliferation, and/or pruritus generation in MF would involve SP directly activating NK1R on malignant T cells (3, 5, 6). Fl-NK1R was not detected in T cells in normal skin or MF skin lesions, including in 5 MF skin samples with known and active pruritus of the specific lesion biopsied at the time of biopsy. Our findings are potentially limited by the inability of the C-terminus antibody to detect the shorter NK1R isoform

1The specific lesion biopsied at the time of biopsy. Our findings are potentially limited by the inability of the C-terminus antibody to detect the shorter NK1R isoform

http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2097

© 2015 The Authors. doi: 10.2340/00015555-2097
Journal Compilation © 2015 Acta Dermato-Venereologica. ISSN 0001-5555
ACKNOWLEDGMENTS
The authors thank Natalie Adams and Lynne Morrison, who consented MF patients and collected blood samples at DFCI and AZCC; Oksana Hradyska and Phillip Vartanian for technical assistance; and Dr. Michael Kirber, Boston University Cellular Imaging Core, for imaging assistance. This study was supported in part by CTSA NIH grant UL1-TR000157 and by NIH R01CA122737-01A2.

REFERENCES

missing the last 96 amino acids of the C-terminus (7). Given the absence of a functioning N-terminal antibody (see Appendix S1), we cannot exclude expression of truncated NK1R in MF subjects. Nevertheless, we found concordance between the expression pattern we obtained and that reported using labeled SP (9). SP/NK1R signaling in MF skin lesions may play a biological role independent of fl-NK1R in skin T cells. The skin remains an important site for generation of pruritogens in MF, and SP may contribute through fl-NK1R-expressing keratinocytes or mast cells, or through malignant T cells using an NK1R-independent mechanism (12). The biological significance of the elevated systemic SP levels in MF is still unknown. In MF subjects, elevated SP levels occurred in the absence of a proliferation of SP-expressing papillary dermal nerves. Elevated SP levels correlated with itch intensity in atopic dermatitis (13). In MF, both the degree of pruritus (1) and systemic SP levels increased with disease stage. Our study is limited by the absence of prospective quantitation of pruritus severity to correlate with serum SP measurements. Nevertheless, our data provide biologic rationale for a future such investigation to assess the contribution of systemic SP to MF itch.

In conclusion, elevated systemic SP levels may contribute to the pathophysiology of MF using fl-NK1R-expressing skin cells, central nervous system cells (7), and now circulating lymphocytes. This complex distribution of NK1R expression highlights the need for both in vitro and prospective in vivo studies to ascertain further the contribution of SP and NK1R signaling to MF pathogenesis and pruritus.