

## EDITORIAL

## INTERLEUKIN-31: A NEW CYTOKINE INVOLVED IN INFLAMMATION OF THE SKIN

M.L. CASTELLANI, V. SALINI, S. FRYDAS<sup>1</sup>, J. DONELAN<sup>2</sup>,  
B. MADHAPPAN<sup>2</sup>, C. PETRARCA<sup>3</sup>, J. VECCHIET<sup>4</sup>, K. FALASCA<sup>4</sup>, G. NERI<sup>5</sup> and S. TETE<sup>6</sup>

*Department of Medicine and Science of Aging, University of Chieti, Chieti, Italy;*

*'Department of Parasitology, Veterinary School, Aristotelian University, Thessaloniki, Greece;*

*<sup>2</sup>Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, U.S.A.; <sup>3</sup>Division of Immunology, <sup>4</sup>Infectious Diseases <sup>5</sup>Otolaryngology Division, and <sup>6</sup>Dental School, University of Chieti, Chieti, Italy*

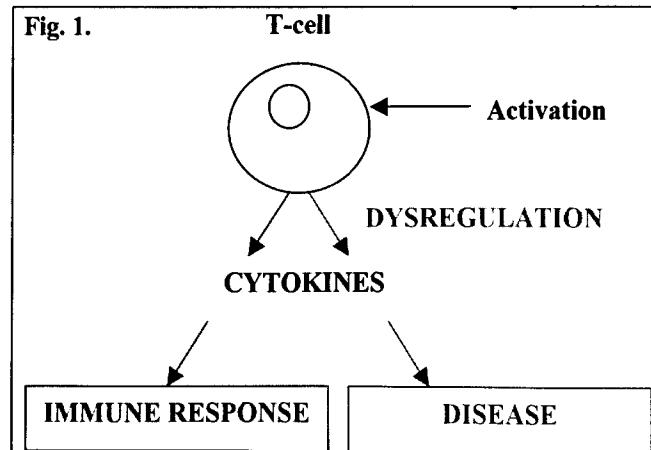
Received December 16, 2004 – Accepted January 13, 2006

Cytokines affect immune functions involved in motility, chemotaxis, phagocytosis, cytotoxicity and antigen presentation (1). Interleukins (IL) are pleiotropic cytokines with diverse receptor signaling pathways whose expression is controlled at multiple levels (2). Interleukin receptors (ILR) have intrinsic roles in regulating and amplifying the inflammatory response (3-12).

Skin is the largest organ of the body with the specific immune defense and its inflammatory conditions include atopic dermatitis, allergies, psoriasis etc. (13-19). Infiltrated lymphocytes proliferate in an activated state in the skin lesion in an autocrine and/or paracrine manner and produce TH2-type cytokines that might evoke immunologic abnormalities (20-23). The skin lesion is characterized by massive infiltration of mononuclear cells including CD4<sup>+</sup> T helper cells and mast cells (24-27). Several cytokines exhibit the capacity to induce T cell response (28-30). It has been reported that GM-CSF plays an important role in the development and perpetuation of atopic dermatitis (31). In addition, psoriasis is regarded as a type-1 T cell-mediated, chronic inflammatory skin disease where IL-15 triggers inflammatory cell recruitment, angiogenesis and production of other inflammatory cytokines (32-33). Interferon-gamma (IFN-gamma),

TNF-alpha and IL-17 are up-regulated in psoriatic lesions. Transforming growth factor- alpha (TGF-alpha) is also highly expressed in the suprabasal layers of epidermis where neutrophils tend to collect in psoriatic lesions. Moreover, increased expression of IL-23, a cytokine which shares the p40 chain with IL-12, is found in psoriatic lesions (34-39).

IL-31 is a newly described immunoregulatory cytokine that is mainly produced by activated TH<sub>2</sub> cells. IL-31 acts through the heterodimeric receptors IL-31R A and oncostatin receptor (OSMR) which are expressed on IL-31 activated monocytes and expressed on epithelial cells and keratinocytes respectively. Recently



**Key words:** cytokine, IL-31, inflammation, dermatitis, T cell response

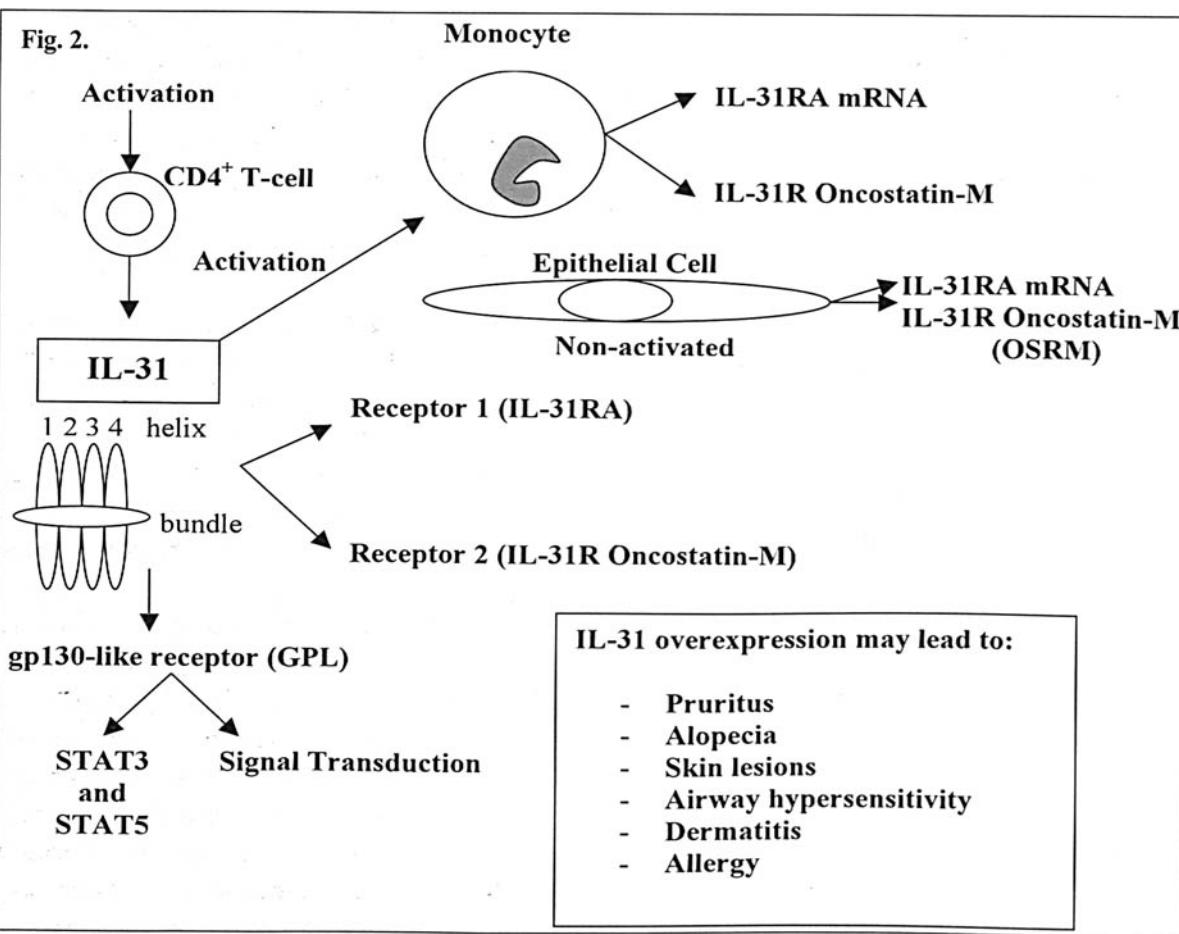
*Mailing address:*

Dr. M.L. Castellani  
Department of Medicine  
Faculty of Medicine  
University of Chieti  
Via dei Vestini 66013 Chieti, Italy  
Tel: +39-0871-3555293  
E-mail: mlcastellani@unich.it

0394-6320 (2006)

Copyright © by BIOLIFE, s.a.s.

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder.  
Unauthorized reproduction may result in financial and other penalties



it has been found that IL-31 is involved in dermatitis, pruritic skin lesions, allergy and airway hypersensitivity. IL31R A is highly homologous with the gp 30-like receptor (GPL), which mediates signal transduction and activate the signal transducer and activator transcription factor 3 (STAT3) and 5 (STAT5). It has been reported that CD4<sup>+</sup> T cells are a very important source of IL-31. Since the development of dermatitis is mediated by gamma delta T cells, it is likely that IL-31 is involved in the proliferation and activation of these cells in skin diseases.

IL-31 is an important player of T cell mediated immune response and underlines the important implications of this cytokine in inflammation and degenerative skin diseases.

The involvement of IL-31 in dermatitis offers the potential of serving as a useful tool for investigating the immunological role of cutaneous gamma/delta T cells. The importance of IL-31 as a mediator of the skin inflammatory diseases is not known; however, we believe that a single cytokine may not explain the pathogenesis of dermatitis.

## REFERENCES

1. Oppenheim J.J and F.W. Ruscetti. 1997. Cytokines. In *Medical Immunology*, 9<sup>th</sup> ed. D.P. Stites, A.I. Terr and T.G. Parslow. Appleton and Lange Stamford, Connecticut, p.146.
2. Abbas A.K., A.H. Lichtman and J.S. Pober. 1991. Cells and tissues of the immune system. In *Cellular and Molecular Immunology*. A.K. Abbas, ed. W.B. Saunders Company Philadelphia, p. 14.
3. Sodin-Semrl S., A. Spagnolo, R. Mikus, B. Barbaro, J. Varga and S. Fiore. 2004. Lipoxin A<sub>4</sub> and serum amyloid A elicit opposite interleukin-8 and NF-κB responses via the common ALX receptor. *Int. J. Immunopathol. Pharmacol.* 17:145.
4. Lo Iacono M., F. Cavallo, E. Quaglino, S. Rolla, M. Iezzi, S. M. Pupa, C. De Giovanni, P-L. Lollini, P. Musiani, G. Forni and R. A. Calogero. 2005. A limited autoimmunity to p185<sup>neu</sup> elicited by DNA and allogeneic cell vaccine hampers the progression of preneoplastic lesions in her-2/neu transgenic mice. *Int.*

- J. Immunopathol. Pharmacol.* 18:351.
5. Kempuraj D., J. Donelan, S. Frydas, T. Iezzi, P. Conti, W. Boucher, N. G. Papadoopoulou, B. Madhappan, L. Letourneau, G. Sabatino and T.C. Theoharides. 2004. Interleukin-28 and 29 (IL-28 and IL-29): new cytokines with anti-viral activities. *Int. J. Immunopathol. Pharmacol.* 17:103.
  6. Kempuraj D., S. Frydas, E. Karagouni, M. Hatzistilianou, P. Boscolo, F. Ferro, M. Di Giannantonio, C.M.V. Conti, D. Merlini R. Doyle, C. Petrarca, M.L. Castellani and T.C. Theoharides. 2004. Cytokines and the brain. *Int. J. Immunopathol. Pharmacol.* 17:229.
  7. Diaco M., F. Ancarani, M. Montalto, E. Verrecchia, A. Evoli, S. Servidei, G. Gasbarrini and R. Manna. 2004. Association of myasthenia gravis and antisynthetase syndrome: a case report. *Int. J. Immunopathol. Pharmacol.* 17:395.
  8. Marchisio M., G.M. Sabatino, A. Albanese, E. Santavenere, R. Buonaguidi and S. Miscia. 2004. Novel evidence of PLC d2 involvement in the regulation of the differential evolution of human aneurysms. *Int. J. Immunopathol. Pharmacol.* 17:381.
  9. Peene I., L. De Rycke, D. Baeten, I. Hoffman, E.M. Veys and F. De Keyser. 2004. History and diagnostic value of antibodies to citrullinated proteins in rheumatoid arthritis. *Int. J. Immunopathol. Pharmacol.* 17:107.
  10. Franchi C., G. Cainelli, E. Frigerio, C. Garutti and G.F. Altomare. 2004. Association of Cyclosporine and 311 nm UVB in the treatment of moderate to severe forms of psoriasis: a new strategic approach. *Int. J. Immunopathol. Pharmacol.* 17:401.
  11. Mastrangelo F., M. Piccirilli, M. Dolci, S. Teté, L. Speranza, A. Patruno, F. Gizzi, M. Felaco, L. Artese and M.A. De Lutiis. 2005. Vascular endothelial growth factor (VEGF) in human tooth germ center. *Int. J. Immunopathol. Pharmacol.* 18:587.
  12. Kalogeromitros D., D. Kempuraj, A. Katsarou-Katsari, S. Gregoriou, M. Makris, W. Boucher and T.C. Theoharides. 2005. Theophylline as "add-on" therapy in patients with delayed pressure urticaria: a prospective self-controlled study. *Int. J. Immunopathol. Pharmacol.* 18:595.
  13. Dillon S.R., C. Sprecher, A. Hammond, et al. 2004. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat. Immunol.* 5:752.
  14. Dreuw A., S. Radtke, S. Pfanz, et al. 2004. Characterization of the signaling capacities of the novel gp130-like cytokine receptor. *J. Biol. Chem.* 279:36112.
  15. Matalon R., S. Surendran, J.D. McDonald, A.O. Okorodudu, S.K. Tyring, K. Michals-Matalon and P. Harris. 2005. Abnormal expression of genes associated with development and inflammation *Int. J. Immunopathol. Pharmacol.* 18:557.
  16. Liu Q. and M. R. Hamblin. 2005. Macrophage-targeted photodynamic therapy: scavenger receptor expression and activation state *Int. J. Immunopathol. Pharmacol.* 18:391.
  17. Ottonello L., M. Bertolotto, F. Montecucco, P. Dapino and F. Dallegrì. 2005. Dexamethasone - induced apoptosis of human monocytes exposed to immune complexes. Intervention of CD95- and XIAP-dependent pathways *Int. J. Immunopathol. Pharmacol.* 18:403.
  18. Cross M.L. 2004. Immune-signalling by orally-delivered probiotic bacteria: effects on common mucosal immunoresponses and protection at distal mucosal sites. *Int. J. Immunopathol. Pharmacol.* 17:127
  19. Marinova S., P. Nenkov, R. Markova, S. Nikolaeva, R. Kostadinova, I. Mitov and M. Vretenarska. 2005. Cellular and humoral systemic and mucosal immune responses stimulated by an oral polybacterial immunomodulator in patients with chronic urinary tract infections. *Int. J. Immunopathol. Pharmacol.* 18:457.
  20. Moseley T.A., D.R. Haudenschild, L. Rose and A.H. Reddi. 2003. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev.* 14:155.
  21. Montalto M., L. Santoro, M. Vastola, V. Curigliano, R. Ricci, F.M. Vecchio, R. Manna and G. Gasbarrini. 2005. Normalisation of high CA 19-9 values in autoimmune hepatitis after steroid treatment. *Int. J. Immunopathol. Pharmacol.* 18:603.
  22. Esposito I., F. Perna, A. Ponticello, M. Perrella, M. Gilli and A. Sanduzzi. 2005. Natural killer cells in bland peripheral blood of patients with idiopathic pulmonary fibrosis (IPF). *Int. J. Immunopathol. Pharmacol.* 18:541.
  23. Gorbunov N.V., S.J. McFaul, A. Janusziewicz and J.L. Atkins. 2005. Pro-inflammatory alterations and status of blood plasma iron in a model of blast-induced lung trauma. *Int. J. Immunopathol. Pharmacol.* 18:547.
  24. Ballerini P., R. Ciccarelli, F. Caciagli, M.P. Rathbone,

- E.S. Werstiuk, U. Traversa, S. Buccella, P. Giuliani, S. Jiang, E. Nargi, D. Visini, C. Santavenere and P. Di Iorio.** 2005. P2X7 receptor activation in rat brain cultured astrocytes increases the biosynthetic release of cysteinyl leukotrienes *Int. J. Immunopathol. Pharmacol.* 18:417.
- 25. D'Haene N., C. Maris, F. Sandras, M.-F. Dehou, M. Remmeliink, C. Decaestecker and I. Salmon.** 2005. The differential expression of Galectin-1 and Galectin-3 in normal lymphoid tissue and non-Hodgkin's and Hodgkin's lymphomas *Int. J. Immunopathol. Pharmacol.* 18:431.
- 26. Bonsi L., L. Pierdomenico, M. Biscardi, C. Marchionni, S. Gavazzi, V. Fossati, B. Ghinassi, F. Alviano, D. Rondelli, M. Franchina, G.P. Bagnara and A. Grossi.** 2005. Constitutive and stimulated production of VEGF by human megakaryoblastic cell lines: effect on proliferation and signaling pathway *Int. J. Immunopathol. Pharmacol.* 18:445.
- 27. Cavàlieri B., M. Mosca, P. Ramadori, M.-G. Perrelli, L. De Simone, F. Colotta, R. Bertini, G. Poli and J.C. Cutrín.** 2005. Neutrophil recruitment in the reperfused-injured rat liver was effectively attenuated by repertaxin, a novel allosteric noncompetitive inhibitor of CXCL8 receptors: a therapeutic approach for the treatment of post-ischemic hepatic syndromes *Int. J. Immunopathol. Pharmacol.* 18:475.
- 28. Petrarca C., S. Frydas, J. Donelan, W. Boucher, N. Papadopoulou, J. Cao, M.L. Castellani, P. Conti, E. Toniato, I. Robuffo, J. Vecchiet, T. Iezzi, B. Madhappan and D. Kempuraj.** 2005. Interleukin 27 (IL-27): a novel pleiotropic cytokine involved in T cell differentiation and T cell response modulation. *Int. J. Immunopathol. Pharmacol.* 18:191.
- 29. Appert-Collin A., F.H.T. Duong, P. Passilly DeGrace, A. Bennasroune, P. Poindron, J-M. Warter and J.P. Gies.** 2005. Xaliproden (SR57746A) induces 5-HT1A receptors-mediated Map kinase activation in PC12 cells. *Int. J. Immunopathol. Pharmacol.* 18:233.
- 30. Brunetti L., C. Di Nisio, G. Orlando, C. Ferrante and M. Vacca.** 2005. The regulation of feeding: a cross talk between peripheral and central signalling. *Int. J. Immunopathol. Pharmacol.* 18:201.
- 31. Trubiani O., R. Di Primio, T. Traini, J. Pizzicannella, A. Scarano, A. Piattelli and S. Caputi.** 2005. Morphological and cytofluorimetric analysis of adult mesenchymal stem cells expanded *ex vivo* from periodontal ligament. *Int. J. Immunopathol. Pharmacol.* 18:213.
- 32. Riccioni G., V. Di Pietro, T. Staniscia, L. De Feudis, G. Traisci, F. Capani, G. Ferrara, E. Di Ilio, G. Di Tano and N. D'Orazio.** 2005. Community acquired pneumonia in internal medicine: a one-year retrospective study based on pneumonia severity index. *Int. J. Immunopathol. Pharmacol.* 18:575.
- 33. Martini F., C. Agrati, G. D'Offizi and F. Poccia.** 2005. HLA-E Up-regulation induced by HIV infection may directly contribute to CD94-mediated impairment of NK cells. *Int. J. Immunopathol. Pharmacol.* 18:26925.
- 34. Alexandrakis M.G., F.H. Passam, C.A. Pappa, J. Damilakis, G. Tsirakis, E. Kandidaki, E.N. Stathopoulos and D.S. Kyriakou.** 2005. Serum evaluation of angiogenic cytokines basic fibroblast growth factor, hepatocyte growth factor and TNF- $\alpha$  in patients with myelodysplastic syndromes: correlation with bone marrow microvascular density. *Int. J. Immunopathol. Pharmacol.* 18:287.
- 35. Fioriti D., A.M. Degener, M. Mischtitelli, M. Videtta, A. Arancio, S. Sica, F. Sorà and V. Pietropaolo.** 2005. BKV infection and hemorrhagic cystitis after allogeneic bone marrow transplant. *Int. J. Immunopathol. Pharmacol.* 18:309.
- 36. Longhi C., M.P. Conte, S. Ranaldi, M. Penta, P. Valenti, A. Tinari, F. Superti and L. Seganti.** 2005. Apoptotic death of *listeria monocytogenes*-infected human macrophages induced by lactoferricin B, a bovine lactoferrin-derived peptide. *Int. J. Immunopathol. Pharmacol.* 18:317.
- 37. Lesma E., E. Riva, M. Giovannini, A.M. Di Giulio and A. Gorio.** 2005. Amelioration of neutrophil membrane function underlies granulocyte-colony stimulating factor action in glycogen storage disease 1b. *Int. J. Immunopathol. Pharmacol.* 18:297.
- 38. Lo Iacono M., F. Cavallo, E. Quaglino, S. Rolla, M. Iezzi, S.M. Pupa, C. De Giovanni, P-L. Lollini, P. Musiani, G. Forni and R. A. Calogero.** 2005. A limited autoimmunity to p185<sup>neo</sup> elicited by DNA and allogeneic cell vaccine hampers the progression of preneoplastic lesions in her-2/neu transgenic mice. *Int. J. Immunopathol. Pharmacol.* 18:351.
- 39. Rossi R.E. and G. Monasterolo.** 2005. A pilot study of feasibility of ultra-rush (20-25 minutes) sublingual-swallow immunotherapy in 679 patients (699 sessions) with allergic rhinitis and/or asthma. *Int. J. Immunopathol. Pharmacol.* 18:277.