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EDITORIAL

IL-31 A TH2 CYTOKINE INVOLVED IN IMMUNITY AND INFLAMMATION

M.L. CASTELLANI, P. FELACO[1], R.J. GALZIO[2], D. TRIPODI[3], E. TONIATO, M.A. DE LUTIIS[1], M. FULCHERI[4], A. CARAFFA[5], P. ANTINOLFI[5], S. TETÈ[3], M. FELACO[1], F. CONTI[6], F. PANDOLFI[7], T.C. THEOHARIDES[8] and Y.B. SHAIK-DASTHAGIRISAHEB[9]

Immunology Division, University of Chieti, Chieti, Italy; [1]Department of Human Dynamics, University of Chieti, Italy; [2]Neurosurgery Division, University of L'Aquila, Italy; [3]School of Dentistry, University of Chieti, Italy; [4]Department of Clinical Psychology, University of Chieti, Italy; [5]Orthopaedics Division, University of Perugia, Perugia, Italy; [6]Vasto Hospital, Chieti, Italy; [7]Institute of Internal Medicine, Catholic University, Rome, Italy; [8]Department of Pharmacology and Experimental Therapeutics, Biochemistry and Internal Medicine Tufts University School of Medicine, Tufts-New England Medical Center, Boston, MA, USA; [9]Department of Medicine, Boston University School of Medicine, Boston, MA, USA

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Cytokines are immunal regulatory proteins, however they also play a relevant role in inflammatory diseases. IL-31 is a newly discovered cytokine expressed primarily in TH2 cells, introduced by activated CD4⁺ T cells. IL-31 is capable of inducing chemokines and other cytokines in several inflammatory diseases via its surface receptor. This cytokine is also produced by mast cells and mast cell line, suggesting a role in allergic diseases. In this editorial we revisit the biological role of IL-31 in immunity and inflammation.

Cytokines are inflammatory proteins and essential mediators of the interactions between activated immune cells (1-6) and non-immune cells (7-10), therefore, they are one of the therapeutic targets of chronic inflammatory disorders (11-13). Cytokines play a critical role in the control of the innate and adaptive immune responses (14-17).

Th1 and Th2 subsets are characterized by a distinct activity of transcription factor and pattern of cytokine-secretion phenotype. The differentiation of CD4⁺ T-cells towards Th1, Th2 and other subsets depends on an appropriate signal through the TCR and generated cytokine milieu is an important factor that influences CD4 cell lineage commitment. It is accepted that CD4 T-helper lymphocytes are essential regulators of immune responses and inflammatory diseases (18-20). Innate immune cells, by signals through STAT6, secrete IL-4 that induces naïve CD4⁺ T cells to become Th2 cells. T helper type 2 (Th2) cells are activated to produce proinflammatory cytokine and chemokine patterns to sustain the persistence of inflammation (21-24). The most recent additions to the ever-growing family of cytokines include interleukin (IL)-27, IL-28A, IL-28B, IL-29, IL-31, IL-32, IL-33, IL-34 and IL-35. Th2 cells produce IL-4, IL-5, IL-13, IL-21 and IL-31, which are important for host defense against parasites and contribute to the pathogenesis

Key words: interleukin, TH2 cell, immunity, inflammation, IL-31, cytokine

Mailing address: M.L. Castellani,
Immunology Division,
University of Chieti,
Via dei Vestini,
66100 Chieti, Italy
Tel: ++39 0871 355 4805 Fax: ++39 0871 355 4804
e-mail: mlcastellani@unich.it

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Table I. *IL-31: biological activities.*

- Possesses potential pleiotropic physiological functions
- Regulates hematopoiesis and immune response
- Acts on a broad range of immune and non-immune cells
- Appears to be an important regulator of Th2 responses
- Seems to drive airway hypersensitivity and dermatitis
- Contributes to the pathogenesis of asthma and allergy
- Plays a role through interaction with TNF-alpha in the pathophysiology of inflammatory bowel disease
- Does not engage gp130
- Sustains the survival of hematopoietic stem cells
- Contributes to effects on the cycling and numbers of hematopoietic stem cells
- Plays a role in the immune responses of the intestine
- Is involved in the recruitment of Jak1, Jak2, STAT-1, STAT-3, STAT5 signaling pathways, and PI3-kinase/AKT cascade
- Stimulates inflammatory responses in colon myofibroblasts
- Activates eosinophil-keratinocyte system
- Induces the secretion of chemokines CXCL8 (IL-8), CXCL1 (growth-related oncogene; GRO-α), CCL7 (monocyte chemoattractant protein-3; MCP-3), CXCL3, CCL13, CCL15)
- Increases proinflammatory cytokines (IL-6, IL-16 and IL-32), and matrix metalloproteinases (MMP-1, MMP-3, MMP-25 and MMP-7)
- Shows an additive effect with IL-17A on IL-6, IL-8, secretion
- In bronchial epithelial cells it elevates gene and protein expressions of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein-1 (MCP-1/CCL2)
- In combination with IL-4 or IL-13 enhances VEGF and CCL2 production
- Contributes to increase the activation of the MAP kinase pathway, ERK and JNK
- Plays an important role in the induction of autoimmune diseases
- Induces pruritus and dermatitis in mice
- Is involved in the proliferation of B and T cells

of asthma and allergy (25-30). Furthermore, a novel subpopulation of memory $CD4^+$ T-lymphocytes was recently identified that produces high levels of IL-17, which plays a major role in the induction of inflammation and tissue destruction in various autoimmune disorders (31-32).

IL-31 is a newly discovered member of the gp130/IL-6 cytokine family, expressed primarily in Th2 cells, produced mainly by activated $CD4^+$ T cells, in particular CD45RO+ (memory) T cells (30, 33). Human IL-31 genes are located on chromosome 12q24.31 and IL-31 cDNA is composed of an open reading frame encoding a 164 amino acid (aa) precursor and a predicted 141 aa mature polypeptide containing the four-α-helix structure. IL-31 mRNA is preferentially, but not exclusively, expressed by Th2 $CD4^+$ T cells after activation. IL-31 mRNA was found in testis, bone marrow, skeletal muscle, kidney, colon, thymus, small intestine, trachea, dorsal root ganglia and it may be involved in promoting the dermatitis and epithelial responses that characterize allergic and non-allergic diseases (7, 33-34).

The interleukin (IL)-17 cytokine family is a group of T cell-derived cytokines. IL-17A was originally cloned and named CTLA8 and the stimulatory effects of IL-31 on cytokine/chemokine stimulation is comparable to the effects of IL-17A. It was subsequently renamed IL-17, and was more recently termed IL-17A. Interleukin (IL)-17 cytokine family, such as IL-31, plays a role through interaction with TNF-alpha in the pathophysiology of some inflammatory diseases, such as inflammatory bowel disease, ulcerative colitis, and Crohn's disease, characterized by ongoing mucosal inflammation. Among the IL-17 family members, IL-17F has the highest degree of homology with IL-17A (40-55%), followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (also named IL-25) which is the

most distantly related (17%).

IL-31-induces cytokine and chemokine release such as pro-inflammatory cytokines IL-1beta, IL-6 and atopic dermatitis-related chemokines CXCL1, CXCL8, CCL2 and CCL18 from eosinophils, via its surface receptor (14). IL-31 is produced by T cells skewed towards a Th2 phenotype; however, in certain conditions Th1 T cells also produce substantial amounts of IL-31. Experimental animals that overexpress IL-31 exhibit a skin phenotype similar to atopic dermatitis in human subjects and IL-31 mRNA expression can be widely detected in many different organs. IL-31 is involved in the proliferation of B and T cells and is most closely related to the IL-6 cytokine family according to its structure and receptor which is very important in the acute-phase response. IL-31 is a member of the four-alpha-helix bundle cytokine family, and histamine receptor agonist(s) upregulates IL-31 mRNA in PBMCs and Th2 cells (15).

IL-31 protein production and release in the human mast cell line LAD2, as well as in peripheral blood-derived cultured mast cells, suggests that mast cells are another source of IL-31, and it has been found that the expression of IL-31 is elevated in psoriatic skin mast cells. The release of IL-31 by human mast cells provides a novel mechanism by which skin-derived antimicrobial peptides/proteins may contribute to inflammatory reactions and suggests a central role of these peptides in the pathogenesis of skin disorders (3).

A potent IL-31 antagonist, consisting of 720 amino acids counteracts the binding of IL-31 to its membrane receptor complex and the subsequent signaling events involving the STATs and MAPK pathways. Neutralizing effects of IL-31 antagonist are found in IL-31-sensitive cell lines, including brain-derived cells and primary cultures of keratinocytes (29).

These findings suggest that IL-31 may be a target for a new potential therapeutic approach for allergic and inflammatory diseases.

Several studies indicate that IL-31 sustains the survival of hematopoietic stem cells and recruits the Jak1, Jak2, STAT-1, STAT-3 and STAT5 signaling pathways, as well as the PI3-kinase (33-38).

Recent studies revealed that IL-31 stimulates inflammatory responses in myofibroblasts and induces the generation of chemokines such as IL-8, GRO-α, MCP-3, CXCL3, CCL13, CCL15, IL-6, IL-16 and IL-32, and matrix metalloproteinases (MMP-1, MMP-3, MMP-25 and MMP-7) (14). In epithelial cells, IL-31 can activate p38 MAPK, ERK and JNK, and also increases protein expressions of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and MCP-1 (39-50).

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