EDITORIAL

INTERLEUKIN 27 (IL-27): A NOVEL PLEIOTROPIC CYTOKINE INVOLVED IN T CELL DIFFERENTIATION AND T CELL RESPONSE MODULATION

C. PETRARCA, S. FRYDAS[1], J. DONELAN[2], W. BOUCHER[2], N. PAPADOPOULOU[2], J. CAO[2], M.L. CASTELLANI[3], P. CONTI, E. TONIATO[4], I. ROBUFFO[5], J. VECCHIET[6], T. IEZZI[7], B. MADHAPPAN[2] and D. KEMPURAJ[2]

Division of Immunology, University of Chieti, 66013 Chieti, Italy; [1]Department of Parasitology, Veterinary School, Aristotelian University, Thessaloniki, Greece; [2]Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111, U.S.A.; [3]Department of Medicine and Science of Ageing and [4]Department of Oncology and Neurosciences, University of Chieti, Italy; [5]Institute for Organ Transplant and Immunocytology, CNR, Section of Chieti, Italy; [6]Infectious Diseases Section, University of Chieti Hospital, Chieti, Italy and [7]Department of Biomedical Sciences, University of Chieti, Italy

Received January 4, 2005 – Accepted February 11, 2005

IL-27 is a recently discovered cytokine belonging to the long-chain four-helix bundle family, which shows structural and functional similarity to IL-12. IL-27 is a heterodimeric complex consisting in the EBI3 (Epstein-Barr virus induced gene 3; IL12p40 related protein) and p28 (IL12p35 related polypeptide) subunits. IL-27 is produced by activated monocytes and dendritic cells. The expression of IL-27 by dendritic cells is critically regulated and concerted with the other members of the IL-12 family. Dendritic cells express IL-27 upon activation by the ligands of the Toll-like receptors 3 and 4 and intact E.coli bacteria, but not by CD40L engagement. The extracellular nucleotide signalling via P2 receptors inhibits IL-27.

The IL-27 receptor, the WSX1/gp130 complex, is expressed on immature and mature T cells, and also on primary human mast cells and monocytes (1). The IL-27/IL-27R signaling system is involved in the T-cell mediated immune response against parasitic (2-5) and bacterial infections (6-9), intracellular pathogens (10) and tumor cells (11-17). However, IL-27 is able to elicit the production of pro-inflammatory and anti-inflammatory cytokine patterns in both CD4+ and CD8+ cells in different experimental and pathologic conditions (18-34). These apparently discordant properties of IL-27 on the immune system need to be further investigated.

IL-27 plays e relevant function in initiating the differentiation pathway of naive T cells towards the IFN gamma-producing CD4+ cells of the Th1 subset (35). The Th1 differentiation is also driven by the IL-27-related cytokine IL-12. However, the IL-27 activity is anterior to that of IL-12 and only partially overlapping. In fact, IL-27 alone is not sufficient for IFN-gamma polarization of T cells but, during the initial Th1 commitment, it induces the expression of the IL-12 receptor on naïve T cells (Fig. 1).

Therefore, IL-27 contributes in a paracrine manner to determine the responsiveness to IL-12 and, consequently, to the production of IFN gamma. On the other hand, the IL-27 receptor is an inhibitor of innate and adaptive elements of the type 2 immunity (36). Engagement of the IL-27R expressed on T cells by IL-27 activates the intracellular transducing pathway JAK1/STAT1 (phosphokinase/signal tranducer and activator of transcription) which in turn induce the transcription of T-bet, the major Th1 specific transcription factor. T-bet determines the transcription of its downstream target IL-12Rbeta2

Key words: interleukin, cytokine, T cells, lymphocyte, immune response, IFN, CD4

Mailing address: Dr. Claudia Petrarca,
Division of Immunology,
University of Chieti,
Via dei Vestini, 66013 Chieti, Italy
e-mail: c.petrarca@unich.it

0394-6320 (2005)

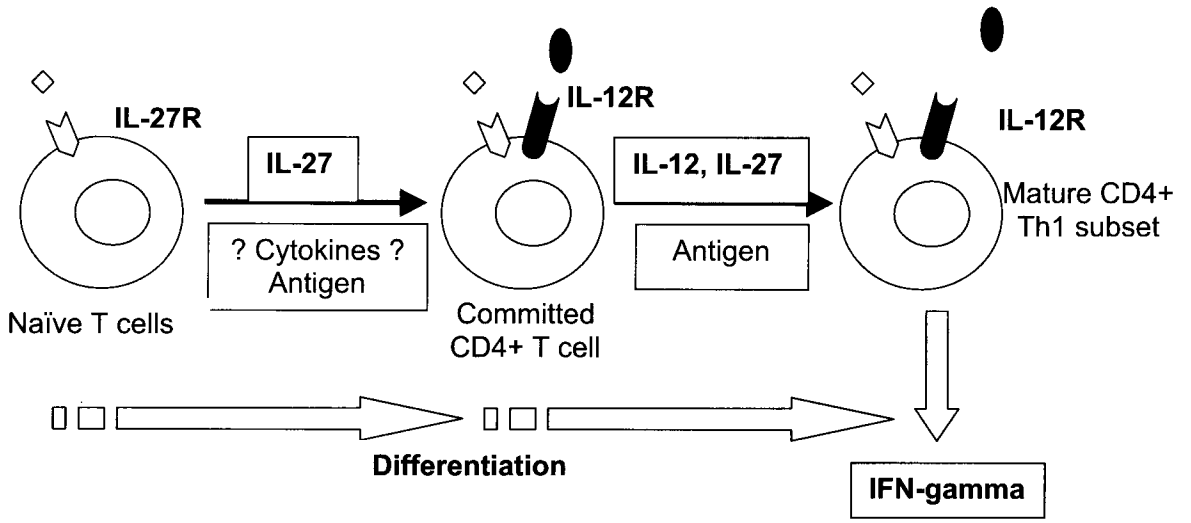

Fig. 1.

and the suppression of the basal expression of GATA-3, the critical Th2 transcription factor (36). However, IFN-gamma can be produced in a STAT1-independent manner (36). IL27R signaling probably also acts through other intracellular pathways since Th2 cytokine expression pattern (37) and both CD8+ T cell activation and cytotoxicity can be evoked.

IL-27 is not only involved in directing the polarization of naive T cells, but also affects the proliferative response and cytokine production of Ag-specific effector/memory Th1 cells. This may explain, in part, its important role in the regulation of inflammatory autoimmune diseases, and also suggest novel ways of therapy.

The IL-12 cytokine family plays important roles in the orchestration of innate and adaptive immunity by dendritic cells (DC). The regulation of IL-12 expression has been thoroughly studied, but little is known about factors governing the expression of IL-23 and IL-27, two novel IL-12-family members acting on memory and naive T cells, respectively. We report that the expression of these cytokines by DC was critically dependent on the mode of activation. DC activation via CD40L predominantly induced IL-12, ligands of the Toll-like receptors (TLR) 3 and TLR4 induced both IL-12 and IL-27, whereas exposure to intact E.coli bacteria resulted in high expression of IL-12, IL-27, and IL-23. The nucleotide, ATP, has been shown to inhibit IL-12 production via P2 receptors. We found that ATP also inhibited IL-27 but enhanced IL-23 expression. Interestingly, the reciprocal regulation of IL-12/IL-27 and IL-23 by ATP was mediated via two distinct P2 receptors and was also induced by prostaglandin E2 via cAMP-elevating EP2/EP4 receptors. As a consequence, DC were selectively impaired in their ability to induce IFN-gamma in naive T cells, but continued to promote IFN-gamma and IL-17 production in memory T cells. These studies identify P2 receptors as promising targets for the design of novel strategies to manipulate specific stages of T cell responses and to treat IL-12- and IL-23-mediated disorders.

REFERENCES

1. **Pflanz S., L. Hibbert, J. Mattson, R. Rosales, E. Vaisberg, J.F. Bazan, J.H. Phillips, T.K. McClanahan, R. de Waal Malefyt and R.A. Kastelein.** 2004. WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J. Immunol. 172:2225.*
2. **Frydas S., M. Hatzistilianou, E. Karagouni, B. Madhappan, N. D'Orazio, G. Riccioni, F. Conti, G. Carratelli and D. Kempuraj.** 2003. Chemokines and parasites. *Int. J. Immunopathol. Pharmacol. 16:221.*
3. **Hunter C.A., A. Villarino, D. Artis and P. Scott.** 2004. The role of IL-27 in the development of T-cell responses during parasitic infections. *Immunol. Rev.*

202:106.

4. **Cooper E.L., T.M. Hrzenjak and M. Grdisa.** 2004. Alternative sources of fibrinolytic, anticoagulative, antimicrobial and anticancer molecules. *Int. J. Immunopathol. Pharmacol. 17:237.*
5. **Kempuraj D., S. Frydas, P. Conti, K. Kandere, W. Boucher, R. Letourneau, B. Madhappan, S.H. Huang, S. Koreaki, S. Christodoulou and T.C. Theoharides.** 2003. Interleukin-25: a new IL-17 family member with growth factor/inflammatory action. *Int. J. Immunopathol. Pharmacol. 16:185.*
6. **Pearl J.E., S.A. Khader, A. Solache, L. Gilmartin, N. Ghilardi, F. Desauvage and A.M. Cooper.** 2004. IL-27 signaling compromises control of bacterial growth in mycobacteria-infected mice. *J. Immunol. 173:7490.*
7. **Kempuraj D., S. Frydas, E. Karagouni, M. Hatzistilianou, P. Boscolo, F. Ferro, M. Di Giannantonio, C.M.V. Conti, D. Merlitti R. Doyle, C. Petrarca, M.L. Castellani and T.C. Theoharides.** Cytokines and the brain. 2004. *Int. J. Immunopathol. Pharmacol. 17:229.*
8. **Sessa R., M. Di Pietro, G. Schiavoni, M. Nicoletti, G. Soda, S. Nardoni, D. Bosco, I. Santino, P. Cipriani and M. del Piano.** 2004. Detection of *Chlamydia pneumoniae* in atherosclerotic coronary arteries. *Int. J. Immunopathol. Pharmacol. 17:301.*
9. **Salcedo R., J.K. Stauffer, E. Lincoln, T.C. Back, J.A. Hixon, C. Hahn, K. Shafer-Weaver, A. Malyguine, R. Kastelein and J.M. Wigginton.** 2004. IL-27 mediates complete regression of orthotopic primary and metastatic murine neuroblastoma tumors: role for CD8+ T cells. *J. Immunol. 173:7170.*
10. **Goldberg R., Y. Zohar, G. Wildbaum, Y. Geron, G. Maor and N. Karin.** 2004. Suppression of ongoing experimental autoimmune encephalomyelitis by neutralizing the function of the p28 subunit of IL-27. *J. Immunol. 173:6465.*
11. **Parruti G., E. Ballone, P. Tarquini, K. Falasca, G. D'Amico, A. Agostinone, G. Placido, V. Graziani, D. Di Giammartino, M. Dalessandro, J. Vecchiet, M. Di Nicola, F. Schioppa, L. Alterio, A. Consorte and G. Marani Toro.** 2003. Dual nucleoside therapy for HIV infection: analysis of results and factors influencing viral response and long term efficacy. *Int. J. Immunopathol. Pharmacol. 16:81.*
12. **Vojdani A., J. B. Pangborn, E. Vojdani and E.L. Cooper.** 2003. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. *Int. J. Immunopathol. Pharmacol. 16:189.*
13. **Kaneider N.C., A. Kaser , H. Tilg, G. Ricevuti and C.J. Wiedermann.** 2003. CD40 ligand-dependent maturation of human monocyte-derived dendritic cells by activated platelets. *Int. J. Immunopathol. Pharmacol. 16:225.*
14. **Arena A., B. Enzo, G. Enrico, B. Marco and R. Graziella.** 2003. Specific immunotheraphy of allergic diseases: a three years perspective observational study. *Int. J. Immunopathol. Pharmacol. 16:277.*
15. **Acharya A. and V. Tripathi**. 2003. Novel peptides enhance the production of nitric oxide and inducible nitric oxide synthase (iNOS) gene expression in murine macrophage. *Int. J. Immunopathol. Pharmacol. 16:241.*
16. **Pannone G., P. Bufo, M.F. Caiaffa, R. Serpico, L. Lo Muzio, C. Rubini, S. Staibano, M. Petruzzi, M. De Benedictis, A. Tursi, G. De Rosa and L. Macchia.** 2004. Cyclooxygenase-2 expression in oral squamous cell carcinoma. *Int. J. Immunopathol. Pharmacol. 17:273.*
17. **Trubiani O., S. Guarnieri, M. Orciani, E. Salvolini and R. Di Primio.** 2004. Sphingolipid microdomains mediate CD38 internalization: Topography of the endocytosis. *Int. J. Immunopathol. Pharmacol. 17:293.*
18. **Prosperi C., C. Scali, M. Barba, A. Bellucci, M.G. Giovannini, G. Pepeu and F. Casamenti.** 2004. Comparison between flurbiprofen and its nitric oxide-releasing derivatives HCT-1026 and NCX-2216 on αβ (1-42)-induced brain inflammation and neuronal damage in the rat. *Int. J. Immunopathol. Pharmacol. 17:317.*
19. **Frydas S., E. Karagouni, M. Hatzistilianou, D. Kempuraj, S. Comani, C. Petrarca, T. Iezzi, N. Verna, P. Conti and M.L. Castellani.** 2004. Chemokines and allergic disorders: a revised study. *Int. J. Immunopathol. Pharmacol. 17:233.*
20. **A. Romano, C. Mondino , M. Viola and P. Montuschi.** 2003. Immediate allergic reactions to β-lactams: diagnosis and therapy. *Int. J. Immunopathol. Pharmacol. 16:19.*
21. **Gioia C., C. Agrati, D. Goletti, D. Vincenti, S.**

Carrara, M. Amicosante, M. Casarini, S. Giosue, G. Puglisi, A. Rossi, V. Colizzi, L.P. Pucillo and F. Poccia. 2003. Different cytokine production and effector/memory dynamics of $\alpha\beta^+$ or $\gamma\delta^+$ T-cell subsets in the peripheral blood of patients with active pulmonary tuberculosis. *Int. J. Immunopathol. Pharmacol. 16:247*

22. **Zorzetto M., G. Ricevuti, M. Martinetti, D. Gritti, C. Gasparetto, A. De Silvestri, L. Salvaneschi and M. Cuccia.** 2004. HLA and hypocomplementemia: the disadvantage of carrying the HLA-b35 and the silent alleles of the C4 complement component. *Int. J. Immunopathol. Pharmacol. 17:307.*
23. **Trubiani O., E. Salvolini, R. Staffolani, R. Di Primio and L. Mazzanti.** 2003. DMSO modifies structural and functional properties of RPMI-8402 cells by promoting programmed cell death. *Int. J. Immunopathol. Pharmacol. 16:253.*
24. **W.G. Austen Jr., L. Kobzik, M.C. Carroll, H.B. Hechtman and F.D. Moore Jr.** 2003. The role of complement and natural antibody in intestinal ischemia-reperfusion injury. *Int. J. Immunopathol. Pharmacol. 16:1.*
25. **Pietropaolo V., D. Fioriti, P. Simeone, M. Videtta, C. Di Taranto, A. Arancio, N. Orsi and A.M. Degener.** 2003. Detection and sequence analysis of human polyomaviruses DNA from autoptic samples of HIV-1 positive and negative subjects. *Int. J. Immunopathol. Pharmacol. 16:269.*
26. **G. Riccioni, A. De Santis, V. Cerasa V. Menna, C. Di Ilio, C. Schiavone, E. Ballone and N. D'Orazio.** 2003. Atherosclerotic plaque formation and risk factors. *Int. J. Immunopathol. Pharmacol. 16:25.*
27. **N. Gianotti and A. Lazzarin.** 2003. Managing failure to antiretroviral drugs in HIV-1-infected patients. *Int. J. Immunopathol. Pharmacol. 16:9.*
28. **R. Manna, L. Miele, M. La Regina, A. Greco and G. Gasbarrini.** 2003. Cryoglobulinaemia: a true internistic disease? *Int. J. Immunopathol. Pharmacol. 16:33.*
29. **Pannellini T., M. Iezzi, E. Di Carlo, E. Eleuterio, A. Coletti, A. Modesti, S. Rosini, M. Neri and P. Musiani.** 2004. The expression of LEC/CCL16, a powerful inflammatory chemokine, is upregulated in ulcerative colitis. *Int. J. Immunopathol. Pharmacol. 17:171.*
30. **M.G. Alexandrakis, D.S. Kyriakou, D. Seretakis, W. Boucher, R. Letourneau, D. Kempuraj and T.C. Theoharides.** 2003. Inhibitory effect of retinoic acid on proliferation, maturation and tryptase level in human leukemic mast cells (Hmc-1). *Int. J. Immunopathol. Pharmacol. 16:43.*
31. **E. Camera, S. Lisby, M.L. Dell'Anna, B. Santucci, R. Paganelli, O. Baadsgaard and M. Picardo.** 2003. Mononuclear cell antioxidant pattern and skin reactivity to irritants. *Int. J. Immunopathol. Pharmacol. 16:49.*
32. **G. Bruno, F. Tega, A. Bruno, U. Graf, F. Corelli, R. Molfetta and M. Barucco.** 2003. The role of substance P in the cerebral ischemia. *Int. J. Immunopathol. Pharmacol. 16:67.*
33. **Sardella G., D. Accapezzato, A. Di Roma, C. Iacoboni, V. Francavilla, G. Benedetti, C. Musto, F. Fedele, G. Bruno and M. Paroli.** 2004. Integrin β_2-chain (CD18) over-expression on $CD4^+$ T cells and monocytes after ischemia/reperfusion in patients undergoing primary percutaneous revascularization. *Int. J. Immunopathol. Pharmacol. 17:165.*
34. **Sodin-Semrl S., A. Spagnolo, R. Mikus, B. Barbaro, J. Varga and S. Fiore.** 2004. Lipoxin A_4 and serum amyloid A elicit opposite interleukin-8 and NF-κB responses via the common ALX receptor. *Int. J. Immunopathol. Pharmacol. 17:145.*
35. **Robinson D.S. and A. O'Garra.** 2002. Further checkpoints in Th1 development. *Immunity 16:755.*
36. **Artis D., A. Villarino, M. Silverman, W.. He, EM. Thornton, S. Mu, S. Summer, T.M. Covey, E. Huang, H. Yoshida, G. Koretzky, M. Goldschmidt, G.D. Wu, F. de Sauvage, H.R. Miller, C.J. Saris, P. Scott and C.A. Hunter.** 2004. The IL-27 receptor (WSX-1) is an inhibitor of innate and adaptive elements of type 2 immunity. *J. Immunol. 173:5626.*
37. **Redecke V., H. Hacker, S.K. Datta, A. Fermin, P.M. Pitha, D.H. Broide and E. Raz.** 2004. Cutting edge: activation of Toll-like receptor 2 induces a Th2 immune response and promotes experimental asthma. *J. Immunol. 172:2739.*