

# Th17 and Interleukin 23 in the Pathogenesis of Psoriatic Arthritis and Spondyloarthritis

ALBERTO CAULI and ALESSANDRO MATHIEU

**ABSTRACT.** Psoriatic arthritis and spondyloarthritis (SpA) are complex immune-mediated diseases affecting peripheral and axial joints. T cells have been considered fundamental in triggering the disease and maintaining the process in the chronic phase. The recent discovery of the CD4+ Th17 lymphocyte subset and the interleukin 23/interleukin 17 axis has further contributed to the definition of unknown pathways, challenging previous models and the role of Th1/Th2 T cells in immune mediated diseases, including SpA. (J Rheumatol 2012;39 Suppl 89:15–18; doi:10.3899/jrheum.120234)

*Key Indexing Terms:*

PSORIATIC ARTHRITIS  
INTERLEUKIN 17

SPONDYLOARTHRITIS  
INTERLEUKIN 23R

TH17  
INTERLEUKIN 23

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by skin and joint involvement that strongly affects the daily life of patients<sup>1</sup>. Apart from skin inflammation and peripheral or axial arthritis, the main clinical manifestations are enthesitis, dactylitis, and other extraarticular features common to the spectrum of the spondyloarthropathies (SpA), including uveitis and inflammatory bowel diseases (IBD)<sup>2</sup>. The early events in PsA pathogenesis as well as in other SpA conditions are believed to occur in predisposed subjects<sup>3</sup> and to be mediated by T cells<sup>4</sup> interacting with other cells such as antigen-presenting cells (APC)<sup>5</sup>. This process gives rise to the inflammatory cascade that then activates a wide range of effector mechanisms, leading ultimately to joint damage and repair mechanisms. Recently, increasing evidence has linked a new subset of T lymphocyte, Th17, according to its signature cytokine, to the pathogenesis of PsA and SpA.

## INTERLEUKIN 17 AND THE Th17 SUBSET

Interleukin 17 (IL-17) is the signature cytokine of a recently described CD3+/CD4+ T lymphocyte subset, Th17. IL-17 is an inflammatory cytokine involved in host defense against bacteria, fungi, and protozoa<sup>6</sup>. IL-17 secretion by CD4 T cells was described in 1995<sup>7</sup>, but only later was it determined that CD4+ T cells producing IL-17 represent a separate T cell lineage termed Th17<sup>8,9</sup>, similarly to the first described Th1 and Th2 subsets. Before the definition of the Th17 subset it was believed that antigenic stimulation of naive CD4+ T cells could give rise to either Th1 lympho-

cytes secreting interferon  $\gamma$  (IFN- $\gamma$ ), defending against intracellular pathogens and involved in autoimmunity, or Th2 lymphocytes secreting IL-4, IL-5, IL-6, and IL-13, defending against extracellular organisms and involved in humoral immunity and allergy.

Th1 development is mainly driven by the cytokine IL-12; an initial innate immune response, possibly driven by activated natural killer (NK) cells, may activate the T-bet transcription factor through STAT1, enhancing responsiveness to IL-12<sup>10</sup>. On the other hand, Th2 development is mainly driven by the cytokine IL-4 and by activation of STAT3 and GATA-3<sup>10</sup>. IL-23, together with IL-1, tumor necrosis factor (TNF)- $\alpha$ , and IL-6, plays a key role in polarizing naive CD4+ T cells toward the Th17 subset. The role of transforming growth factor (TGF)- $\beta$ , primarily in mice, is still under debate in humans, showing contrasting results in its ability to induce Th17 differentiation<sup>11,12</sup>. It is noteworthy that TGF- $\beta$  and IL-6 are able to induce retinoic acid orphan receptors (ROR $\gamma$ t and ROR $\alpha$ ) in naive T lymphocytes, causing the upregulation of IL-23 receptor (IL-23R)<sup>13</sup>, thus facilitating Th17 polarization. IL-23 is part of the IL-12 family and is a dimeric molecule composed of the subunits IL-12p40 and IL-23p19, while IL-12 is composed of IL-12p35 and IL-12p40 subunits (IL-12p70). This has important implications when targeting these cytokine subunits for therapeutic purposes. Further, similarly to IL-12 and IL-23 cytokines, IL-12 and IL-23 receptors also share a common subunit. IL-23R is a heterodimeric molecule composed of IL-12Rb1 and IL-23R; on the other hand, IL-12R is composed of IL-12Rb1 in association with the IL-12Rb2 subunit. IL-23 therefore appears to be the primary cytokine involved in the amplification and differentiation of the Th17 subset and in the induction of IL-17 secretion<sup>14</sup>.

The balance between the Th17 subset and regulatory T cells (Treg) is regulated by several mechanisms: IFN- $\gamma$  and IL-4 inhibit IL-17 production<sup>8,9,15</sup>, IL-2 inhibits Th17 cell differentiation by downregulating ROR $\gamma$  $\delta$ <sup>16</sup>, and IL-27 (a

*From the Rheumatology Unit, Department of Medical Sciences, Policlinico of the University of Cagliari, Monserrato, Italy.*

*A. Cauli, MD, PhD; A. Mathieu, MD, Professor of Rheumatology, Rheumatology Unit, Department of Medical Sciences, Policlinico of the University of Cagliari.*

*Address correspondence to Dr. A. Cauli, Department of Medical Sciences, Rheumatology Unit, Policlinico of the University of Cagliari, ss 554, Monserrato 090142, Cagliari, Italy. E-mail: cauli@medicina.unica.it*

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

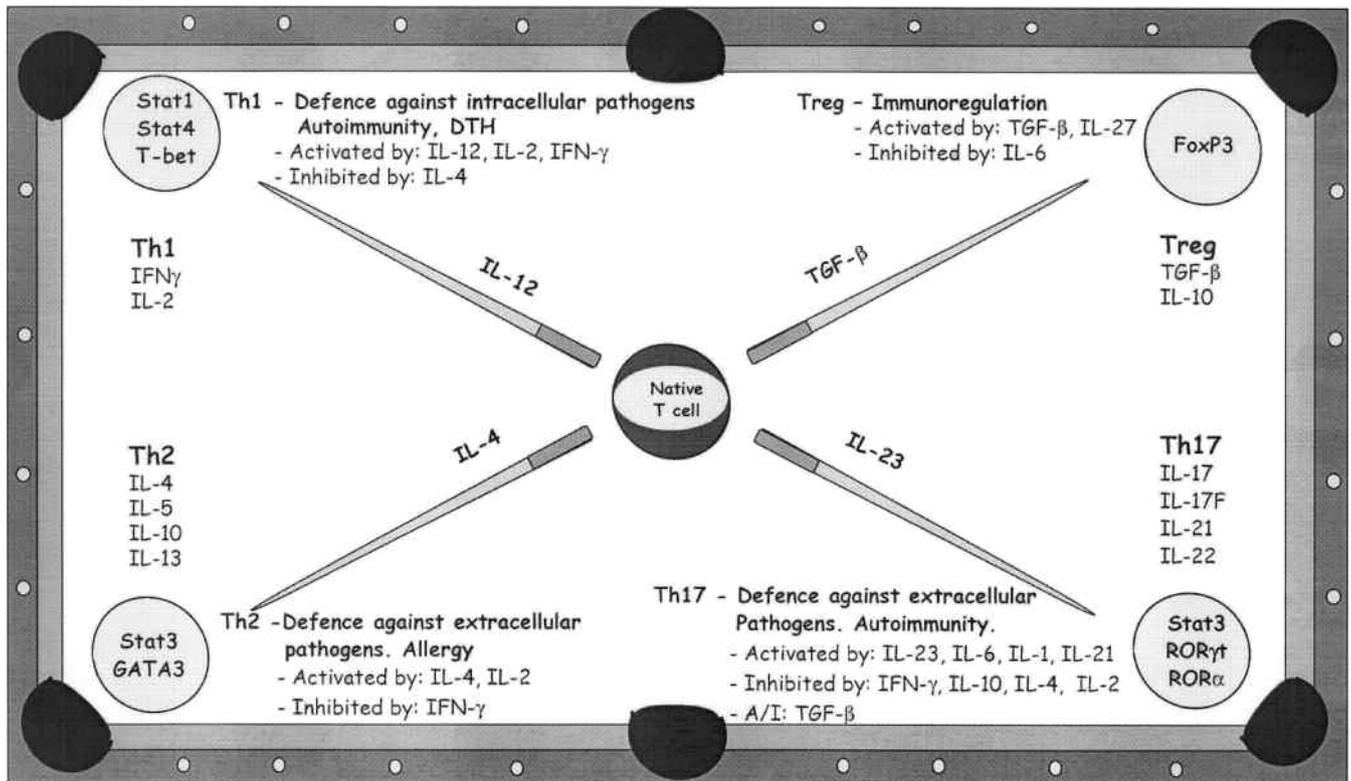


Figure 1. T lymphocyte “balls” are “shot” by cytokines in “inflammatory billiards.”

cytokine belonging to the IL-12 family mainly produced by APC) inhibits IL-17 production by T cells inducing IL-10 secretion from Treg cells<sup>17</sup>. Human Th17 cells secrete IL-17A and IL-17F, but other leukocytes are able to produce IL-17. Among them, NK cells, CD8+ lymphocytes,  $\gamma\delta$  T cells, and neutrophils can produce other IL-17 family cytokines<sup>18</sup>. In the already complex inflammatory milieu, CD4+ T lymphocytes secreting IL-17 may also produce other cytokines including TNF- $\alpha$ , IL-6<sup>19</sup>, and IL-22<sup>20</sup>. It is noteworthy for implications in the pathogenesis of psoriasis that IL-22 has been reported to stimulate epidermal hyperplasia and dermal inflammation<sup>21</sup>. The biological effects of IL-17 are diverse and directed to different cell populations, such as monocytes and macrophages, osteoblasts, fibroblasts, and endothelial and epithelial cells. IL-17 is able to induce the production of proinflammatory cytokines such as IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and IL-8, the expression of homing receptors and chemokines, colony stimulating factors, and matrix metalloproteinase<sup>18</sup>.

### Th17 IN PsA AND SpA

In the last decade, Th17 cells and IL-17 have been implicated in the pathogenesis of chronic arthritis conditions such as rheumatoid arthritis (RA), PsA, and SpA in general, including IBD and skin psoriasis. These diseases were previously considered Th1-mediated diseases, with IFN- $\gamma$  and IL-2 playing important roles in the generation of the inflammatory cascade.

Susceptibility to both skin psoriasis and PsA is associated with alleles of the *IL-12B* and *IL-23R* genes<sup>22,23</sup>. Similarly, *IL23R* alleles predispose genes also to other SpA such as ankylosing spondylitis and Crohn's disease<sup>24,25</sup>. This shared association suggests common inflammatory pathways involving IL-23R in all SpA. Further, IL23p19 and p40 (shared by IL-12p70 and IL-23 cytokines) subunits, but not IL-12p35 (only present in IL-12), are increased in lesional psoriatic skin compared to nonlesional skin<sup>26</sup>. Notably, serum levels of IL12/23 p40 subunit are significantly higher in patients with PsA compared to controls<sup>27</sup>. Given the importance of IL-23R and IL-23 stimulation for the Th17 subset, this experimental evidence suggests a primary role of the Th17 subset in PsA and SpA. This is confirmed by a randomized controlled trial by Gottlieb, *et al*<sup>28</sup> that showed that treatment with human IL-12/23 p40 monoclonal antibody reduces the signs and symptoms of joint inflammation in PsA.

In RA, IL-17 and IL-23 have been found in synovial membrane, synovial fluid, and serum samples<sup>29</sup>; further, a correlation of messenger RNA expression of the receptor activator of nuclear factor- $\kappa$ B ligand (RANK ligand; RANKL) with IL-23 expression has been shown<sup>30</sup>. RANKL may be induced by IL-17 and also by TNF- $\alpha$ , and may interact with osteoclasts to activate their erosive capabilities at sites of inflammation<sup>18</sup>. This may support the concept that the IL-23/IL-17 axis takes part in the mechanisms leading to bone destruction. IBD are part of the SpA spectrum. It is

therefore noteworthy that IL-17 has been found over-expressed in the sera and colon of these patients<sup>31</sup> and that an increased number of Th17 cells were found in the gut tissue from patients with Crohn's disease<sup>32</sup>.

Recently, Bowness and colleagues provided an explanation that links the well-known associations found in axial SpA patients with HLA-B27, and the association with IL-23R and the Th17 subset<sup>33</sup>. HLA-B27 is a heterotrimeric molecule that tends to dissociate from bound peptide and  $\beta_2$ -microglobulin ( $\beta_2m$ ), giving rise to free heavy chains which aggregate in  $\beta_2m$ -free heavy chain homodimers (B27<sub>2</sub>). Bowness, *et al* have shown that B27<sub>2</sub>-expressing APC stimulate the survival, proliferation, and IL-17 production of KIR3DL2+ CD4+ Th-17 cells, demonstrating that this is mediated by the KIR3DL2/B27<sub>2</sub> pair interaction. The B27<sub>2</sub> responsive IL-17 producing CD4+ T cells expressed IL-23R, and were also able to produce TNF- $\alpha$  and/or IFN- $\gamma$ . T lymphocyte with an overlapping Th17 and Th1 phenotype (plasticity) are found in SpA and may therefore be involved in the disease process.

The precise immune mechanisms that determine and drive PsA and SpA and the role of the Th17 subset need further research. In particular, the complex network of the different T cell subsets and cytokines in the inflammatory milieu of PsA and SpA (Figure 1) at an early stage as well as at established stages of disease will be fundamental to understanding the precise pathogenesis of SpA and the opportunity for treatment. Modulation of the Th17 pathway, with or without TNF- $\alpha$  antagonism, appears to be a promising approach in the attempt to achieve satisfactory control of disease activity and to block disease progression and damage.

## ACKNOWLEDGMENT

The authors thank Dr. Grazia Dessolet for her scientific and artistic contribution in creating Figure 1.

## REFERENCES

1. Cauli A, Gladman DD, Mathieu A, Olivieri I, Porru G, Tak PP, et al. GRAPPA 3PPSA Study Group. Patient global assessment in psoriatic arthritis: a multicenter GRAPPA and OMERACT study. *J Rheumatol* 2011;38:898-903.
2. Gladman DD. Psoriatic arthritis. In: Harris ED, Budd RC, Firestein GS, Genovese MC, Sergent JS, Ruddy S, et al, editors. *Kelly's textbook of rheumatology*, 7th ed. Philadelphia: W.B. Saunders Co.; 2005:1155-64.
3. Reveille JD. The genetic basis of spondyloarthritis. *Ann Rheum Dis* 2011;70 Suppl 1:i44-50.
4. Pitzalis C, Cauli A, Pipitone N, Smith C, Barker J, Marchesoni A, et al. Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. *Arthritis Rheum* 1996;39:137-45.
5. Cauli A, Pitzalis C, Yanni G, Hawad M, Panayi GS. CD1 positive antigen presenting cells in psoriatic and rheumatoid arthritis. *Rheumatology* 2000;6:666-73.
6. Lubberts E. Th17 cytokines and arthritis. *Seminars Immunopathol* 2010;32:43-53.
7. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, et al. Human IL-17: a novel cytokine derived from T cells. *J Immunol* 1995;155:5483-6.
8. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;6:1123-32.
9. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 2005;6:1133-41.
10. Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ, et al. IL-12 and IL-23: master regulators of innate and adaptive immunity. *Immunol Rev* 2004;202:96-105.
11. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, et al. TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. *Nat Immunol* 2007;8:1390-7.
12. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007;8:950-7.
13. Yang XO, Pappu BP, Nurieva R, Akimzhanov A, Kang HS, Chung Y, et al. T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma. *Immunity* 2008;28:29-39.
14. Kastelein RA, Hunter CA, Cua DJ. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 2007;25:221-42.
15. Hoeve MA, Savage ND, de Boer T, Langenberg DM, de Waal Malefyt R, Ottenhoff TH, et al. Divergent effects of IL-12 and IL-23 on the production of IL-17 by human T cells. *Eur J Immunol* 2006;36:661-70.
16. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 2007;26:371-81.
17. Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA, et al. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat Immunol* 2007;8:1380-9.
18. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007;25:821-52.
19. Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, McKenzie B, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest* 2006;116:1310-6.
20. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006;203:2271-9.
21. Ma HL, Liang S, Li J, Napierata L, Brown T, Benoit S, et al. IL-22 is required for Th17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. *J Clin Invest* 2008;118:597-607.
22. Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet* 2008;4:e1000041.
23. Nair RP, Ruetter A, Stuart PE, Jenisch S, Tejasvi T, Hiremagalore R, et al. Polymorphisms of the IL12B and IL23R genes are associated with psoriasis. *J Invest Dermatol* 2008;128:1653-61.
24. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, et al. Wellcome Trust Case Control Consortium. Australo-Anglo-American Spondylitis Consortium (TASC). Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nature Genetics* 2007;39:1329-37.
25. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006;314:1461-3.
26. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23 p19 and

- p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004;199:125–30.
27. Szodoray P, Alex P, Chappell-Woodward CM, Madland TM, Knowlton N, Dozmorov I, et al. Circulating cytokines in Norwegian patients with psoriatic arthritis determined by a multiplex cytokine array system. *Rheumatology* 2007;46:417–25.
28. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009;373:633–40.
29. Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, Ishiyama S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest* 1999;103:1345–52.
30. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med* 2006;203:2673–82.
31. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* 2003;52:65–70.
32. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, et al. Phenotypic and functional features of human Th17 cells. *J Exp Med* 2007;204:1849–61.
33. Bowness P, Ridley A, Shaw J, Chan AT, Wong-Baeza I, Fleming M, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. *J Immunol* 2011;186:2672–80.