

## Transforming Growth Factor- $\beta$ : An Indirect Inducer of Th17 Cell Differentiation both in Human and Murine System

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**Abstract:** Since their first description only some years ago Th17 cells have become of vital importance in immunological research. However, the role of TGF- $\beta$  in Th17 cell development is still a matter of controversial discussion. Predicted to have a key function in Th17 cell differentiation in the mouse TGF- $\beta$  was shown to inhibit IL-17 production of human CD4<sup>+</sup> T cells. Moreover, recent data indicate TGF- $\beta$  signaling in T cells to be dispensable for Th17 cell differentiation in the murine system. Hence, rather being a specie-specific factor TGF- $\beta$  is likely to act as an indirect inducer of Th17 cell differentiation both in mice and men.

**Key words:** Transforming growth factor, T helper cell, mice and men, murine system

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### INTRODUCTION

Th17 cells are a subset of T helper cell lymphocytes producing IL-17, TNF- $\alpha$  and IL-6, but not IFN- $\gamma$  or IL-4 (McKenzie *et al.*, 2006; Iwakura and Ishigame, 2006). Via secretion of IL-17 Th17 cells enhance the expression of G-CSF (Fossiez *et al.*, 1996; Cai *et al.*, 1998; Schwarzenberger *et al.*, 1998; 2001), IL-8 (Fossiez *et al.*, 1996; Laan *et al.*, 1999; Yao *et al.*, 1995a; Kawaguchi *et al.*, 2001; Katz *et al.*, 2001; Jones and Chan, 2002; Prause *et al.*, 2003) and ICAM-1 (Yao *et al.*, 1995a; Albanesi *et al.*, 1999) thereby promoting chemotaxis of neutrophils and monocytes to sites of inflammation. In addition, IL-17 stimulates the production of IL-6 (Fossiez *et al.*, 1996; Yao *et al.*, 1995a; 1995b; Katz *et al.*, 2001; Chabaud *et al.*, 1998), matrix metalloproteinases (Chabaud *et al.*, 2000), prostaglandin E2 (Fossiez *et al.*, 1996), NO (Shalom-Barak *et al.*, 1998; Attur *et al.*, 1997) as well as the complement components C3 and factor B (Katz *et al.*, 2000). Hence, Th17 cells represent potent pro-inflammatory mediators crucial in the regulation of inflammatory responses.

In a number of inquiries using murine models of host defense Th17 cells have been described to be important in the pathogenesis of chronic inflammatory diseases including arthritis (Lubberts *et al.*, 2005; Latham *et al.*, 2005), colitis (Zhang *et al.*, 2006; Ogawa *et al.*, 2004), encephalitis (Komiyama *et al.*, 2006; Hofstetter *et al.*, 2005) as well as asthma and allergy (Hellings *et al.*, 2003). In humans IL-17 producing T cells have been isolated from synovial membranes and synovial fluid of patients suffering

from rheumatoid arthritis (Chabaud *et al.*, 1999). At this, severity of inflammation is reported to be consistent to the IL-17 concentration detectable in serum and tissue of the arthritis patients. Furthermore, a correlation between IL-17 serum levels and the degree of inflammatory processes has been described in the context of autoimmune encephalomyelitis (Lock and Heller, 2003) and inflammatory bowel disease (Fujino *et al.*, 2003). Thus, IL-17 especially if produced by T cells is a likely candidate for intervention in chronic inflammatory diseases in men.

### Th17 cell differentiation: Proceeding specie-specific?

In the murine system the synergistic action of TGF- $\beta$  and IL-6 has been considered to be essential for Th17 cell development, so far (Veldhoen *et al.*, 2006; Mangan *et al.*, 2006; Bettelli *et al.*, 2006). In contrast, differentiation of human naïve T helper cells into Th17 cells has been reported not to depend on TGF- $\beta$  (Chen *et al.*, 2007; Wilson *et al.*, 2007; Acosta-Rodriguez *et al.*, 2007; Manel *et al.*, 2008; Santarlasci *et al.*, 2009; Cosmi *et al.*, 2008). Moreover, TGF- $\beta$  has been predicted to act suppressive on IL-17 production of human CD4<sup>+</sup> T cells (Acosta-Rodriguez *et al.*, 2007; Manel *et al.*, 2008). Due to the divergent observations made in murine and human systems Th17 cells development in mice and men has been assumed to be regulated differentially (Annunziato *et al.*, 2009; Annunziato and Romagnani, 2009). However, recent data provide evidence that TGF- $\beta$  is not directly required for the molecular orchestration of Th17 cell differentiation in

the mouse as well (Das *et al.*, 2009; Schumann, 2008). Thus, the situation seen in the murine system is closer related to the human situation as previously thought.

**What role for TGF- $\beta$  in Th17 differentiation?** TGF- $\beta$  initially has been published as a growth factor (De Larco and Todaro, 1978). Thereinafter it was found, that TGF- $\beta$  not only influences differentiation of cells but is also crucial in inflammatory processes (Kehrl *et al.*, 1986a; 1986b). TGF- $\beta$  regulates the innate and the adaptive immunity affecting macrophages (Ashcroft, 1999), dendritic cells (Strobl and Knapp, 1999), T cells (Cerwenka and Swain, 1999), B cells (Lebman and Edmiston, 1999) and NK cells (Horwitz *et al.*, 1999). The cytokine acts both pro- and antiinflammatory depending on genetic background, cell type, state of differentiation, extracellular matrix as well as the presence of other regulatory factors (McCartney-Francis and Wahl, 1994; Wahl, 1994). Hence, TGF- $\beta$  shows a distinctive pleiotropy playing a complex role in immunomodulation.

At present time the role of TGF- $\beta$  in T helper cell differentiation has become of special interest. Depending on cytokine milieu naïve T helper cells differentiate into four known T helper cell subsets. TGF- $\beta$  interacts in this process by several ways. Both Th1 (Gorelik *et al.*, 2002; Lin *et al.*, 2005) and Th2 cells (Chen *et al.*, 2003a; Gorelik *et al.*, 2000; Heath *et al.*, 2000) are inhibited by TGF- $\beta$ . Concomitantly, TGF- $\beta$  represents the direct inducer of Treg cells, which themselves are considerable producers of the cytokine (Chen *et al.*, 2003b).

Beside its clear role in Treg cell development conflicting data have been published concerning the relevance of TGF- $\beta$  in Th17 cell generation in mice and men. In murine system cytokines critically for Th17 cell differentiation were propagated to be TGF- $\beta$  and IL-6 (Veldhoen *et al.*, 2006; Mangan *et al.*, 2006; Bettelli *et al.*, 2006). However, TGF- $\beta$  has not been shown to directly promote the generation of IL-17 producing T cells from naïve precursors. Rather, a beneficial effect of TGF- $\beta$  was seen, when naïve CD4<sup>+</sup> T cells were co-cultivated with Treg cells plus dendritic cells and stimulated with anti-CD3-antibody as well as Lipopolysaccharid (LPS) (Veldhoen *et al.*, 2006). LPS is known as strong inducer of Th1 reactions via a release of IL-12 by dendritic cells (Pearce *et al.*, 2006). The effect of TGF- $\beta$  in such a setting might therefore rather be based on the prevention of a Th1 cell development. Consistently to this assumption, using a mouse model unable to generate Th1 and Th2 cells, the cytokine IL-6 has been reported to be sufficient to drive

Th17 cell generation (Das *et al.*, 2009). In addition, TGF- $\beta$  was shown not to affect the expression of the retinoic acid receptor-Related Orphan Receptor  $\gamma$  (ROR  $\gamma$ t), a Th17 cell specific transcription factor (Das *et al.*, 2009). Beyond that, Th17 cells could be detected in a transgene mouse strain T cell specific insensitive for TGF- $\beta$  signaling (Schumann, 2008). Visualization of Th17 cells succeeded both *ex vivo* after re-stimulation of lymph node cells of *B. burgdorferi*-infected mice as well as *in vitro* after T cell specific stimulation of splenocytes and purified CD4<sup>+</sup> lymphocytes (Schumann, 2008). In contrast, stimulation of T cells over-expressing TGF- $\beta$  resulted in decreased Th17 cell numbers in comparison to the wild type (Schumann, 2008). Hence, there is compelling evidence that TGF- $\beta$  does not act as a direct inducer of Th17 cell development in the mouse.

The dispensability of TGF- $\beta$  signaling on T cells for Th17 cell development in the murine system is consistent to publications dealing with effects of TGF- $\beta$  on human T helper cell differentiation. In human system TGF- $\beta$  has been shown to inhibit IL-17 production by T cells (Acosta-Rodriguez *et al.*, 2007; Manel *et al.*, 2008). According hitherto existing literature rather than TGF- $\beta$ , cytokines such as IL-1 $\beta$  and IL-23 drive Th17 cell development from human CD4<sup>+</sup> precursors (Chen *et al.*, 2007; Wilson *et al.*, 2007; Acosta-Rodriguez *et al.*, 2007).

**TGF- $\beta$  affects Th17 cell differentiation in an indirect way:** TGF- $\beta$  is part of a complex regulatory system critically in immune homeostasis. The cytokine is of vital importance in T helper cell differentiation influencing all four known T helper cell subsets. In addition to interference in T helper cell development TGF- $\beta$  represents the main product of Treg cells thereby mediating the immunosuppressive and anti-inflammatory function of these cells (Chen *et al.*, 2003b).

Of note, the cytokine accomplishes its effects both directly and indirectly. TGF- $\beta$  directly induces Treg cell differentiation via promotion of the transcription factor FoxP3 (Chen *et al.*, 2003b). TGF- $\beta$  directly blocks Th1 as well as Th2 cell development via inhibition of T-bet (Gorelik *et al.*, 2002; Lin *et al.*, 2005) and GATA-3 (Chen *et al.*, 2003a; Gorelik *et al.*, 2000; Heath *et al.*, 2000) expression, respectively. By contrast, Th17 cell differentiation is affected indirectly by TGF- $\beta$ . IFN- $\gamma$  and IL-4, the cytokines produced by Th1 and Th2 cells, are well known inhibitors of Th17 cell development. Hence, blocking of Th1 and Th2 cells linked with the absence of IFN- $\gamma$  and IL-4 provides a milieu optimal for naïve CD4<sup>+</sup> precursors to

differentiate into Th17 cells (Veldhoen *et al.*, 2006; Mangan *et al.*, 2006; Bettelli *et al.*, 2006; Infante-Duarte *et al.*, 2000). Taken together, the impact of TGF- $\beta$  in T helper cell specification both in human and murine system is due to its inhibitory action on Th1 and Th2 cells in addition to its direct promotion of Treg cell amplification.

**Conflict of interest:** The author discloses any financial and personal relationships with other people or organizations that could inappropriately influence her work.

## REFERENCES

- Acosta-Rodriguez, E.V., G. Napolitani, A. Lanzavecchia and F. Sallusto, 2007. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nat. Immunol.*, 8: 942-949. PMID: 17676045
- Albanesi, C., A. Cavani and G. Girolomoni, 1999. IL-17 is produced by nickel-specific T lymphocytes and regulates ICAM-1 expression and chemokine production in human keratinocytes: Synergistic or antagonist effects with IFN-gamma and TNF-alpha. *J. Immunol.*, 162: 494-502. PMID: 9886425
- Annunziato, F. and S. Romagnani, 2009. Do studies in humans better depict Th17 cells? *Blood*, 114: 2213-2219. PMID: 19494349
- Annunziato, F., L. Cosmi, F. Liotta, E. Maggi and S. Romagnani, 2009. Human Th17 cells: Are they different from murine Th17 cells? *Eur. J. Immunol.*, 39: 637-640. PMID: 19283714
- Ashcroft, G.S., 1999. Bidirectional regulation of macrophage function by TGF-beta. *Microbes Infect.*, 1: 1275-1282. PMID: 10611755
- Attur, M.G., R.N. Patel, S.B. Abramson and A.R. Amin, 1997. Interleukin-17 up-regulation of nitric oxide production in human osteoarthritis cartilage. *Arthritis Rheum.*, 40: 1050-1053. DOI: 10.1002/art.1780400609
- Bettelli, E., Y. Carrier, W. Gao, T. Korn and T.B. Strom *et al.*, 2006. Reciprocal developmental pathways for the generation of pathogenic effector Th17 and regulatory T cells. *Nature*, 441: 235-238. DOI: 10.1038/nature04753
- Cai, X.Y., C.P. Gommoll, Jr., L. Justice, S.K. Narula and J.S. Fine, 1998. Regulation of granulocyte colony-stimulating factor gene expression by interleukin-17. *Immunol. Lett.*, 62: 51-58. DOI: 10.1016/S0165-2478(98)00027-3
- McCartney-Francis, N.L. and S.M. Wahl, 1994. Transforming growth factor beta: A matter of life and death. *J. Leukoc. Biol.*, 55: 401-409. PMID: 8120457
- Cerwenka, A. and S.L. Swain, 1999. TGF- $\beta$ 1: Immunosuppressant and viability factor for T lymphocytes. *Microbes Infect.*, 1: 1291-1296. DOI: 10.1016/S1286-4579(99)00255-5
- Chabaud, M., F. Fossiez, J.L. Taupin and P. Miossec, 1998. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J. Immunol.*, 161: 409-414. <http://www.jimmunol.org/cgi/reprint/161/1/409.pdf>
- Chabaud, M., J.M. Durand, N. Buchs, F. Fossiez and G. Page *et al.*, 1999. Human interleukin-17: A T cell-derived proinflammatory cytokine produced by the rheumatoid synovium. *Arthritis Rheum.*, 42: 963-970. DOI: 10.1002/1529-0131(199905)42:5<963::AID-ANR15>3.0.CO;2-E
- Chabaud, M., P. Garnero, J.M. Dayer, P.A. Guerne and F. Fossiez *et al.*, 2000. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine*, 12: 1092-1099. DOI: 10.1006/cyto.2000.0681
- Chen, C.H., C. Seguin-Devaux, N.A. Burke, T.B. Oriss and S.C. Watkins *et al.*, 2003a. Transforming growth factor  $\beta$  blocks Tec kinase phosphorylation, Ca<sup>2+</sup> influx and NFATc translocation causing inhibition of T cell differentiation. *J. Exp. Med.*, 197: 1689-1699. DOI: 10.1084/jem.20021170
- Chen, W.J., W.W. Jin, N. Hardegen, K.J. Lei and L. Li *et al.*, 2003b. Conversion of peripheral CD4<sup>+</sup>CD25<sup>-</sup> Naive T Cells to CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells by TGF- $\beta$  induction of transcription factor Foxp3. *J. Exp. Med.*, 198: 1875-1886.
- Chen, Z., C.M. Tato, L. Muul, A. Laurence and J.J. O'Shea, 2007. Distinct regulation of interleukin-17 in human T helper lymphocytes. *Arthritis Rheum.*, 56: 2936-2946. DOI: 10.1002/art.22866
- Cosmi, L., R.D. Palma, V. Santarlasci, L. Maggi and M. Capone *et al.*, 2008. Human interleukin 17-producing cells originate from a CD161<sup>+</sup>CD4<sup>+</sup> T cell precursor. *J. Exp. Med.*, 205: 1903-1916. <http://jem.rupress.org/content/205/8/1903.full.pdf>
- Das, J., G. Ren, L. Zhang, A.I. Roberts and X. Zhao *et al.*, 2009. Transforming growth factor beta is dispensable for the molecular orchestration of Th17 cell differentiation. *J. Exp. Med.*, 206: 2407-2416. DOI: 10.1084/jem.20082286120409c
- De Larco, J.E. and G.J. Todaro, 1978. Growth factors from murine sarcoma virus-transformed cells. *Proc. Natl. Acad. Sci. USA.*, 75: 4001-4005. <http://www.pnas.org/content/75/8/4001.full.pdf>

- Fossiez, F., O. Djossou, P. Chomarat, L. Flores-Romo and S. It-Yahia *et al.*, 1996. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med.*, 183: 2593-2603. DOI: 10.1084/jem.183.6.2593
- Fujino, S., A. Andoh, S. Bamba, A. Ogawa and K. Hata *et al.*, 2003. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut*, 52: 65-70. DOI: 10.1136/gut.52.1.65
- Gorelik, L., P.E. Fields and R.A. Flavell, 2000. Cutting edge: TGF-beta inhibits Th type 2 development through inhibition of GATA-3 expression. *J. Immunol.*, 165: 4773-4777. <http://www.jimmunol.org/cgi/reprint/165/9/4773.pdf>
- Gorelik, L., S. Constant and R.A. Flavell, 2002. Mechanism of transforming growth factor  $\beta$ -induced inhibition of T helper type 1 differentiation. *J. Exp. Med.*, 195: 1499-1505. DOI: 10.1084/jem.20012076
- Heath, V.L., E.E. Murphy, C. Crain, M.G. Tomlinson and A. O'Garra, 2000. TGF- $\beta$ 1 down-regulates Th2 development and results in decreased IL-4-induced STAT6 activation and GATA-3 expression. *Eur. J. Immunol.*, 30: 2639-2649. DOI: 10.1002/1521-4141(200009)30:9<2639::AID-IMMU2639>3.0.CO;2-7
- Hellings, P.W., A. Kasran, Z. Liu, P. Vandekerckhove and A. Wuyts *et al.*, 2003. Interleukin-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. *Am. J. Respir. Cell Mol. Biol.*, 28: 42-50. DOI: 10.1165/rcmb.4832
- Hofstetter, H.H., S.M. Ibrahim, D. Koczan, N. Kruse and A. Weishaupt *et al.*, 2005. Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. *Cell Immunol.*, 237: 123-130. PMID: 16386239
- Horwitz, D.A., J.D. Gray and K. Ohtsuka, 1999. Role of NK cells and TGF- $\beta$  in the regulation of T-cell-dependent antibody production in health and autoimmune disease. *Microbes Infect.*, 1: 1305-1311. DOI: 10.1016/S1286-4579(99)00253-1
- Infante-Duarte, C., H.F. Horton, M.C. Byrne and T. Kamradt, 2000. Microbial lipopeptides induce the production of IL-17 in Th cells. *J. Immunol.*, 165: 6107-6115. PMID: 11086043
- Iwakura, Y. and H. Ishigame, 2006. The IL-23/IL-17 axis in inflammation. *J. Clin. Invest.*, 116: 1218-1222. DOI: 10.1172/JCI28508
- Jones, C.E. and K. Chan, 2002. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha and granulocyte-colony-stimulating factor by human airway epithelial cells. *Am. J. Respir. Cell Mol. Biol.*, 26: 748-753. <http://ajrcmb.atsjournals.org/cgi/content/full/26/6/748>
- Katz, Y., O. Nadiv and Y. Beer, 2001. Interleukin-17 enhances tumor necrosis factor  $\alpha$ -induced synthesis of interleukins 1, 6 and 8 in skin and synovial fibroblasts: A possible role as a "fine-tuning cytokine" in inflammation processes. *Arthritis Rheum.*, 44: 2176-2184. DOI: 10.1002/1529-0131(200109)44:9<2176::AID-ART371>3.0.CO;2-4
- Katz, Y., O. Nadiv, M.J. Rapoport and M. Loos, 2000. IL-17 regulates gene expression and protein synthesis of the complement system, C3 and factor B, in skin fibroblasts. *Clin. Exp. Immunol.*, 120: 22-29. DOI: 10.1046/j.1365-2249.2000.01199.x
- Kawaguchi, M., F. Kokubu, H. Kuga, S. Matsukura and H. Hoshino *et al.*, 2001. Modulation of bronchial epithelial cells by IL-17. *J. Allergy Clin. Immunol.*, 108: 804-809. DOI: 10.1067/mai.2001.119027
- Kehrl, J.H., A.B. Roberts, L.M. Wakefield, S. Jakowlew and M.B. Sporn *et al.*, 1986a. Transforming growth factor beta is an important immunomodulatory protein for human B lymphocytes. *J. Immunol.*, 137: 3855-3860. PMID: 2878044
- Kehrl, J.H., L.M. Wakefield, A.B. Roberts, S. Jakowlew and M. Varez-Mon *et al.*, 1986b. Production of transforming growth factor beta by human T lymphocytes and its potential role in the regulation of T cell growth. *J. Exp. Med.*, 163: 1037-1050. PMID: 2871125
- Komiyama, Y., S. Nakae, T. Matsuki, A. Nambu and H. Ishigame *et al.*, 2006. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J. Immunol.*, 177: 566-573. PMID: 16785554
- Laan, M., Z.H. Cui, H. Hoshino, J. Lotvall and M. Sjostrand *et al.*, 1999. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. *J. Immunol.*, 162: 2347-2352. PMID: 9973514
- Latham, K.A., K.B. Whittington, R. Zhou, Z. Qian and E.F. Rosloniec, 2005. *Ex vivo* characterization of the autoimmune T cell response in the HLA-DR1 mouse model of collagen-induced arthritis reveals long-term activation of type II collagen-specific cells and their presence in arthritic joints. *J. Immunol.*, 174: 3978-3985. PMID: 15778354
- Lebman, D.A. and J.S. Edmiston, 1999. The role of TGF-beta in growth, differentiation and maturation of B lymphocytes. *Microbes Infect.*, 1: 1297-1304. PMID: 10611758
- Lin, J.T., S.L. Martin, L. Xia and J.D. Gorham, 2005. TGF-beta 1 uses distinct mechanisms to inhibit IFN-gamma expression in CD4<sup>+</sup> T cells at priming and at recall: Differential involvement of Stat4 and T-bet. *J. Immunol.*, 174: 5950-5958. PMID: 15879087

- Lock, C.B. and R.A. Heller, 2003. Gene microarray analysis of multiple sclerosis lesions. *Trends Mol. Med.*, 9: 535-541. DOI: 10.1016/j.molmed.2003.10.008
- Lubberts, E., M.I. Koenders and W.B. van den Berg, 2005. The role of T-cell interleukin-17 in conducting destructive arthritis: Lessons from animal models. *Arthritis Res. Ther.*, 7: 29-37. PMID: 15642151
- Manel, N., D. Unutmaz and D.R. Littman, 2008. The differentiation of human T (H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgamma. *Nat. Immunol.*, 9: 641-649. PMID: 18454151
- Mangan, P.R., L.E. Harrington, D.B. O'Quinn, W.S. Helms and D.C. Bullard *et al.*, 2006. Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature*, 441: 231-234. PMID: 16648837
- McKenzie, B.S., R.A. Kastelein and D.J. Cua, 2006. Understanding the IL-23-IL-17 immune pathway. *Trends Immunol.*, 27: 17-23. PMID: 16290228
- Ogawa, A., A. Andoh, Y. Araki, T. Bamba and Y. Fujiyama, 2004. Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice. *Clin. Immunol.*, 110: 55-62. PMID: 14962796
- Pearce, E.J., C.M. Kane and J. Sun, 2006. Regulation of dendritic cell function by pathogen-derived molecules plays a key role in dictating the outcome of the adaptive immune response. *Chem. Immunol. Allergy*, 90: 82-90. PMID: 16210904
- Prause, O., M. Laan, J. Lotvall and A. Linden, 2003. Pharmacological modulation of interleukin-17-induced GCP-2-, GRO-alpha- and interleukin-8 release in human bronchial epithelial cells. *Eur. J. Pharmacol.*, 462: 193-198. PMID: 12591113
- Santarlaschi, V., L. Maggi, M. Capone, F. Frosali and V. Querci *et al.*, 2009. TGF-beta indirectly favors the development of human Th17 cells by inhibiting Th1 cells. *Eur. J. Immunol.*, 39: 207-215. PMID: 19130583
- Schumann, J., 2008. Transformierender Wachstumsfaktor-beta (TGF-beta) und Granulozyten-Makrophagen Kolonie-Stimulierender Faktor (GM-CSF) in der Pathogenese der Lyme-Borreliose und der Spezifizierung von T-Helferzell-Populationen. Schwarzenberger, P., R. La, A. Miller, P. Ye and W. Huang *et al.*, 1998. IL-17 stimulates granulopoiesis in mice: Use of an alternate, novel gene therapy-derived method for in vivo evaluation of cytokines. *J. Immunol.*, 161: 6383-6389. PMID: 9834129
- Schwarzenberger, P., W. Huang, P. Oliver, P. Byrne and R. La *et al.*, 2001. Il-17 mobilizes peripheral blood stem cells with short-and long-term repopulating ability in mice. *J. Immunol.*, 167: 2081-2086. PMID: 11489991
- Shalom-Barak, T., J. Quach and M. Lotz, 1998. Interleukin-17-induced gene expression in articular chondrocytes is associated with activation of mitogen-activated protein kinases and NF-kappaB. *J. Biol. Chem.*, 273: 27467-27473. PMID: 9765276
- Strobl, H. and W. Knapp, 1999. TGF-beta1 regulation of dendritic cells. *Microbes Infect.*, 1: 1283-1290. PMID: 10611756
- Veldhoen, M., R.J. Hocking, C.J. Atkins, R.M. Locksley and B. Stockinger, 2006. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity*, 24: 179-189. PMID: 16473830
- Wahl, S.M., 1994. Transforming growth factor beta: the good, the bad and the ugly. *J. Exp. Med.*, 180: 1587-1590. PMID: 7964446
- Wilson, N.J., K. Boniface, J.R. Chan, B.S. McKenzie and W.M. Blumenschein *et al.*, 2007. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat. Immunol.*, 8: 950-957. PMID: 17676044
- Yao, Z., S.L. Painter, W.C. Fanslow, D. Ulrich and B.M. Macduff *et al.*, 1995a. Human IL-17: A novel cytokine derived from T cells. *J. Immunol.*, 155: 5483-5486. PMID: 7499828
- Yao, Z., W.C. Fanslow, M.F. Seldin, A.M. Rousseau and S.L. Painter *et al.*, 1995b. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity*, 3: 811-821. PMID: 8777726
- Zhang, Z., M. Zheng, J. Bindas, P. Schwarzenberger and J.K. Kolls, 2006. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. *Inflamm. Bowel. Dis.*, 12: 382-388. PMID: 16670527