World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i29.3638

World J Gastroenterol 2010 August 7; 16(29): 3638-3641
ISSN 1007-9327 (print)

GUIDELINES FOR BASIC SCIENCE

Interleukin-21 triggers effector cell responses in the gut

Daniela De Nitto, Massimiliano Sarra, Francesco Pallone, Giovanni Monteleone

Daniela De Nitto, Massimiliano Sarra, Francesco Pallone, Giovanni Monteleone, Department of Internal Medicine, University "Tor Vergata" of Rome, 00133 Rome, Italy
Author contributions: All authors contributed drafting the paper.
Supported by Fondazione Umberto di Mario, Rome, the Broad Medical Research Program Foundation (Grant No. IBD-0154R), and Giuliani SpA, Milan, Italy
Correspondence to: Giovanni Monteleone, MD, PhD, Department of Internal Medicine, University "Tor Vergata" of Rome, 00133 Rome, Italy. gi.monteleone@med.uniroma2.it
Telephone: +39-6-72596158 Fax: +39-6-72596391
Received: April 2, 2010 Revised: April 22, 2010
Accepted: April 29, 2010
Published online: August 7, 2010

Abstract

In the gut of patients with Crohn's disease and patients with ulcerative colitis, the major forms of inflammatory bowel diseases (IBD) in humans, the tissue-damaging immune response is mediated by an active cross-talk between immune and non-immune cells. Accumulating evidence indicates also that cytokines produced by these cells play a major role in initiating and shaping this pathologic process. One such cytokine seems to be interleukin (IL)-21, a member of the common γ-chain-receptor family. IL-21 is produced in excess in the inflamed intestine of patients with IBD mostly by activated CD4+ T helper cells co-expressing interferon-γ and follicular T helper cells. Moreover, both *in vitro* and *in vivo* studies indicate that excessive IL-21 production leads to the activation of multiple signaling pathways that expand and sustain the ongoing mucosal inflammation. In this article, we review the available data supporting the pathogenic role of IL-21 in IBD.

Key words: Interleukin-21; Gut; T cells; Epithelial cells; Fibroblasts

Peer reviewer: Tamara Vorobjova, Senior Researcher in Immunology, Department of Immunology, Institute of General and Molecular Pathology, University of Tartu, Ravila, 19, Tartu, 51014, Estonia

De Nitto D, Sarra M, Pallone F, Monteleone G. Interleukin-21 triggers effector cell responses in the gut. *World J Gastroenterol* 2010; 16(29): 3638-3641 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i29/3638.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i29.3638

INTRODUCTION

The organized lymphoid tissue of the gastrointestinal tract contains large numbers of immune cells that are deputed both to protect from infectious diseases and to evoke immune tolerance[1,2]. Perturbations in this delicately balanced microenvironment can promote the collapse of tolerance, thus leading to chronic inflammation that alters the integrity and function of the gut[3]. This occurs for example in patients with Crohn's disease (CD) and patients with ulcerative colitis (UC), the major forms of inflammatory bowel diseases (IBD) in humans[4]. In both these conditions, the tissue damage is mediated by an excessive and poorly controlled immune-inflammatory reaction directed against components of the normal bacterial flora[5,6]. Evidence also indicates that an active and dynamic interplay between immune and non-immune cells plays a major role in initiating and shaping this pathologic process, and that cytokines are essential mediators of this cross-talk[7-9]. One such cytokine seems to be interleukin (IL)-21, a product of activated CD4+ T helper (Th) cells, follicular Th cells (TFH), and Natural killer (NK) T cells, which exerts regulatory effects on multiple cell types[10-13]. In this article, we review the available data supporting the pathogenic role of IL-21 in IBD.

IL-21 IS MADE BY TH1 CELLS AND FOLLICULAR TH CELLS IN THE HUMAN GUT

Initial studies conducted in our laboratory showed that IL-21 protein is over-produced in the inflamed gut of

patients with CD and patients with UC as compared to normal controls[14]. These data were confirmed by a recent study showing that IL-21 mRNA expression is increased in rectal mucosa from patients with active UC compared to UC patients in remission and healthy controls and that, in UC, IL-21 gene expression correlates with histological activity of the disease[15]. A genome-wide association study for IBD has identified risk variants in the chromosomal 4q27 region harbouring the *IL-2* and *IL-21* genes, suggesting that polymorphism(s) in this region might contribute to regulation of IL-21 production/function[16-18]. However, it is noteworthy that expression of IL-21 in the uninflamed mucosa of IBD patients does not differ from that seen in the normal colonic mucosa, and that peripheral blood T cells isolated from IBD patients and healthy controls express similar levels of IL-21[14]. Therefore, it is plausible that up-regulation of IL-21 in IBD is strictly linked to the ongoing mucosal inflammation.

In both CD and UC, IL-21 is made by CD4+ but not CD8+ T cells[14]. By flow-cytometry it was also shown that the majority of IL-21-producing CD4+ T-LPL co-express interferon (IFN)-γ, and to a lesser extent IL-17A, supporting the hypothesis that, in IBD, IL-21 is preferentially made by Th1 rather than Th17 cells[19]. At the present time, it remains unclear how IL-21-positive cells co-expressing IFN-γ differentiate in the human gut. Since Th1 cells are abundant in the human gut, and particularly in CD mucosa[20-22], it is conceivable that Th1 cells can acquire the ability to make IL-21 in response to specific stimuli. Indeed, we have recently shown that *in vitro* stimulation of intestinal lamina propria (LP) CD4+ T cells with IL-12, the major inducer of Th1 cell response, enhances the fraction of cells producing IL-21 or both IL-21 and IFN-γ[19].

IL-21 is also produced by TFH cells in the human gut, and the fraction of IL-21-producing TFH cells is significantly higher in CD than in UC and controls[19]. Interestingly, activation of mucosal T cells with IL-12 leads to enhanced production of IL-21 by TFH cells[19], thus confirming that IL-12-driven signals positively regulate IL-21 production in the gut.

IL-21 ENHANCES INFLAMMATORY PATHWAYS IN THE GUT

A large body of evidence supports the concept that excessive production of IL-21 in the gut has deleterious consequences for the host. IL-21 is highly produced in the gut of wild-type mice with dextran sulfate sodium (DSS)- and trinitrobenzene sulfonic acid-relapsing (TNBS)-induced colitis[23]. Notably, IL-21-deficient mice are largely protected against disease in both models[23]. Amelioration of both DSS- and TNBS-induced colitis in IL-21-knockout mice is associated with a marked decrease in Th17-related molecules, such as IL-17 and IL-17F. Administration of IL-21R/Fc, a fusion protein that binds to IL-21 and prevents it activating cell-surface receptors, in wild-type mice attenuates DSS-colitis, confirming the pro-inflammatory role of IL-21 in this model[23]. A similar scenario emerges from studies in human IBD[19]. Stimulation of intestinal mucosal T cells with IL-21 results in enhanced activation of transcription factors (i.e. Stat3, Stat4 and T-bet) and marked synthesis of IFN-γ and IL-21 itself[14]. Moreover, treatment of CD mucosal cells with IL-21R/Fc reduces Stat4 and T-bet and inhibits IFN-γ production. Neutralization of IL-21 in CD mucosal cell cultures leads also to a decreased expression of IL-17A[23]. Taken together these data indicate that IL-21 is able to expand Th1 and Th17 cell responses in the gut, even though further experimentation is needed to elucidate the basic mechanism by which IL-21 exerts these regulatory effects.

Initially described as an important regulator of the function of immune cells[24,25], IL-21 has been recently shown to also regulate the activity of non-immune cells. Gut myofibroblasts and epithelial cells express constitutively IL-21R and are able to respond to IL-21[26]. In particular, stimulation of colonic myofibroblasts with IL-21 enhances the synthesis of matrix metalloproteinases (MMPs)[26], a family of proteases that are supposed to participate in the tissue damage and remodelling occurring in IBD[27,28]. The IL-21-driven induction of MMPs can be potentiated by tumor necrosis factor α, and associates with no change in the production of tissue inhibitors of MMPs[26]. Regulation of MMPs by IL-21 does not however seem to occur at the transcriptional level, because stimulation of fibroblasts with IL-21 does not alter the MMP RNA expression[26]. Additionally, the intracellular level of MMP proteins is not increased by IL-21, and the IL-21-induced MMP synthesis is not affected by inhibitors of gene transcription and *de novo* protein synthesis[26]. Therefore, it is plausible that IL-21 preferentially increases the secretion of either pre-constituted or newly synthesized MMPs. The *in vivo* relevance of these findings relates to the demonstration that supernatants of CD mucosal cells induce myofibroblasts to secrete MMP and this is partially inhibitable by IL-21R/Fc[26].

IL-21 induces activation of mitogen activated protein kinases in colonic epithelial cells thereby promoting the secretion of macrophage inflammatory protein (MIP)-3α[29], a chemokine up-regulated on the inflamed gut epithelium of IBD patients and involved in the recruitment of T cells in the gut mucosa[30,31]. In line with these observations, blockade of endogenous IL-21 in cultures of IBD mucosal explants reduces MIP-3α synthesis by epithelial cells[29].

IL-21 INHIBITS REGULATORY T CELL DIFFERENTIATION AND MAKES CD4+ T CELLS RESISTANT TO TREGS-MEDIATED IMMUNE-SUPPRESSION

Regulatory T cells (Tregs) play an important role in maintaining homeostasis and preventing autoimmunity in various organs, including the gut[32,33]. Tregs specifically express the transcription factor forkhead winged helix transcription factor gene (Foxp3), which is also functionally required for their regulatory activity[32]. In addition to naturally occur-

ring Tregs that are produced by the thymus as a functionally distinct and mature population of T cells[33], Tregs can arise in the periphery upon conversion of CD4+CD25- T cells into Foxp3-positive-CD4+CD25+ cells in response to activating stimuli and transforming growth factor (TGF)-β1[34,35]. This phenomenon seems to occur in the normal gut, where TGF-β1 synergizes with other regulatory molecules (e.g. IL-10, retinoic acid) in mounting an effective counter-regulatory response[36,37]. However, if activation of naïve CD4+CD25- T cells occurs in the presence of TGF-β1 and inflammatory stimuli, they tend to differentiate into effector Th17 cells rather than into Tregs[38]. IL-21 seems to accomplish this function, given that it can cross-regulate Tregs induction and direct the development of Th17 cells[39]. Interestingly, colitis induced by the transfer of naïve T cells into severe combined immunodeficient mice is suppressed by TGF-β1-induced Tregs generated *in vitro* in the absence of IL-21 but not by T cells generated in the presence of TGF-β1 and IL-21[40]. By contrast, these latter T cells exacerbate colitis with increased expression of IL-17 and a reduced number of Foxp3-expressing cells in the gut mucosa[40]. Consistent with this is the demonstration that blockade of IL-21 associates with high numbers of Foxp3-positive Tregs and reduced tissue damage in the colon and small intestine of mice with acute graft *vs* host disease[41].

IL-21 is also able to counteract the regulatory effects of Tregs by providing human CD4+ T cells signals that raise their threshold for suppression by Tregs[42]. Collectively these observations delineate another mechanism by which IL-21 contributes to amplify the ongoing inflammation in IBD.

CONCLUSION

There is no doubt that IL-21 modulates the activity of several cell types that orchestrate the tissue damage in IBD, and that blockade of IL-21 signalling attenuates the ongoing mucosal inflammation in experimental models of IBD. Therefore, it is conceivable that the near future will witness the use of novel therapeutic strategies aimed at inhibiting IL-21 activity in IBD. However, some important issues related to the blockade of IL-21 function must be taken into consideration before moving into the clinic. For instance, we should not forget that IL-21 plays a decisive role in the control of B cell and plasma cell function, and that IL-21 signalling may attenuate the course of IgE-mediated diseases[24,25]. Moreover, blockade of IL-21 could potentially enhance the risk of malignancies and exacerbate chronic viral infections given the ability of IL-21 to trigger CD8+ T cell-dependent immune reactions against tumors and viruses[43-48]. At least in some circumstances, IL-21 stimulates IL-10 production, thereby promoting tolerogenic rather than inflammatory responses. If so, anti-IL-21 therapy could paradoxically enhance the risk of autoimmunity.

REFERENCES

1 **Mowat AM**, Parker LA, Beacock-Sharp H, Millington OR, Chirdo F. Oral tolerance: overview and historical perspectives. *Ann N Y Acad Sci* 2004; **1029**: 1-8
2 **Mowat AM**. Dendritic cells and immune responses to orally administered antigens. *Vaccine* 2005; **23**: 1797-1799
3 **Macdonald TT**, Monteleone G. Immunity, inflammation, and allergy in the gut. *Science* 2005; **307**: 1920-1925
4 **Podolsky DK**. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429
5 **Strober W**, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. *J Clin Invest* 2007; **117**: 514-521
6 **Abraham C**, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; **361**: 2066-2078
7 **Elson CO**, Cong Y, McCracken VJ, Dimmitt RA, Lorenz RG, Weaver CT. Experimental models of inflammatory bowel disease reveal innate, adaptive, and regulatory mechanisms of host dialogue with the microbiota. *Immunol Rev* 2005; **206**: 260-276
8 **MacDonald TT**, Bajaj-Elliott M, Pender SL. T cells orchestrate intestinal mucosal shape and integrity. *Immunol Today* 1999; **20**: 505-510
9 **Fantini MC**, Monteleone G, Macdonald TT. New players in the cytokine orchestra of inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 1419-1423
10 **Parrish-Novak J**, Dillon SR, Nelson A, Hammond A, Sprecher C, Gross JA, Johnston J, Madden K, Xu W, West J, Schrader S, Burkhead S, Heipel M, Brandt C, Kuijper JL, Kramer J, Conklin D, Presnell SR, Berry J, Shiota F, Bort S, Hambly K, Mudri S, Clegg C, Moore M, Grant FJ, Lofton-Day C, Gilbert T, Rayond F, Ching A, Yao L, Smith D, Webster P, Whitmore T, Maurer M, Kaushansky K, Holly RD, Foster D. Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. *Nature* 2000; **408**: 57-63
11 **Nurieva R**, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 2007; **448**: 480-483
12 **Vogelzang A**, McGuire HM, Yu D, Sprent J, Mackay CR, King C. A fundamental role for interleukin-21 in the generation of T follicular helper cells. *Immunity* 2008; **29**: 127-137
13 **Coquet JM**, Kyparissoudis K, Pellicci DG, Besra G, Berzins SP, Smyth MJ, Godfrey DI. IL-21 is produced by NKT cells and modulates NKT cell activation and cytokine production. *J Immunol* 2007; **178**: 2827-2834
14 **Monteleone G**, Monteleone I, Fina D, Vavassori P, Del Vecchio Blanco G, Caruso R, Tersigni R, Alessandroni L, Biancone L, Naccari GC, MacDonald TT, Pallone F. Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. *Gastroenterology* 2005; **128**: 687-694
15 **Yamamoto-Furusho JK**, Miranda-Pérez E, Fonseca-Camarillo G, Sánchez-Muñoz F, Barreto-Zuñiga R, Dominguez-Lopez A. Interleukin 21 expression is increased in rectal biopsies from patients with ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 1090
16 **Márquez A**, Orozco G, Martínez A, Palomino-Morales R, Fernández-Arquero M, Mendoza JL, Taxonera C, Díaz-Rubio M, Gómez-García M, Nieto A, López-Nevot MA, de la Concha EG, Martín J, Urcelay E. Novel association of the interleukin 2-interleukin 21 region with inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 1968-1975
17 **van Heel DA**, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, Wapenaar MC, Barnardo MC, Bethel G, Holmes GK, Feighery C, Jewell D, Kelleher D, Kumar P, Travis S, Walters JR, Sanders DS, Howdle P, Swift J, Playford RJ, McLaren WM, Mearin ML, Mulder CJ, McManus R, McGinnis R, Cardon LR, Deloukas P, Wijmenga C. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet* 2007; **39**: 827-829
18 **Festen EA**, Goyette P, Scott R, Annese V, Zhernakova A, Lian J, Lefèbvre C, Brant SR, Cho JH, Silverberg MS, Taylor KD, de Jong DJ, Stokkers PC, Mcgovern D, Palmieri O, Achkar JP, Xavier RJ, Daly MJ, Duerr RH, Wijmenga C, Weersma RK,

Rioux JD. Genetic variants in the region harbouring IL2/IL21 associated with ulcerative colitis. *Gut* 2009; **58**: 799-804
19 **Sarra M**, Monteleone I, Stolfi C, Fantini MC, Sileri P, Sica G, Tersigni R, Macdonald TT, Pallone F, Monteleone G. Interferon-gamma-expressing cells are a major source of interleukin-21 in inflammatory bowel diseases. *Inflamm Bowel Dis* 2010; **16**: 1332-1339
20 **Fuss IJ**, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, Fiocchi C, Strober W. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996; **157**: 1261-1270
21 **Neurath MF**, Weigmann B, Finotto S, Glickman J, Nieuwenhuis E, Iijima H, Mizoguchi A, Mizoguchi E, Mudter J, Galle PR, Bhan A, Autschbach F, Sullivan BM, Szabo SJ, Glimcher LH, Blumberg RS. The transcription factor T-bet regulates mucosal T cell activation in experimental colitis and Crohn's disease. *J Exp Med* 2002; **195**: 1129-1143
22 **Monteleone G**, Biancone L, Marasco R, Morrone G, Marasco O, Luzza F, Pallone F. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. *Gastroenterology* 1997; **112**: 1169-1178
23 **Fina D**, Sarra M, Fantini MC, Rizzo A, Caruso R, Caprioli F, Stolfi C, Cardolini I, Dottori M, Boirivant M, Pallone F, Macdonald TT, Monteleone G. Regulation of gut inflammation and th17 cell response by interleukin-21. *Gastroenterology* 2008; **134**: 1038-1048
24 **Monteleone G**, Pallone F, Macdonald TT. Interleukin-21 (IL-21)-mediated pathways in T cell-mediated disease. *Cytokine Growth Factor Rev* 2009; **20**: 185-191
25 **Spolski R**, Leonard WJ. IL-21 and T follicular helper cells. *Int Immunol* 2010; **22**: 7-12
26 **Monteleone G**, Caruso R, Fina D, Peluso I, Gioia V, Stolfi C, Fantini MC, Caprioli F, Tersigni R, Alessandroni L, MacDonald TT, Pallone F. Control of matrix metalloproteinase production in human intestinal fibroblasts by interleukin 21. *Gut* 2006; **55**: 1774-1780
27 **Kruidenier L**, MacDonald TT, Collins JE, Pender SL, Sanderson IR. Myofibroblast matrix metalloproteinases activate the neutrophil chemoattractant CXCL7 from intestinal epithelial cells. *Gastroenterology* 2006; **130**: 127-136
28 **Pender SL**, Fell JM, Chamow SM, Ashkenazi A, MacDonald TT. A p55 TNF receptor immunoadhesin prevents T cell-mediated intestinal injury by inhibiting matrix metalloproteinase production. *J Immunol* 1998; **160**: 4098-4103
29 **Caruso R**, Fina D, Peluso I, Stolfi C, Fantini MC, Gioia V, Caprioli F, Del Vecchio Blanco G, Paoluzi OA, Macdonald TT, Pallone F, Monteleone G. A functional role for interleukin-21 in promoting the synthesis of the T-cell chemoattractant, MIP-3alpha, by gut epithelial cells. *Gastroenterology* 2007; **132**: 166-175
30 **Kwon JH**, Keates S, Bassani L, Mayer LF, Keates AC. Colonic epithelial cells are a major site of macrophage inflammatory protein 3alpha (MIP-3alpha) production in normal colon and inflammatory bowel disease. *Gut* 2002; **51**: 818-826
31 **Teramoto K**, Miura S, Tsuzuki Y, Hokari R, Watanabe C, Inamura T, Ogawa T, Hosoe N, Nagata H, Ishii H, Hibi T. Increased lymphocyte trafficking to colonic microvessels is dependent on MAdCAM-1 and C-C chemokine mLARC/CCL20 in DSS-induced mice colitis. *Clin Exp Immunol* 2005; **139**: 421-428
32 **Hori S**, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science* 2003; **299**: 1057-1061
33 **Sakaguchi S**, Ono M, Setoguchi R, Yagi H, Hori S, Fehervari Z, Shimizu J, Takahashi T, Nomura T. Foxp3+ CD25+ CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. *Immunol Rev* 2006; **212**: 8-27
34 **Fantini MC**, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF. Cutting edge: TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. *J Immunol* 2004; **172**: 5149-5153
35 **Chen W**, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G, Wahl SM. Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med* 2003; **198**: 1875-1886
36 **Coombes JL**, Siddiqui KR, Arancibia-Cárcamo CV, Hall J, Sun CM, Belkaid Y, Powrie F. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med* 2007; **204**: 1757-1764
37 **El-Asady R**, Yuan R, Liu K, Wang D, Gress RE, Lucas PJ, Drachenberg CB, Hadley GA. TGF-{beta}-dependent CD103 expression by CD8(+) T cells promotes selective destruction of the host intestinal epithelium during graft-versus-host disease. *J Exp Med* 2005; **201**: 1647-1657
38 **Mucida D**, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H. Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. *Science* 2007; **317**: 256-260
39 **Yang L**, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, Kuchroo VK, Hafler DA. IL-21 and TGF-beta are required for differentiation of human T(H)17 cells. *Nature* 2008; **454**: 350-352
40 **Fantini MC**, Rizzo A, Fina D, Caruso R, Becker C, Neurath MF, Macdonald TT, Pallone F, Monteleone G. IL-21 regulates experimental colitis by modulating the balance between Treg and Th17 cells. *Eur J Immunol* 2007; **37**: 3155-3163
41 **Bucher C**, Koch L, Vogtenhuber C, Goren E, Munger M, Panoskaltsis-Mortari A, Sivakumar P, Blazar BR. IL-21 blockade reduces graft-versus-host disease mortality by supporting inducible T regulatory cell generation. *Blood* 2009; **114**: 5375-5384
42 **Peluso I**, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, Pallone F, Monteleone G. IL-21 counteracts the regulatory T cell-mediated suppression of human CD4+ T lymphocytes. *J Immunol* 2007; **178**: 732-739
43 **Fröhlich A**, Kisielow J, Schmitz I, Freigang S, Shamshiev AT, Weber J, Marsland BJ, Oxenius A, Kopf M. IL-21R on T cells is critical for sustained functionality and control of chronic viral infection. *Science* 2009; **324**: 1576-1580
44 **Yi JS**, Du M, Zajac AJ. A vital role for interleukin-21 in the control of a chronic viral infection. *Science* 2009; **324**: 1572-1576
45 **Elsaesser H**, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. *Science* 2009; **324**: 1569-1572
46 **Andorsky DJ**, Timmerman JM. Interleukin-21: biology and application to cancer therapy. *Expert Opin Biol Ther* 2008; **8**: 1295-1307
47 **Spolski R**, Leonard WJ. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. *Curr Opin Immunol* 2008; **20**: 295-301
48 **Skak K**, Kragh M, Hausman D, Smyth MJ, Sivakumar PV. Interleukin 21: combination strategies for cancer therapy. *Nat Rev Drug Discov* 2008; **7**: 231-240

S- Editor Tian L **L- Editor** O'Neill M **E- Editor** Ma WH