Review

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Rheumatoid arthritis and the alpha-chemokine IP-10

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Abstract

Interferon(IFN)-gamma-induced protein 10 (IP-10) and its receptor, CXCR3, appear to contribute to the pathogenesis of rheumatoid arthritis (RA). IP-10 has been detected in sera, synovial fluid (SF), and synovial tissue in RA patients. IP-10 is mainly expressed by infiltrating macrophage-like cells and fibroblast-like synoviocytes in RA synovium. The elevated expression of CXCR3 on T cells from SF has been associated with high levels of IFN-gamma, which suggest a preferential Th1 phenotype. A human phase II clinical trial using an anti-IP-10 monoclonal antibody (MDX-1100) for RA patients who had an inadequate response to methotrexate treatment has shown that blocking IP-10 significantly increased response rate compared to the placebo group, suggesting a possible therapeutic use in humans. ***Clin Ter 2014; 165(6):e447-451. doi: 10.7417/CT.2014.1791***

Key words: *CXCR3, IP-10, rheumatoid arthritis*

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disorder, causing symmetrical polyarthritis of large and small joints. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated (1). The key pieces of evidence relating the pathogenesis of RA to autoimmunity and inflammation are the following:

1. A genetic link with HLA-DR4 and related allotypes of major histocompatibility complex (MHC) Class II and the T cell-associated protein PTPN22 (2).
2. An undeniable link to the pathogenesis of vascular disease of many types, including the possibility of a strong causal connection to rheumatoid vasculitis.
3. A remarkable reduction of disease progression in many cases by blockade of the cytokine Tumor Necrosis Factor (TNF)-alpha (3).
4. A similar dramatic response in many cases to depletion of B lymphocytes.
5. The presence of rheumatoid factors (RF), and antibodies to citrullinated peptides (ACPA) (4).
6. Initial site of disease is synovial membrane.
7. Women (30 to 50 years) are more commonly affected.

These data suggest that the disease involves abnormal B cell–T cell interaction, with presentation of antigens by B cells to T cells via HLA-DR eliciting T cell help and consequent production of RF and ACPA. Inflammation is then driven either by B cell or T cell products stimulating release of TNF and other cytokines and chemokines (5-8).

Chemokines

Chemokines are small proteins which play a significant role in leukocyte trafficking (9) by producing chemotactic activity in cells expressing chemokine receptors. Based on the position of the first and second conserved cysteine residues within the N-terminal domain, the chemokines are divided into two major (CX3C and CXC) and two minor (CC and C) subfamilies (10-13). The CX3C subfamily has three intervening residues separating the two N-terminal cysteines, whereas the CXC subfamily only has one non-conserved amino acid residue separating the N-terminal cysteines. CC chemokines are those in which two cysteines are adjacent to each other, and a single known C chemokine lacks the first cysteine of the N-terminal pair. The Interferon (IFN)-gamma-induced protein 10 (IP-10) is a member of the CXC subfamily. CXC chemokines bind to CXC chemokine receptors. IP-10 specifically activates CXCR3 receptor which is a seven trans-membrane-spanning G protein-coupled receptor predominantly expressed on activated T helper 1 (Th1) lymphocytes (14), natural killer (NK) cells, macrophages and B cells (15, 16). The other IFN-gamma-induced CXC chemokines, monokine induced by IFN-gamma (Mig) and IFN-inducible T-cell chemoattractant (I-TAC), also activate CXCR3. These CXC chemokines are preferentially expressed on Th1 lymphocytes (17-19). IP-10 is highly expressed in a diverse range of human diseases. It has been shown to be involved in the pathological processes of the main human disorders, as infectious, inflammatory (20, 21) and autoimmune diseases (10), and cancer. Since IP-10 plays a significant role in leukocyte homing to inflamed tissues, it exacerbates inflammation and causes significant tissue

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damage (10). IP-10 is an ELR-negative CXC chemokine that attenuates angiogenesis and has anti-tumor action (22, 23). However, an increased expression of IP-10 and its corresponding receptor CXCR3 have also been associated with advanced human cancers, including malignant melanoma (24), ovarian carcinoma (25), B-cell lymphoma (26), basal cell carcinoma (27), and thyroid cancer (28, 29).

Under proinflammatory conditions, IP-10 is secreted from a variety of cells, such as activated neutrophils, monocytes, epithelial cells, endothelial cells, fibroblasts and keratinocytes in response to IFN-gamma (27, 30). This crucial regulator of the IFN response, preferentially attracts activated Th1 lymphocytes to the area of inflammation and its expression is associated with Th1 immune responses (31-33).

The determination of high level of IP-10 in peripheral liquids is therefore a marker of host immune response, especially Th1 orientated T-cells.

Circulating levels of IP-10 are increasing with age (34). Furthermore, recent reports have shown that the serum and/or the tissue expression of IP-10 are increased in organ specific autoimmune diseases, such as type 1 diabetes (T1D) (35-38), Graves' disease (GD), or Graves' ophthalmopathy (GO) (39-41), autoimmune thyroiditis (42-44), or systemic rheumatic disorders like systemic lupus erythematosus (SLE) (45), systemic sclerosis (SSc) (46, 47), psoriasis or psoriatic arthritis (48-50), sarcoidosis (51, 52), Hepatitis C Virus (HCV)-related cryoglobulinemia (53-55), other HCV immune mediated disorders (56-61), and also in cancers (28, 29, 62-66).

Here, we review IP-10 in RA and other arthritis.

IP-10 in rheumathoid arthritis

RA is a chronic inflammatory arthritis characterized by joint inflammation, synovial hyperplasia, and bone destruction. A Th1/Th2 cytokine imbalance with a predominance of Th1 cytokines, including IFN-gamma, has been suggested to be of pathogenetic importance in RA (67, 68).

A study was aimed to quantify the Th1 cytokine IFN-gamma-positive and the Th2 cytokine interleukin (IL)-4-positive cells in synovial fluid (SF) and synovial membrane at the single-cell level in RA in comparison to reactive arthritis (67). In SF of the RA patients, the mean percentage of IFN-gamma+/CD4+ T cells was almost 4-fold higher than the number of IL-4+/CD4+ T cells, while the ratio of IFN-gamma/IL-4+ CD4+ T cells was only 1.59 in reactive arthritis, suggesting that the Th1 pattern in the joint of RA patients demonstrated at the single-cell level may be important for the pathogenesis of RA and may provide a target for future immunotherapy (67).

The expression and regulation of chemokines that signal through CXCR3 (IP-10 and Mig) in RA synovial fluids, synovial tissues, and blood, was evaluated in a first study (69). SF protein levels of IP-10 and Mig were 2-fold elevated in SF of RA patients compared to control SF. Tissue levels of IP-10 and Mig were significantly higher in RA than in osteoarthritis (OA). Serum levels of IP-10 were higher in patients with seropositive RA compared to controls. This study suggested that IP-10 and Mig may participate in the selective recruitment of CXCR3(+) T cells to the inflamed synovium (69).

It was shown that IP-10 expression within inflamed joints appears to be regulated not only by inflammatory cytokines but also by the physical interaction of activated leukocytes with fibroblast-like synoviocytes, contributing to the recruitment of specific subpopulations of T cells (Th1 type) from the bloodstream into the synovial joints (70).

In another study synovial tissue cells from RA patients more strongly expressed mRNAs for CXCR3 ligands and spontaneously secreted larger amounts of these chemokine proteins than the cells from OA patients (71). The mRNA expression of all CXCR3 ligands was induced in synovial fibroblasts from RA patients after stimulation with IFN-gamma, TNF-alpha, or IL-1beta. However, synovial fibroblasts significantly secreted Mig and IP-10 proteins, but not I-TAC protein, after IFN-gamma stimulation and secreted only IP-10 protein after TNF-alpha or IL-1beta stimulation. When stimulated with a combination of IFN-gamma and TNF-alpha, these cells were able to secrete large amounts of all three chemokines. These results indicate that synovial fibroblasts may be involved in perpetuating the Th1 immune response by producing the Th1-associated CXCR3 ligands, and the synergistic effect of IFN-gamma and TNF-alpha may be important for their chemokine production in RA joints (71).

Stimulation of fibroblasts and human microvascular endothelial cells with the inflammatory cytokines IL-1beta or TNF-alpha combined with either IFN-alpha, IFN-beta or IFN-gamma resulted in a synergistic induction of the CXC chemokine IP-10, but not of the neutrophil chemoattractant CXCL8 (72). Synovial concentrations of CXCL8 and IP-10 were compared in patients suffering from crystal arthritis, ankylosing spondylitis, psoriatic arthritis and RA. All three groups of autoimmune arthritis patients (ankylosing spondylitis, psoriatic arthritis and RA) had significantly increased synovial IP-10 levels compared with crystal arthritis patients (72).

IP-10 was detected in sera of SF and synovial tissue (ST) in RA patients (70).

IP-10 is mainly expressed by infiltrating macrophage-like cells and fibroblast-like synoviocytes in RA synovium (73).

CXCR3 is expressed in T-cell rich areas of inflamed ST, and the majority of T cells (in RA, SF express CXCR3) (74).

The elevated expression of CXCR3 on T cells of SF has been associated with high levels of IFN-gamma, which suggests a preferential Th1 phenotype. CXCR3 is also expressed on endothelial cells of ST from RA and on dendritic cells (75).

Recently, it was found that serum and tissue levels of IP-10 were increased in collagen-induced arthritis, an animal model of RA (73).

Available evidence shows that nuclear factor kappa-B ligand (RANKL) promotes IP-10 expression in osteoclast precursors, and that IP-10 mediates RANKL expression in CD4+ T cells via Gαi subunit of CXCR3 in RA synovium. Importantly, this cross-talk between IP-10 and RANKL, or other cytokines such as TNF-alpha may be responsible for the initiation and/or aggravation of inflammation and bone erosion in RA (73).

Treating collagen-induced arthritis mice with neutralizing anti-IP-10 antibody suppressed clinical arthritis

progression, infiltration of CD4+ T cells and F4/80+ macrophages, serum concentration of RANKL and TNF-alpha, and histological bone loss (73).

A study was aimed to evaluate gene expression in the microdissected synovial lining cells of RA patients, using those of OA patients as the control. Expression levels of signal transducer and activator of transcription 1 (STAT1), IFN regulatory factor 1 (IRF1), and the chemokines Mig, IP-10, and CCL5 were statistically significantly higher in the synovium of RA than in that of OA, indicating an important role for lining synovial cells in the inflammatory and proliferative processes of RA (76).

In synovial fibroblasts and monocyte-derived macrophages ML3000, a competitive inhibitor of the cyclooxygenase and the lipoxygenase pathway, inhibited the TNF induced expression of Mig, IP-10 and I-TAC, providing the basis for further clinical studies testing the application of ML3000 in RA (77).

Infliximab, a monoclonal antibody that blocks the effects of TNF, is used for the treatment of RA. A study analysed the effects on chemokines and their receptors on peripheral mononuclear cells of anti-TNF treatment in RA patients. The chemokines IP-10, CCL2/MCP-1, and CCL4/MIP-1beta, mainly targeting the Th1 immune response, decreased after treatment with anti-TNF, suggesting a more pronounced effect on Th1 activity than on Th2-mediated response (78).

A human phase II clinical trial using an anti-IP-10 monoclonal antibody (MDX-1100) for RA patients who had an inadequate response to methotrexate (MTX) treatment has been published (79). Patients with active RA receiving stable doses of MTX (10-25 mg weekly) were randomized to receive intravenous doses of 10 mg/kg MDX-1100 (n = 35) or placebo (n = 35) every other week. The ACR20 response rate was significantly higher among MDX-1100-treated patients than among placebo-treated patients (54% versus 17%; P = 0.0024). This study showed that MDX-1100 was well tolerated and demonstrated clinical efficacy in RA patients whose disease responded inadequately to MTX. This was the first study to demonstrate clinical efficacy of a chemokine inhibitor in RA and supports the notion of a potential role of IP-10 in the immunopathogenesis of RA (79).

Conclusion

IP-10 and its receptor, CXCR3, appear to contribute to the pathogenesis of RA. IP-10 has been detected in sera, SF, and ST in RA patients. IP-10 is mainly expressed by infiltrating macrophage-like cells and fibroblast-like synoviocytes in RA synovium. The elevated expression of CXCR3 in SF T cells has been associated with high IFN-gamma levels, which suggests a preferential Th1 phenotype. A human phase II clinical trial using an anti-IP-10 monoclonal antibody (MDX-1100) for RA patients who had an inadequate response to MTX treatment has shown that blocking IP-10 significantly increased response rate compared to the placebo group, suggesting a possible therapeutic use in humans.

References

1. Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med 2007; 120:936-9
2. Yarwood A, Huizinga TW, Worthington J. The genetics of rheumatoid arthritis: risk and protection in different stages of the evolution of RA. Rheumatol (Oxford), 2014; Sep 18 (Epub ahead of print)
3. Alghasham A, Rasheed Z. Therapeutic targets for rheumatoid arthritis: Progress and promises. Autoimmun 2014; 47:77-94.
4. Sakkas LI, Bogdanos DP, Katsiari C, et al. Anti-citrullinated peptides as autoantigens in rheumatoid arthritis-relevance to treatment. Autoimmun Rev 2014; Aug 23 (Epub ahead of print)
5. Niu X, Chen G. Clinical Biomarkers and Pathogenic-Related Cytokines in Rheumatoid Arthritis. J Immunol Res 2014; Aug 21 (Epub ahead of print)
6. Calabrese LH, Rose-John S. IL-6 biology: implications for clinical targeting in rheumatic disease. Nat Rev Rheumatol 2014; Aug 19 (Epub ahead of print)
7. Kerekes G, Nurmohamed MT, González-Gay MA, et al. Rheumatoid arthritis and metabolic syndrome. Nat Rev Rheumatol 2014; Aug 5 (Epub ahead of print)
8. Blandizzi C, Gionchetti P, Armuzzi A, et al. The role of tumour necrosis factor in the pathogenesis of immune-mediated diseases. Int J Immunopathol Pharmacol 2014; 27(suppl.1):1-10
9. Moser B, Loetscher P. Lymphocyte traffic control by chemokines. Nat Immunol 2001; 2:123-8
10. Lee EY, Lee ZH, Song YW. CXCL10 and autoimmune diseases. Autoimmun Rev 2009; 8:379-83
11. Antonelli A, Ferrari SM, Giuggioli D, et al. Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. Autoimmun Rev 2014; 13:272-80
12. Swaminathan GJ, Holloway DE, Colvin RA, et al. Crystal structures of oligomeric forms of the IP-10/CXCL10 chemokine. Structure 2003; 11:521-32
13. Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000; 12:121-7
14. Sallusto F, Lenig D, Mackay CR, et al. Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. J Exp Med 1998; 187:875-83
15. Loetscher M, Loetscher P, Brass N et al. Lymphocyte-specific chemokine receptor CXCR3: regulation, chemokine binding and gene localization. Eur J Immunol 1998; 28:3696-705
16. Qin S, Rottman JB, Myers P, et al. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. J Clin Invest 1998; 101:746-54
17. Loetscher M, Gerber B, Loetscher P, et al. Chemokine receptor specific for IP10 and mig: structure, function, and expression in activated T-lymphocytes. J Exp Med 1996; 184:963-9
18. Cole KE, Strick CA, Paradis TJ, et al. Interferon-inducible T cell alpha chemoattractant (I-TAC): a novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. J Exp Med 1998; 187:2009-21
19. Clark-Lewis I, Mattioli I, Gong JH, et al. Structure- function relationship between the human chemokine receptor CXCR3 and its ligands. J Biol Chem 2003; 278:289-95

20. Kanda N, Shimizu T, Tada Y, et al. IL-18 enhances IFN-gamma-induced production of CXCL9, CXCL10, and CXCL11 in human keratinocytes. Eur J Immunol 2007; 37:338-50
21. Kanda N, Watanabe S. Prolactin enhances interferon-gamma induced production of CXC ligand 9 (CXCL9), CXCL10, and CXCL11 in human keratinocytes. Endocrinol 2007; 148:2317-25
22. Persano L, Crescenzi M, Indraccolo S. Anti-angiogenic gene therapy of cancer: current status and future prospects. Mol Aspects Med 2007; 28:87-114
23. Belperio JA, Keane MP, Arenberg DA, et al. CXC chemokines in angiogenesis. J Leukoc Biol 2000; 68:1-8
24. Monteagudo C, Martin JM, Jorda E, et al. CXCR3 chemokine receptor immunoreactivity in primary cutaneous malignant melanoma: correlation with clinicopathological prognostic factors. J Clin Pathol 2007; 60:596-9
25. Furuya M, Suyama T, Usui H, et al. Up-regulation of CXC chemokines and their receptors: implications for proinflammatory microenvironments of ovarian carcinomas and endometriosis. Hum Pathol 2007; 38:1676-87
26. Jones D, Benjamin RJ, Shahsafaei A, et al. The chemokine receptor CXCR3 is expressed in a subset of B-cell lymphomas and is a marker of B-cell chronic lymphocytic leukemia. Blood 2000; 95:627-32
27. Lo BK, Yu M, Zloty D, et al. CXCR3/ligands are significantly involved in the tumorigenesis of basal cell carcinomas. Am J Pathol 2010; 176:2435-46
28. Antonelli A, Bocci G, La Motta C, et al. Novel pyrazolopyrimidine derivatives as tyrosine kinase inhibitors with antitumoral activity in vitro and in vivo in papillary dedifferentiated thyroid cancer. J Clin Endocrinol Metab 2011; 96:288-96
29. Antonelli A, Fallahi P, Ferrari SM, et al. Dedifferentiated thyroid cancer: a therapeutic challenge. Biomed Pharmacother 2008; 62:559-63
30. Luster AD, Ravetch JV. Biochemical characterization of a gamma interferon-inducible cytokine (IP-10). J Exp Med 1987; 166:1084-97
31. Bonecchi R, Bianchi G, Bordignon PP, et al, Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. J Exp Med 1998; 187:129-34
32. Hancock WW, Gao W, Csizmadia V, et al. Donor-derived IP-10 initiates development of acute allograft rejection. J Exp Med 2001; 193:975-80
33. Khan IA, MacLean JA, Lee FS, et al. IP-10 is critical for effector T cell trafficking and host survival in Toxoplasma gondii infection. Immunity 2000; 12:483-94
34. Antonelli A, Rotondi M, Fallahi P, et al. Increase of CXC chemokine CXCL10 and CC chemokine CCL2 serum levels in normal ageing. Cytokine 2006; 34:32-8
35. Antonelli A, Fallahi P, Ferrari SM, et al. Serum Th1 (CXCL10) and Th2 (CCL2) chemokine levels in children with newly diagnosed Type 1 diabetes: a longitudinal study. Diabet Med 2008; 25:1349-53
36. Antonelli A, Baj G, Marchetti P, et al. Human anti-CD38 autoantibodies raise intracellular calcium and stimulate insulin release in human pancreatic islets. Diabetes 2001; 50:985-91
37. Antonelli A, Ferrari SM, Corrado A, et al. CXCR3, CXCL10 and type 1 diabetes. Cytokine Growth Factor Rev 2014; 25:57-65
38. Corrado A, Ferrari SM, Ferri C, et al. Type 1 diabetes and (C-X-C motif) ligand (CXCL) 10 chemokine. Clin Ter 2014; 165:e181-5
39. Antonelli A, Ferrari SM, Frascerra S, et al. CXCL9 and CXCL11 chemokines modulation by peroxisome proliferator-activated receptor-alpha agonists secretion in Graves' and normal thyrocytes. J Clin Endocrinol Metab 2010; 95:E413-20
40. Baschieri L, Antonelli A, Nardi S, et al. Intravenous immunoglobulin versus corticosteroid in treatment of Graves' ophthalmopathy. Thyroid 1997; 7:579-85
41. Antonelli A, Ferrari SM, Fallahi P, et al. Cytokines (interferon-γ and tumor necrosis factor-α)-induced nuclear factor-κB activation and chemokine (C-X-C motif) ligand 10 release in Graves disease and ophthalmopathy are modulated by pioglitazone. Metabolism 2011; 60:277-83
42. Antonelli A, Ferrari SM, Frascerra S, et al. Circulating chemokine (CXC motif) ligand (CXCL)9 is increased in aggressive chronic autoimmune thyroiditis, in association with CXCL10. Cytokine 2011; 55:288-93
43. Antonelli A, Ferrari SM, Frascerra S, et al. Increase of circulating CXCL9 and CXCL11 associated with euthyroid or subclinically hypothyroid autoimmune thyroiditis. J Clin Endocrinol Metab 2011; 96:1859-63
44. Ruffilli I, Ferrari SM, Colaci M, et al. CXCR3 and CXCL10 in autoimmune thyroiditis. Clin Ter 2014; 165:e237-42
45. Lacotte S, Brun S, Muller S, et al. CXCR3, inflammation, and autoimmune diseases. Ann N Y Acad Sci 2009; 1173:310-7
46. Antonelli A, Ferri C, Fallahi P, et al. Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis. Eur J Endocrinol 2007; 156:431-7
47. Antonelli A, Ferri C, Fallahi P, et al. Th1 and Th2 chemokine serum levels in systemic sclerosis in the presence or absence of autoimmune thyroiditis. J Rheumatol 2008; 35:1809-11
48. Antonelli A, Delle Sedie A, Fallahi P, et al. High prevalence of thyroid autoimmunity and hypothyroidism in patients with psoriatic arthritis. J Rheumatol 2006; 33:2026-8
49. Antonelli A, Fallahi P, Delle Sedie A, et al. High values of Th1 (CXCL10) and Th2 (CCL2) chemokines in patients with psoriatic arthtritis. Clin Exp Rheumatol 2009; 27:22-7
50. Antonelli A, Fallahi P, Delle Sedie A, et al. High values of alpha (CXCL10) and beta (CCL2) circulating chemokines in patients with psoriatic arthritis, in presence or absence of autoimmune thyroiditis. Autoimmunity 2008; 41:537-42
51. Su R, Nguyen ML, Agarwal MR, et al. Interferon-inducible chemokines reflect severity and progression in sarcoidosis. Respir Res 2013; 14:121
52. Antonelli A, Fazzi P, Fallahi P, et al. Prevalence of hypothyroidism and Graves disease in sarcoidosis. Chest 2006;130:526-32
53. Antonelli A, Ferri C, Fallahi P, et al. High values of CXCL10 serum levels in mixed cryoglobulinemia associated with hepatitis C infection. Am J Gastroenterol 2008; 103:2488-94
54. Fallahi P, Ferrari SM, Giuggioli D, et al. Mixed cryoglobulinemia and thyroid autoimmune disorders. Clin Ter 2013; 164:e337-41
55. Ferri C, Antonelli A, Mascia MT, et al. B-cells and mixed cryoglobulinemia. Autoimmun Rev 2007;7:114-20
56. Ferrari SM, Fallahi P, Mancusi C, et al. HCV-related autoimmune disorders in HCV chronic infection. Clin Ter 2013; 164:e305-12
57. Fallahi P, Di Domenicantonio A, Mazzi V, et al. Hepatitis C virus and type 1 diabetes. Clin Ter 2013; 164:e437-44
58. Antonelli A, Ferri C, Fallahi P, et al. High values of CXCL10 serum levels in patients with hepatitis C associated mixed cryoglobulinemia in presence or absence of autoimmune thyroiditis. Cytokine 2008; 42:137-43

59. Antonelli A, Ferri C, Fallahi P, et al. Alpha-chemokine CXCL10 and beta-chemokine CCL2 serum levels in patients with hepatitis C-associated cryoglobulinemia in the presence or absence of autoimmune thyroiditis. Metabolism 2008; 57:1270-7
60. Coppola N, Gentile I, Pasquale G, et al. Anti-HBc positivity was associated with histological cirrhosis in patients with chronic hepatitis C. Ann Hepatol 2014; 13:20-6
61. Coppola N, Marrone A, Pisaturo M, et al. Role of interleukin 28-B in the spontaneous and treatment-related clearance of HCV infection in patients with chronic HBV/HCV dual infection. Eur J Clin Microbiol Infect Dis 2014; 33:559-67
62. Antonelli A, Ferri C, Fallahi P, et al. Thyroid Cancer in HCV-related chronic hepatitis patients: a case-control study. Thyroid 2007; 17:447-51
63. Antonelli A, Ferri C, Fallahi P, et al. Thyroid cancer in HCV-related mixed cryoglobulinemia patients. Clin Exp Rheumatol 2002; 20:693-6
64. Mollica MP, Lionetti L, Moreno M, et al. 3,5-diiodo-l-thyronine, by modulating mitochondrial functions, reverses hepatic fat accumulation in rats fed a high-fat diet. J Hepatol 2009; 51:363-70
65. Pacini F, Antonelli A, Lari R, et al. Unsuspected parathyroid cysts diagnosed by measurement of thyroglobulin and parathyroid hormone concentrations in fluid aspirates. Ann Intern Med 1985; 102:793-4
66. Antonelli A, Ferrari SM, Fallahi P, et al. Variable modulation by cytokines and thiazolidinediones of the prototype Th1 chemokine CXCL10 in anaplastic thyroid cancer. Cytokine 2012; 59:218-22
67. Yin Z, Siegert S, Neure L, et al. The elevated ratio of interferon gamma-/interleukin-4-positive T cells found in synovial fluid and synovial membrane of rheumatoid arthritis patients can be changed by interleukin-4 but not by interleukin-10 or transforming growth factor beta. Rheumatology (Oxford) 1999; 38:1058-67
68. Lee EY, Lee ZH, Song YW. The interaction between CXCL10 and cytokines in chronic inflammatory arthritis. Autoimmun Rev 2013; 12:554-7
69. Patel DD, Zachariah JP, Whichard LP. CXCR3 and CCR5 ligands in rheumatoid arthritis synovium. Clin Immunol 2001; 98:39-45
70. Hanaoka R, Kasama T, Muramatsu M, et al. A novel mechanism for the regulation of IFN-gamma inducible protein-10 expression in rheumatoid arthritis. Arthritis Res Ther 2003; 5:R74-81
71. Ueno A, Yamamura M, Iwahashi M, et al. The production of CXCR3-agonistic chemokines by synovial fibroblasts from patients with rheumatoid arthritis. Rheumatol Int 2005; 25:361-7
72. Proost P, Struyf S, Loos T, et al. Coexpression and interaction of CXCL10 and CD26 in mesenchymal cells by synergising inflammatory cytokines: CXCL8 and CXCL10 are discriminative markers for autoimmune arthropathies. Arthritis Res Ther 2006; 8:R107
73. Kwak HB, Ha H, Kim HN, et al. Reciprocal cross-talk between RANKL and interferon-gamma-inducible protein 10 is responsible for bone-erosive experimental arthritis. Arthritis Rheum 2008; 58:1332-42
74. Wedderburn LR, Robinson N, Patel A, et al. Selective recruitment of polarized T cells expressing CCR5 and CXCR3 to the inflamed joints of children with juvenile idiopathic arthritis. Arthritis Rheum 2000; 43:765-74
75. Ruth JH, Rottman JB, Katschke KJ Jr, et al. Selective lymphocyte chemokine receptor expression in the rheumatoid joint. Arthritis Rheum 2001; 44:2750-60
76. Yoshida S, Arakawa F, Higuchi F, et al. Gene expression analysis of rheumatoid arthritis synovial lining regions by cDNA microarray combined with laser microdissection: up-regulation of inflammation-associated STAT1, IRF1, CXCL9, CXCL10, and CCL5. Scand J Rheumatol 2012; 41:170-9
77. Ospelt C, Kurowska-Stolarska M, Neidhart M, et al. The dual inhibitor of lipoxygenase and cyclooxygenase ML3000 decreases the expression of CXCR3 ligands. Ann Rheum Dis 2008; 67:524-9
78. Eriksson C, Rantapää-Dahlqvist S, Sundqvist KG. Changes in chemokines and their receptors in blood during treatment with the TNF inhibitor infliximab in patients with rheumatoid arthritis. Scand J Rheumatol 2013; 42:260-5
79. Yellin M, Paliienko I, Balanescu A, et al. A Phase II, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of MDX-1100, a fully human anti-CXCL10 monoclonal antibody, in combination with methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2012; 64:1730-9