Hepatitis B virus infection and interferon-inducible protein-10

S. Fabiani

Department of Experimental Pathology, M.B.I.E., School of Medicine, Università di Pisa, Italy

Abstract

Interferon (IFN)-inducible protein-10 (IP-10) is a proinflammatory chemokine, binding the chemokine (C-X-C motif) receptor 3 (CXCR3), which is found mainly on activated T cells and natural killer (NK) cells, and plays an important role in T helper (Th) 1 type inflammatory disorders (autoimmune, neoplastic, and infectious diseases). Concerning viral hepatitis, IP-10 appears to be involved in the pathogenesis of liver damage as well as on the extra-hepatic manifestations either protecting or promoting infection, depending on host immune status and genetic background. During chronic hepatitis B, IP-10 is specifically produced by hepatocytes in inflammatory areas. Here, IP-10 leads to recruitment of T cells, production of IFN-gamma by activated NK T cells, and then monokine induced by IFN-gamma (MIG) and IP-10 secretion by parenchymal and non-parenchymal cells, with a final positive feedback, perpetuating the immune cascade. The increased levels of IP-10 and IP-10 mRNA in the peripheral blood of patients with cirrhosis are closely correlated with the load of HBV DNA in serum, and seem to play a key role in the progression of post-hepatic cirrhosis. Higher pre-treatment IP-10 levels, and dynamic down-regulation, are associated with an increased probability of hepatitis B e antigen (HBeAg) loss after Peg-IFN therapy. Hepatitis B surface antigen (HBsAg) drop in patients treated with nucleos(t)ide analogues (NAs) is associated with higher baseline IP-10.

The prevalence ranges from over 10% in Asia to less than 1% in North America and Western Europe. The virus is transmitted by exposure to infectious blood or body fluids. Routes of infection are vertical transmission, and early life and adulthood horizontal transmission, including “inapparent parenteral” spread (4-7), hence the importance of screening of donated blood, plasma, organ tissue and semen, risk-reduction counseling and implementation of infection control practices, and overall the routine immunization for infants and high-risk individuals (8, 9).

The infection by HBV may be oligosymptomatic or even entirely asymptomatic, going unrecognized. Symptoms of clinically manifest forms of acute viral B hepatitis include loss of appetite, nausea, vomiting, mild fever, and then jaundice. The acute viral B hepatitis lasts for a few weeks, gradually improving in most affected people without need of treatment, with the exception of immunocompromised patients and/or patients with more severe liver disease (fulminant hepatic failure), that occur in less than 1%, and may lead up to death as a result (10-13).

Chronic forms may be also silent, but the association with a chronic liver inflammation (chronic hepatitis), over a period of several years, may lead to cirrhosis (14, 15) and increased incidence of liver cancer (16, 17).

Extra-hepatic manifestations occur in up to 20% of HBV-infected people and include dermatitis, poly-arthralgias and arthritis, pulmonary disease, aplastic anemia, glomerulonephritis, and vasculitis (18-20).

HBV-related cryoglobulinemic vasculitis is rare, but it has also been described (21, 22).

HBV is a member of the Hepadnaviridae family. The genome of HBV is organized as a encapsidated circular partially double-stranded DNA, covalently attached to HBV polymerase, a specialized reverse transcriptase (23, 24). HBV is defined as para-retrovirus: a non-retrovirus still using reverse transcription in the replication process (25).

HBV replicates in liver cells, leading liver pathology as the result of complex interactions between virus and host
immune system, according to the three, not necessarily sequential, major phases of the chronic HBV infection (CHB): 1) immune tolerance, 2) activation [a] “immune reactive hepatitis B e antigen (HBeAg)-positive phase” and b) “HBeAg-negative CHB”], and 3) immune control [a] “inactive HBV carrier state” and b) “hepatitis B surface antigen (HBsAg)-negative phase”] (26). Both innate and adaptive mechanisms are involved during the different phases of HBV infection, including during therapy-induced immune control. In particular, growing data underline the potential contribution of the innate immune response through Toll-like receptors (TLRs) and TLR-signaling pathways, and microRNA (miRNA) in the pathogenesis and outcome of HBV infection (27, 28).

Better characterized is the adaptive immune response with its complex web of effector cell types: CD4 T cells, or T helper (Th) cells, produce cytokines and induce efficient development of effector cytotoxic CD8 T cells and B cell antibody production; CD8 T cells, or cytotoxic T lymphocytes (CTLs), clear HBV-infected hepatocytes through cytolytic and cytokine-induced non-cytolytic mechanisms (4, 29-32).

Detection and correct interpretation of HBV antigens (HBsAg and HBeAg) and antibodies (anti-HBs, anti-Hbc and anti-HBe), together with HBV DNA serum monitoring (33-35) and biochemical and histological evolution features (36), assess the phase and activity of CHB and the candidacy for antiviral therapy, and allow clinicians to determine response to treatment.

The ideal approach to antiviral therapy in CHB remains uncertain. However, the available treatment strategies include peg-interferon (Peg-IFN) alpha or nucleos(t)ide analogues (NAs) (26) and the key issue for the future will be the efficacy of combined and/or sequential treatment with oral agents and IFN, tailoring treatment at the single-patient level (37), with the main goal of sustained suppression of HBV replication and then reduction in histological activity, leading to prevention of disease progression to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death (38).

Even in presence of a response to the antiviral therapy, these patients are still at risk for complications, as HBV cannot be completely eradicated due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes, which may explain HBV reactivation (39-41). Moreover, the HBV genome integrates into the host genome and might favor oncogenesis and the development of HCC (42-44).

Chemokines and IP-10

Chemokines (chemotactic cytokines) are small heparin-binding proteins that constitute a large family of peptides (60–100 amino acids) structurally related to cytokines, whose main function is to regulate leukocytes, as well as non-hematopoietic cells trafficking (45, 46).

They are subdivided into four families on the basis of the number and spacing of the conserved cysteine residues in the N-terminus of the protein: C, CC, CX3C, and CXC (47). While CXC chemokines with an N-terminal ELR (Glu-Leu-Arg) motif are specific chemoattractants for neutrophils, those lacking the N-terminal ELR motif do not act as chemoattractants for neutrophils, but do act as chemoattractants for activated T cells (48).

Besides the structural criteria, chemokines may be categorized into several functional groups (49): inflammatory chemokines, homeostaticchemokines, and dual-function chemokines.

The chemokine IP-10 (IFN-inducible protein of 10 kDa, CXCL10) is a proinflammatory chemokine lacking the N-terminal ELR motif. It binds the G protein-coupled receptor CXCR3, which is found mainly on activated T cells and NK cells, and plays an important role in Th1 type inflammatory diseases (50). IP-10 is defined as IFN-gamma-inducible protein, hence, in response to IFN-gamma, it is secreted from a variety of cells (endothelial, monocyte, fibroblast, and keratinocyte) (51, 52). IP-10 secretion can also be induced by other different inflammatory stimuli, including IFN-alpha and IFN-beta as well as tumor necrosis factor (TNF)-alpha (53, 54).

Elevated peripheral fluids IP-10 levels are a marker of Th1 orientated immune response, as recruited Th1 lymphocytes lead to increased IFN-gamma and TNF-alpha production, which in turn stimulates Th1 lymphocytes IP-10 secretion, producing a positive feedback and finally perpetuating the immune cascade (55).

High serum and/or tissue IP-10 levels, and, as a consequence, Th1 immune response are involved in pathogenesis and progression of different disorders (autoimmune, neoplastic, and infectious diseases).

Concerning some “demonstrated or presumed” autoimmune processes, IP-10 high levels have been detected both in organ specific disorders, such as type 1 diabetes mellitus (56-60), Graves’ disease (61, 62) and ophthalmopathy (63), and autoimmune thyroiditis (64-71), and systemic disorders, such as rheumatoid arthritis, psoriasis or psoriatic arthritis (72), systemic lupus erythematosus, mixed cryoglobulinemia, Sjögren syndrome, systemic sclerosis (73), and sarcoidosis.

Chemokines network, including IP-10, seems also to be involved in neoplastic microenvironment, playing a multifaceted role in tumor pathogenesis and progression with potential advantage for new therapeutic strategies (74-83).

IP-10 roles in the initiation and progression of infectious diseases remain unclear and the potential utilization as a therapeutic target is still discussed (84).

However IP-10 has been implicated in infectious diseases due to viruses (i.e. Rhinovirus, Coronavirus, respiratory syncytial virus, Coxsackie virus, Ebola virus, Dengue virus, EBV, Herpes simplex virus type 2, HIV, and hepatitis virus B and C), bacteria (i.e. Helicobacter pylori, Mycoplasma, Chlamydia, Legionella pneumophila, Leptospira, and Mycobacterium tuberculosis), fungi (i.e. Candida albicans, Pneumocystis jiroveci, and Cryptococcus neoformans), and parasites (i.e. Cryptosporidium, Trypanosoma brucei, Plasmodium falciparum and Plasmodium vivax, Toxoplasma gondii, and Leishmania) (85-104).

IP-10 either protects or promotes infection, depending on host immune status and genetic background (84).

Concerning viral hepatitis, IP-10 appears to be involved on the pathogenesis of liver damage as well as on the extra-
hepatic manifestations (105-117).

The predictive value of IP-10 on treatment outcome of hepatopathic patients has been described, too (118).

Here we review the scientific literature on HBV virus infection and IP-10.

In March 2015, we searched MEDLINE from 1997 to the present using the Medical Subject Headings terms “hepatitis B virus infection” or “HBV” and “interferon-inducible protein-10” or “CXCL10” or “IP-10”.

Full papers and abstracts without language restrictions were considered.

**HBV infection and IP-10**

In 1997, Narumi et al. reported that the mRNA of IP-10 was expressed in hepatocytes in CHB and chronic hepatitis C virus infection (CHC) patients using in situ hybridization (119).

To clarify whether or not the production of IP-10 is related to the hepatic inflammation in autoimmune and viral liver diseases the work has been continued studying the serum levels of IP-10 in autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), CHB and CHC patients, and assessing the cell type-specific expression of IP-10 mRNA in their liver tissue.

The serum level of IP-10 was significantly \( P < 0.02 \) higher in patients with AIH, PBC, and CHB than in healthy controls, and it was significantly correlated \( P < 0.05 \) with the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

After successful treatment of AIH and CHC, the serum level of IP-10 decreased to the same level as in healthy volunteers.

Even in this study, in cases with CHB or CHC, in situ hybridization continued to demonstrate the expression of IP-10 mRNA in hepatocytes around focal or lobular necrosis surrounded by infiltrating mononuclear cells. These results suggested that IP-10 was specifically produced by hepatocytes in inflammatory areas of hepatitis B, and that IP-10 may help to recruit T cells to the hepatic lesions in chronic viral hepatitis (120).

Intrahepatic NK T cells activated by alpha-galactosylceramide inhibit HBV replication non-cytopathically in the liver of transgenic mice. This effect was mediated by antiviral cytokines directly produced by activated NK T cells and/or by other cytokine-producing inflammatory cells that are recruited into the liver. It was demonstrated that IFN-gamma produced by activated NK T cells induced parenchymal and non-parenchymal cells of the liver to produce high levels of monokine induced by IFN-gamma (MIG) and IP-10, which mediated the intrahepatic recruitment of lymphomononuclear inflammatory cells (121).

Using transgenic mice that replicate HBV in the liver as recipients of HBV-specific CTLs, it was shown that the chemokines responsive IFN-gamma are rapidly and strongly induced in the liver after CTL transfer. The transferred CTLs activate (via the secretion of IFN-gamma) hepatocytes and non-parenchymal cells of the liver to produce IP-10 and MIG. Blocking these chemokines in vivo reduces the recruitment of host-derived lymphomononuclear cells into the liver and the severity of the liver disease without affecting the IFN-gamma-dependent antiviral potential of the CTLs (122).

Interestingly, it was also shown that the severity of the CTL-initiated liver disease is also ameliorated by the depletion of neutrophils (123).

Expression of IP-10 was investigated both in serum and in the liver of patients with CHC and CHB. Patients with liver diseases of non-viral etiologies served as controls. IP-10 expression was highest in hepatitis C. In CHC, but not in CHB, IP-10 expression was strongly correlated with the amount of transcripts for IFN-gamma and to the amount of transcripts for the constitutively expressed macrophage-derived cytokine interleukin (IL)-18 (124).

In another study the levels of IP-10 mRNA in peripheral blood mononuclear cells (PBMCs) of patients with CHB were detected by real-time polymerase chain reaction (PCR). Furthermore the level of IP-10 in serum was measured by enzyme linked immunosorbent assay, and the expression of IP-10 in hepatic biopsy tissue was detected by streptavidin-peroxidase immunohistochemistry.

The level of IP-10 mRNA in the PBMCs of patients was significantly higher in patients with CHB than that in normal controls. The level of IP-10 in the serum of patients with CHB was higher than in normal controls \( P < 0.05 \). In patients with CHB, the level of IP-10 mRNA in PBMCs was correlated with the IP-10 plasma level, and the IP-10 plasma level was correlated with the levels of ALT and HBV-DNA plasma. IP-10 was found by immunohistochemical analysis to be selectively upregulated on sinusoidal endothelium. These data suggest that IP-10 may play an important role in trafficking inflammatory cells to the local focus in the liver and induces the development of the chronicity of hepatitis B (125).

A further study investigated whether the naturally occurred sequence variations in the IP-10 gene impact liver damage and disease progression of CHB in a total of 613 and 1787 unrelated Han Chinese HBV carriers. It was systematically screened sequence variations in the IP-10 gene and examined the association between the variations in this gene and susceptibility to disease progression of chronic HBV infection. The polymorphism G-201A, located in the promoter region of IP-10, was associated with susceptibility to disease progression in male HBV carriers. Functional analyses show that the G-201A polymorphism alters the binding affinity of nuclear protein and regulates IP-10 expression. Higher IP-10 transcription was observed in IFN-gamma-stimulated PBMCs with the disease-susceptible genotypes.

These results suggested this novel regulatory polymorphism G-201A in the promoter of IP-10 gene could be a part of the genetic variation underlying the susceptibility of individuals to disease progression of CHB (126).

It was also investigated the kinetics of innate and adaptive immune activation during hepatic flares (HF) in patients chronically infected with HBV.

Soluble (IFN-alpha, IL-1beta, TNF-alpha, IL-6, IL-8, IL-10, CCL-2, CCL-3, MIG, IP-10) and cellular (HBV-specific T cells, NK, Treg) immunological parameters were measured longitudinally in patients who developed HF after therapy withdrawal and cross-sectionally in chronic and acute hepatitis B patients. A progressive increase of HBV
replication precedes HF but occurs without detection of innate immune activation, with the exception of increased serum IL-8. Despite the absence of increased circulatory HBV-specific T or activated NK cells, HF were temporally associated with high serum levels of IFN-gamma inducible chemokines MIG and IP-10 (but not CCL-2 or CCL-3). These results suggest that MIG and IP-10 play a major role in the development of HF (127).

Another study reported a novel molecular mechanism of HBV infection inducing IP-10 expression, which involves viral protein HBx affecting NF-kappaB pathway, leading to transactivation of the IP-10 promoter (128).

A study was aimed to detect the relationship between the expression of IP-10 in serum, IP-10 mRNA in PBMCs, and the levels of HBV DNA in the serum of patients, and to explore their role in the pathogenesis of cirrhosis. The levels of IP-10 in serum and IP-10 mRNA in PBMCs of patients with cirrhosis higher than those of controls. The increased levels of IP-10 and IP-10 mRNA in the peripheral blood of patients with cirrhosis were closely correlated with the load of HBV DNA in serum, and seem to play a key role in the progression of post-hepatitic cirrhosis (129).

A study explored the association between intra-hepatic IL-22 expression, its relevant associated cytokines and the severity of liver inflammation/fibrosis in CHB patients. In CHB patients, the expression of IL-22, IL-6, MIG and IP-10 were significantly higher with ALT levels ≤ twice the upper limit of normal (ULN), compared with those with ALT levels > twice the ULN. Furthermore, immunofluorescent labeling demonstrated a close spatial association of IL-22, MIG, IP-10 or I-TAC in the CHB liver. It was speculated that IL-22 and non-ELR-CXC chemokines, such as IP-10, synergistically may provide protection in liver inflammation/ fibrosis during CHB infection (130).

Several studies have demonstrated that HBV affects the expression and function of TLRs.

The natural history of CHB infection is distinctly different in children, since 90% of children become chronic carriers compared to 5% of adults when infected with HBV. A study evaluated the function of TLRs and cytotoxic DNA receptors in children with CHB infection compared to healthy children. Stimulation with ligands for TLR2, TLR3 and TLR9 induced IL-6, CCL3 and IP-10 to a significantly higher level in PBMCs of children with CHB compared to healthy children (131).

The mechanism underlying the chronicity of HBV infection was investigated by hydrodynamic injection to introduce HBV replicon DNA into livers of three different mouse strains: BALB/c, C57BL/6, and FVB/N. It was found that an HBV clone persistently replicated in the livers of FVB/N mice but was rapidly cleared from the livers of BALB/c and C57BL/6 mice. Flow cytometric analysis and PCR of the mouse livers indicated that after DNA injection, FVB/N mice had few intrahepatic activated CTLs and produced low levels of IFN-gamma, TNF-alpha, and the MIG and IP-10 chemokines. These findings were in sharp contrast with those observed in BALB/c and C57BL/6 mice, reflecting a strong correlation between the degree of liver inflammation and viral clearance (132).

HBV escapes antiviral immunity, by altering plasmacytoid dendritic cells (pDC) functions, to disrupt interactions between pDC and NK cells. It has been shown that high level of IP-10 and hepatitis B surface and e antigens might induce these defective pDC functions (133).

The expression profile in the mouse hepatitis B virus X (HBx)-transfected model was investigated in order to lay a foundation for further study on the implication of cytokines expression in HBV infection. IFN-gamma protein levels were reduced in pCMV-tag2B-transfected mice as compared with the untreated mice, which was consistent with the up-regulation of MIG and IP-10. It was suggested HBx transfection could induce the expression of MIG and IP-10 in the liver tissues, which might play the roles in HBV-related liver immunity and cytokines-mediated antiviral effect (134).

A further study was aimed to investigate the impact of the single nucleotide polymorphisms G-201A (rs1439490) in IP-10 gene on disease progression of HBV infection. G-201A in promoter region of IP-10 gene was associated with liver disease progression in patients with HBV infection through upregulating IP-10 expression (135). Acute exacerbation of CHB infection was prospectively studied in HBV patients. In these patients, serum HBV DNA level surged before the peak of serum ALT, and coincided with the peak of ALT. The upsurge of serum viral load significantly correlated with the increase of IL-10 and IP-10 (136).

A further study confirmed that in comparison to healthy individuals and asymptomatic HBV carriers, expression of MIG, IP-10, I-TAC, and IL-10 were elevated in patients with active CHB and had positive correlation with ALT levels (137).

**Chronic Hepatitis B therapy and IP-10**

The role of IP-10 in patients treated for CHB infection has been also investigated (138). HBsAg loss is the ultimate goal of antiviral therapy. A study was aimed to investigate potential factors predictive for HBsAg loss: 42% of patients with a strong HBsAg decrease, 2 years after virological response cleared HBsAg. Importantly, no patient without a late HBsAg decrease > 0.5 log(10) cleared HBsAg. By contrast, early HBsAg decrease after 6 months of NA therapy was not associated with HBsAg loss. Baseline serum IP-10 levels were associated with late but not early HBsAg kinetics and were highest in patients with HBsAg loss (139). To evaluate if serum levels of IP-10 may predict response to Peg-IFN therapy in CHB, IP-10 was measured at baseline and on-treatment week 12 in 210 HBeAg-positive patients treated with Peg-IFN for 52 weeks. Higher baseline IP-10 was associated with more HBV DNA, HBeAg and HBsAg decline from week 4 onwards, and IP-10 was higher in patients who achieved HBeAg loss and combined response. A combination of high IP-10 (> 150 pg/ml) with absence of pre-core and core promoter mutants strongly predicted combined response and HBsAg loss: 48% of patients with high IP-10 and no detectable mutants achieved a combined response. These data suggest that higher pre-treatment IP-10 levels are associated with an increased probability of HBeAg loss after Peg-IFN therapy. A combination of high baseline IP-10 and absence of pre-core and core promoter mutants identified
patients with the highest probability of combined response and HBsAg loss (140).

The unclear dynamics of programmed death-1 (PD-1) as well as cytokine/chemokine expression and its correlation with virological response in patients with CHB were also studied. IP-10 expression was positively correlated with viral load, level of ALT and PD-1 expression on CD8+ T cells at baseline. Moreover, the decrease in IP-10 in serum directly correlated with a decrease in ALT levels. At weeks 24 and 25, IP-10 expression was significantly lower than baseline in virological responders; however, this was not observed in non-responders. These results suggested that PD-1 and IP-10 may be used as predictors for virological response, and blockade of their pathway may improve the outcome of patients with CHB (141).

The changes of HBsAg and IP-10 serum levels in HBeAg-negative CHB patients treated with entecavir were evaluated. Virological remission rates were high (year-1: 94%, after year-2: 97-98%). Median IP-10 levels (pg/ml) did not change from baseline to year-1 or -2 (245 vs 229 or 251), but increased at year-3 and -4 (275 and 323, P<0.030). HBsAg drop ≥ 0.5 log(10) was associated with baseline IP-10 or IP-10 > 350 pg/ml (P≤0.002).

These results suggested that serum IP-10 levels represent a promising predictor of HBsAg decline in this setting (142).

Another study evaluated the associations between serum cytokines and chemokines, HBsAg, hepatitis B core-related antigen (HBcAg), and HBV DNA and response to entecavir therapy in CHB. Serum IL-6 (P=0.031), MIG (P=0.002), and IP-10 (P=0.001) were high in CHB and correlated positively with ALT, AST, and bilirubin. Before treatment, elevated IL-22 and lower HBsAg and HBcAg were associated with a favorable treatment outcome (143).

Serum IP-10 level changes were evaluated during the pre-, on- and post-treatment periods for CHB patients receiving Peg-IFN therapy in another study. Serum IP-10 levels were positively correlated with the hepatic inflammation activity score and ALT level, but negatively with the HBV DNA load and HBsAg quantification. The CHB patients achieving HBeAg clearance or HBsAg decline > 1 log(10) IU/ml had higher pre-treatment IP-10 levels and more obvious on-treatment reduction of the IP-10 level than did patients with HBeAg persistent-positive or HBsAg decline <1 log(10) IU/ml. The data confirm that higher pre-treatment serum IP-10 expression and dynamic down-regulation might be associated with an increased probability of HBeAg clearance and HBsAg decline in CHB patients during Peg-IFN alpha therapy.

Conclusions

IP-10 plays an important role in HBV infection. IP-10 is specifically produced by hepatocytes in inflammatory areas of hepatitis, and may help to recruit T cells to the hepatic lesions in chronic viral hepatitis. IFN-gamma, produced by activated NK T cells, induces parenchymal and non-parenchymal cells of the liver to produce high levels of MIG and IP-10, which mediate the intrahepatic recruitment of lymphomononuclear inflammatory cells. Blocking these chemokines in vivo reduces the recruitment of host-derived lymphomononuclear cells into the liver and the severity of the liver disease without affecting the IFN-gamma-dependent antiviral potential of the CTLs. Furthermore, the levels increase of IP-10 and IP-10 mRNA in the peripheral blood of patients with HBV-related cirrhosis is closely correlated with the load of HBV DNA in serum, and seems to play a key role in the progression of post-hepatic cirrhosis. Higher pre-treatment IP-10 levels, and dynamic down-regulation, are associated with an increased probability of HBeAg loss after Peg-IFN alpha therapy. HBsAg drop in patients treated with NAs is associated with higher baseline IP-10.

These results suggest that IP-10 may be used as predictor for virological response, and that is of particular relevance considering the key issue for the future on treatment of CHB, based on tailoring treatment strategies at the single-patient level.

References

10. Wright TL, Lau JY. Clinical aspects of hepatitis B virus infection. Lancet 1993; 342:1340-4
HBV and IP-10

B. World J Gastrointest Pharmacol Ther 2014; 5:175-82


29. Guidotti LG, Chisari FV. To kill or to cure: options in host defense against viral infection. Curr Opin Immunol 1996; 8:478-83


34. Tong Hv, Bock CT, Velavan TP. Genetic insights on host and hepatitis B virus in liver diseases. Mutat Res Rev Mutat Res 2014; 762:65-75


36. Lok A, McMahon B. Chronic hepatitis B. Hepatology 2001; 34:1225-41


for therapeutic purposes mobilizes differently interferon-gamma-inducible alpha-chemokine CXCL10 serum levels in patients with active Graves' disease or toxic nodular goiter. J Clin Endocrinol Metab 2007; 92:1485-90


65. Antonelli A, Fallahi P, Rotondi M, et al. Increased serum CXCL10 in Graves' disease or autoimmune thyroiditis is not associated with hyper- or hypothyroidism per se, but is specifically sustained by the autoimmune, inflammatory process. Eur J Endocrinol 2006; 154:651-8


