Recent studies have shown macrophage activation states in parallel to the Th cell type 1/2 paradigm. IFN-\(\gamma\) has long been known as the classical macrophage activating factor inducing cytokine secretion by macrophages to support Th1-driven immune responses. IL-4 which was historically regarded as macrophage deactivators is now thought to induce alternative immunological activation of macrophages[9], in that it enhances the capacity of macrophages for endocytosis and antigen presentation by the induction of mannose receptor expression[10]. In normal immunological process, classical and alternative macrophage activation maintains the balance of macrophage.

**IMBALANCE of Th1/Th2**

Th1 and Th2 type cytokines in patients with hepatitis

Chronic hepatitis is characterized by incomplete clearance of virus and damage hepatocytes. Since hepatitis B virus (HBV) is known to have no cytopathic effect on the infected hepatocytes, cell-mediated immunity is thought to play an important role in the pathogenesis of hepatocellular damage and HBV clearance[11]. Although immune evading mechanisms used by HBV are largely unknown, defects in T cell response have been suspected as a major factor involved in the pathogenesis of chronic hepatitis[11-13]. Different from acute self-limited hepatitis in which protective immunity develops after elimination of HBV, immune response fails to remove HBV-infected hepatocytes in chronic hepatitis B. Th1 type pattern of secreted immunity can be considered as an appropriate response of the immune system to inhibit viral replication and HBV eradication. Mechanisms by which IFN-\(\gamma\) favors the elimination of HBV may include enhancement of cytotoxic T lymphocyte (CTL) activation, direct anti-viral activity, increased expression of major histocompatibility complex class I molecules on infected cells, and activation of macrophages[16-18]. It has been shown in a transgenic mouse model that adoptive transfer of CTLs producing IFN-\(\gamma\)-could inhibit HBV replication without cytolysis[19].

Studies have shown[18] that predominant Th1 (IFN-\(\gamma\)) cytokine profile of hepatitis B core Ag (HbcAg)-specific and hepatitis B surface Ag (HbsAg)-reactive T cells is associated with acute self-limited hepatitis B. In most patients with acute hepatitis, CTL responses to epitopes of HbsAg, while there are no such responses in patients with chronic hepatitis[20]. Thus, Th1 might be insufficient for complete removal of HBV in chronic hepatitis and positively correlated with hepatic inflammatory activity.

Meanwhile, Barnaba et al. cloned CD4+ HBV envelope antigen (HbeAg)-reactive T cells and showed signs of cytotoxicity only when they produced IFN-\(\gamma\)[21]. This is in agreement with findings that production of IFN-\(\gamma\) by peripheral blood mononuclear cells (PBMCs) upon HbsAg stimulation was associated with higher level of hepatocyte damage. The dissociation between the mechanisms responsible for the immune-mediated hepatocytolysis, and for viral clearance in HBV infection was proposed[23]. It has been demonstrated that the interaction between Ag-specific CTL and target hepatocytes results in spotty necrosis which is limited to a very few hepatocytes[24]. Instead, the antiviral effect is mediated by IFN-\(\gamma\). IL-2, and TNF-\(\alpha\) released by HBV-specific CTLs or by antigen nonspecific macrophages, and these
cytokines profoundly suppress HBV gene expression in infected hepatocytes by noncytolytic mechanisms through eliminating HBV nucleocapsid particles and destabilizing the viral RNA. Thus, after recognition of HBV antigens on the surface of infected hepatocytes, CTLs perform two distinct functions; they kill a small fraction of infected hepatocytes and secrete IFN-γ and TNF-α, which exert antiviral effects without destruction of hepatocytes. Effective clearance of duck HBV and woodchuck hepatitis virus has also been shown to occur without massive hepatocellular necrosis.

In addition, a cytokine balance favoring Th2 type cytokine production such as IL-4 and IL-10 has been associated with progressive virus infections. Co-activation of Th3 cells with Th2 cells can negatively regulate immune responses and may be associated with the immune tolerant state of chronic HBV infection. The shift from Th1 to Th2 or Th0 profiles was observed in acquired immune deficiency syndrome (AIDS). Result also indicates the existence of a Th2 type response to HBsAg in chronic hepatitis B patients with more severe liver damage. Th2 cells may be associated with the persistence of HBV infection. Probably the virus can mutate effectively and evade T-cell immune defense mechanisms. Persistent infection upsets the balance between immunostimulatory and inhibitory cytokines which can prolong inflammation and lead to necrosis, fibrosis, and chronic liver disease.

In chronic hepatitis C virus (HCV) infection, Fan et al. observed that the elevated levels of Th2 cytokines were greater than Th1 cytokines measured by ELISA. This result is in agreement with Kobayashi et al. who showed a significant increase in number of IL-4 producing Th2 cells and a significant decrease in number of IFN-γ-producing Th1 cells (PBMC stimulated by anti-CD3 antibody). They suggested that, theoretically, stimulation with anti-CD3 antibody results in the expansion of T lymphocytes, whereas stimulation with HCV core protein results in the expansion of T lymphocytes responsive to HCV core antigen. The stimulation of PBMC with anti-CD3 antibody could reflect the patient’s real situation better than that with HCV core protein. In addition, they measured the IFN-γ after the depletion of CD8+ T cells—one of the major sources of IFN-γ production. This could explain that the increased production of IFN-γ (Th1) shown in others studies were due to IFN-γ secretion by CD8+ T lymphocytes.

However, Iwata et al. found that in patients with chronic hepatitis C there was the increasing production of IFN-γ (Th1) by PBMC after stimulation with HCV core protein. Bergamini et al. obtained the similar result that the percentage of Th1 cells was significantly increased in CD4+, CD8+, ‘naïve’-CD45RA+ and ‘memory’-CD45RO+ T-cell subsets (PBMC by mitogen-stimulation) from patients versus controls, and Sobue et al. also found that a shift to Th1 cytokine profile correlated with the progress of liver damage, which could be related to the higher proportion of CD4+ T cells. Although in chronic hepatitis C infection, the levels of mononuclear cells derived from peripheral blood reflected the level of mononuclear cells derived from liver, the profile of Th1/Th2 in liver tissue and in peripheral blood was different. In liver tissue, a predominance of Th1 type cytokines was seen in CD4+ T cells while a predominance of Th1 type cytokines was observed in CD8+ cells in peripheral blood. Thus, the elevated cytokine production may also have been caused by a higher proportion of CD4+ T cells in the liver tissue of patients with chronic HCV infection compared with that in healthy controls, and intrahepatetic CD4+ T cells may be more important than CD8+ T cells in the pathogenesis of liver damage in chronic hepatitis C infection. In addition, the percentage of CD4+ T cells in liver correlated with the histological activity of hepatitis. These results may indicate a preferential compartmentalization of Th1 cytokine-producing CD4+ T cells in the liver, suggesting that some liver-derived CD4+ T cells had a direct cytotoxic effect. Meanwhile cytokines produced may inhibit viral replication, such as IFN-γ and TNF-α.

The probable mechanism of Th1 predominance in HCV infection is that in order to eliminate HCV and inhibit viral replication, the compartmentalized CD4+ T cells may shift to a Th1 profile and induce nonspecific immune responses to activate nonspecific immune cells and effector molecules, resulting in liver cell damage. Nevertheless, further studies are needed to investigate the significance of CD4+ T cells in liver tissue.

The different result was observed regarding Th1 or Th2 predominance in patients with chronic hepatitis C, which was probably due to the administration of PBMC and the measurement for Th1 cytokines from CD4+ T, or both CD4+ and CD8+ T cells. It is also possible that the HCV-related antigen influences Th helper cells to produce a different cytokine profile from that in healthy subjects. For example, in transgenic mice with HBeAg, the T cell response against peptide 120-31 of HBeAg was predominantly Th1, whereas the response against peptide 129-40 was predominantly Th2-like. Moreover, escaping variants of HCV epitope attenuate or fail to stimulate T-cell proliferation, which is accompanied by a shift in cytokine secretion patterns from one characteristic of a Th1 antiviral responses to a Th2 form. Recent evidence suggests that the polymorphic nature of the MHC binding sites and differences in the T-cell repertoire among persons lead to highly variable binding affinity for the immunodominant HBV peptides, which in turn determines the outcome after acute HBV infection.

The role of IL-12 in hepatitis disease

IL-12, a heterodimer composed of 2 subunits of p40 and p35 and secreted mainly by antigen-presenting cells (APC) such as activated macrophages and dendritic cells (DCs), is a crucial mediator between innate and adaptive immune responses. The transcriptional factor T-bet, which can induce transcription of an IFN-γ reporter gene and is specifically expressed in Th1 cells generated in the presence of IL-12, suppresses the expression of genes encoding IL-4, IL-5 and induces the synthesis of IFN-γ. These studies suggest that Th1 development process is governed by cytokine IL-12 to a great degree.

IL-12 is a key cytokine not only promoting Th1—synergizing with IL-2, IL-12 induces rapid and efficient production of IFN-γ by stimulation of the TCR–CD3 complex and activation of the CD28 receptor, but also maintaining Th1 responses (Figure 1), in that Th-cell differentiation is determined most probably early after infection by the balance between IL-12 and IL-10, IL-4, which favours Th1- and Th2-cell development, respectively. In addition, IL-12 correlates with virus clearance. In HBV-infected patients, a significant increase in IL-12 production was observed only in patients who cleared the virus. The peak of serum IL-12 associated with Th1 cytokines (IFN-γ) occurred after the ALT flare and preceded or coincided with the time of HBe seroconversion. Thus, the findings in patients with chronic HBV infection support a proposed combination strategy for therapy with IL-12 plus vaccination. After the ALT flare, the occurrence of IL-12 peak would be the reason that hepatocellular necrosis induced by CTL leads to the recruitment of macrophages and noncommitted T helper cells in the liver. Then the native particles of HBeAg are released from damaged hepatocytes and provide potent antigenic stimulation for these cells. In patients who are able to respond with an increase in IL-12 production, this will promote Th1 cell development and stimulate the production of IFN-γ and TNF-α, which will exert their noncytolytic antiviral effects.

IL-12 may be instrumental in the defense mechanism against HBV infection, and the elevation of its level can be indicative of hepatitis recovery. The enhancing effect of IL-12 on IFN-γ production of PBMC in patients with chronic hepatitis B virus...
infection is increased during IFN-α treatment. Therefore, IFN-α and IL-12 may enhance the efficacy for the treatment of chronic HBV infection[52], and HCV-related cellular immune defect in patients with hepatitis C can be restored in most patients by IL-12[53]. However, Quiroga et al[54] found that HCV-infected patients with greater necro-inflammatory activity of liver showed greater IL-12 production by PBMC than those with minimal or mild activity and normal donors. Massive induction of the proinflammatory cytokines IL-12 and IFN-γ in liver specimens is apparently not counterbalanced by the anti-inflammatory cytokine IL-10, which may play an important role in promoting inflammatory reactions leading to massive liver damage in murine models of fulminant hepatitis B[55].

**Figure 1** Development of Th1/Th2 From Marc and Weeber.

**BALANCE OF MACROPHAGE IN PATIENTS WITH HEPATITIS**

**Macrophage and macrophage activation**

Macrophages can be segregated into two broad groups: resident tissue macrophages and inflammatory macrophages. Tissue macrophages are heterogeneous, and those isolated from different anatomical sites differ in function presumably because of adaptive responses to the local micro-environment[56]. Inflammatory macrophages are derived largely from circulating monocytes, which infiltrate damaged tissue, but some arise by local cell division[57]. There is now increasing evidence for the heterogeneity of macrophages that have infiltrated inflamed or otherwise damaged tissue, depending on the type and severity of injury, the stage of its evolution and the localization of the macrophages within the tissue[58].

One major function of macrophages is to provide a defense line against microbial invasion and to recognize and kill tumor cells. Macrophages can accomplish this in a direct manner, involving the release of products such as oxygen radicals and tumor necrosis factor that are harmful to microorganisms or cancer cells. On the other hand, they play an indirect role in these anti-microbial or anti-tumor processes by secretion of cytokines or by antigen processing and presentation, thereby regulating the immune system[59].

The macrophage presents HBV-derived proteins which activates CD4+ T cells. The effects of stimulation on macrophages include increased cytokine production (TNF-α, IFN-γ, IL-1), expression of inducible nitric oxide synthase, nitric oxide secretion, and up-regulation of adhesion molecules. All these processes can lead, directly or indirectly, to increased cytotoxicity of the macrophages. We also found the higher expression level of granulate and activation –linked surface antigen CD69 by CD14 macrophage from peripheral blood in patients with chronic hepatitis than in controls[60]. This activity was associated with high level transcription of IL-1, IL-6 and TNF-α (unpublished data). Probably, plasma HBV antigens activate macrophages from peripheral blood. Subsequently, such cytokines are produced. In addition, the increasing number of macrophage functions and heterogeneity in *vivo* and *in vitro* has led to the definition of macrophage activation states in parallel to the Th 1/2 paradigm. IFN-γ has long been known as the classical macrophage activating factor inducing cytokine secretion by macrophages supporting Th1-driven immune responses. IL-4 which was historically regarded as macrophage deactivators is now thought to induce alternative immunological activation of macrophages[61], in that it enhances the capacity of macrophages for endocytosis and antigen presentation by the induction of mannose receptor expression[62]. In normal immunological process, classical and alternative macrophage activation maintains the balance of macrophage.

**Balanced macrophage activation hypothesis**

Figure 2 shows a macrophage activation cycle wherein multiple steps occur during various forms of activation and recycling of macrophage function so as to achieve balanced macrophage activation (Steps 1-5)[63]. When hepatitis virus invades the body, tissue-resident macrophages undergo local activation and engulf the virus or antigen and enhanced recruitment of monocytes and precursors from bone-marrow pools results in the accumulation of tissue macrophages that have enhanced turnover and an altered phenotype[64]. After the antigen presentation, Th cells are activated through MHC class II. Th1 (stand for active Th) cell produces IL-2 and IFN-γ and Th2 (stand for inhibitor T) cell secretes IL-4 and IL-10, which is involved in B cell activation as well as providing signals for balanced macrophage activation. Production of IL-4 is known to activate the alternative macrophage activation pathway[65] (step 5). Although IL-4 induces mannose receptor expression and enhance the capacity of macrophages for endocytosis and antigen presentation[66], alternative pathway activated macrophages *in vitro* actively inhibit mitogen-induced proliferation of peripheral blood lymphocytes[67] and CD4+ T cells[68-66]. These findings convincingly confirm that alternative activation generates immunosuppressive macrophage populations. In fact, co-induction of IL-10 with IL-4 secreted by Th2 cells, mainly contributes to the inhibition effect. The net result of excess IL-10 production shuts off the Th1 activation pathway[61]. Therefore, the balance of macrophage and these cytokines are closely related to viral infectious diseases such as AIDS and viral hepatitis.

**Figure 2** Blanced macrophage activation cycles From Michael[62].

Macrophages may contribute either directly or indirectly to the hepatonecrosis with fulminant virus infection[67] through classical macrophage pathway. Macrophages in the liver called Kupffer cells activate Th1 (IFN-γ), IFN-γ will activate Kupffer cell[68,69]. This results in Kupffer overactivation, which in turn promotes cytokines production (TNF-α, IFN-γ) of inducible NOS (iNOS), nitric oxide (NO) secretion. These processes can lead, directly or indirectly, to increased cytotoxicity of the macrophages-this is the classical macrophage activation pathway.

IL-12 is a cytokine secreted by APCs such as activated macrophages and DCs[70]. It has an important role against intracellular pathogens by promoting Th1 cell development, cell mediated cytotoxicity and IFN-γ production[71,72]. For
example, a significant increase in IL-12 production was observed only in patients with chronic hepatitis C who cleared the virus.[72]

On the one hand, IFN-γ, activating macrophage and TNF-α secreted by macrophage, exert their noncytolytic antiviral effects. On the other hand, macrophage kills small fraction of infected hepatocytes. As mentioned above, the increase of serum IL-12 and Th1 cytokines always followed the ALT flare[73] confirming the function of IL-12 in promoting Th1 cell development, and binary function of macrophage. This also explains that HCV-infected patients with greater necro-inflammatory activity of liver showed greater IL-12 production by PBMC than those with minimal or mild activity in normal donors, and why Th1 predominance in HCV infection was correlated with the direct cytotoxic effect[81,21] and the inhibition of viral replication.

The greater production of IL-12 associated with greater necro-inflammatory activity of liver in HCV-infected patients[80] and response of IFN-γ to HCV core protein with chronic liver disease suggest a cellular immune response to the onset of the necroinflammatory process of hepatitis[80]. In murine model of fulminant hepatitis B, massive liver damage was associated with the massive induction of IL-12 and IFN-γ in liver specimens. Probably, the proinflammatory cytokines are apparently not counterbalanced by the anti-inflammatory cytokine IL-10. Thus IL-12 may play an important role in promoting inflammatory reactions[80]. These cases suggest that the macrophages are in the hyperactive situation, probably due to the imbalance of Th1/Th2 and failing to establish the alternative macrophage activation, which results in the imbalance of macrophage. Thus massive hepatocytes are killed by macrophages or overactivated CTLs.

The steps 2 and 3 in Figure 2 are continually stimulated when foreign virus can not be cleared by successful immune response for Lack of optimal T-cell reactivity that would reestablish balanced macrophage activation. The immunologoc overstimulation overpredicts lead to pathologic sequelae such as cirrhosis and hepatitis in chronic hepatitis B and C infections[74].

After long periods of time during which steps 2 and 3 are overemphasized, there would be a predicted shortage of cells to accomplish steps 5 and 1. There would also be an initial overdrive of Th1 cell population. Patients with HIV also have been observed to have a dramatic Th1 to Th2 shift as described in step 4 and patients with chronic hepatitis B appeared to be Th2 predominant[80]. The balanced macrophage activation theory predicts that this shift is compensatory in nature with the T cells attempting to regulate balanced macrophage activation through production of IL-4 which induces step 5. Th2 predominance would be suffered by patients with chronic viral disease, which would cause secondary immunopathogenic changes, such as HCV-related liver cirrhosis (HCC)[73], while patients with histology of inflammation showed a significantly higher CD4+Th1 response to the HCV core antigen as compared to patients with histology of fibrosis/cirrhosis[80]. These findings suggest that Th1/Th2 imbalance in HCV-related cirrhosis would decrease the antitumor immunity and its improvement might present the protective effect from HCC[77]. At the same time, there exists the exhaustion of cells in steps 5 and 1. This would decrease the rate of phagecysis.

Alternative macrophage pathway (step 4) has the following features: (1) the production of angiogenic factors, (2) inhibition of T cell responses, (3) associated downregulation of inflammatory-mediator production characteristic of classical activated macrophages, and (4) with the alternative macrophage activation chemokine-1 (AMAC-1)[77], also known as macrophage inflammatory protein-4 (MIP-4). But few studies were performed in aspect of macrophage, and little is known about the mechanism of the balanced macrophage theory in chronic virus liver infection.

CONCLUSION

Recent data have made a major shift in the role of macrophages in HIV[78] and inflammatory kidney disease. They can no longer be regarded solely as causing injury but rather as cells that can also promote resolution[90,91]. This means that strategies to prevent macrophage influx may be beneficial to patients with hepatitis. Future experiments will need to define methods for determining the functional attributes of macrophages in clinical liver biopsies, and effective ways to manipulate the function of inflammatory macrophages in vivo.

Given the diverse range of functions macrophages can assume, it becomes possible to modulate disease by altering macrophage activity. The classic view would be that the overall inflammatory environment is a balance between pro- and anti-inflammatory cytokines, determining infiltrating and resident cell function. An increase of pro-inflammatory cytokines from macrophages such as TNF-α or IL-1β thus worsens inflammation, whereas antagonists of these molecules such as IL-1 receptor antagonist (IL-1ra), IL-1 type II decoy receptor (IL-1RII) and soluble TNF receptor result in reduced injury[91]. A number of cytokines are described as anti-inflammatory, including the Th2 cytokines IL-4, IL-10 and IL-13, IL-6 and TGF-β. rIL-10-treatment of patients with advanced fibrosis who had failed antiviral therapy appeared to decrease disease activity[82]. TGF-β2 significantly suppressed IFN-γ production at the single-cell level, indicating that the enhanced down-regulation of Th1 by TGF-β2 in patients with HCV-related liver cirrhosis might be effective against hepatoma[83]. But not all anti-inflammatory cytokines are equal in their ability to modulate macrophage function in vivo. In contrast to the results with the Th2 cytokines, IL-4 and IL-10, infusions of TGF-β do not modulate inflammatory macrophage function in glomerulonephritis. For example, Infusion of TGF-β3 in rats with NTN (nephrotic nephritis RANTES) before the onset of disease did not alter the degree of proteinuria, although the number of infiltrating macrophages was reduced[84]. The study about TGF-β treatment of animal models and patients with hepatitis is still unknown.

Advanced clinical studies of WF10 (completely blocked antigen activation of T cells responsiveness –in step 2) are currently underway in the USA for treatment of patients with HIV disease. The patients who received two cycles of WF10 showed chronic immunological changes by downregulating inflammatory macrophages and reestablished alternative macrophage activation, which was consistent with induction of balanced macrophage activation[85]. Similarly, it is possible to modify inflammatory virus liver disease using a range of cytokines (Th1/Th2 types) with well-defined effects on macrophage activation. For example, defects in T cell response have been suspected as a major factor involved in the pathogenesis of chronic hepatitis B[81,14] and favoring Th2 type cytokine may lead to chronic infections with HBV. Recent study has shown that activation of Th1 immunity accompanied by enhancement of CTL activity during therapy is a common immune mechanism for the successful treatment of hepatitis B and C[96]. Using HBV core gene transduced DCs as APCs, HBcAg specific CTLs and Th1 type immune responses could be generated in the mice, which would be a new way to deal with the viral hepatitis[97]. Thus, treatment with IL-12 to drive T cell reactivity[88], and usage of IL-4 receptor antagonist are probably the practicable way to clear virus and remove HBV-infected hepatocytes. Although IL-12 as monotherapy in patients with HCV did not alter the production of regulatory cytokines produced by Th1/2 cells[99] and had low efficacy[90,91]. IL-12 combining with IFN-α may enhance the efficacy for the treatment of chronic hepatitis B virus infection[92] and may be a predisposition for elimination of HBcAg and successful treatment of hepatitis B[93].
Sun QL et al. Cytokine profiles in patients with hepatitis

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