association. Geographic differences in HCV genotype have been thought to cause these discrepancies [66] although this remains controversial. Large-scale, population-based, well-controlled studies are necessary to reach a robust conclusion. It can be concluded that, at least in areas with a high prevalence of HCV carriage, HCV is an important risk factor for B-cell lymphomagenesis.

In this paper, we propose a novel hypothesis that peripheral B cells serve as reservoirs for persistent HCV infection. We also suggest that long-lasting HCV infection in B cells may induce lymphoproliferative disorders that may eventually evolve into B-cell NHL, although little is known about the mechanism responsible for B-cell lymphomagenesis. In the remainder of this section, the possible mechanisms of B-NHL tumorigenesis induced by HCV infection will be discussed based on current knowledge of lymphomagenesis-related genes.

Activation-induced cytidine deaminase (AID) is essential for somatic hypermutation (SHM) and class switch recombination of immunoglobulin genes in B cells [67–69]. Recently, it has been proposed that AID may be instrumental in the initiation and progression of B-NHL. This is because a malfunction in either of the two processes stated above is apparently responsible for chromosomal translocations and aberrant SHM, which are the two main causes of genetic lesions associated with B-NHL [70, 71]. Several oncogenes have been demonstrated to be targets for SHM with immunoglobulin genes. In many cases, these anomalies activate the DNA damage response system that either allows DNA repair or eliminates the aberrant B-cell clones [72]. Failure of these repair systems may be a cause of B-cell malignancies. Specific features of SHM are the predominance of single-based substitution, the preference for transitions over transversion, and the specific targeting of the RGYW/WRCY motif. Pasqualucci et al. showed that hypermutation of proto-oncogenes exists in DLBCL [71]. However, in HCV-associated NHL, the number of mutations in some proto-oncogenes was lower than that already found in HCV-negative B-cell NHL patients [73]. Because there is a close association between HCV infection and the incidence of B-NHL, as described above [6, 7], analyzing the expression levels of AID in CHC B cells is of great interest.

Lai et al. established a B-cell line (SB) from HCV-infected B-NHL cells. The virus particles produced from SB cell culture could infect primary human hepatocytes, Raji cells, and PBMC in vitro [74]. They examined the expression of AID in Raji cells and PBMC after HCV infection in vitro. It was found that HCV infection activated the expression of AID in Raji cells. AID expression level was also higher in PBMC of patients infected with HCV than in uninfected individuals [75]. However, their study did not assess which cell population showed an enhancement of AID expression. It was observed in our recent study that expression levels of AID mRNA were markedly enhanced in the $CD19^+$, but not in the $CD19^-$ subset of patients with CHC [32]. Furthermore, the enhanced expression of AID protein was detected in the $CD19^+$ B-cell subset of patients with CHC [32]. The fact that this enhancement of AID expression is confined to the B-cell subset is extremely intriguing because several reports have demonstrated the augmented expression of AID in B-NHL [26, 76, 77].

Using an AID-deficient mouse model, Pasqualucci et al. concluded that AID is required for germinal center-derived lymphomagenesis [78]. They addressed the issue of errors in AID-mediated antigen receptor gene modification processes being the principal contributors to the pathogenesis of human B-NHL. Increasing epidemiological evidence has highlighted the close correlation between HCV infection and B-NHL [6, 7, 79]. Thus, it is tempting to hypothesize that the enhancement of AID in CHC B cells is at least partly responsible for the initiation of lymphomagenesis. In fact, several recent studies suggest that AID is deeply involved in tumorigenesis [80–84]. Notably, HCV enhanced AID expression by NF-κB activation through the expression of viral core proteins. Furthermore, NF-κB expression was upregulated and activated by HCV NS2 proteins in HepG2 cells [85]. These findings suggest that inappropriate expression of AID acts as a DNA mutator that enhances genetic susceptibility to mutagenesis [86].

Additionally, enhanced expression of other lymphomagenesis-related genes including cyclin D1, cyclin D2, BAL, STK15, and galectin-3 in CHC B cells is worth considering [32]. Overexpression of CCND1, which alters cell-cycle progression, is frequently observed in various tumors and may contribute to tumorigenesis [87, 88], whereas CCND2 is known to be expressed at constitutively high levels in B-NHL [89]. BAL is a novel risk-related gene in DLBCL, a typical B-NHL [90], while STK15 is a gene highly expressed in a histologically aggressive type of NHL [91]. Galectin-3 is an antiapoptotic protein, highly expressed in DLBCL [92]. Presumably, the enhanced expression of these genes in CHC B cells [32] may also correlate with B-cell lymphomagenesis.

Tumor necrosis factor alpha-induced protein 3, also called A20, was first identified in 1990 as a TNF-induced cytoplasmic protein with zinc finger motifs [93], which thereafter has been described as a key player in the negative regulation of inflammation by terminating NF-κB signaling [94–96]. Recently, A20 has gained much attention as a novel tumor suppressor [97, 98]. Honma et al. first reported that A20 is frequently inactivated or even deleted in mantle cell lymphoma and DLBCL, and they raised the possibility that inactivation of A20 may be at least partly responsible for lymphomagenesis [99, 100]. Other investigators have subsequently supported their findings [101, 102]. Moreover, A20 also regulates antiviral signaling as well as programmed cell death [103–105]. Currently, the expression, biological activities, and mechanisms of action of A20 have been the focus of attention on a wide scale [106]. Interestingly, Ngueyn et al. reported [107] that the HCV core protein induced an increased expression of A20 in the human hepatocyte cell line HepG2, which has generated a genuine interest in the expression of A20 in peripheral B cells of patients with CHC. Our preliminary data suggests that the A20 molecule is partially cleaved in CHC B cells (Kusunoki et al.; in preparation). An intriguing possibility is that the A20 gene interacts with and is mutated by AID, the expression of which is dramatically enhanced in CHC B cells [32]. In

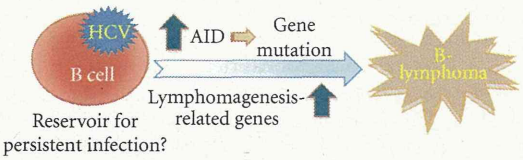

FIGURE 2: Role of HCV infection in B-cell lymphomagenesis, a hypothesis.

this regard, the expression levels of A20 in patients with B-NHL suffering from chronic HCV infection are worth investigating.

5. Conclusion

In this paper, we summarized recent studies illuminating the possible role of HCV infection in B-cell lymphomagenesis. We proposed a hypothesis that HCV utilizes B cells as reservoirs for persistent infection, which could result in the enhanced expression of lymphomagenesis-related genes, particularly AID, which is thought to be crucial for the initiation and progression of B-NHL (Figure 2). Elimination of HCV in plasma by antiviral reagents as well as in peripheral B cells by specific antibodies would be beneficial for patients with CHC to achieve a complete viral clearance. Finally, although a positive association between HCV infection and B-NHL occurrence is still being debated [108–111], it is worthwhile to investigate the possible mechanisms by which B-cell lymphoproliferative disorders, which may evolve into B-NHL, are induced in patients with CHC.

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