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TOPIC HIGHLIGHT

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Hepatitis C virus-related mixed cryoglobulinemia: Is genetics to blame?

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Abstract

Mixed cryoglobulinemia (MC) is the extrahepatic manifestation most strictly correlated with hepatitis C virus (HCV) infection; it is a benign autoimmune and lymphoproliferative disorder that evolves to lymphoma in 5%-10% of cases. MC is reputed to be a multistep and multifactorial process whose pathogenicity is still poorly understood. It is still unknown why only some chronically infected HCV patients develop MC and only some of these exhibit systemic symptoms (MC syndrome). Several studies have investigated the pathogenetic basis of MC and the most recent ones suggest that the virus is able to trigger such a disorder only in the presence of genetic factors that are still unknown. Here, we try to clarify the complex relationship between HCV-related MC and the host's genetic background. The data that we report are heterogeneous and sometimes even conflicting. Therefore, large, multicenter studies are clearly needed. The identification of a characteristic genetic signature of cryoglobulinemic patients would be an important step toward a personalized approach in their clinical care. The new wide-ranging genomics technologies will hopefully help to resolve these complex issues.

Key words: Hepatitis C virus; Mixed cryoglobulinemia; Genetics; Viral pathogenetic factors; Host pathogenetic factors

Core tip: Mixed cryoglobulinemia (MC) is the extrahepatic manifestation most strictly correlated with hepatitis C virus (HCV) infection; it is a benign autoimmune/lymphoproliferative disorder that evolves to lymphoma in 5%-10% of cases. MC pathogenesis is still poorly understood. Several studies have tried to clarify the pathogenetic basis of MC and have suggested that HCV can trigger such a disorder only in the presence of still-undetermined genetic factors. Here, we attempt to clarify the relationship between HCV-related MC and the host's genetic background. The data that we report are heterogeneous and sometimes conflicting, so large, multicenter studies are clearly needed.

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INTRODUCTION

Mixed cryoglobulinemia (MC) is the extrahepatic manifestation most strictly correlated with hepatitis C virus

(HCV) infection[1], as well as being an autoimmune and B cell lymphoproliferative disorder that evolves to lymphoma in 5%-10% of patients. Defined as a systemic vasculitis, MC is caused by intravascular immune complexes named cryoglobulins (CGs). The term "mixed" refers to the simultaneous involvement of immunoglobulin G (IgG) and IgM in generating the CGs that can include partially monoclonal (type Ⅱ MC) or totally polyclonal (type Ⅲ MC) immunoglobulins. The IgM has rheumatoid factor activity and is produced by clonally expanded autoreactive B cells[2-5].

The pathogenesis of MC is still poorly understood, although it is certain that several subsequent events contribute to disease onset, when they occur in a favorable host genetic substrate[1,6-8]. The reasons why only some chronically infected HCV patients develop MC and why only some of these exhibit systemic symptoms, the so-called MC syndrome (MCS), are unknown. One of the most obvious explanations, the genetic factor, has only recently been seriously contemplated, when the impact of this disease on chronic HCV infection and its role in predisposing to lymphoid malignancies has been recognized. Since then, several studies have tried to clarify the complex pathogenesis of MC and the most recent have focused on genetics.

Together with genetic predisposition, epigenetic factors such as the expression of specific miRNAs can be a major contribution to the pathogenesis of HCV-related lymphoproliferative disorders[9]. In particular, miR-26b is downregulated in peripheral blood mononuclear cells from HCV-related MC but totally restored after complete virological and clinical response to anti-HCV therapy[10,11]. However, this review focuses on the numerous attempts to define the specific genetic background predisposing to development of MC.

We try to clarify this topic by reporting all the attempts to define the genetic basis of HCV-related MC, starting from studies that failed to attribute a direct role in triggering this condition to viral factors, and ending with studies proposing an association between some particular host genetic variants and the development of MC. Other studies have shown a relationship between chronic HCV infection and lymphoma or other autoimmune diseases, which are worth considering for their resemblance to MC.

MC AND HCV FACTORS

Viral genotype and MC

Since the mid-1990s, several studies have analyzed the relationship between HCV factors, such as genotype and viremia, and MC susceptibility. Although results are often conflicting, most studies conclude that the distribution of viral genotypes in MC patients without clinical manifestations does not significantly differ from those observed in HCV patients with no evidence of lymphoproliferation[12-14]. The patients in the cited papers had asymptomatic MC and, as speculated by Sinico *et al*[14], these studies leave open the possibility that HCV genotype or subtype could influence progression to symptomatic MC. However, the analysis of 60 MC patients, including 22 with symptoms, reported by Frangeul *et al*[15], did not show a significant association between MCS and HCV genotype.

Specific HCV hypervariable region 1 and 2 mutations and MC

Some authors have thoroughly investigated the possible role of mutations in the N-terminal hypervariable regions 1 and 2 (HRV1 and HRV2) of the E2 envelope glycoprotein in predisposition to MC.

The initial results about the relationship between E2 mutational pattern and MC pathogenesis suggest an association of particular HVR1 variants (insertion at codon 385 and deletion at codon 384) with type Ⅱ MC[16]. The authors focused on 385 insertions responsible for improved ability of E2 to bind the HCV putative receptor CD81, with consequent higher stimulation of CD81 itself leading to augmented lymphoproliferation[16].

Another attempt, published some years later, did not confirm these data, but correlated different viral mutations with MC (positions 389 and 398 for HVR1 and positions 474, 493 and 497 for HVR2)[17]. Conversely, a study published by Rigolet *et al*[18], after an accurate approach of cloning and sequencing HVR1 regions isolated from HCV-positive MC patients, clearly concluded that any particular motif of E2 coding sequence could be associated with MC. These data were confirmed in a study conducted on a population of 80 MC patients by Bianchettin *et al*[7]. A similar experimental plan and accurate statistical and bioinformatic approaches suggested that MC arose by as-yet-unidentified host rather than virus-specific factors, meaning that attention should be focused on the host.

Convincing proof of the role played by host genetics in determining HCV-related MC onset appeared in an epidemiological study by Pozzato *et al*[19], which demonstrated that there were ethnic differences in the prevalence of asymptomatic HCV-associated monoclonal B-cell expansion. Based on an observational suspicion of a high prevalence of MC in Italy versus a low prevalence in Japan, the authors investigated 60 Italian and 44 Japanese HCV patients and concluded that there were no differences in the two groups apart from ethnicity. This clearly suggests that HCV is able to induce B-cell expansion only in the presence of unidentified genetic factors.

MC AND GENETIC FACTORS

MC and HLA polymorphisms

The first studies regarding the host genetic factors conditioning susceptibility to development of MC during chronic HCV infection analyzed human leukocyte antigen (*HLA*) gene cluster variants. *HLA* gene products are responsible for presenting viral antigens to T cells, therefore, it has been speculated that some HLA variants could be implicated in driving the immune response against the virus to produce autoreactive antibodies (the CGS). An early attempt to investigate the genetic predisposition to MC was published even before the discovery

of HCV and HLA class Ⅱ polymorphisms. Migliorini *et al*[20] did not find any association between MC and either class I or class Ⅱ HLA molecules. Since then, several studies and some controversial data have been published. Ossi *et al*[21], studying 16 MC patients, showed a higher expression of HLA-B51 and B35 antigens, previously correlated with other autoimmune disorders, as well as the presence of HLA-A9 with its A24 split in 50% of the same population.

An almost contemporary study performed in a large cohort of multi-transfused patients, including 116 HCV-positive ones, showed no association between a specific HLA pattern and MC. The authors conclude that the HLA class Ⅱ DR2 subtype (DRB1*1601, DQB1*0502), which is characteristic of multi-transfused patients who maintain HCV negativity after years of blood transfusions, could be considered as a sort of protection against HCV infection[22].

A meticulous study, mostly for the accuracy of the statistical analysis, showed a higher frequency of HLA-B8 and HLA-DR3 in a group of 25 HCV-positive cryo-patients[23]. The odds ratio was also calculated and the highest corresponded to the presence of both B8 and DR3, suggesting the existence of an HLA-B8-DR3 haplotype associated with HCV-infected MC patients. These results were partially confirmed in a Chinese study in which HLA-DR3 was significantly associated with the presence of HCV-related cryoglobulinemia that was mostly asymptomatic[24].

The absence of an association between HLA and MC was demonstrated by another Italian group. Analysis of HLA-DRB1 alleles in 46 patients with HCV infection concluded that HLA class Ⅱ polymorphisms did not distinguish patients with MC from those without MC[25].

Cacoub *et al*[26] also evaluated *HLA-DRB1* and *HLA-DQB1* polymorphisms in a cohort of 76 symptomatic or asymptomatic MC patients. Multivariate logistic regression analysis of several features indicated the presence of HLA-DR11 as a positive predictor of MC, together with the already known female sex and age. The same HLA class Ⅱ alleles were evaluated in another study that focused on the association between particular HLA-DR-DQ combinations and HCV-positive non-Hodgkin's lymphoma (NHL) with and without a background of MC[27]. Various HLA Ⅱ associations have been found for HCV-positive NHL in the presence of MC (higher frequency of DR5-DQ3 HLA) and for HCV-positive and MC-negative NHL (higher frequency of DR1-DQ1), suggesting the presence of alternative pathogenetic processes for similar but different HCV lymphomas.

MC and cytokine mutations

Alterations in the cytokine/chemokine patterns, also involving proinflammatory and Th1 chemokines, have been demonstrated in MC and other extrahepatic disorders induced by HCV infection[28]. These previous studies have investigated genetic variants of this complex class of immune response regulators.

Several studies have shown that interleukin (IL)-10 may be involved in the pathogenesis of lymphoid disorders; moreover, three different mutations in the IL-10 promoter (-1082G→A, -819C→T and -592C→A) were associated with higher IL-10 production. In a study by Persico *et al*[29], conducted on 270 well-characterized patients with NHL and/or HCV-related chronic hepatitis, a high prevalence of IL10-1082GG genotype was significantly associated with NHL in HCV-infected patients.

Polymorphisms of inflammatory chemokines are also significantly correlated with the outcome of HCV infection, because chronic hepatitis itself is closely associated with inflammation.

Recent reports have shown high levels of a B-cell-specific cytokine, namely B-cell-activating factor (BAFF; or B lymphocyte stimulator), in the serum of HCV patients with lymphoproliferative disorders but could not define the mechanisms underlying this phenomenon[30-33]. BAFF is a tumor necrosis factor α family member and a key regulator of B-cell differentiation, survival, and immunoglobulin secretion, and the mutated genotype of its promoter (-871T) is associated with higher BAFF mRNA levels in monocytes[34,35]. Two consecutive studies conducted on a well-characterized MC population indicated a significantly higher prevalence of T allele homozygosity in patients with MCS, as well as the presence of the T allele (homozygous TT plus heterozygous TC) compared to HCV carriers without MC[8,36]. These results are consistent with the serum BAFF levels found in the different groups. Therefore, the transcriptional activation induced by the BAFF promoter variant could be considered one of the mechanisms contributing to the pathogenesis of HCV-related lymphoproliferative disorders.

MC and IgG Fc receptors

Two independent studies have evaluated the role of the genetic variability of IgG Fc receptors (FcGRs) in the susceptibility to MC during the course of HCV infection. The FcGRs, present on leukocytes, are responsible for the clearance of immune complexes, phagocytosis, antibody-dependent cellular cytotoxicity, and regulation of the release of inflammatory mediators and B-cell activation, mainly in phagocytes. Their polymorphic variants are associated with reduced affinity for immune complexes, autoimmune diseases, and cancer[37]. In the first study, Vassilopoulos *et al*[38] analyzed a cohort of HCV patients with different autoimmune/lymphoproliferative disorders, including MC, discriminating between symptomatic and asymptomatic individuals and investigating FcRⅢA and the *NA1/NA1 FcGRⅢB* genotypes. They did not find any increased frequency of particular alleles in the autoimmune manifestations group compared to historical controls. In the second study, a more numerous cohort of cryoglobulinemic patients was evaluated. Despite the wider and better characterized MC population, this recent screening of FcGR2A 131R/H, FcGR2B 232 I/T, FcGR3A 176 V/F and FcGR3B NA1/NA2 confirmed the previous results, with the distribution of *FcGR* genotypes not being significantly different compared to the controls[8]. We reported in 21 HCV-MC patients treated

Table 1 Association between hepatitis C virus-related lymphoproliferative disorders and host genetic factors

Factors	References
HLA polymorphisms	
HLA-A9	[21]
HLA-B8	[23]
HLA-DR3	[23,24]
HLA-DR11	[26]
HLA-DR5-DQ3	[27]
Cytokine mutations	
IL-10 promoter (-1082GG)	[29]
BAFF promoter (-871T)	[8]
Sporadic associations	
Fibronectin Msp I and HaeⅢb	[40]
CYP27B1	[41]

HLA: Human leukocyte antigen; IL: Interleukin; BAFF: B-Lymphocyte activating factor.

with rituximab (anti-CD20 monoclonal antibody) that the response was strictly related to the F allele homozygosity of FcGR3A, suggesting that this genotype could be involved in response to rituximab therapy.

Sporadic associations

The role of mutations within Fas and Fas-L genes has been described in mice with an increased prevalence of autoimmune manifestations, therefore, some authors have postulated that such mutations could be related to autoimmune diseases and lymphoproliferation. Results obtained from a small number of patients with Sjögren's syndrome or type Ⅱ MC do not support such a hypothesis, suggesting that the germline mutations of the Fas receptor and its ligand are probably not involved in the pathogenesis of HCV-related type Ⅱ MC[39].

A possible relationship between two fibronectin polymorphisms (called *Msp* I and *Hae*Ⅲb) and type Ⅱ MC has been investigated, in order to define the risk of lymphoma development. Fabris *et al*[40] analyzed 74 patients with MC, including 21 who developed B-cell NHL and 72 with HCV-negative and MC-unrelated NHL. None of the major MC-related clinical manifestations was significantly linked with a particular allele or genotype of the *Msp* I and *Hae*Ⅲb fibronectin gene polymorphisms. However, the two genetic sites seem to confer an independent increased risk of NHL in MC patients.

As a result of the critical role of vitamin D in the regulation of the immune system, the analysis of the serum vitamin D status in HCV-infected patients with extrahepatic manifestations seems particularly interesting. Terrier *et al*[41] found a strong association between low serum levels of vitamin D and the presence of MC and systemic vasculitis in patients with chronic HCV infection. Regarding the B-cell compartment, they observed significant correlations between serum 1,25-dihydroxyvitamin D and the B-cell activation status.

Lange *et al*[42] previously found that 1,25-dihydroxyvitamin D serum concentrations were higher in HCV patients with *CYP27B1* AA genotype compared to patients with *CYP27B1* AC or CC genotype, thus, it is conceivable that MC patients harbor these latter genotypes. Unfortunately, no further studies have been published on this topic but an abstract of Terrier Benjamin *et al*[43] reports an exactly opposite association between phenotype and genotype in patients with HCV-related systemic vasculitis.

Recent important advances in the HCV field strongly suggest that the polymorphic variants of the *IL-28B* gene should be analyzed. Indeed, in 2009 several independent studies have shown that single nucleotide polymorphisms near the IL-28B coding region are closely associated with HCV clearance. IL-28B is involved in innate immunity and a recent study evaluated the influence of these genetic variations in the development of HCV-related MC[44]. The allele distribution reported in the study was similar in patients with or without MC, and does not support the hypothesis that these polymorphisms influence the development of MC.

The associations between HCV-related lymphoproliferative disorders and host genetic factors are summarized in Table 1.

CONCLUSION

It is clear from the reports described in this review that the role of genetics in HCV-related MC is a current and compelling research topic. Each patient is genetically unique, which can affect the evolution of chronic HCV infection towards benign lymphoproliferation predisposing to lymphoma. The identification of a characteristic genetic signature of cryoglobulinemic patients could be a step towards personalized approaches in the clinical care of HCV infection, which are useful for targeted follow-up of high-risk individuals. The above data are heterogeneous and sometimes even conflicting, thus, there is a clear need for multicenter studies including large numbers of patients, and the future application of the new genomic and proteomic wide-range technologies will surely assist in this direction.

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