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Review Article

Chemokine Receptor *CCR5* Gene Polymorphism and Clinical Outcomes in Individuals with Chronic Hepatitis C and *Shistosoma Mansoni* Infection

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Abstract

Chemokine receptor CCR5 is a receptor for proinflammatory chemokines which plays key roles in host responses, especially to viruses. The 32-bp deletion mutation in the *CCR5* coding region (CCR5□32) abolishes the receptor from the cell surface, and in homozygous individuals there is no functional CCR5. Homozygosity for this deletion (CCR5□32/□32) is found in 1% of Caucasians, who are protected against HIV infection, whereas the heterozygous state (CCR5□32/WT) is found in 10% of Caucasians, who show slower HIV progression. A number of studies of Hepatitis C Virus (HCV) infection have explored the association between the CCR5Δ32 mutation and HCV susceptibility and severity in people with and without schistosomiasis. Discrepant results have been reported, with positive, negative, or zero effects of the CCR5Δ32 mutation on liver fibrosis or inflammation, response to treatment, or spontaneous viral clearance in patients with HCV infection. This article summarizes the findings of these studies and discusses their limitations and discrepancies. Much work remains to be done to fully elucidate the association between the CCR5□32 mutation and HCV outcomes, and to identify the mechanisms of this association in different groups of patients groups in different localities. A generalizable association between the CCR5□32 mutation and HCV disease would provide new insights for the development of therapeutic options.

Keywords: HCV; Hepatitis C; *Schistosoma mansoni*; Chemokine Receptors; CCR5Δ32 Mutation; HCV Prognosis

Abbreviations

HCV: Hepatitis C virus; HIV: Human Immunodeficiency Virus; CCR5: Chemokine Receptor 5

Introduction

Chemokine receptor CCR5 is a receptor for proinflammatory chemokines which plays key roles in host responses, especially to viruses. Chemokines are small polypeptides with a significant role in leukocyte recruitment and trafficking during inflammation. In addition, chemokines play an important role in T cell differentiation: CD4+ T cells can differentiate into Th1 or Th2 cells depending on their exposure to chemokines. It has been shown that CCR5 is expressed at higher levels on Th1 cells than Th2 clones [1]. In CCR5 knockout mice, T cell response to a variety of antigens is increased [2,3]. The CCR5 receptor has been found to influence T cell trafficking and host immune responses in both human and marine viral diseases [4]. In intracellular parasitic diseases, where control of the infection is dependent on the Th1 immune response, mice deficient in CCR5 had low antigen-specific Interferon-gamma (IFN-gamma) responses especially during the early phase of antigen stimulation. Of further interest in this connection is the association found between CCR5 deficiency and the suppressed progression of leishmaniasis and malaria [5,6].

In the *CCR5* gene, CCR5Δ32 is the mutant allele which causes the CCR5 delta 32 mutation. This deletion mutation alters the receptor's amino acid sequence and thus affects the ability of CCR5 to act as a chemokine receptor. In addition, the mutation may encode a nonfunctional truncated protein that is not transported to the cell surface. The 32-bp deletion in the CCR5 coding region (CCR5Δ32) abolishes the receptor from the cell surface, and in homozygous individuals there is no functional CCR5. It was proposed that the CCR5Δ32 mutation emerged 700 years ago during the European smallpox epidemics as a protective mechanism against the *Variola* virus, which exploits CCR5 as an entry receptor [7].

Chemokine receptor CCR5 in viral and parasitic infections

Viral and intracellular parasitic infections such as leis mania and malaria are controlled by an adequate specific Th1 cell response, in which T cells and other effecter cells migrate to the infected site and perform their unique immunological functions. When a nonspecific T cell population is recruited to the infection site, these cells fail to remove the infecting pathogen in most patients, and this is presumably responsible for chronic disease damage. The migration of T cells to the infection site is controlled by the chemokines secreted by the infected cells, and which subsequently interact with their receptors, such as CCR5 expressed on the attracted T cells. In Hepatitis C Virus (HCV) infection, antiviral T cells express CCR5; the recruitment of these T cells to the liver is a crucial step in the immune response to the disease. As one of the most important chemokine receptors, CCR5 is expressed on CD8+ and CD4+ T cells and is responsible for the

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recruitment of these essential immune cells required to produce a competent immune response against HCV infection [28]. Although the role of the CCR5Δ32 mutation in antiviral immunity remains unclear, IFN-gamma responses to HCV proteins are known to be slightly greater in CCR5 wild-type patients than in CCR5Δ32 carriers. In contrast, people with different CCR5 genotypes do not differ in T cell migration, proliferation of peripheral blood mononuclear cells, or Interleukin-4 (IL-4) production. Interruption of the CCR5 signaling pathway by the CCR5Δ32 mutation may potentially result in a slight reduction in the HCV-specific IFN-gamma response in HCV-positive patients [29]. In this connection, several chemokine and chemokine receptor polymorphisms, the most important of which is the CCR5Δ32 polymorphism, have been associated with different outcomes of HCV infection.

Recently, scientists have proposed that the eradication of smallpox and the cessation of vaccinia immunization may be among the reasons for the sudden spread of Human Immunodeficiency Virus (HIV) infection, because both HIV and smallpox viruses were found to utilize CCR5 receptors for cell entry [8]. This is the first instance in which a virus other than HIV had been shown to exploit this chemokine receptor [8]. Homozygosity for this deletion (CCR5Δ32/Δ32) is found in 1% of Caucasians, who are protected against HIV infection, and the heterozygous state (CCR5Δ32/WT) is found in 10% of Caucasians, in whom it may slow HIV progression [30,31]. It was suggested that protection against HIV infection by the CCR5Δ32 mutation may occur through immunological mechanisms and through blockage of viral entry into the cells.

Chemokine receptor CCR5 and HCV infection with or without schistosomiasis

Scientists believe that viruses other than HIV may also use CCR5 receptors as an entry point to infect cells. In HCV, we still do not know the exact method the virus uses to enter cells, or whether CCR5 is involved in cell entry by this virus. Like HIV, HCV has also shown a recent inexplicably wide distribution in many parts of the world. The role of the CCR5 receptor in the rapid spread of HCV, either through immunological mechanisms or by acting as an entry receptor, remains to be determined.

In a country like Egypt, which has the highest prevalence of HCV infection worldwide (with a prevalence ranging from 6% to more than 40% among different regions and demographic groups [9,10]), co infection with HCV has been reported to be more common in patients with schistosomiasis than in the general population. This leads to a worse prognosis and a greater burden on society and health services [11-13]. Schistosomiasis has long ranked first in Egypt among human parasitic diseases of socioeconomic and public health importance and the disease are still endemic in many foci [14,15]. Schistosomiasis has always been incriminated in the significant increase in HCV infection rates, although this association has not been satisfactorily explained. It might be related with the use of inject able anti-bilharzial drugs before the 1980s [16]. The reusable syringes and frequent blood transfusions for patients with *Schistsoma mansoni* infection might constitute the main mechanism for the dramatic increase of HCV infection among schistosomiasis patients [16]. Moreover, immunological responses to chronic schistosomiasis were suggested to interfere with the development of a curative immune response to hepatitis. Also, the soluble egg antigens of *S. mansoni* were proposed to enhance the multiplication of HCV [17].

Regardless of the causes, the HCV infection rate remains high and many new cases are diagnosed continuously despite the cessation of parenteral anti-bilharzial drugs and strict infection control measures for blood transfusions. Scientists have suggested that the genetic background of individuals may be involved in the marked spread of HCV worldwide. Mutations in the chemokine receptor 5 genes (CCR5Δ32 mutations) were suggested by some to be associated with increased susceptibility to or protection against HCV infection or with progression in patients with either HCV infection alone or in those infected with HCV and schistosomiasis.

Chemokine receptor CCR5 polymorphism and the outcomes of HCV infection

Some studies have explored the association between the CCR5Δ32 mutation and HCV disease susceptibility and severity. The association between the presence of the heterozygous CCR5Δ32 variant and HCV clearance was supported by the findings of Golding et al [18] and Nansen et al [19]. Also, polymorphism in RANTES, one of the chemokines that binds CCR5, was associated with HCV treatment response according to Ahlenstiel et al [20]. Moreover, among individuals with HCV infection, Golding et al [18] found a trend towards less severe scores for hepatic inflammation in CCR5WT/Δ32 heterozygous vs. CCR5WT/WT homozygous patients. Yilmaz et al. [32] found that the histological activity index was significantly lower in HCV-positive patients with the mutated form of CCR5Δ32 than in the non mutated group, and the former group also had decreased levels of liver inflammation and fibrosis. Katsonas et al [33] found that the *CCR* gene is one of the important determinants of clinical and treatment-related outcomes in patients with HCV infection. Scientists have explored the association between the CCR5Δ32 mutation in schistosomiasis-infected patients and protection against HCV infection or progression. El-Moamly et al. [21] concluded that the CCR5Δ32 mutation in patients with schistosomiasis was not associated with increased HCV disease susceptibility. However, schistosomiasis patients with the CCR5Δ32 mutation and HCV infection were less prone to severe hepatic fibrosis and more likely to have spontaneous viral clearance than patients with the non mutant genotype. Although this study did not prove whether the CCR5Δ32 mutation in schistosomiasis patients increases their susceptibility to HCV infection or protects against it, the results nonetheless suggested that the CCR5Δ32 mutation has an effect on HCV clearance and liver disease prognosis in patients with schistosomiasis.

On the other hand, the association of CCR5Δ32 genotype with HCV viral clearance was not supported in work by Prom rat et al [22] or Hellier et al [23]. Goyal et al [25] concluded that the CCR5Δ32 mutation did not influence the susceptibility to or severity of liver disease in patients with chronic hepatitis C, and did not influence their response to therapy. Moreover, Woitas et al [24] observed a higher frequency of CCR5Δ32 homozygotes among patients with chronic HCV infection. Yilmaz et al [32] also found that CCR5 polymorphism was more frequent in HCV-positive patients than in healthy individuals in the Turkish population. The CCR5 WT/Δ32 genotypes were observed in 8.6% of HCV-positive patients and 1.7% of those in the HCV-negative group [32]. Omran et al [34] showed a significant association between the functional Single Nucleotide Polymorphism (SNP) of the *CCR5* gene and the viral response to

interferon in Egyptian patients with chronic hepatitis C. They also found that the presence of the G allele in patients with HCV infection showed a highly significant association with nonresponsive to treatment, higher stage of hepatic fibrosis and poorer grade of liver activity; the A allele, on the other hand, showed a highly significant association with constant treatment response, low hepatic fibrosis stage and comparatively better liver activity grade [34]. Huik et al [35] examined the association between *CCR5* haplotypes and HCV seropositivity, and found that HHG*1-bearing *CCR5* genotypes influenced HCV seropositivity in a group of Caucasian intravenous drug users. Suppiah et al [36] found that the CCR5Δ32 mutation did not influence treatment-induced recovery in patients with HCV infection who received IFN-α and ribavirin, and did not increase the likelihood of sustained virological response in the context of *IL28B* polymorphisms in a multivariate model. The homozygous CCR5Δ32 mutations were significantly more frequent in patients with HCV infection than in healthy controls in European cohorts but not in Australians of European ancestry [36]. Nettermann et al [37] found that the predictive value of *IL28B* gene polymorphism for spontaneous HCV clearance in a single-source outbreak cohort was limited in patients carrying the CCR5Δ32 mutation.

The discrepancies in the results of these studies of the role of the CCR5Δ32 mutation in HCV infection and disease outcomes may be explained by the low frequency of this mutation in the populations studied to date. This low frequency, noted in all studies, makes it difficult to undertake informative statistical analyses between different groups. Moreover, the lack of statistical power prevents researchers from drawing definite conclusions concerning their findings. For example, an earlier study reported a single heterozygous individual for the CCR5Δ32 mutation in a sample of 100 healthy Indian participants, while the rest had wild-type alleles [26]. In addition, disagreement between published articles may result from the presence of different confounding variables which may interfere with the accurate measurement of various outcomes. For instance, one study which found no association between HCV and the CCR5Δ32 mutation included participants from multiple European populations and included a low number of virus-negative persons [23]. Moreover, the HCV genotypes in the participants of that study were not specified, and the infections came from multiple sources. These factors suggest that the results were affected by a high degree of genetic HCV heterogeneity. In another study which found no association between HCV clearance and the CCR5Δ32 mutation, significant co morbid illnesses such as hepatitis B infection and other risk factors for liver disease were not excluded or reported [25]. However, in other studies such as one reported by El-Moamly et al [21], where the CCR5Δ32 mutation showed a positive effect on HCV clearance and liver fibrosis, patients with other causes of chronic liver diseases were excluded, a single viral genotype (genotype 4) was considered, and *Schistosoma* infection was present in both the test and control groups. In addition, the study by El-Moamly et al [21] was the first to explore the association between CCR5 receptor polymorphism and clinical outcomes in Egyptian patients with schistosomiasis alone or with HCV co infection. However, this study, like other studies, was also limited by the low frequency of the CCR5Δ32 mutation in the participants.

Conclusion

To date, the available evidence regarding a possible association between chemokine receptor *CCR5* gene polymorphism and the clinical outcome in individuals with chronic hepatitis C has been contradictory and inconclusive. Positive, negative, and zero effects of CCR5Δ32 mutations have been reported on HCV disease susceptibility, liver fibrosis and inflammation, response to treatment, and spontaneous clearance of the virus. Much work remains to be done to fully elucidate the association between CCR5Δ32 mutations and HCV susceptibility and outcomes. If such an association is proved, studies will be needed to explore whether this association can be generalized to other patients in different localities, to those with various co infections, or to other HCV genotypes. Further studies involving larger groups of participants will also be needed to substantiate the results given the low prevalence of the CCR5Δ32 mutation in the population. In addition, we need studies to fully investigate the mechanisms at work in the protective or exacerbating effect of the CCR5Δ32 mutation in people with HCV infection. If a generalizable association between the CCR5Δ32 mutation and HCV disease is proved, this would provide new insights for the development of therapeutic options. Such new knowledge would constitute an important advance in the management of patients with HCV, particularly as we know that anti-CCR5 agents are already being investigated for the treatment of HIV [27].

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