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Review

Beyond HIV infection: Neglected and varied impacts of CCR5 and CCR5Δ32 on viral diseases



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ABSTRACT

The interactions between chemokine receptors and their ligands may affect susceptibility to infectious diseases as well as their clinical manifestations. These interactions mediate both the traffic of inflammatory cells and virus-associated immune responses. In the context of viral infections, the human C-C chemokine receptor type 5 (CCR5) receives great attention from the scientific community due to its role as an HIV-1 co-receptor. The genetic variant CCR5Δ32 (32 base-pair deletion in CCR5 gene) impairs CCR5 expression on the cell surface and is associated with protection against HIV infection in homozygous individuals. Also, the genetic variant CCR5Δ32 modifies the CCR5-mediated inflammatory responses in various conditions, such as inflammatory and infectious diseases. CCR5 antagonists mimic, at least in part, the natural effects of the CCR5Δ32 in humans, which explains the growing interest in the potential benefits of using CCR5 modulators for the treatment of different diseases. Nevertheless, beyond HIV infection, understanding the effects of the CCR5Δ32 variant in multiple viral infections is essential to shed light on the potential effects of the CCR5 modulators from a broader perspective. In this context, this review discusses the involvement of CCR5 and the effects of the CCR5Δ32 in human infections caused by the following pathogens: West Nile virus, Influenza virus, Human papillomavirus, Hepatitis B virus, Hepatitis C virus, Poliovirus, Dengue virus, Human cytomegalovirus, Crimean-Congo hemorrhagic fever virus, Enterovirus, Japanese encephalitis virus, and Hantavirus. Subsequently, this review addresses the impacts of CCR5 gene editing and CCR5 modulation on health and viral diseases. Also, this article connects recent findings regarding extracellular vesicles (e.g., exosomes), viruses, and CCR5. Neglected and emerging topics in “CCR5 research” are briefly described, with focus on Rocio virus, Zika virus, Epstein-Barr virus, and Rhinovirus. Finally, the potential influence of CCR5 on the immune responses to coronaviruses is discussed.

1. Introduction

Inflammatory cells play a crucial role in protecting the host from viral infections. Leukocyte migration is a fundamental step of the inflammatory response to viruses, a process regulated by the interaction between chemokines and their receptors. Therefore, dysregulations in the chemokine-mediated inflammatory process may contribute to viral pathogenesis (Glass et al., 2003). The C-C chemokine receptor type 5 (CCR5) interacts primarily with the chemokines CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES), which act as CCR5 agonists by stimulating cell migration and mediating

inflammatory responses. On the other hand, the chemokine MCP-3/CCL7 is the main CCR5 antagonist ligand (Blanpain et al., 1999; Zlotnik and Yoshie, 2000; Glass et al., 2003; Alkhatib, 2009).

In addition to regulating the migration of non-specific leukocytes during inflammatory responses, CCR5 controls the action of specific cell types, including natural killer (NK) cells (Khan et al., 2006; Weiss et al., 2011) and regulatory T (Treg) cells (Wysocki et al., 2005; Tan et al., 2009; Dobaczewski et al., 2010). CCR5 is also expressed by tissue-resident memory T cells. These CCR5⁺ cells support barrier immunity (Davis et al., 2019).

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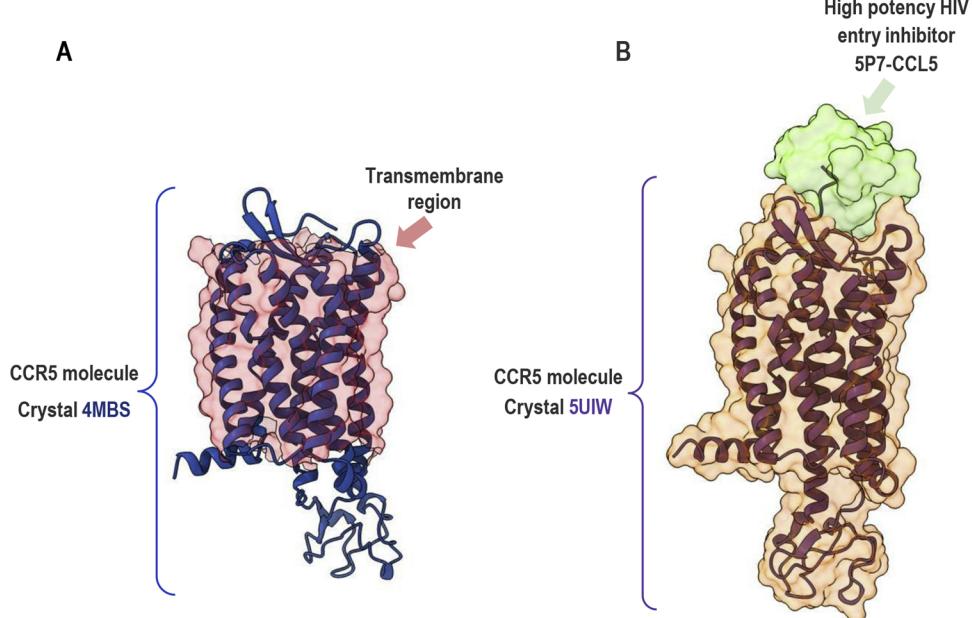


Fig. 1. Crystal structure of CCR5. Crystal structure of CCR5 from RCSB PDB data bank (<https://www.rcsb.org/>) presented with ChimeraX molecular visualization program. A) 4MBS (CCR5, resolution 2.71 Angstroms) molecule, without contact with any ligand/inhibitor, display of the entire domain is shown in cartoon mode and colored in blue. The surface with transparency in red highlights only transmembrane regions of CCR5. B) 5UIW (CCR5 in complex with high potency HIV entry inhibitor 5P7 – CCL5, resolution 2.20 Angstroms) molecule display of the entire domain is shown in cartoon mode and colored in purple. The surface with transparency (colored in orange) emphasizes subtle changes in the spatial conformation of the molecule when in contact with the inhibitor colored in green. Crystallography: Tan et al. (2013) for 4MBS and Zheng et al. (2017) for 5UIW.

The CCR5 is a G-protein-coupled receptor (GPCR), containing seven transmembrane α -helices, three extracellular loops, and three intracellular loops (Tan et al., 2013). Fig. 1 shows the structure of CCR5, highlighting its transmembrane domains and extra and intracellular loops. The specificity of interaction between CCR5 and chemokines is mediated by the second extracellular loop (Samson et al., 1997). Helices 2 and 3 have a fundamental role in chemokine-induced CCR5 activation (Govaerts et al., 2003). The steps required from ligand binding culminating in cell migration encompass a series of intracellular interactions, including the G-protein heterotrimer and downstream effectors (Lacalle et al., 2017). After stimulation by chemokines or natural reactive antibodies and subsequent triggering of chemotaxis, CCR5 is phosphorylated and internalized in the cytoplasm (Signoret et al., 2000; Venuti et al., 2015, 2016; Lacalle et al., 2017; Venuti et al., 2017, 2018).

The number of available receptors on the cell surface is related to the rate of internalization and recycling of CCR5, which affects the activation of CCR5 and consequent signaling of specific pathways that culminate in chemotaxis processes (Mueller et al., 2002). Of note, intracellular pools of CCR5 can be detected in the cells. These pools are probably formed by internalized or immature/precursor forms of CCR5 molecules (Mirzabekov et al., 1999; Kohlmeier et al., 2008; Achour et al., 2009; Guglielmi et al., 2011; Shirvani et al., 2011) that can be rapidly expressed on the cell surface in response to viral stimuli and inflammatory responses (Kohlmeier et al., 2008). In other words, CCR5 molecules are recycled by cells. Specifically, CCR5 recycling can be mediated by degradation followed by *de novo* synthesis (in response to stimulation by natural antibodies) or occur in the classic short-term system without *de novo* synthesis (in response to stimulation by CCL5, for example) (Venuti et al., 2015, 2016). The traffic of CCR5 between the plasma membrane and the intracellular medium is mediated by different molecules, including clathrins, β -arrestin 2, and extracellular signal-regulated kinase (ERK) 1 (Venuti et al., 2015, 2016; Venuti et al., 2018). Also, intracellular CD4 regulates the expression of CCR5 on the cell surface (Achour et al., 2009).

The human CCR5 protein (352 residues) is encoded by the *CCR5* gene [Chromosome 3 (3p.21.31)], which is very polymorphic (Blanpain et al., 2000; Hoover, 2018). Among polymorphisms of the *CCR5*, the *CCR5Δ32* (rs333) has been intensively studied in different human populations. The frequency of the *CCR5Δ32* is quite variable. In general, the $\Delta 32$ allele frequency is high in European-derived populations (for

example, 16 % in Norway and 11 % in Germany) and low or absent in African and Asian populations (Solloch et al., 2017). However, although the $\Delta 32$ allele is more frequent in European populations, there are exceptions due to migratory events. For example, the frequency of the $\Delta 32$ allele is high in South Africa (13 %) and Chile (12 %) (Solloch et al., 2017). Also, the frequency of the $\Delta 32$ allele can be quite variable within the same country. In Brazil, the frequency of the allele in the general population is around 4–5 % (Silva-Carvalho et al., 2016; Solloch et al., 2017). In the southern region of the country, the frequency can reach up to 9 % due to the past migration of European populations to this region (Boldt et al., 2009; Pena et al., 2011; Schauren et al., 2013). Fig. 2 summarizes basic aspects of CCR5 and shows the frequency of the $\Delta 32$ allele in various countries.

The *CCR5Δ32* is the most studied genetic variant of the *CCR5* gene because of its strong protective effect against HIV infection (considering susceptibility to CCR5-tropic strains). HIV entry into $CD4^+$ T cells is mediated by the interaction of the virus with CD4 and with a co-receptor, usually CCR5. The *CCR5Δ32* variant is a 32 base-pair deletion in the *CCR5* coding region, which causes a frameshift, resulting in a truncated protein that is not directed to the cell surface. *CCR5Δ32* in heterozygosity promotes a decrease in the expression of functional CCR5 on the cell surface compared to *CCR5* wild-type cells. Therefore, individuals with heterozygous genotype for *CCR5Δ32*, if infected with HIV, have a small protection against disease progression due to the reduced expression of CCR5 on the surface of $CD4^+$ T cells (reduced HIV – CCR5 interaction). In *CCR5Δ32* homozygous cells, no CCR5 is expressed in the plasmatic membrane. Therefore, homozygous individuals for this polymorphism ($\Delta 32/\Delta 32$) show virtually total protection against HIV type 1 infection, since no CCR5 expression is verified on cell surface (no HIV – CCR5 interaction at cell surface is possible) (Deng et al., 1996; Dragic et al., 1996; Huang et al., 1996; Samson et al., 1996; Wu et al., 1997; Proudfoot, 2002; Venkatesan et al., 2002; Picton et al., 2012). Fig. 3 illustrates the phenotypic effects of *CCR5Δ32* in human cells.

The main results involving the triad “*CCR5*, HIV, and *CCR5Δ32*” were published in 1996 in *Nature*, *Cell* and *Science* papers by different groups (Parmentier, 2015). Since then, the research involving CCR5 has explored the role of the CCR5 protein and *CCR5Δ32* polymorphism in different diseases, as well as the therapeutic potentials of CCR5 blockade. Currently, the physical interaction of CCR5 with HIV is known in detail (Shaik et al., 2019) and the research involving the

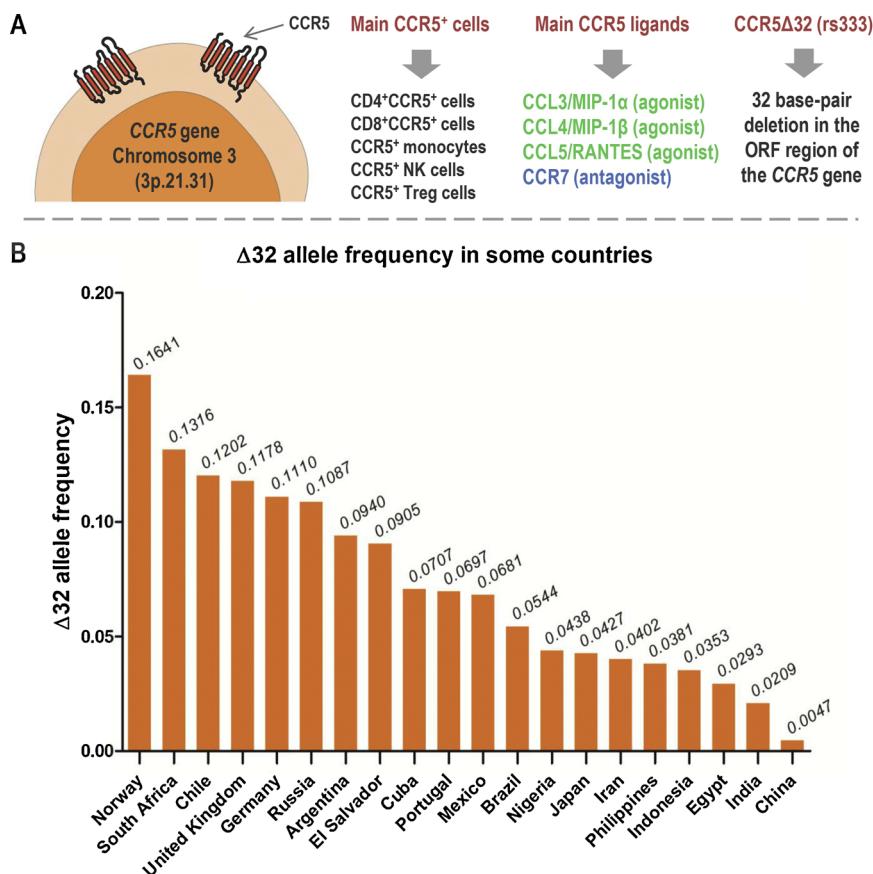


Fig. 2. Fundamental aspects of CCR5 (panel A) and frequency of the Δ32 allele in selected countries (panel B). This figure was created using Servier Medical Art illustrations (available at <https://smart.servier.com>, under a Creative Commons Attribution 3.0 Unported License). The bar chart was plotted using GraphPad Prism 5.01 software (GraphPad Software, Inc., San Diego, CA, USA). The Δ32 allele frequencies were obtained from Solloch et al. (2017).

impacts of CCR5Δ32 on HIV infection has led to the development of CCR5 antagonists: quite effective drugs used in the treatment of HIV-infected individuals, especially the licensed drug Maraviroc (Pfizer, Inc.), an allosteric modulator approved for clinical use in 2007 (Van Der Ryst, 2015; Latinovic et al., 2019). Also, a recent study has shown that molecules that inhibit CCR5 trafficking to the plasma membrane also have a therapeutic potential against HIV infection (Boncompain et al., 2019). Research involving CCR5 has also brought other important advances in combating HIV infection. Of note, there are already two cases of sustained remission of HIV infection following stem-cell transplantation using CCR5Δ32 homozygous donor, the “Berlin Patient” (Hütter et al., 2009) and the “London Patient” (Gupta et al., 2019, 2020). Fig. 4 summarizes the effects of CCR5Δ32 (homozygous genotype) on HIV infection and the main achievements of the research involving CCR5 and HIV infection.

Beyond the effects of CCR5/CCR5Δ32 on HIV infection, CCR5Δ32 impacts non-viral infectious diseases (Ungvári et al., 2007; Salnikova et al., 2013) and inflammation-related conditions (Chies and Nardi, 2001; Balistreri et al., 2009; Muntinghe et al., 2012; Kaminski et al., 2019a; Kulmann-Leal et al., 2020). Therefore, both the CCR5 molecule *per se* as well as the CCR5Δ32 variant, through the interference on the interaction of CCR5 with its ligands, may impact CCR5-mediated anti-viral cellular activity and inflammatory reactions during host response against pathogens. Indeed, the CCL5 – CCR5 axis influences virus-associated immune responses (Tyner et al., 2005; Grayson et al., 2007; Chen et al., 2017). Although the effects of CCR5Δ32 on CCR5 expression are clear, CCR5 and CCR5Δ32 have varied and even contrasting roles in different diseases. Due to interactions with other genetic variants as well as with environmental factors, the role of CCR5Δ32 may differ even within the same disease, depending on the ethnic group or population assessed (Rautenbach and Williams, 2020). Studying the involvement of CCR5 and the effects of CCR5Δ32 on infectious diseases may contribute to the understanding of the genetic factors involved in

the susceptibility and progression of multiple viral diseases. Also, these studies can shed light on the use of CCR5 modulators/blockers in a broader perspective, beyond HIV infection. In this context, the aim of this review is to discuss the involvement of CCR5 and the effects of the CCR5Δ32 in human viral infections, covering West Nile virus, Influenza viruses, Human papillomavirus, Hepatitis B virus, Hepatitis C virus, Poliovirus, Dengue virus, Human cytomegalovirus, Crimean-Congo hemorrhagic fever virus, Enterovirus, Japanese encephalitis virus, and Hantavirus. This review also addresses the impacts of CCR5 gene editing and the CCR5 modulation on health and viral diseases. Recently, the role of extracellular vesicles has brought complexity to the fields of both immunology and virology. Therefore, this article connects recent findings regarding extracellular vesicles, viruses, and CCR5. In the last part of the review, neglected and emerging topics in “CCR5 research” are briefly discussed, with a focus on Rocio virus, Zika virus, Epstein-Barr virus, and Rhinovirus.

Studies involving HIV will not be included in this article because different aspects of the relationship between HIV and CCR5/CCR5Δ32 are well established and have already been intensely explored in different reviews (Allen et al., 2018; Breton and Chakrabarti, 2018; Ndung'u et al., 2019). Also, the impacts of CCR5 and CCR5Δ32 on tick-borne encephalitis virus (TBEV) infection will not be addressed in this article because our group has recently reviewed these topics in a recent publication (Ellwanger and Chies, 2019a).

2. Methodological notes

This article is characterized as a narrative review. The selection of the articles was carried out from an initial search on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), using the terms “CCR5”, “CCR5Δ32”, “virus”, “viral infection”, “exosomes”, and “extracellular vesicles” (separately and in association). After extensive analysis of article abstracts, it was established that the review would address the following viruses:

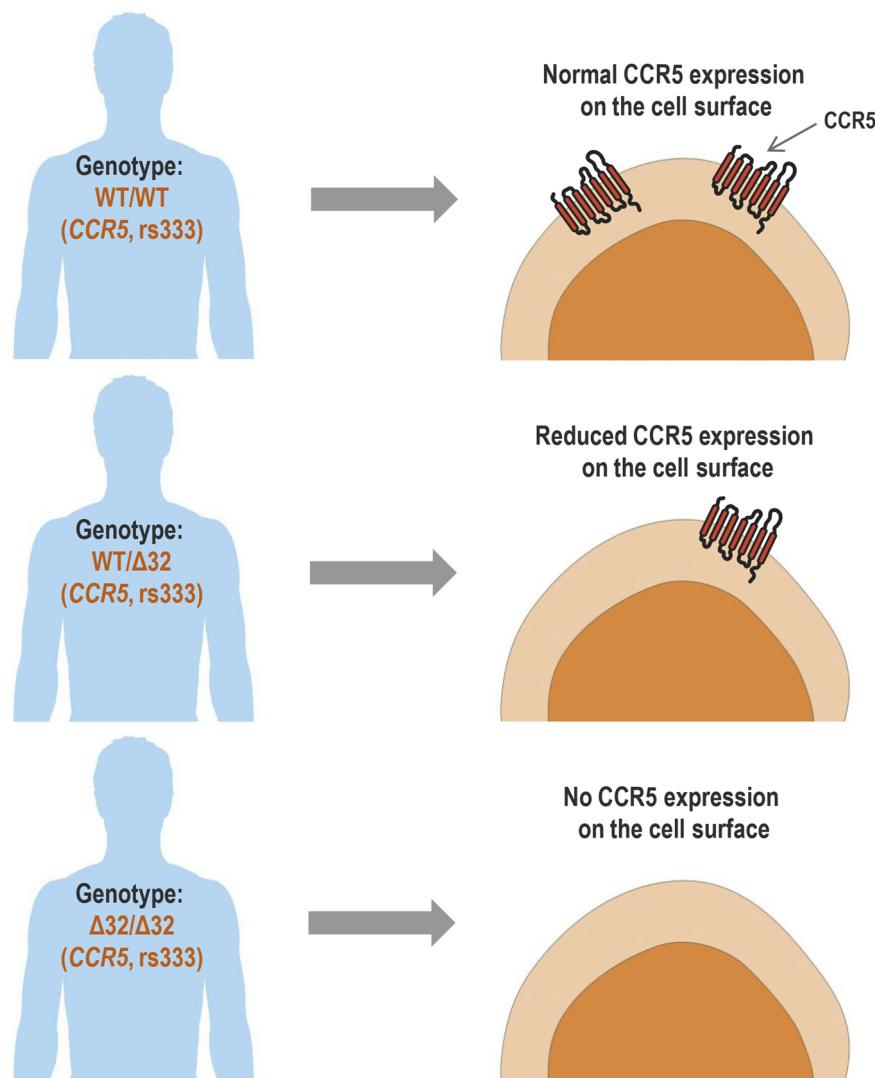


Fig. 3. Phenotypic effects of the polymorphism CCR5Δ32 in human cells. WT/WT: wild-type homozygous genotype. WT/Δ32: heterozygous genotype. Δ32/Δ32: variant homozygous genotype. This figure was created using Servier Medical Art illustrations (available at <https://smart.servier.com>, under a Creative Commons Attribution 3.0 Unported License).

West Nile virus, Influenza viruses, Human papillomavirus, Hepatitis B virus, Hepatitis C virus, Poliovirus, Dengue virus, Human cytomegalovirus, Crimean-Congo hemorrhagic fever virus, Enterovirus, Japanese encephalitis virus, Hantavirus, Rocio virus, Zika virus, Epstein-Barr virus, and Rhinovirus. All original articles that evaluated the involvement of CCR5 or CCR5Δ32 in the infections caused by the mentioned viruses were analyzed. Subsequently, the Google Scholar (<https://scholar.google.com.br/>) was consulted to detect relevant papers that were not indexed in PubMed, using the terms “CCR5” in association with the name of each of the viruses covered in the review. The authors of this review tried to include the largest number of original articles that addressed the topic covered in this work, intending to write a broad and complete article. However, some papers were not included because it was not possible to obtain clear conclusions from the studies. The reference lists of the consulted articles were also used to complement the selection of articles for this review.

As previously mentioned in the introduction, a discussion addressing the involvement of CCR5 in TBEV infection was not included in this work. Articles addressing the involvement of CCR5 and CCR5Δ32 in HIV infection were included only to present to the reader some basic and historical aspects related to such topics, cited mainly in the introduction section and figures, but not included as a major section of

the article. Considering the importance of the coronavirus disease 19 (COVID-19) pandemic, a section addressing the potential influence of CCR5 on the immune responses to coronaviruses was included in this article. Review articles were also selected in PubMed and Google Scholar for writing the sections and paragraphs that address the basic aspects of viruses, exosomes, and diseases (e.g., epidemiological, molecular, clinical aspects). Exceptionally, review articles with outstanding discussions regarding the role of CCR5 in viral infections were also cited in this work. Regarding tables, it is important to note that the data available in the “Population” columns are limited and often represent only general characteristics of the evaluated population. In many studies, a population can be composed of individuals from various ethnic groups. This limitation must be taken into account when evaluating the results of the studies cited in the tables. Finally, also in “Population” columns, “information not available” was used when this information was not clearly described in the cited article.

3. CCR5Δ32 and viral infections

3.1. West Nile virus

West Nile virus (WNV) is a neurotropic positive-sense single-

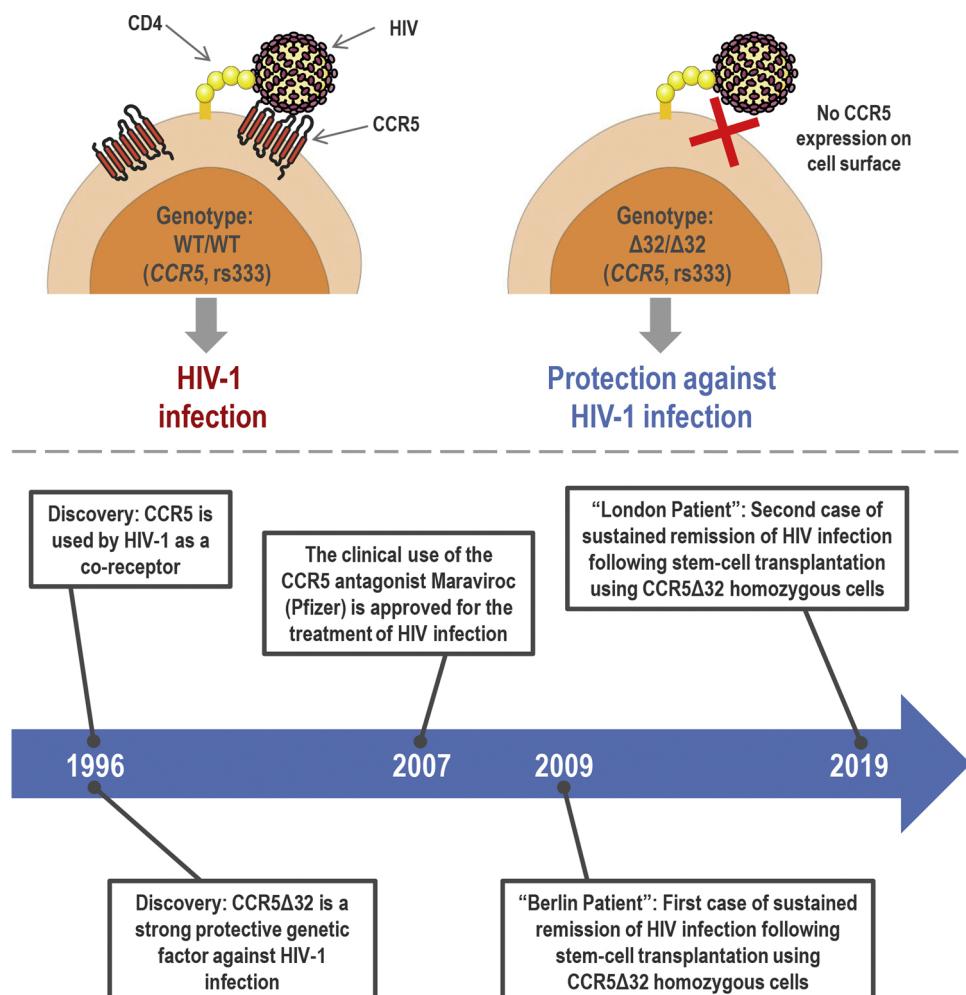


Fig. 4. Effects of the CCR5 Δ 32 (homozygous genotype) on HIV infection (upper panel) and the main achievements of the research involving CCR5 and HIV infection (bottom panel). This figure was created using Servier Medical Art illustrations (available at <https://smart.servier.com>, under a Creative Commons Attribution 3.0 Unported License).

stranded RNA flavivirus endemic in various parts of the world. WNV transmission to humans occurs through the bite of infected mosquitoes, especially species of the *Culex* genus (Suthar et al., 2013). Although different animals can participate in the WNV transmission cycle, birds are the classic amplifier hosts. Humans, horses and other mammals are dead-end hosts (Kramer et al., 2008; CDC, 2018). Among humans, blood transfusion, organ transplantation, and breast milk can also transmit the virus. Vertical transmission may also occur. However, compared to transmission by mosquito bites, these routes of transmission are rare (Kramer et al., 2008).

About 25 % of WNV-infected individuals develop West Nile fever, a clinical condition with variable symptoms and severity. In less than 1% of the infected individuals, WNV invades the central nervous system (CNS), causing neurological manifestations (neuroinvasive disease), including meningitis, encephalitis, and acute flaccid paralysis. Of note, West Nile neuroinvasive disease shows a 10%–20% fatality rate. Severe illness is associated with older age and other factors, including genetic traces (Petersen et al., 2013; Sejvar, 2016). WNV infection is considered the leading cause of arboviral encephalitis in the world (Ciota, 2017). The treatment of WNV infection is supportive (Petersen et al., 2013).

It is known that the CCR5 protein interferes in the clinical course of WNV infection (Glass et al., 2005; Diamond, 2009; Michlmayr and Lim, 2014), but the effects of CCR5 Δ 32 on the susceptibility to this infection and disease progression are different. According to Lim et al. (2010) and Danial-Farran et al. (2015), CCR5 Δ 32 has no important effect on

susceptibility to WNV infection. In accordance, Loeb et al. (2011) found no association between CCR5 Δ 32 and WNV infection. Conversely, there is robust population-based data showing a strong association between the CCR5 Δ 32 homozygous genotype and increased risk of developing symptomatic WNV infection (Glass et al., 2006; Lim et al., 2008, 2010). Also, Bigham et al. (2011) showed that the CCR5 Δ 32 variant was associated with symptomatic WNV infection when the dominant model of inheritance was considered in the analysis. A recent meta-analysis confirmed the role of the CCR5 gene in WNV infection, specifically the association between the CCR5 Δ 32 with severe disease (Cahill et al., 2018). Table 1 summarizes the results of the studies that evaluated the CCR5 Δ 32 genetic variant in the context of human WNV infection.

In agreement with studies showing that CCR5 Δ 32 homozygous genotype is a risk factor for symptomatic WNV infection in humans, *Ccr5* $^{-/-}$ WNV-infected mice showed a reduced capacity of viral control, increased disease severity, impaired leukocyte trafficking towards the brain, and high mortality rates than *Ccr5* wild-type mice. These findings reinforce that *Ccr5* is a key molecule in the immune response against WNV (Glass et al., 2005; Durrant et al., 2015). Taking together, these pieces of evidence robustly support the role of CCR5 as a protective molecule on WNV pathogenesis. Specifically, CCR5 $^{+}$ leukocytes play a fundamental role in combating WNV in the brain (Glass et al., 2005; Lim et al., 2006; Michlmayr and Lim, 2014; Durrant et al., 2015). In this sense, CCR5 plays a specific and non-redundant role in controlling WNV infection (Lim and Murphy, 2011; Durrant et al., 2015; Ellwanger et al., 2020a).

Table 1
Impacts of CCR5 Δ 32 on West Nile virus (WNV) infection.

Population	Sample	Main findings	References
American	395 symptomatic WNV + individuals; 145 symptomatic but non-infected individuals; 1318 controls (blood donors)	The CCR5 Δ 32 homozygous genotype was strongly associated with increased risk of symptomatic WNV infection	Glass et al. (2006)
American	224 symptomatic WNV + individuals; 1318 controls (blood donors)	Corroborating data from Glass et al. (2006), the CCR5 Δ 32 homozygous genotype was strongly associated with increased risk of symptomatic WNV infection	Lim et al. (2008)
American	634 WNV + individuals; 422 non-infected individuals	CCR5 Δ 32 homozygous genotype was associated with clinical symptoms of WNV infection; No association between CCR5 Δ 32 and susceptibility to WNV infection	Lim et al. (2010)
American, Canadian	385 symptomatic WNV + individuals; 328 asymptomatic WNV + individuals; 1318 controls [blood donors from Glass et al. (2006)]	No association of CCR5 Δ 32 and WNV infection considering symptomatic and asymptomatic WNV + individuals; Considering a dominant model of inheritance of CCR5 Δ 32 and using controls from Glass et al. (2006), the CCR5 Δ 32 was associated with symptomatic WNV infection and infection risk	Bigham et al. (2011)
American, Canadian	821 WNV + individuals with severe infection; 1233 individuals with non-severe infection	No association between CCR5 Δ 32 and WNV infection severity	Loeb et al. (2011)
Israeli (Ashkenazi Jews)	39 symptomatic WNV + individuals; 61 non-infected individuals	No association between CCR5 Δ 32 and WNV infection	Danial-Farran et al. (2015)

Based on the data mentioned above, the lack of CCR5 expression linked to CCR5 Δ 32 homozygosity is an important risk factor for increased severity of WNV-associated disease. The opposite effects of the CCR5 Δ 32 genetic variant on both HIV and WNV infections are summarized in Fig. 5. Hereupon, individuals homozygous for CCR5 Δ 32 and living in endemic areas of the WNV should take additional care to prevent WNV infection (e.g., use of repellents, mosquito nets). Also, the use of CCR5 blockers to treat HIV infection may have a negative impact on populations living in WNV-endemic areas. To avoid this negative impact, HIV-infected individuals who live in such areas and who use CCR5 blockers must apply robust measures against mosquito bites (Glass et al., 2006; Lim et al., 2006; Lim and Murphy, 2011).

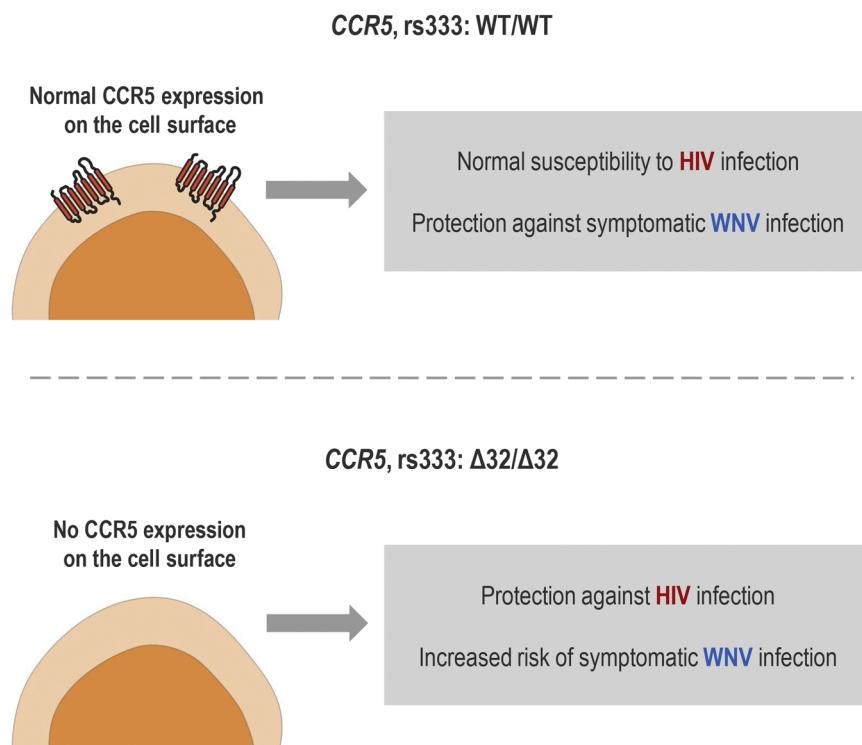
3.2. Influenza virus

Influenza infection affects humans seasonally, causing recurrent epidemics and even pandemics in some years. In humans, the infection

is caused basically by influenza A and influenza B, both enveloped negative-sense single-stranded RNA viruses belonging to *Orthomyxoviridae* family (Krammer et al., 2018; Petrova and Russell, 2018). Influenza A is a zoonotic disease, and influenza B circulates primarily in humans. Influenza infection affects mainly the respiratory tract, which can cause mild to severe disease depending on viral and host characteristics. Secondary bacterial infection may also occur (Krammer et al., 2018). Human co-infection with multiple influenza types is an important neglected problem (Gregianini et al., 2019). Influenza is a prevalent infection worldwide, and new vaccines are produced annually, based on strains circulating each year in the Northern and Southern hemispheres (Krammer et al., 2018; Petrova and Russell, 2018). Antivirals can be used in the treatment of influenza infection (Krammer et al., 2018). Investments in new vaccines, antiviral drugs, and surveillance systems are needed to reduce the global burden associated with influenza infection (Petrova and Russell, 2018).

The severity of influenza infection is related to the intensity of

Fig. 5. Effects of the polymorphism CCR5 Δ 32 on HIV and WNV infections. Upper panel: effects observed in individuals with the wild-type homozygous genotype (WT/WT). Bottom panel: effects observed in individuals with the homozygous genotype variant (Δ 32/ Δ 32). This figure was created using Servier Medical Art illustrations (available at <https://smart.servier.com>, under a Creative Commons Attribution 3.0 Unported License).



proinflammatory responses and the predominant profile of cytokine production by the host (Liu et al., 2016). A body of evidence has shown that both CCL5 and CCR5 participate in the modulation of the immune response to influenza virus infection (Matsukura et al., 1998; Tyner et al., 2005; Sládková and Kostolanský, 2006; Kohlmeier et al., 2008; Oslund and Baumgarth, 2011). Of note, CCR5 mediates the recruitment of NK cells to the lungs in influenza A infection (Carlin et al., 2018) and participates in neutrophil action in the lungs during influenza pneumonia (Rudd et al., 2019).

Although flow cytometry data did not indicate significant changes regarding CCR5 expression on the surface of human monocytes after experimental influenza A infection (Salentin et al., 2003), various studies have shown that, in mice, the lack of CCR5 expression is associated with a higher risk of death by influenza infection (Dawson et al., 2000; Tyner et al., 2005; Fadel et al., 2008; Tavares et al., 2020). Based on these findings, it was postulated that pharmacological CCR5 blockade may have some undesirable effect on the immune response against the influenza virus in humans (Fadel et al., 2008). Importantly, more research on this aspect is needed since this data suggests that, in humans, the CCR5 absence due to the CCR5Δ32 polymorphism could affect pathogenesis and the lethality rate of influenza infection.

Falcon et al. (2015) evaluated the frequency of the CCR5Δ32 in pandemic H1N1-infected Spanish individuals and revealed an association between the polymorphism with fatal outcome. The CCR5Δ32 was also associated with increased disease severity in other studies (Keynan et al., 2010; Rodriguez et al., 2013). However, these results should be interpreted with caution since both studies were based on very small sample sizes (Keynan et al., 2010; Rodriguez et al., 2013). Importantly, other studies addressing humans reported no association between CCR5Δ32 and severity of influenza infection (Sironi et al., 2014; Maestri et al., 2015; Matos et al., 2019). Taking together, the body of evidence suggests that CCR5Δ32 has little influence on severity of influenza infection (Table 2). Results described by Falcon et al. (2015) seem to be specific to that studied population, composed of individuals from 13 regions of Spain.

3.3. Human papillomavirus

Human papillomavirus (HPV) is a double-stranded DNA virus belonging to the papillomavirus family. HPV is transmitted by direct contact (for example, through sexual intercourse). The HPV infection is quite common worldwide, and is usually controlled by the immune system. Viral clearance occurs in most cases within 1–2 years after infection. However, if the infection is not controlled, HPV can cause non-cancerous mucosal lesions or different types of malignant lesions such as anal cancer, penile cancer, vulvar cancer, head cancer, neck cancer, and especially cervical cancer. HPV is an oncogenic pathogen because it inhibits the activity of p53 and Prb (retinoblastoma protein) tumor suppressor molecules through the action of E6 and E7 viral proteins, respectively. These proteins also exhibit other oncogenic mechanisms.

Table 2
Impacts of CCR5Δ32 on Influenza virus infection.

Population	Sample	Main findings	References
Canadian	20 individuals infected with 2009 pandemic H1N1	The CCR5Δ32 allele was considered a risk factor for severe infection among Caucasian individuals	Keynan et al. (2010)
Spanish	1 fatal case and 1 mild disease case (2009 pandemic H1N1)	The patient who died from the infection had CCR5Δ32 homozygous genotype	Rodriguez et al. (2013)
Mostly European	29 individuals (27 Italian; 1 Spanish; 1 Chinese) infected with 2009 pandemic H1N1	No association between the CCR5Δ32 and H1N1 infection	Sironi et al. (2014)
Spanish	171 individuals infected with 2009 pandemic H1N1	The CCR5Δ32 was associated with increased risk for fatal outcome	Falcon et al. (2015)
Brazilian	156 infected/hospitalized individuals; 174 infected (mild symptoms) but non-hospitalized individuals (2009 pandemic Influenza A H1N1)	No association between the CCR5Δ32 and H1N1 infection severity	Maestri et al. (2015)
Brazilian	153 influenza-like illness cases; 173 severe acute respiratory infection cases; 106 fatal cases (2009 pandemic H1N1)	No association between the CCR5Δ32 and H1N1 infection severity or mortality	Matos et al. (2019)

Worldwide, between 5–10 % of all cancers in women are due to HPV infection (Schiffman et al., 2016; Sanjosé et al., 2018). There are several HPV genotypes (> 200), and those most associated with cancer are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and probably 68 (Schiffman et al., 2016). Of note, the genotype 16 (HPV16) has a prominent role in cancer development. Vaccination is one of the most effective ways to prevent HPV infection, having important positive impacts on multiple aspects of population health. HPV vaccine protects the vaccinated individual from infection *per se* and from HPV-related cancer (Schiffman et al., 2016; Sanjosé et al., 2018).

The expression of CCR5 is increased in cervical cancer tissues (Sales et al., 2014; Che et al., 2016). Also, *in vitro* growth, proliferation, and invasive capacity of cervical cancer cells can be inhibited through CCR5 downregulation (Che et al., 2016). These findings suggest the involvement of CCR5 in the development of cervical lesions. In a study performed with Indian individuals (Singh et al., 2008), the genotype and allele frequencies of CCR5Δ32 were not different between cervical cancer patients and controls. However, when the patients were stratified by cancer stage (stages 1B to 4), the CCR5 heterozygous genotype was associated with stage 1B of cervical cancer. The HPV positivity rate among the evaluated patients was not described (Singh et al., 2008).

The relationship between CCR5Δ32, HPV infection, and cervical lesions is addressed in other studies (Table 3). CCR5Δ32 homozygous genotype was associated with increased susceptibility to HPV infection in a study performed with Swedish individuals (Zheng et al., 2006). Mangieri et al. (2019) investigated the potential influence of CCR5Δ32 on susceptibility to HPV infection and cervical lesions in Brazilian women. However, the genetic variant was not significantly associated with susceptibility to HPV infection (considering allele frequency, co-dominant model and dominant model) or HPV-associated lesions (Mangieri et al., 2019). In accordance, previous studies performed with Brazilian women did not find an association between CCR5Δ32 and susceptibility to HPV infection (Suzuki et al., 2008) or between the polymorphism and HPV-related cervical lesions (Suzuki et al., 2008; Santos et al., 2016). Lastly, CCR5Δ32 did not affect susceptibility to HPV infection in Lithuanian individuals with laryngeal cancer (Stumbrytė-Kaminskiene et al., 2020). In conclusion, although tissue analysis and evidence obtained *in vitro* suggest that the CCR5 is potentially involved in the pathogenesis of HPV, most studies point to a lack of involvement of CCR5Δ32 in susceptibility to HPV infection or HPV-associated diseases.

3.4. Hepatitis B virus

The Hepatitis B virus (HBV) is a hepatotropic DNA virus member of the *Hepadnaviridae* family. In adults, approximately 95 % of HBV infections are resolved naturally (viral clearance). Individuals who have not cleared the virus after acute infection become chronic HBV carriers. Of note, chronic HBV infection affects 3.5 % of the world population. A portion of individuals who develop chronic infection have a variety of

Table 3

Impacts of CCR5Δ32 on Human papillomavirus (HPV) infection.

Population	Sample	Main findings	References
Swedish	126 HPV-infected individuals; 173 non-infected individuals	CCR5Δ32 homozygous genotype was associated with increased risk of HPV infection	Zheng et al. (2006)
Brazilian	74 HPV-infected individuals; 43 non-infected individuals	No association between CCR5Δ32 and HPV infection; No association between CCR5Δ32 and HPV-related cancer	Suzuki et al. (2008)
Brazilian	139 HPV-infected individuals with cervical intraepithelial neoplasia or cervical cancer; 151 HPV-infected individuals without cervical lesions	No association between CCR5Δ32 and HPV-related lesions; No association between CCR5Δ32 and HPV genotypes	Santos et al. (2016)
Brazilian	164 HPV-infected individuals; 185 non-infected individuals	No statistically significant effect of CCR5Δ32 on susceptibility to HPV infection or HPV-related cervical lesions (low-grade squamous intraepithelial lesion or high-grade squamous intraepithelial lesion)	Mangieri et al. (2019)
Lithuanian	49 laryngeal squamous cell carcinoma patients (21 HPV-infected patients and 28 non-infected patients)	No statistically significant effect of CCR5Δ32 on susceptibility to HPV infection, clinical-pathological characteristics or surviving rates	Stumbrytė-Kaminskienė et al. (2020)

liver diseases: different levels of inflammation and fibrosis, cirrhosis, and cancer. The outcome of the infection (acute or chronic) as well as the course of liver diseases, depends on the interaction between host and viral factors. The pharmacological therapies available to treat HBV are not satisfactory, since frequently the infection is only controlled, and cure is rarely achieved. There is, therefore, a need to develop new anti-HBV therapies. Currently, HBV infection can be prevented through vaccination (Yuen et al., 2018; Lang et al., 2019; Lee and Banini, 2019).

The CCR5 and its ligands regulate the action of T cells and other leukocytes in the liver. Thus, CCR5 regulates liver inflammation and participates in the local immune response against viruses (Ajuebor et al., 2006; Sanchooli et al., 2014). In mice models of hepatitis, CCR5 deficiency was associated with increased liver inflammation, tissue injury, and liver failure (Ajuebor et al., 2005; Moreno et al., 2005; Stevens et al., 2019). Deficiency of CCR5 expression is generally associated with reduced migration of inflammatory cells, which would translate into less inflammation. This reasoning is correct and applies to different situations and tissues (Braunersreuther et al., 2007; Muntinghe et al., 2009; Kaminski et al., 2019a). However, CCR5 is an immunoregulatory molecule (Doodes et al., 2009; Dobaczewski et al., 2010; Christmann et al., 2011; Hütter et al., 2011) and therefore its deficiency can also cause deregulation in the action of various immune cell types (e.g., NK and Treg cells), increasing the inflammatory status in some tissues. In humans, multiple evidence has shown the involvement of CCR5 (protein and gene) in distinct aspects of HBV infection (Ahn et al., 2006; TrehanPati et al., 2009; Ahmadabadi et al., 2013; Yang et al., 2018). Interestingly, CCR5Δ32 and other host genetic factors can affect the immunogenicity of the HBV vaccine (Ganczak et al., 2017; Ellwanger and Chies, 2019b). Considering these aspects, the influence of the CCR5Δ32 on susceptibility/resistance to HBV and disease severity is quite plausible.

Several studies investigated the role of the CCR5Δ32 polymorphism in HBV infection. Some of them found no association between those variables (Arababadi et al., 2010; Khorramdelazad et al., 2013; Safari et al., 2017; Zhang et al., 2018; Moudi et al., 2019). In other studies, the absence of CCR5Δ32 allele in the sample, due to ethnic features of the evaluated population, precluded the analysis concerning the potential impact of this genetic variant on HBV infection (Ahn et al., 2006; Li et al., 2011).

Some authors have observed significant influences of CCR5Δ32 on HBV infection. Suneetha et al. (2006) reported an association between the CCR5Δ32 heterozygous genotype and chronic HBV infection. In contrast, Thio et al. (2007) found an association between the CCR5Δ32 allele and infection recovery in a study that analyzed individuals with persistent HBV infection and individuals who recovered from the infection. Subsequently, Thio et al. (2008) associated the HBV infection recovery with an epistatic effect between the CCR5Δ32 and the RANTES-403A promoter polymorphisms. Finally, Abdolmohammadi et al. (2016) found a protective effect of the CCR5Δ32 genetic variant

against HBV infection, once the Δ32 allele was more frequent in controls compared to HBV-infected individuals.

Recently, we investigated the frequency of CCR5Δ32 in HBV mono-infected and HBV/HIV co-infected Brazilian individuals (Ellwanger et al., 2020b). A control group and HIV mono-infected individuals were also evaluated in our study. A total of 1113 individuals were studied, which represents the largest study involving CCR5Δ32 and HBV infection to date (see Table 4 for comparisons with other studies). We found a significant protective effect of CCR5Δ32 on HBV/HIV co-infection, a result probably due to the partial protective effect of CCR5Δ32 against HIV infection since no important impact of CCR5Δ32 on susceptibility to HBV mono-infection was observed (Ellwanger et al., 2020b).

3.5. Hepatitis C virus

The Hepatitis C virus (HCV) was formally described in 1989 (Choo et al., 1989) and, currently, HCV infection is one of the most important infectious diseases in terms of global public health burden. HCV is an enveloped single-stranded positive-sense RNA virus, has seven genotypes, and belongs to the *Flaviviridae* family, *Hepacivirus* genus (Pietschmann and Brown, 2019). It is estimated that 71 million individuals are chronically infected by HCV worldwide (Viganò et al., 2019).

Similar to the HBV infection, HCV-infected individuals can eliminate the virus naturally or develop chronic infection, which occurs in 55–85 % of the cases. Chronic infection can cause liver inflammation, cirrhosis, and hepatocarcinoma (Lingala and Ghany, 2015). In addition to liver damage, HCV causes a series of immune-mediated extrahepatic manifestations, including rheumatologic, dermatologic, ophthalmologic, renal, pulmonary, neuropsychiatric, cardiovascular, and hematologic manifestations, especially mixed cryoglobulinemia (Romano et al., 2018). HCV therapy using direct-acting antivirals (DAAs) shows cure rates over 95 % (Pietschmann and Brown, 2019). Early treatment of infected patients decreases death rates from HCV-associated liver disease, reduces disease transmission, and alleviates extrahepatic health problems. Focusing the efforts on HCV treatment is extremely important because there is no effective HCV vaccine (Viganò et al., 2019).

HCV seropositivity is an important risk factor for HIV infection (Zwolinska et al., 2013). Like HIV, HCV is primarily transmitted through blood transfusion and sexual intercourse, and HCV/HIV co-infection is a major problem worldwide. Depression of the immune system due to uncontrolled HIV infection may contribute to HCV progression (Schlabe and Rockstroh, 2018). Both susceptibility to HCV infection and disease progression are affected by viral and environmental factors and physio-metabolic, immune, and genetic components of the host (Ellwanger et al., 2018a).

Infiltration of inflammatory cells in the hepatic tissue is a classic observation in HCV infection. Chemokines and chemokine receptors

Table 4
Impacts of CCR5Δ32 on HBV infection.

Population	Sample	Main findings	References
Korean	349 chronic HBV-infected individuals; 243 individuals with spontaneous recover; 106 non-infected individuals	The CCR5Δ32 allele was not found in any studied individual	Ahn et al. (2006)
Information not available	214 chronic HBV-infected individuals; 408 non-infected individuals	The CCR5Δ32 heterozygous genotype was associated with chronic HBV infection; The CCR5Δ32 wild-type allele was associated with severe liver disease when analyzed in combination with other genetic variants (a/a-T/T-Wt/Wt model from VDR-Apa1/Taq1/CCR5Δ32 polymorphisms)	Suneetha et al. (2006)
American	190 individuals with persistent HBV infection; 336 individuals with infection recover	The CCR5Δ32 allele was associated with recovery from the infection	Thio et al. (2007)
American	181 individuals with persistent HBV infection; 316 individuals with infection recover	Infection recovery was associated with an epistatic interaction between the CCR5Δ32 and the RANTES-403A polymorphism	Thio et al. (2008)
Iranian	57 individuals with occult HBV infection; 100 non-infected individuals	The CCR5Δ32 heterozygous genotype was found in 3 controls and no individuals with occult HBV infection carried the allele (small sample size study); No association between the CCR5Δ32 and occult HBV infection	Arababadi et al. (2010)
Chinese	185 individuals who underwent liver transplantation due to HBV-related disease	The CCR5Δ32 allele was not found in any studied individual	Li et al. (2011)
Iranian	60 chronic HBV-infected individuals; 60 non-infected individuals	The CCR5Δ32 heterozygous genotype was found in 3 controls and no infected individual carried the allele (small sample size study); No association between the CCR5Δ32 and HBV infection	Khorramdelazad et al. (2013)
Iranian	357 HBV-infected individuals; 455 non-infected individuals	The CCR5Δ32 was associated with protection against HBV infection	Abdolmohammadi et al. (2016)
Iranian	60 chronic HBV-infected individuals; 120 individuals with infection recover	The CCR5Δ32 heterozygous genotype was found in 1 individual with infection recover and no HBV-infected individual carried the allele (small sample size study); No association between the CCR5Δ32 and HBV infection	Safari et al. (2017)
Chinese	263 HBV-infected individuals; 141 non-infected individuals	No association between the CCR5Δ32 and HBV infection	Zhang et al. (2018)
Iranian	100 chronic HBV-infected individuals; 40 individuals with infection recover; 100 non-infected individuals	No association between the CCR5Δ32 (as an individual factor) and HBV infection; The WtAGCC haplotype (from CCR5Δ32, CCR5 – 2459A/G, MCP-1 – 2518A/G, VDR-APa1A/C and VDR-Taq1T/C polymorphisms, respectively) was associated with HBV infection	Moudi et al. (2019)
Brazilian	335 HBV mono-infected individuals; 144 HBV/HIV co-infected individuals; 300 HIV mono-infected individuals; 334 non-infected individuals	The CCR5Δ32 was a protective factor against HBV/HIV co-infection, but the CCR5Δ32 did not affect susceptibility or resistance to HBV mono-infection	Ellwanger et al. (2020b)

participate in the recruitment and activity of inflammatory cells in the liver, acting on anti-HCV immune responses and ultimately modifying the rate of inflammation and other histological manifestations observed during infection. Based on this rationale, the CCR5 molecule was postulated as having an impact on HCV-induced liver injury, susceptibility to HCV infection, and modulation of the possibilities of viral clearance. The downregulation of CCR5 due to CCR5Δ32 may interfere in these processes (Ahlenstiel et al., 2004; Coenen and Nattermann, 2010). In agreement, several polymorphisms in other immune system genes [especially human leukocyte antigen (HLA), mannose-binding lectin (MBL), toll-like receptor (TLR), interleukins (IL), and interferon (IFN) gene families] indeed modify both susceptibility to HCV infection and disease progression (Ellwanger et al., 2018a). Especially the focus of this review, clinical response to HCV therapy is influenced by CCR5 gene polymorphisms (Konishi et al., 2004; Omran et al., 2013). Also, there is evidence showing that CCR5 haplotypes can affect susceptibility to HCV infection (Huik et al., 2013).

A recent *in vitro* study suggested that CCR5 blockage could have a beneficial effect on the treatment of HCV infection since CCR5 antagonists (maraviroc and cenicriviroc) inhibit HCV replication (Blackard et al., 2019). The use of CCR5 antagonists in humans is safe (Fätkenheuer et al., 2010; Gulick et al., 2014; Giaquinto et al., 2018) and these drugs have the potential to treat a number of diseases in which CCR5 is involved, including HCV-associated liver disease. Although the use of CCR5 antagonists on HCV mono-infection is not yet approved, it can be useful specifically for co-infected HIV/HCV patients, where CCR5 blocking (maraviroc) is already recommended (Haïm-Boukobza et al., 2013; Blackard et al., 2019). However, the detailed patterns of CCR5 expression in different tissues and at various

points in the clinical course of HCV infection are still poorly understood. According to a recent study, the expression of CCR5 in CD8⁺ T cells is increased in the liver of chronic HCV-infected patients (Pirozyan et al., 2019), but other studies have found mixed results regarding CCR5 expression on T cells in the context of HCV infection (Lichterfeld et al., 2002; Vincent et al., 2005; Larrubia et al., 2007; Zahran et al., 2020). Therefore, considering that the role of CCR5 in HCV infection is still uncertain, the potential use of CCR5 blockers to treat HCV mono-infection should be cautious.

The influence of the CCR5Δ32 variant on HCV infection susceptibility was investigated by several studies. Woitas et al. (2002) found a significantly higher frequency of the CCR5Δ32 homozygous genotype in HCV-infected individuals compared to controls, HIV-infected and HIV/HCV co-infected individuals, suggesting the CCR5Δ32 as a risk factor for HCV infection. In agreement, the Δ32 allele was a significant risk factor for infection when the authors compared the HCV-infected group to both controls and HIV-infected individuals. Moreover, the CCR5Δ32 homozygous genotype was associated with increased HCV loads. In their study, it was observed an important deviation from the Hardy-Weinberg equilibrium in data from HCV-infected individuals; and a high portion of the individuals included in the study was hemophiliac (Woitas et al., 2002). Hemophiliac individuals were at high risk of exposure to HCV and HIV until the mid-1980s (Promrat et al., 2003; Zhang et al., 2003). Considering that the CCR5Δ32 homozygous genotype provides protection against HIV infection, a high frequency of this genotype in an HCV-infected group may be due to HIV resistance, but not to HCV, among individuals highly exposed to both viruses. Due to those and other reasons, the results of Woitas et al. (2002) were criticized by different authors (Klein, 2003; Mangia et al., 2003; Poljak

Table 5
Impacts of CCR5Δ32 on HCV infection.

Population	Sample	Main findings	References
German	153 HCV-infected individuals; 102 HIV-infected individuals; 130 HCV/HIV co-infected individuals; 102 non-infected individuals	The CCR5Δ32 polymorphism (Δ32 allele and homozygous genotype) was associated with increased susceptibility to HCV infection; The CCR5Δ32 homozygous genotype was associated with increased HCV loads	Woitas et al. (2002)
German	156 chronic HCV-infected individuals	The CCR5Δ32 allele was associated with reduced response rates to interferon- α monotherapy	Ahlensti et al. (2003)
Caucasian	62 chronic HCV-infected individuals; 119 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection, HCV-related liver disease or therapy response	Glas et al. (2003)
European	544 HCV-infected individuals with persistent infection; 128 individuals who cleared the virus (547 individuals were genotyped for CCR5Δ32)	The CCR5Δ32 polymorphism was associated with reduced portal inflammation and increased liver fibrosis	Hellier et al. (2003)
Information not available	235 chronic HCV-infected individuals; 96 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection or HCV-related disease progression	Mangia et al. (2003)
Slovenian	150 HCV-infected individuals; 101 HIV-infected individuals; 385 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection	Poljak et al. (2003)
American	417 individuals with liver disease (including 339 HCV-infected individuals); 2380 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection, HCV-related liver disease or therapy response	Promrat et al. (2003)
Caucasian (American; European)	1419 hemophiliacs (stratified in the analyzes according to serological status for HCV and HIV)	No association between the CCR5Δ32 and susceptibility to HCV infection; This study indicated that the results of Woitas et al. (2002) was affected by the inclusion of hemophiliacs in the HCV-infected group	Zhang et al. (2003)
Japanese	105 chronic HCV-infected individuals; 53 non-infected individuals	The CCR5Δ32 allele was not detected in any individuals included in the study	Konishi et al. (2004)
German	257 chronic HCV-infected individuals; 250 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection, HCV-related liver disease or therapy response	Mascheretti et al. (2004)
Spanish	139 HCV-infected individuals; 100 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection or liver injury	Ruiz-Ferrer et al. (2004)
Israeli	127 chronic HCV-infected individuals; 48 HCV-infected individual who had undergone liver transplantation due to liver cirrhosis; 75 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection; The CCR5Δ32 allele was associated with reduced liver inflammation	Wald et al. (2004)
German	333 HCV-infected individuals; 125 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection; No major association between the CCR5Δ32 and HCV-related liver disease or therapy response	Wasmuth et al. (2004)
Irish	196 chronic HCV-infected individuals; 88 individuals who cleared the virus; 120 non-infected individuals	The CCR5Δ32 polymorphism was associated with HCV clearance and less severe hepatic inflammatory scores	Goulding et al. (2005)
Belgian	163 HCV-infected individuals; 310 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection	Thoelen et al. (2005)
Information not available	252 chronic HCV-infected individuals; 408 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection, HCV-related liver disease or therapy response	Goyal et al. (2006)
Information not available	21 HCV-infected hemophiliacs	The CCR5Δ32 allele was associated with reduced anti-viral (mediated by interferon- γ) response	Ahlensti et al. (2009)
German	277 chronic HCV-infected individuals; 119 individuals who cleared the virus; 105 non-infected individuals	The CCR5Δ32 wild-type genotype was associated with spontaneous viral clearance. Therefore, CCR5Δ32 allele can be considered a risk factor for persistent infection	Nattermann et al. (2011)
Egyptian	190 <i>Schistosoma mansoni</i> /HCV co-infected individuals; 220 <i>S. mansoni</i> -infected individuals	The CCR5Δ32 allele was associated with spontaneous viral clearance in co-infected individuals	El-Moamly et al. (2013)
Australian; European	813 chronic HCV-infected individuals; 836 non-infected individuals	The CCR5Δ32 homozygous genotype was associated with chronic HCV infection (especially in Europeans); No association between the CCR5Δ32 and therapy response	Suppiah et al. (2013)
Swiss; Italian	1290 chronic HCV-infected individuals; 160 individuals who cleared the virus	The CCR5Δ32 allele was associated with decreased rates of spontaneous viral clearance; No association between the CCR5Δ32 and HCV-related liver disease or therapy response	Morard et al. (2014)
Turkish	58 chronic HCV-infected individuals; 58 non-infected individuals	The CCR5Δ32 allele was associated with higher HCV load and reduced histology activity index in liver samples	Yilmaz et al. (2014)
Iranian	100 HCV-infected individuals; 100 non-infected individuals	The CCR5Δ32 was not detected in any individuals included in the study	Bineshian et al. (2018)
Brazilian	674 HCV-infected individuals; 104 HCV/HIV co-infected individuals; 300 HIV-infected individuals; 274 non-infected individuals	No association between the CCR5Δ32 and susceptibility to HCV infection or HCV/HIV co-infection; No association between the CCR5Δ32 and HCV-related fibrosis, cirrhosis or hepatocarcinoma	Ellwanger et al. (2018b)

et al., 2003; Promrat et al., 2003; Zhang et al., 2003). In this sense, no influence of CCR5Δ32 on susceptibility to HCV infection were reported in studies performed with various populations (Glas et al., 2003; Mangia et al., 2003; Poljak et al., 2003; Promrat et al., 2003; Zhang et al., 2003; Ruiz-Ferrer et al., 2004; Wald et al., 2004; Wasmuth et al., 2004; Thoelen et al., 2005; Goyal et al., 2006). Reinforcing the observations of those different studies, our group found no association between the CCR5Δ32 and susceptibility to HCV infection or HCV/HIV co-infection in a study that evaluated a large number of Brazilian individuals (Ellwanger et al., 2018b). Bineshian et al. (2018) did not detect the CCR5Δ32 allele in any Iranian HCV-infected individual and

controls included in their study, preventing any conclusion in terms of susceptibility in that population. Finally, it is important to mention that in addition to the study by Woitas et al. (2002), a study performed in 2013 also found an association between the CCR5Δ32 homozygous genotype with chronic HCV infection in Europeans, but the authors of the study mentioned that specific factors regarding selection bias (e.g., co-exposure to HIV) may have influenced their results (Suppiah et al., 2013). Taken together, the above-mentioned results called attention for the importance of performing genetic variant studies in different populations, exposed to different social and environmental factors and presenting distinct ethnic backgrounds.

Considering multiple clinical and histological parameters, two main different results were obtained when the CCR5Δ32 genetic variant was evaluated in the context of HCV-related diseases: reduced liver inflammation in Δ32 allele carriers (Hellier et al., 2003; Wald et al., 2004; Goulding et al., 2005); and no association between the CCR5Δ32 and clinical variables (Glas et al., 2003; Mangia et al., 2003; Promrat et al., 2003; Goyal et al., 2006; Mascheretti et al., 2004; Ruiz-Ferrer et al., 2004; Morard et al., 2014; Ellwanger et al., 2018b).

In the context of persistence/resolution of HCV infection and viral control, in the one hand, studies described association of the CCR5Δ32 allele with reduced rates of spontaneous viral clearance (Nattermann et al., 2011; Morard et al., 2014), higher viral load (Yilmaz et al., 2014), and reduced anti-HCV immune response (Ahlenstiel et al., 2009). On the other hand, studies have reported association between the CCR5Δ32 variant and increased rates of spontaneous viral clearance (Goulding et al., 2005; El-Moamly et al., 2013). No significant effect of the CCR5Δ32 on viral clearance was reported by other authors (Mascheretti et al., 2004).

The potential impact of the CCR5Δ32 polymorphism on response to HCV therapy was also evaluated by some authors. Ahlenstiel et al. (2003) found an association between the CCR5Δ32 allele and reduced response rates to interferon- α monotherapy, but the polymorphism did not affect the response to the combined interferon/ribavirin therapy. This finding shows that the use of more robust therapeutic regimens compensates the undesirable effects of CCR5Δ32 on HCV therapy with interferon- α monotherapy. Of note, the effect of CCR5Δ32 may be negligible in the context of modern HCV therapies (Ahlenstiel et al., 2003). Other studies did not report significant effects of the polymorphism on response to HCV therapy (Glas et al., 2003; Promrat et al., 2003; Goyal et al., 2006; Mascheretti et al., 2004; Suppiah et al., 2013; Morard et al., 2014). Again, it is important to mention that the ethnic distribution of the CCR5Δ32 allele could interfere with study results. Konishi et al. (2004), for example, did not detect the CCR5Δ32 allele in any Japanese individual included in their study focused on host genetic factors involved in the response to interferon therapy. Lastly, the polymorphism also does not appear to be associated with any specific HCV genotype (Glas et al., 2003; Wasmuth et al., 2004; Goyal et al., 2006).

Already in 2004, Ahlenstiel et al. (2004) highlighted that the impact of CCR5 on HCV infection was controversial. In 2020, many controversies remain, although some points are better defined. Table 5 summarizes the main findings of the studies that evaluated CCR5Δ32 on HCV infection. Although some studies indicate an influence of the polymorphism on susceptibility to infection, most studies indicate that the Δ32 allele has little (or no) influence on HCV susceptibility. The impact of the CCR5Δ32 on HCV-related liver disease is quite variable and context-dependent. Finally, available data suggest some benefit of CCR5 antagonists for the treatment of HCV mono-infection. However, these data are still limited and further studies evaluating this topic are needed.

3.6. Poliovirus

Poliovirus (PV) is a single-stranded RNA enterovirus of the family Picornaviridae. There are three types of PV: wild PV type 1 (WPV1), type 2 (WPV2), and type 3 (WPV3). The PV replicates in the tonsils and intestinal tract. In few infection cases (~1%), the virus invades the CNS and can cause poliomyelitis resulting in paralysis. Poliomyelitis is a condition characterized by inflammation of the gray matter of the spinal cord and muscle paralysis unleashed by PV replication in motor neurons (Racaniello, 2006; Kew and Pallansch, 2018; Keohane et al., 2020). Polioencephalitis can also occur and is characterized by the inflammation of the gray matter of the brain (Keohane et al., 2020). PV infection is preventable through vaccination. The global PV vaccination program (Global Polio Eradication Initiative) has virtually eliminated cases of PV-derived paralysis, which currently occur to a limited extent

in some countries, such as Pakistan and Afghanistan, and are caused by WPV1, while WPV2 and WPV3 have not circulated in human populations since 1999 and 2012, respectively (Kew and Pallansch, 2018).

Host genetics and profile of immune responses affect the course of PV infection, determining if a particular individual will have neurological impairment (Andersen et al., 2019). Considering that CCR5 affects the course of other neuroinvasive viral infections such as TBEV and WNV, it was hypothesized that CCR5Δ32 could influence the development of neurological impairment associated with PV infection, as this only occurs in a portion of infected individuals (Rosenberg et al., 2013). In this context, Rosenberg et al. (2013) evaluated the effect of the CCR5Δ32 on severe cases of PV infection through a retrospective study performed in Finland, including rare samples of individuals with neurological symptoms from the 1984–1985 PV outbreak occurred in that country (Table 6). The authors found no statistically significant effect of the CCR5Δ32 on PV infection; only a trend of association between the Δ32 allele and increased risk of PV infection was observed (Rosenberg et al., 2013). However, this study had a very small sample size (only seven cases of severe PV infection were evaluated) and therefore the results were not conclusive. In addition, due to the declining number of PV infection cases in the world, the effect of CCR5Δ32 will be increasingly difficult to be assessed in population-based studies.

3.7. Dengue virus

Dengue virus (DENV) is a single-stranded RNA virus that belongs to the Flaviviridae family, *Flavivirus* genus. There are four DENV serotypes, being all transmitted to humans by *Aedes* mosquitoes (*Aedes aegypti* and *Aedes albopictus*) (Guzman et al., 2016). DENV infection is a global health problem with huge impacts on public health systems, especially in tropical countries (Bhatt et al., 2013), being considered the most common arbovirosis in the world (Stanaway et al., 2016). Globally, the incidence of symptomatic DENV infection is within the range of 50–100 million cases per year, resulting in ~10,000 deaths each year (Stanaway et al., 2016).

Clinically, dengue illness is divided into three basic phases: acute febrile phase, critical phase, and recovery (convalescent) phase. Dengue disease occurs with/without warning signs or severe dengue. Warning signs (suggestive signs or symptoms of important fluid loss, capillary leakage, and shock, such as severe abdominal pain and mucosal bleeding; observed at the end of the febrile phase) allow the rapid identification of patients who need more clinical attention and supportive therapy, in an attempt to avoid severe dengue. When severe disease occurs, this condition can lead to serious organ involvement, shock, and hemorrhage, among other signals and symptoms (Guzman et al., 2016). Infection with a DENV serotype triggers long-term immunity to that specific serotype (homotypic DENV). Immunity to heterotypic DENV also occurs, but it is transitory. Therefore, an individual can have dengue disease more than once. Severe dengue occurs more frequently in recurrent infection with a different viral serotype (Murphy and Whitehead, 2011; St John and Rathore, 2019).

The immune response mediates DENV clearance and the resolution of dengue diseases, but it is also involved in the disease pathogenesis (Murphy and Whitehead, 2011). Some evidence suggests the participation of CCL5/CCR5 axis in the protection against DENV (Sierra et al., 2014), as well as in the pathogenesis of Dengue disease (Islam et al., 2019). Indeed, DENV infection is associated with increased frequency of human CCR5⁺ T cells (de-Oliveira-Pinto et al., 2012; Badolato-Correa et al., 2018). In a study performed by Marques et al. (2015), lower viral replication was found in macrophages treated with CCR5 blockers. In the same study, CCR5^{-/-} mice were protected from DENV infection. These findings suggest that CCR5Δ32 could be a protective factor against DENV infection. However, Xavier-Carvalho et al. (2013) found no statistical difference in the frequency of CCR5Δ32 polymorphism between Brazilian children with severe DENV infection and healthy controls. In the same direction, no effect of CCR5Δ32 on

Table 6
Impacts of CCR5Δ32 on various viral infections.

Pathogen/Disease	Population	Sample	Main findings	References
Poliiovirus (PV) infection	Finnish	7 PV-infected individuals with neurological symptoms; 79 non-infected individuals or asymptomatic infected individuals	No association between CCR5Δ32 and severe PV-associated neurological disease (small sample size study)	Rosenberg et al. (2013)
Dengue virus (DENV) infection	Brazilian	87 DENV-infected children (severe cases); 326 controls	No statistical association between CCR5Δ32 and DENV infection	Xavier-Carvalho et al. (2014)
Human cytomegalovirus (CMV) infection	Australian Indian	56 DENV-infected individuals; 91 non-infected individuals 42 DENV-infected individuals (33 mild cases and 9 severe cases); 90 non-infected individuals	No statistical association between CCR5Δ32 and DENV infection The CCR5Δ32 allele was not detected in any individuals included in the study	Brestovac et al. (2014)
Crimean-Congo hemorrhagic fever virus (CCHFV) infection	European-American; African-American Polish	123 European-American and 117 African-American individuals with AIDS and CMV retinitis 72 children with intrauterine CMV infection; 398 non-infected children 3 CCHFV fatal cases; 12 CCHFV non-fatal cases 133 CCHFV-infected individuals; 97 non-infected individuals	No statistical association between CCR5Δ32 (as an individual factor) and mortality, retinitis progression or retinal detachment No statistical association between CCR5Δ32 and CMV infection All individuals had the wild-type genotype The CCR5Δ32 heterozygous genotype and the Δ32 allele were associated with protection against CCHFV infection (both factors found in increased frequency in control group)	Kasztelicz et al. (2017) Engin et al. (2009), Rustemoglu et al. (2017)
Enterovirus (EV) infection	German	97 individuals with enteroviral cardiomypathy (23 individuals with persistent EV infection; 42 individuals who spontaneously cleared the virus; 32 individuals with persistent EV infection who received interferon-β therapy to clear the virus) 183 JEV-infected individuals; 361 non-infected individuals	CCR5Δ32 was associated with spontaneous viral clearance and better clinical outcome (all Δ32 allele carriers showed viral clearance and none of them died during the study period)	Lassner et al. (2018)
Japanese encephalitis virus (JEV) infection	Indian	98 nephropathia epidemica cases; 592 controls	No statistical association between the CCR5Δ32 and Japanese encephalitis considering the CCR5Δ32 as an individual factor	Deval et al. (2019)
Nephropathia epidemica (linked to hantavirus infection)	Russian (Republic of Tatarstan)		CCR5Δ32 did not affect susceptibility to hantavirus infection. However, the wild-type homozygous genotype was associated with more severe disease	Kletenkov et al. (2019)

susceptibility to DENV infection was found in a small sample-size study performed with individuals from Western Australia (Brestovac et al., 2014) and recent data suggested no important involvement of *CCR5* gene or *CCR5* polymorphisms in DENV infection (Cahill et al., 2018; Ornelas et al., 2019). Finally, the CCR5Δ32 allele was not identified in a small group of Indian DENV-infected individuals (Islam et al., 2019). Table 6 shows some details of the studies involving CCR5Δ32 and DENV infection.

Taking together, the data mentioned above indicate that the effects of *CCR5* on DENV infection are very different between humans and rodents. However, it should be noted that the approach of each mentioned study is quite particular, and we cannot exclude some potential effects of *CCR5* and CCR5Δ32 on DENV infection in humans.

3.8. Human cytomegalovirus

Human cytomegalovirus (CMV) is an enveloped double-stranded DNA virus belonging to the *Herpesviridae* family (Crough and Khanna, 2009; Herbein, 2018). The infection in immunocompetent adults is usually asymptomatic. However, in some cases, it can cause mononucleosis syndrome or other rare complications, including meningitis and myocarditis. CMV is an opportunistic pathogen and, therefore, symptomatic infection occurs more frequently in immunocompromised individuals (HIV infected or transplanted patients on immunosuppressive drugs). Congenital CMV infection is associated with morbidity and mortality in newborns, being associated with neurodevelopmental problems (Crough and Khanna, 2009). CMV is also linked to cancer development, once several CMV proteins (e.g., pUL122, pUL123, pUS28, pUL83, pUL111A) activate pro-oncogenic pathways, including angiogenesis, escape of immune control and tumor suppressors, tumoral inflammation, invasion and metastasis, genome instability, and increased cell survival and proliferation (Herbein, 2018). Poor socioeconomic condition favors CMV infection. Antibodies indicating past CMV infection are found in ~60 % of adults from high-income countries. In low-income countries, the rate of past infections can reach 100 % (Griffiths et al., 2015).

CMV can manipulate the immune system producing virokines (virus-encoded cytokine/chemokine homologs) and viroceptors (virus-encoded cytokine/chemokine receptor homologs), molecules that enable the virus to evade host immune defenses. Such molecules can also facilitate viral replication (Lucas et al., 2001; Froberg, 2004; Vomaske et al., 2012). Importantly, CMV-encoded proteins can interact with *CCR5*, modulating its function and cell migration (Tadagaki et al., 2012; Vomaske et al., 2012), potentially affecting the pathogenesis of diseases in which *CCR5* have an involvement, especially HIV infection. CMV infection in immunocompromised HIV/AIDS patients can cause different problems, including retinitis, esophagitis, gastritis, pneumonitis, and hepatitis (Crough and Khanna, 2009). CMV proteins can have an inhibitory effect on HIV–*CCR5* interaction, hampering cell infection by HIV (Tadagaki et al., 2012). In the opposite direction, Johnson et al. (2018) have shown that CMV upregulates *CCR5* expression *in vitro*, suggesting a potential contribution to HIV susceptibility *in vivo*. In accordance, a previous study has indicated that CMV infection upregulates *CCR5* expression (Johnson et al., 2015). However, mixed results were reported regarding the effect of CMV on *CCR5* expression since there is evidence indicating that CMV infection may reduce *CCR5* expression in various cell types (Lecointe et al., 2002; Varani et al., 2005). Interestingly, these mixed results may not be contradictory. CMV-infected cells may indeed exhibit decreased *CCR5* expression, limiting HIV infection in these cells. However, CMV-infected cells release CMV-associated soluble factors that increase *CCR5* expression in non-infected bystander cells, then facilitating HIV replication in such cells and, consequently, contributing to HIV pathogenesis (King et al., 2006).

There is evidence showing that variants in the *CCR5* gene can influence multiple aspects of CMV infection (Loeffler et al., 2006; Sezgin et al., 2011). For example, the *CCR5* promoter polymorphism

rs1800023 affects CMV replication (Bravo et al., 2014; Corrales et al., 2015). In a study evaluating children, Kasztelewicz et al. (2017) found no influence of CCR5Δ32 on susceptibility to congenital CMV infection, severity of congenital CMV disease, or CMV-related sensorineural hearing loss at birth. As an individual genetic factor, CCR5Δ32 was not statistically associated with the progression of CMV retinitis, a condition that CMV can cause in immunocompromised individuals (Sezgin et al., 2011) (Table 6).

3.9. Crimean-Congo hemorrhagic fever virus

Crimean-Congo hemorrhagic fever virus (CCHFV) belongs to the genus *Nairovirus*, family *Bunyaviridae*. CCHFV circulates in Africa, Europe, Middle East, and Asia countries, and can infect a variety of domestic animals and wild species, but without causing symptomatic illness. Humans are accidental hosts of CCHFV, for which the virus is transmitted mainly by tick-bites (especially ticks of the genus *Hyalomma*), although other routes of transmission also exist, such as exposure to blood of infected animals. Most CCHFV-infected individuals have no symptoms or have mild nonspecific febrile syndrome. However, in some individuals, the infection can cause the Crimean-Congo hemorrhagic fever, a severe disease characterized by fever, myalgia, hemorrhage, among other manifestations. Neurological complications can also occur, being the spectrum and intensity of the disease quite variable (Ergönül, 2006; Bente et al., 2013; Garrison et al., 2019).

Deregulation of several cytokines and chemokines is involved in the pathogenesis of Crimean-Congo hemorrhagic fever (Ergönül, 2006; Saksida et al., 2010; Bente et al., 2013; Garrison et al., 2019). In a study performed by Arasli et al. (2015), expression of the CCR5 ligands CCL2, CCL3, and CCL4 was increased in CCHFV-infected adults compared to controls. Considering these same chemokines in CCHFV-infected children, only CCL4 was significantly increased compared to pediatric controls (Arasli et al., 2015).

Engin et al. (2009) evaluated the CCR5Δ32 in 15 Turkish CCHFV-infected individuals and observed the wild-type homozygous genotype in all cases. In a subsequent study evaluating the Turkish population, Rustemoglu et al. (2017) found a protective effect of CCR5Δ32 heterozygous genotype and Δ32 allele on CCHFV infection, since the genotype and allele frequencies were higher in controls than in CCHFV-infected individuals. Conversely, the wild-type genotype (normal CCR5 expression) was prevalent among infected individuals. These findings suggest that CCR5 contributes to susceptibility to CCHFV infection and that CCR5 down-regulation due to CCR5Δ32 results in some protection against the infection. However, further studies are needed to explain the mechanisms by which CCR5 participates in CCHFV infection. In the same study, the CCR5Δ32 was not significantly associated with disease severity, clinical parameters, or mortality rate (Rustemoglu et al., 2017). Together, these findings (Table 6) indicate that the effect of CCR5Δ32 is given specifically on resistance against CCHFV infection, without affecting the pathogenesis/outcome of Crimean-Congo hemorrhagic fever.

3.10. Enterovirus

The genus *Enterovirus* is composed of non-enveloped, positive-stranded RNA viruses, belonging to the *Picornaviridae* family. Enteroviruses (EV) can infect the gastrointestinal tract, CNS, and other organs, including heart (Tapparel et al., 2013). Cardiomyopathy is a common consequence of EV infection in the heart. EV infection is associated with myocardial inflammation (myocarditis) and other damages to heart tissues (Badorff et al., 2000; Cooper, 2009; Sagar et al., 2012; Tapparel et al., 2013; Weintraub et al., 2017). A portion of EV-infected individuals clears the virus, while others develop persistent infection that can damage heart tissues. Viral persistence in individuals

with enteroviral cardiomyopathy is associated with an increased mortality rates (Kühl et al., 2005; Lassner et al., 2018).

Some studies suggest that CCR5 influences different aspects of the pathogenesis of viruses belonging to the *Picornaviridae* family, including Encephalomyocarditis virus (Christmann et al., 2011; Shaheen et al., 2015), Coxsackievirus B3 (Valaperti et al., 2013), and Rhinovirus (Muehling et al., 2018), once CCR5 participates in the regulation of the host immune response during infection by these viruses. Considering the effects of the genetic variant CCR5Δ32 on CCR5 expression and CCR5-related immune responses, it is possible that CCR5Δ32 also shows some impact on EV-related diseases.

In a German study that evaluated patients with enteroviral (chronic/inflammatory) cardiomyopathy (Lassner et al., 2018), the CCR5Δ32 was strongly associated with spontaneous viral clearance and better clinical outcome (reduced mortality rate) (Table 6). These findings indicate a critical involvement of the CCR5 molecule in the pathogenesis of EV cardiomyopathy. It was suggested that the CCR5Δ32 genotyping could be used to assist in the prediction of the clinical progression of enteroviral cardiomyopathy: the Δ32 allele as a predictor of a better prognosis, without the need of antiviral interferon-β (IFN-β) therapy; and the wild-type genotype as a predictor of a worse prognosis and immediate need of antiviral IFN-β therapy (Lassner et al., 2018). The clinical use of IFN-β is effective to eliminate the virus, avoid irreversible cardiac injury, and reduce mortality rates, but it is also associated to numerous adverse effects (Kühl et al., 2012; Lassner et al., 2018). Considering the prognostic value of the CCR5Δ32 on the clinical course of enteroviral cardiomyopathy, it is necessary to evaluate the relationship between the CCR5Δ32 and the disease in different human populations, mainly through genetic association studies. If this association is confirmed in other populations, the CCR5Δ32 genotyping will be a broad-spectrum clinical tool, enhancing and driving the treatment of enteroviral cardiomyopathy.

3.11. Japanese encephalitis virus

Japanese encephalitis virus (JEV) contains a single-stranded positive-sense RNA genome and belongs to the family *Flaviviridae*, genus *Flavivirus*. Birds and pigs are the JEV amplifying hosts. JEV is transmitted by *Culex* mosquitoes and occurs especially in Australia and Asian countries. Humans and horses are dead-end JEV hosts. The human infection causes a broad range of clinical manifestations, varying from asymptomatic infection (most cases) to mild febrile syndrome and even lethal meningoencephalitis. JEV is the etiological agent of most cases of viral encephalitis in many countries, reaching ~30% mortality rate (van den Hurk et al., 2009; Tiwari et al., 2012; Le Flohic et al., 2013).

Some evidence obtained in laboratory conditions (*in vitro* analysis and murine models) showed that JEV infection induces the up-regulation of CCR5 gene (Gupta and Rao, 2011; Pareek et al., 2014; Zhang et al., 2019). Also, increased infiltration of CCR5⁺ CD8⁺ T cells was observed in the brains of JEV-infected mice (Zhang et al., 2019). In this context, using a mouse model of Japanese encephalitis, Larena et al. (2012) showed that CCR5 protects the host against JEV infection in the CNS, being essential for disease recovery. CCR5-deficient mice showed higher viral loads in the brain and spinal cord as well as increased mortality rate, as compared to control mice (Larena et al., 2012). Also using a mouse model of Japanese encephalitis, Kim et al. (2016) demonstrated that CCR5 controls the infiltration of CD4⁺ Foxp3⁺ T regulatory (Treg) cells in the CNS, contributing to protection against Japanese encephalitis. The infiltration and action of inflammatory cells in the brain are important to limit neuroinvasive infections, processes that are regulated by multiple factors, especially cytokines, chemokines and their receptors, including CCR5. However, the uncontrolled action of inflammatory cells can cause damage to the CNS. Of note, CD4⁺ Foxp3⁺ Treg cells regulate the immune responses, avoiding

undesirable or excessive action of inflammatory cells (Bardina and Lim, 2012; Veiga-Parga et al., 2013; Simonetta and Bourgeois, 2013; Campbell, 2015; Kim et al., 2016). According to these pieces of evidence, CCR5-mediated action of Treg cells is critical for the control of Japanese encephalitis. However, the role of CCR5 in JEV infection may be more complex than it appears at first. Liu et al. (2018) demonstrated that the use of the CCR5 antagonist maraviroc reduces the JEV-induced inflammation in mice brain, increasing survival rate. This result suggests that potential deleterious effects of CCR5-mediated inflammation in the brain may override the effects of CCR5-mediated action of Treg cells and, therefore, the use of CCR5 antagonists to treat Japanese encephalitis may be beneficial. Based on these complex and contradictory results, it can be concluded that CCR5 indeed has an important influence on Japanese encephalitis, but it is not yet possible to state its specific roles, once they are varied and appear to be context-dependent. Also, the results obtained in animal models may not fully represent the disease course in humans.

Indeed, some evidences suggest the involvement of CCR5 in the pathogenesis of Japanese encephalitis in humans. In Indian individuals with mild cases of Japanese encephalitis, a significant downregulation of the CCR5 gene was observed as compared to healthy controls (Chowdhury and Khan, 2019). However, the CCR5Δ32 does not have a relevant influence on the disease. Deval et al. (2019) investigated the effect of various genetic variants, including CCR5Δ32, on the development of Japanese encephalitis in individuals from North India (Table 6). No statistically significant difference was found when the CCR5Δ32 (as an individual factor) was compared between cases and controls (Deval et al., 2019). Considering that both studies mentioned above were performed in the Indian population, studies evaluating the potential effects of CCR5 and CCR5Δ32 on Japanese encephalitis in other populations are necessary.

3.12. Hantavirus infection

Puumala virus (PUV) infection is a zoonosis endemic in Europe. PUV is an enveloped single-stranded RNA virus, belonging to the Bunyaviridae family, genus *Hantaviridae*. Most PUV infections are mild or subclinical. In some infected individuals, PUV is responsible for the development of nephropathia epidemica, a milder form of hemorrhagic fever with renal syndrome, a condition typically caused by other Hantaviruses (Settergren, 2000; Mustonen et al., 2013; Lebecque and Dupont, 2019). An *in vitro* study found increased CCR5 gene expression in primary monocytes infected by hantaviruses (Hantaan virus, Sin Nombre virus and Andes virus) (Markotić et al., 2007). In this sense, host genetic factors and the immune responses affect different aspects of PUV infection and progression of nephropathia epidemica (Mustonen et al., 2013), although the role of CCR5 in this disease is little known.

Kletenkov et al. (2019) evaluated the potential influence of the CCR5Δ32 on nephropathia epidemica in individuals from Republic of Tatarstan, Russia (Table 6). Of note, in their study, the authors stated hantavirus infection as the cause of Nephropathia epidemica, not specifying the PUV detection. No statistical difference was observed in CCR5Δ32 genotype frequencies between cases and controls, indicating that CCR5Δ32 does not influence the susceptibility to hantavirus infection in the studied population. Considering only nephropathia epidemic cases, the study revealed an association between the wild-type homozygous genotype (functional CCR5) and increased severity of the disease. Conversely, the heterozygous genotype was considered a protective factor against increased disease severity (Kletenkov et al., 2019). To the best of our knowledge, there are no other studies that have evaluated CCR5Δ32 in nephropathia epidemica. However, the results presented by Kletenkov et al. (2019) suggest that further studies evaluating the roles of CCR5 and CCR5Δ32 on hantavirus infection are important.

4. CCR5 gene editing and CCR5 modulation: what would be the effects of CCR5 absence on everyday life?

In 2019, the multiple roles of CCR5 in physiological and pathological conditions gained the attention of the scientific community and lay public due to CCR5 gene editing in human embryos, the “CRISPR babies”, performed by a Chinese biophysicist. The researcher claimed to have used CRISPR gene editing technology to edit the CCR5 of germline cells to mimic the effects of CCR5Δ32, aiming to generate babies resistant to HIV infection. The ethical, safety, and legal aspects related to this procedure have caused an intense and broad discussion in the media and scientific literature (Cohen, 2019; Daley et al., 2019; Greely, 2019; Rosenbaum, 2019), and this case culminated in a three years prison sentence for the biophysicist responsible for the procedure (Cyranoski, 2020). Also, the consequences of the CCR5 absence have brought many concerns to light, once the CCR5 protein participates in tissue development processes, control of immune responses, and several other physiological processes. Considering these concerns, our group and others described some undesirable effects associated to natural CCR5 absence (due to the CCR5Δ32 homozygous genotype) and CCR5 editing (Ellwanger et al., 2019; Wang and Yang, 2019; Xie et al., 2019).

Besides gene editing techniques, the expression of CCR5 can be artificially modulated through the use of pharmacological antagonists (e.g. maraviroc), chemokine ligands, and monoclonal antibodies (Fantuzzi et al., 2019). The use of CCR5 antagonists is well established for the treatment of HIV infection and is currently being tested for the treatment of many other diseases, such as cancer (Pervaiz et al., 2019; Huang et al., 2020a), stroke (Joy et al., 2019), and cocaine addiction-related disorders (Hall et al., 2020; Nayak et al., 2020).

Taking together, it is increasingly clear that the specific inhibition of CCR5 expression through different techniques is gaining pace in different clinical contexts. The pharmacological CCR5 blockade has many benefits in different clinical situations, particularly in the treatment of HIV infection. Also, the potential of gene editing (especially in somatic cells) for the treatment of genetic diseases is very promising. However, considering viral infections, two aspects must be considered, as follows:

I) The non-redundant characteristics of the CCR5 should be taken into consideration when studying the CCR5 protein and the effects of CCR5Δ32 on viral infections: The traditional concepts of redundancy and robustness of the chemokine system consider that the absence of a specific chemokine or chemokine receptor is adequately compensated by other molecules. Although these concepts are generally correct for some chemokines/receptors and for some physiological conditions, the lack of CCR5 expression may affect the host protection against some specific infectious diseases once the CCR5 absence is not perfectly compensated for by other receptors (Ellwanger et al., 2020a). The nonredundancy of CCR5 is relevant especially for infections by neuroinvasive flaviviruses (Bardina and Lim, 2012). For example, the absence of CCR5 due to CCR5Δ32 is considered deleterious in WNV infection (Glass et al., 2006; Lim et al., 2008) and in some aspects of TBEV infection (Ellwanger and Chies, 2019a). The non-redundant role of CCR5 is also likely in JEV infection (Larena et al., 2012).

II) Studies evaluating the actual impact of CCR5 antagonists on neuroinvasive infections are needed: It is possible that those individuals using CCR5 antagonists (e.g., for the treatment of HIV infection) and living in areas endemic for neuroinvasive viruses, especially WNV and TBEV, may be at increased risk of developing viral encephalitis-related problems. However, it is still necessary that studies consistently evaluate this assumption, since the available evidence does not support risks for the use of CCR5 antagonists in endemic areas of flaviviruses (Martin-Blondel et al., 2016). As mentioned in the topic addressing WNV in this review, it is prudent to recommend to individuals using CCR5 antagonists to adopt measures to minimize the risk of neuroinvasive infections, such as the use of mosquito repellents and mosquito nets (considering the risk of WNV infection), and to limit their

exposure to tick-infested areas (considering the risk of TBEV infection). Concerns regarding the use of CCR5 antagonists in areas of JEV circulation have also been raised by other authors (Kim et al., 2016; Larena et al., 2012). If the connection between the use of CCR5 antagonists and increased risk of neuroinvasive infections is confirmed in methodologically well-controlled studies, these recommendations should be considered of essential importance for users of CCR5 antagonists.

5. The triad “extracellular vesicles, viruses, and CCR5”

“Extracellular vesicles” (EVs) is a general term used to designate different membranous vesicles released by various cell types. EVs include microparticles, microvesicles, nanovesicles, nanoparticles, ectosomes, exosomes, exovesicles, exosome-like vesicles, oncosomes, among other vesicle types. EVs act in the transport of different molecules (e.g. microRNAs, mRNAs, proteins) between cells and tissues in a regulated and precise manner. EVs promote the maintenance of physiological processes, also participating in the pathogenesis of various diseases, such as cancer and inflammatory diseases (Colombo et al., 2014; Théry et al., 2018). Besides, the regulation of multiple aspects of the immune system is strongly influenced by EVs (O’Neill and Quah, 2008; Colombo et al., 2014; Ellwanger et al., 2016).

The multiple roles of EVs in viral infections began to be studied more intensively in recent years, representing an emerging topic in the field of infectious diseases. Currently, the relationship between EVs and viral infections has already been explored (to a greater or lesser extent) in the context of the following viruses: Bunyaviruses, Cytomegalovirus, Dengue virus (DENV), Ebola virus, Epstein-Barr virus, Hepatitis A virus, Hepatitis C virus (HCV), Human papillomavirus, Herpes simplex virus, Human T cell lymphotropic virus, Kaposi’s sarcoma-associated herpesvirus, Zika virus (ZIKV), TBEV, HIV (Kaminski et al., 2019b), and Influenza virus (Zheng et al., 2020).

EVs participate in immune evasion processes, ultimately allowing viruses to bypass host defenses (Kaminski et al., 2019b). For example, HIV is likely to usurp the exosome biogenesis pathway in such a way that enhances its infectivity, while increasing its evading strategies from the host immune defenses (Ellwanger et al., 2017a). Regarding TBEV, exosomes were indicated as important participants in both viral infection and pathogenesis; in this case, tick-derived exosomes facilitate TBEV transmission to the host. Also, exosomes derived from TBEV-infected host neurons can facilitate the spread of the virus in the CNS (Zhou et al., 2018). Exosomes have shown multi-dimensional roles in DENV life cycle. They can modulate negatively or positively DENV pathogenesis, where they are suggested as instrumental for Dengue Hemorrhagic Fever development in reason of the transportation of specific microRNAs (Mishra et al., 2019). Since HCV can be found inside exosomes (Liu et al., 2014), it is not surprising that blood-derived exosomes from HCV-infected patients can transmit the virus to other cells (Bukong et al., 2014). These findings suggest that exosomes and other EVs assist in the transport of HCV particles/components between cells, ultimately facilitating viral infection. Of note, EVs can transport multiple viral components or molecules from virus-infected cells that end up facilitating the spread of the virus in the host. On the other hand, EVs can act in favor of the host, transporting molecules that assist host defenses in the elimination or control of infections (Kaminski et al., 2019b).

EVs can transport a range of cytokines and chemokines, such as IL-1, IL-2, IFN- α , IFN- β , CCL2, CCL3, CCL4, and CXCL10 (Chen et al., 2011; Konadu et al., 2015; Hosseinkhani et al., 2018; Kodidela et al., 2018; Gao et al., 2019a, b; Aiello et al., 2020; Chiantore et al., 2020). Besides, EVs and microparticles also transport chemokine receptors (Shen et al., 2016; Li et al., 2018; Liang et al., 2018), including CCR5 (Mack et al., 2000; Tokarz et al., 2019). Interestingly, EVs from CCR5 wild type cells can deliver CCR5 molecules to CCR5 $\Delta 32/\Delta 32$ cells, making them

susceptible to HIV infection (Mack et al., 2000). A similar phenomenon has been reported involving microparticles, HIV, and CXCR4 (Rozmyslowicz et al., 2003). CCR5 expression is also influenced by the release of EVs, specifically microparticles (Renovato-Martins et al., 2017). Therefore, EVs have the potential to attribute greater complexity to CCR5 roles in viral infections. It is possible that the presence of CCR5 in cells is not only dependent on mechanisms of membrane expression and internalization of the receptor. It can also be dependent on CCR5 delivery mediated by EVs. However, the actual impact of EVs on CCR5-mediated immune response in infections remains to be determined and deserves further investigation.

Finally, a truncated CCR5 soluble form (Tsimanis et al., 2005), as well as soluble CXCR4, have also been reported in the plasma of humans (Malvoisin et al., 2011). Of note, the truncated CCR5 soluble form has ~ 22 kDa (half the size of the CCR5 found on cell membranes) and is truncated at the end of the second extracellular loop (the third extracellular loop and the subsequent three transmembrane regions are absent) (Tsimanis et al., 2005). However, the existence of cell-free soluble CCR5 is still controversial and does not represent a consensus in the scientific community. Such doubts occur mainly in consideration of the structure of the receptor, which is highly characteristic of a cell membrane-associated molecule. We believe that EVs-containing CCR5 can explain potential (misleading) detections of soluble CCR5. The importance of circulating EVs-containing CCR5 on viral infections represents an additional and interesting open question to be investigated.

6. Neglected and emerging topics in CCR5 research: Rocio virus, Zika virus, Epstein-Barr virus, and rhinovirus

Chávez et al. (2013) demonstrated an involvement of the CCR5 protein in the infection by Rocio virus (ROCV), a mosquito-borne flavivirus that caused a major human encephalitis outbreak between 1975 and 1980, in the region of Ribeira Valley, São Paulo State, Brazil (Ellwanger et al., 2017b). Specifically, using a mouse model of ROCV-associated encephalitis, CCR5-deficient mice showed increased survival rate and reduced levels of brain inflammation compared to mice expressing CCR5, indicating the participation of CCR5 in ROCV-associated encephalitis (Chávez et al., 2013). Although other studies discussed in this review have shown an important involvement of CCR5 in infection by flaviviruses [especially as an important molecule for the resolution of neuroinfection, in opposition to results of Chávez et al. (2013)], the role of the CCR5 in ROCV infection represents a neglected topic. This knowledge gap should be addressed in further studies since the reemergence of ROCV in Brazil is a concern in terms of public health (Figueiredo, 2007; Ellwanger et al., 2017b). Although no other ROCV outbreaks have been reported in Brazil after the 1980s, there is evidence of ROCV circulation in animals (Casseb et al., 2014; Pauvolid-Corrêa et al., 2014; Silva et al., 2014).

Badolato-Corrêa et al. (2018) reported that Zika virus (ZIKV) infection induces an upregulation of CCR5 expression on T cells. Of note, ZIKV is another mosquito-borne flavivirus that recently reemerged in many countries, affecting Brazil in particular. ZIKV infection is associated with microcephaly and other human development problems (Baud et al., 2017). Zachova et al. (2019) showed that Epstein-Barr virus (EBV)-infected B cells have increased CCR5 expression compared to EBV-non-infected cells. Also, recent evidence points to a pivotal role of the CCR5 in the attenuation of rhinovirus-associated inflammation, by controlling the activity of CD4 $^{+}$ Foxp3 $^{+}$ Treg cells (Hossain et al., 2020). Altered levels of cytokines and chemokines are associated with several aspects of ZIKV (Barros et al., 2018; Naveca et al., 2018; Khaiboullina et al., 2019; Lima et al., 2019), EBV (Piovan et al., 2005; Ehlin-Henriksson et al., 2009; Cohen et al., 2017), and rhinovirus infections (Rajan et al., 2014; Shelfoon et al., 2016; Hansel et al., 2017). However, the potential role of the chemokine receptor CCR5 in the

pathogenesis of ZIKV, EBV, and rhinovirus represents open questions in the field of CCR5 research.

7. CCR5 and coronaviruses: is there a connection?

Coronaviruses are positive-sense RNA viruses that belong to the *Coronaviridae* family (Li et al., 2020). Coronaviruses infect a wide range of species, including humans. Until 2019, humans have faced two major outbreaks of high pathogenic coronaviruses, the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak (Fung and Liu, 2019). In 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan (Hubei province, China) (Wu et al., 2020) and rapidly spread to more than 180 countries/regions (Interactive dashboard of global COVID-19 cases - Johns Hopkins University: <https://arcg.is/0fHmTX>; Dong et al., 2020). Of note, SARS-CoV-2 infection causes the "coronavirus disease 2019" and therefore is also called "COVID-19". Considering the ongoing SARS-CoV-2 pandemic and the clinical variability observed in the affected individuals, ranging from mild to severe respiratory disease (Chen et al., 2020; Huang et al., 2020b), the following question arose: does CCR5 have any clinically relevant influence on SARS-CoV-2 or other coronaviruses infections?

Recent data indicated that SARS-CoV-2 binds to the ACE2 receptor (Andersen et al., 2020), using this receptor for entry into human cells. Therefore, it is unlikely that CCR5 or CCR5Δ32 have some significant effect on the susceptibility or resistance to SARS-CoV-2 infection. However, CCR5 may have some impact on the clinical course of SARS-CoV-2 infection.

The pattern and intensity of the human immune responses regulate the clinical progression and even the outcome of infections by coronaviruses (Li et al., 2020), including SARS-CoV-2 (Qin et al., 2020; Shi et al., 2020). SARS-CoV-infected mice showed increased expression of CCR5 mRNA in lungs along with the production of CCL2, CCL3 and CCL5 chemokines, the major CCR5 natural agonists (Chen et al., 2010). Intracranial infection of mice with Mouse Hepatitis Virus (MHV, a murine coronavirus) induces an increased CCR5 expression, which contributed to MHV-induced demyelination through CCR5-mediated macrophage recruitment to the CNS (Glass et al., 2001). Subsequent studies using MHV-infected mice showed that CCR5 participates in the regulation of CD4⁺ and CD8⁺ T cell activities against the virus in the CNS (Glass and Lane, 2003a, b). Also, SARS-CoV-infected human monocyte-derived dendritic cells showed increased CCR5 expression *in vitro* (Law et al., 2009).

Taking together, the findings mentioned above suggest that CCR5 could have some influence on the clinical course of SARS-CoV-2 infection. However, future studies addressing humans are needed to clarify this suggestion. In this sense, we emphasize that so far, there is no evidence showing a clear involvement of CCR5 in SARS-CoV-2 human infection.

8. Final considerations regarding the phenotypic effects of the CCR5

The CCR5Δ32 is a highly penetrating polymorphism, and exerts a robust phenotypic effect on CCR5. However, the expression of CCR5 is regulated by other polymorphisms in addition to CCR5Δ32 (Mehlotra, 2019). Also, the CCR5 expression is influenced by non-coding genetic elements. The effect of the genetic background of the host can also be exacerbated or diminished depending on the environmental conditions to which the individual is exposed (Ellwanger et al., 2018c; Kulkarni et al., 2019). Taking together, these factors help to explain why many of the effects exerted by CCR5 on a given disease are specific to a certain population, ethnic group, or individual.

9. Conclusions

Research involving CCR5 and HIV began in the mid-1990s. Since then, many achievements in the field of CCR5/HIV research have been made, such as the identification of CCR5Δ32 as a strong protective factor against HIV infection and the development of CCR5 antagonists for the treatment of HIV infection. Currently, these drugs are being tested for the treatment of other inflammatory and infectious diseases. In this context, the use of CCR5 antagonists has raised some concerns, since the blockade of CCR5 can affect or even weaken the host defenses against certain infections, especially neuroinvasive infections by flaviviruses. However, to date, there is no strong evidence indicating that the use of CCR5 antagonists has increased the susceptibility of individuals to problematic flaviviruses infections.

The frequency of CCR5Δ32 is quite varied among human populations, and therefore the effects of the allele in a particular population may not apply to another population. Moreover, the effects of CCR5 and CCR5Δ32 are disease-specific. For instance, the CCR5Δ32 does not significantly affect susceptibility to WNV infection. However, the effect of the CCR5 and CCR5Δ32 on WNV disease progression is very robust. Some animal-derived findings suggest the involvement of the CCR5 in the pathogenesis of DENV infection. However, the effects of CCR5 on DENV infection are very different between humans and rodents. Of note, CCR5Δ32 does not significantly affect susceptibility to DENV infection or disease progression. Moreover, the effect of CCR5Δ32 on HBV-related disease is population-specific. Interestingly, CMV release virokines, which are molecules that can manipulate the host immune response and affect the CCR5 function. The examples cited above highlight the varied impacts of CCR5 and CCR5Δ32 on viral infections.

The few studies involving CCHFV, EV, and Hantavirus infection have indicated important effects of CCR5Δ32 on these conditions. Based on these findings, further studies should investigate the role of CCR5Δ32 and CCR5 protein in such infections, considering populations with distinct genetic backgrounds. Some evidence suggested the participation of CCR5 in infections by ZIKV, EBV, and rhinovirus. Also, a mouse model of ROCV-associated encephalitis suggested an important role for CCR5 in host immune responses against the virus. However, the roles of CCR5 and CCR5Δ32 in infections by ZIKV, EBV, rhinovirus, and ROCV are still poorly understood and need to be investigated in future studies. The role of EVs in the transport of CCR5 between cells indicates that the expression of CCR5 on the cell surface may also depend on the release of EVs containing CCR5. Also, the transport of host molecules and viruses through EVs adds complexity to the topics covered in this review and should be taken into account in future studies that investigate the role of CCR5 in viral infections. Gene editing technologies have the potential to be used to treat different diseases, mainly when applied to somatic cells. However, CCR5 gene editing in human embryos presents a number of ethical problems. Besides, the absence of CCR5 can have deleterious effects in certain conditions, such as increased susceptibility to symptomatic WNV infection. Finally, this article showed that the participation of CCR5 in different viral infections is complex and varied and, therefore, cannot be generalized. This article also pointed out neglected gaps in knowledge involving CCR5 that should be addressed in future studies.

CRediT authorship contribution statement

Joel Henrique Ellwanger: Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Bruna Kulmann-Leal:** Investigation, Validation, Writing - review & editing. **Valéria de Lima Kaminski:** Investigation, Writing - review & editing. **Andressa Gonçalves Rodrigues:** Investigation, Writing - review & editing. **Marcelo Alves de Souza Bragatte:** Visualization, Writing - review & editing. **José Artur Bogo Chies:** Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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