INTRODUCTION

1.1 An overview of CCR5 and CCR5Δ32

The intense and varied interactions between microorganisms and humans shaped, and are still shaping, different resistance mechanisms of the host against pathogens, as well as distinct parasite/pathogens evasion strategies. In this context, cytokines are some of the most important components of innate and adaptative immune responses during infections (Teijaro, 2017). Cytokines are small cell-signalling molecules responsible for promoting and regulating the immune responses (Ferreira, Borba, Bonetti, Leonart, & Pontarolo, 2018).

Abstract

The CCR5 molecule was reported in 1996 as the main HIV-1 co-receptor. In that same year, the CCR5Δ32 genetic variant was described as a strong protective factor against HIV-1 infection. These findings led to extensive research regarding the CCR5, culminating in critical scientific advances, such as the development of CCR5 inhibitors for the treatment of HIV infection. Recently, the research landscape surrounding CCR5 has begun to change. Different research groups have realized that, since CCR5 has such important effects in the chemokine system, it could also affect other different physiological systems. Therefore, the effect of reduced CCR5 expression due to the presence of the CCR5Δ32 variant began to be further studied.

Several studies have investigated the role of CCR5 and the impacts of CCR5Δ32 on autoimmune and inflammatory diseases, various types of cancer, and viral diseases. However, the role of CCR5 in diseases caused by bacteria and parasites is still poorly understood. Therefore, the aim of this article is to review the role of CCR5 and the effects of CCR5Δ32 on bacterial (brucellosis, osteomyelitis, pneumonia, tuberculosis and infection by Chlamydia trachomatis) and parasitic infections (toxoplasmosis, leishmaniasis, Chagas disease and schistosomiasis). Basic information about each of these infections was also addressed. The neglected role of CCR5 in fungal disease and emerging studies regarding the action of CCR5 on regulatory T cells are briefly covered in this review. Considering the “renaissance of CCR5 research,” this article is useful for updating researchers who develop studies involving CCR5 and CCR5Δ32 in different infectious diseases.

KEYWORDS

C-C chemokine receptor type 5, CCR5Δ32, chemokines, host–pathogen interactions, inflammation, regulatory T cells
A group of cytokines is classified as chemokines since these molecules have chemotactic activity and are responsible for leucocyte migration from blood to tissues during inflammatory responses. Chemokine and their receptors are also involved in several biological processes besides cell migration, including those associated with HIV pathogenesis and the development of autoimmune diseases (Dinarello, 2007). Although the role of chemokines and their receptors in different infectious diseases has already been explored by several authors (Chensue, 2001; Murdoch & Finn, 2000), there is still scarce information regarding specific host-pathogen and chemokine interactions, as well as outcomes in a given disease. Moreover, a still little-explored topic concerns how high-penetrance genetic variants influence these interactions. Thus, the C-C chemokine receptor type 5 (CCR5) and the genetic variant CCR5Δ32 will be targeted in this article as a model to dissect, explain and understand such interactions.

CCR5 is a seven-domain transmembrane protein encoded by CCR5 gene (Combadiere, Ahuja, Tiffany, & Murphy, 1996; Raport, Gosling, Schweickart, Gray, & Charo, 1996; Samson, Labbe, Mollereau, Vassart, & Parmentier, 1996) and primarily expressed on leucocytes (Kunkel et al., 2002; Raport et al., 1996; Rottman et al., 1997; Wu et al., 1997), although its expression is also observed in cells of different tissues (Dorf, Berman, Tanabe, Heesen, & Luo, 2000; Raport et al., 1996; Rottman et al., 1997; Simpson et al., 2000; Vaday, Pehl, Kadam, & Lawrence, 2006). CCR5 acts as a receptor for different chemokines, mainly CCL3, CCL4 and CCL5 (Combadiere et al., 1996; Jones, Maguire, & Davenport, 2011; Lin et al., 2008; Murdoch & Finn, 2000; Raport et al., 1996; Samson, Labbe, et al., 1996). MCP-3/CCL7 is a natural CCR5 antagonist (Blanpain et al., 1999). The protein structure of CCR5 is shown in Figure 1 (panel a).

The interaction of chemokines with CCR5 regulates the action of inflammatory cells. For this reason, CCR5 is a crucial regulator on inflammatory responses (Brelot & Chakrabarti, 2018; Lederman, Penn-Nicholson, Cho, & Mosier, 2006). Dysregulation on chemokine-receptor interactions or altered expression of chemokines

![Figure 1: CCR5: fundamental aspects of protein and gene. Panel a: CCR5 polypeptide chain (snake diagram) originated from CCR5 ORF translation. CCR5 contains seven transmembrane domains, three extracellular loops (ECL1, ECL2 and ECL3). CCR5Δ32 affects the ECL2 and subsequent regions. Polypeptide chains of N-terminus (N-term) and C-terminus (C-term) are not shown. Panel b: Structure of the CCR5 gene, showing untranslated and coding regions. CCR5 is located on chromosome 3 (3p.21.31), downstream to CCR2, also indicated in the figure. CCR5 has three exons and two introns. ORF is located in exon 3. Gene location of the polymorphisms that compose the CCR5 human haplogroups are indicated in the figure. Details of each polymorphism are shown in Table 1. Leucocyte and receptor illustrations were obtained from Servier Medical Art (available at https://smart.servier.com, under a Creative Commons Attribution 3.0 Unported License). The structure of CCR5 protein was created using the GPCRdb (G Protein-Coupled Receptor database), available at http://gpcrdb.org/ (Munk et al., 2016; Pándy-Szekeres et al., 2018). Representation of CCR5-CCR2 genes and location of CCR2/CCR5 polymorphisms was created based on Lawhorn et al. (2013).](image-url)
and their receptors are linked to different diseases (Bernardini, Antonangeli, Bonanni, & Santoni, 2016; Chen et al., 2018). Also, pathological conditions such as viral infections can trigger alterations in CCR5 expression on the cell surface (Chenine, Sattentau, & Moulard, 2000; Kohlmeier et al., 2008; Lichterfeld et al., 2002) and therefore influence the dynamics of chemokine–receptor systems.

CCR5 has become widely known throughout the scientific community due to its role as an HIV type 1 (HIV-1) co-receptor, an important finding evidenced in 1996 by different groups (Alkhatib et al., 1996; Choe et al., 1996; Deng et al., 1996; Doranz et al., 1996; Dragic et al., 1996; Samson, Libert, et al., 1996). Also in 1996, it was reported that a 32-base pairs deletion in the coding region of the CCR5 gene, known as CCR5Δ32, was associated with relative resistance to HIV infection (Dean et al., 1996; Liu et al., 1996; Samson, Libert, et al., 1996). Therefore, 1996 can be considered as a landmark for research involving CCR5, a field that has strongly re-emerged in recent years.

Importantly, the frequency of the CCR5Δ32 allele is quite variable in human populations. As a general rule, it is elevated in populations from North Europe and less frequent, or even absent, in African and Asian populations (Martinson, Chapman, Rees, Liu, & Clegg, 1997; Novembre, Galvani, & Slatkin, 2005; Solloch et al., 2017). Within genetically admixed populations, such as the Brazilian population, its allele frequency is intermediate (around 4%–7%) (Ellwanger, Kulmann-Leal, et al., 2020; Ellwanger, Leal, et al., 2018; Silva-Carvalho, Moura, Coelho, Crovella, & Guimarães, 2016; Vargas, Marrero, Salzano, Bortolini, & Chies, 2006; Zambra, Biolchi, Brum, & Chies, 2013). Individuals homozygous for the Δ32 allele have resistance to HIV-1 infection, while heterozygous individuals carrying only one Δ32 allele, when infected by HIV, present a slower progression to AIDS as compared to Δ32 allele noncarriers. This slower disease progression is due to the phenotypic effects of this polymorphism. CCR5Δ32 homozygous individuals do not express CCR5 on the cell surface, while heterozygous individuals have reduced CCR5 expression (Brelot & Chakrabarti, 2018; Venkatesan et al., 2002; Wu et al., 1997). These findings drew much attention from the scientific community looking for genetic resistance factors against HIV infection. Since then, a high number of studies addressing the relationship between CCR5 and HIV have emerged. A PubMed search on February 2020 using the terms “HIV” and “CCR5” resulted in over 6,000 published articles.

The role of CCR5 in conditions unrelated to HIV infection has been neglected for many years. However, recently the research involving the influence of CCR5 on different conditions has been intensified. Such studies address the CCR5 molecule per se (Castanheira et al., 2019; Jiao et al., 2018; Liu et al., 2018; Umansky, Blattner, Gebhardt, & Utikal, 2017), CCR5 pharmacological blockade (Moy et al., 2017; Pervaiz et al., 2019), CCR5 gene editing (Xie, Zhan, Ge, & Tang, 2019) and the genetic variant CCR5Δ32 (Fatica et al., 2019; Kaminski, Ellwanger, Sandrim, Pontillo, & Chies, 2019; Kletenkov et al., 2019; Slomiński et al., 2017; Toson et al., 2017; Troncoso et al., 2018). The resurgence of research involving these different aspects of CCR5 is due to two main factors: the advancement of
gene-editing technologies, which allow the exploration of the metabolic and pathophysiologic effects of CCR5 editing (Allen et al., 2018; Qi et al., 2018; Vangelista & Vento, 2018; Xu et al., 2017), and the development of CCR5 blockers for clinical use (Vangelista & Vento, 2018). Recently, the different effects of CCR5 editing were much debated (Ellwanger, Kaminski, & Chies, 2019; Wang & Yang, 2019; Xie et al., 2019) after a Chinese scientist alleged to have performed this procedure on human embryos (Cryanoski & Ledford, 2019). Such a claim generated a series of criticisms regarding the ethical and clinical issues involved in this procedure (Krimsky, 2019; Wang, Li, Li, Gao, & Wei, 2018; Wang & Yang, 2019). Although the number of studies involving CCR5 over the years has remained relatively stable, interventions such as these have increased attention regarding studies with CCR5.

CCR5Δ32 has complex and variable effects, which may be "deleterious" or "protective" according to the disease or condition evaluated (Ellwanger et al., 2019; Lim, Glass, McDermott, & Murphy, 2006). The absence of CCR5 due to CCR5Δ32 may not be optimally compensated for by other chemokine receptors, inducing undesirable effects on the immune system in the face of specific immune challenges (Ellwanger, Kaminski, & Chies, 2020). These features make the investigation of the roles of CCR5Δ32 on different diseases even more interesting.

On the other hand, the use of CCR5 blockers has been increasingly explored, and several studies support the use of this technology for the treatment of different diseases. For example, CCR5 blockers have a good potential for treating various types of cancer (Halama et al., 2016; Halvorsen et al., 2016; Mencarelli et al., 2013; Nishikawa et al., 2019; Pervaiz et al., 2019; Sicoli et al., 2014; Tanabe, Sasaki, Mukaida, & Baba, 2016; Velasco-Velázquez et al., 2012), graft-versus-host disease (Moy et al., 2017; Reshef et al., 2019), inflammatory bowel disease (Mencarelli et al., 2016) and stroke (Joy et al., 2019). Therefore, the lack of CCR5 is deleterious in some situations, but blocking this receptor may be desirable in specific clinical contexts.

If we understand how the CCR5Δ32 variant is expressed and where and how the truncated molecule acts, it will be possible to infer the effects of CCR5 absence or low expression on different diseases without (or prior to) the need for gene-editing technologies or CCR5 pharmacological blockade. Also, gene–disease association studies are important tools for the discovery of potential therapeutic targets (Hill, 2012; Segal & Hill, 2003), especially considering the existence of CCR5 blockers already approved for use in humans (Vangelista & Vento, 2018). Thus, to investigate the effects of CCR5Δ32 (and potentially of the low expression of CCR5) in distinct physiological and pathologic conditions will help to define where and when the use of CCR5 blockers could be advantageous. Additionally, this type of study allows the discovery of genetic factors of susceptibility or resistance to different infectious diseases (Frodsham & Hill, 2004; Hill, 2012; Segal & Hill, 2003). In this sense, the main objective of this article is to review the role of CCR5 and the impacts of CCR5Δ32 in different bacterial and parasitic infections, which are little-explored fields in the context of CCR5 research. The following bacterial infections are covered in this article: brucellosis, osteomyelitis, pneumonia (Mycoplasma pneumoniae and Streptococcus pneumoniae), tuberculosis and infection by Chlamydia trachomatis. Regarding parasitic infections, toxoplasmosis, leishmaniasis, Chagas disease and schistosomiasis are included in this review. Considering the variety of infections addressed, basic information about each of them is also described. Also, the structure of the CCR5 gene and protein, some relevant CCR5 polymorphisms, and evolutionary aspects of CCR5Δ32 are addressed. Finally, the role of CCR5 in fungal diseases and emerging studies regarding the combined action of CCR5 and regulatory T cells are briefly discussed.

### 1.2 The structure of the CCR5 gene and its polymorphisms

The CCR5 gene is located on chromosome 3 (cytogenetic band 3p.21.31), has a length of 6,065 bases and is composed of three exons and two introns. CCR5 ORF (Open Reading Frame) contains 1,056 bases and is located on exon 3. The protein generated by its translation has a total of 352 residues (Hoover, 2018; Liu et al., 1996; Mummidi et al., 2000). Spatially, the CCR5 is very close to the CCR2, another chemokine receptor gene, the last one being upstream to CCR5 (Lawhorn et al., 2013). Figure 1 (panel b) schematizes CCR5 gene structure and flanking regions. Also, there is a recently described long noncoding RNA (lncRNA) gene overlapping with CCR5, termed CCR5AS, whose expression is positively correlated with CCR5 mRNA levels (Kulkarni et al., 2019). This finding is quite relevant due to the impact of noncoding genetic elements on the susceptibility and progression of infectious diseases (Ellwanger, Zambra, Guimarães, & Chies, 2018).

The human CCR5 is very polymorphic at genetic and protein levels (Blanpain et al., 2000; Carrington et al., 1997; Hoover, 2018; Shioda et al., 2001; Suzuki et al., 2002). According to Hoover (2018), there are approximately 260 single nucleotide variants (SNVs) in the CCR5 gene, being ~40 in the ORF region (Hoover, 2018). Many CCR5 variants were already addressed in viral, bacterial and parasitic infections, and some have a notorious role in particular outcomes. For example, in Trypanosoma cruzi infection, several CCR5 polymorphisms (rs333, rs3176763, rs11575815, rs1799988, rs1800024, rs2856758) were associated to differential clinical outcomes (Batista et al., 2018; Calzada, Nieto, Beraún, & Martín, 2001; Flórez, Martín, & González, 2012; Frade et al., 2013; Machuca, Suárez, Echeverría, Martín, & González, 2014; Nogueira et al., 2012; Oliveira et al., 2015, 2016). Recently, a genetic variant similar to CCR5Δ32, called CCR5Δ42, has been associated with HIV protection in the African population (Arendt et al., 2019). This latter polymorphism also affects the expression of CCR5 on the cell surface and, therefore, may have functional effects in African populations, similar to CCR5Δ32 in Euro-descendant individuals. Of note, eight CCR5 variants, including the above-mentioned rs333 (CCR5Δ32), rs1799988 (CCR5Δ2135), rs1800024 (CCR5Δ1835) and rs2856758 (CCR5Δ2733), compose the CCR5 human haplogroups (Table 1). These haplogroups are of special interest
since they are associated with different phenotypes, along with a variant in the CCR2 gene. The location of these nine polymorphisms in the CCR2-CCR5 gene region is shown in Figure 1 (panel b).

Multiple studies addressing CCR5 haplotypes and their importance in different scenarios were already published (Huik et al., 2013; Malhotra et al., 2011; Pedersen et al., 2007; Picton, Paximadis, & Tiemessen, 2012; Rocco, Mangoano, Pozo, & Sen, 2003; Vega et al., 2017). The analysis addressing the effect of the CCR5 haplotypes on infectious diseases is a very interesting strategy because it considers the influence of different genetic variants on CCR5 expression (Mehlotra, 2019). According to Gonzalez et al. (1999), there are nine different CCR5 human haplogroups (HH): HHA, HHB, HHC, HHD, HHE, HHF*1, HHF*2, HHG*1 and HHG*2. Those haplogroups differ in frequency among different populations. Given the physical proximity of the CCR2 and CCR5 genes, a CCR2 variant (CCR2 +190) is also included in the CCR5 haplotypic analysis (Gonzalez et al., 1999; Lawhorn et al., 2013; Mehlotra, 2019). The details of each haplogroup and the variants analysed are summarized in Table 1.

1.3 | Origin and evolutionary aspects of CCR5Δ32

CCR5Δ32 is a genetic variant originating from a single mutation event that occurred in Europe (Galvani & Novembre, 2005; Libert et al., 1998; Stephens et al., 1998). Due to its European origin, the Δ32 allele frequency is higher in Euro-descendant populations. The highest allele frequencies are observed specifically in populations in northern Europe, in countries such as Denmark, Estonia, Finland, Latvia, Lithuania and Norway. In these specific countries, the allele frequency of the CCR5Δ32 is higher than 12% (Solloch et al., 2017). Migratory flows and miscegenation processes have spread the Δ32 allele among different human populations. For these reasons, the CCR5Δ32 can be found at relatively high frequencies in populations outside the European continent, as in Brazil, where it is not difficult to observe the presence of the variant in the southern region of the country (Ellwanger, Kulmann-Leal, et al., 2020; Silva-Carvalho et al., 2016).

It was estimated that the origin of the CCR5Δ32 in the human population occurred about 700 years ago (considering a range of 275–1,875 years) (Stephens et al., 1998). An origin between 1,400 and 3,500 years ago was estimated in another work (Libert et al., 1998). However, studies evaluating ancient DNA showed that the CCR5Δ32 might be older than these estimates, being prevalent in prehistoric Europeans (Bouwman, Shved, Akgül, Rühli, & Warinmer, 2017; Faure & Royer-Carenzi, 2008; Hedrick & Verrelli, 2006; Hummel, Schmidt, Kremeyer, Herrmann, & Oppermann, 2005; Zawicki & Witas, 2008). Sabeti et al. (2005) estimated that the origin of the CCR5Δ32 in the human population occurred more than 5,000 years ago, which is in agreement with evidence pointing to the presence of the Δ32 allele in samples of ancient DNA. Of note, there is additional evidence pointing to the presence of the Δ32 allele for even 7,000 years ago (Faure & Royer-Carenzi, 2008).

The origin area of the CCR5Δ32 may not be the same as the current areas of the highest Δ32 allele frequency (Novembre et al., 2005). Considering its spread, Vikings may have contributed to the dissemination of the Δ32 allele across Europe (Galvani & Novembre, 2005; Lucotte, 2002; Lucotte & Dieterlen, 2003; Novembre et al., 2005). Negative selection during the Roman expansion may also have played a role in determining the currently observed frequency of the Δ32 allele. Interestingly, Romans could have contributed to the decrease of allele frequency in ancient European populations in which the allele was highly prevalent (Faure & Royer-Carenzi, 2008). Climatic conditions and geographical characteristics may also have affected, directly or indirectly, the distribution and frequency of the Δ32 allele (Balanovsky et al., 2005; Limborska et al., 2002).

Selective pressures can have acted on CCR5Δ32, favouring its expansion in the human population (Libert et al., 1998; Stephens et al., 1998). Although CCR5Δ32 homozygous genotype protects against HIV (an adaptive advantage considering a scenario of high HIV circulation), this pathogen was not responsible for increasing the frequency of the variant in the human population, since the HIV/AIDS pandemic is recent in human history (Galvani & Slatkin, 2003). Different authors have tried to discover the potential selective pressures responsible for the fixation of the CCR5Δ32 in the genome (>1% rate) and subsequent expansion of the Δ32 allele in the European population. It was hypothesized that an epidemic in Europe could have been an essential selective event that acted on the Δ32 allele (Carrington et al., 1997; Stephens et al., 1998). In this case, CCR5Δ32 would have been a protective factor against a particular infectious disease, giving an evolutionary advantage to individuals bearing the Δ32 allele. Consequently, the CCR5Δ32 increased in frequency and spread in the European population. In other words, the allele would have undergone positive selection.

The Black Death occurred between 1,346 and 1,352, representing the historically most important epidemic of bubonic plague, an infectious disease caused by the bacterium Yersinia pestis. During Black Death, 25%–33% of Europeans died from bubonic plague. Black Death and other bubonic plague outbreaks were hypothesized as a central selective pressure on CCR5Δ32, since Y. pestis infection cases occurred in epidemic proportions in the geographical region where the CCR5Δ32 is currently observed in high frequency. The period of occurrence of Black Death (~650 years ago), together with the first estimates that pointed to a recent origin of the CCR5Δ32 (~700 years ago), helped to support this hypothesis (Stephens et al., 1998). The connection between bubonic plague, CCR5Δ32 and HIV has become widely known in the scientific community and among the lay public through the media (Stumpf & Wilkinson-Herbots, 2004). However, various studies based on mathematical models, historical evidence, population data, animal models of Y. pestis infection and ancient DNA analysis did not support this hypothesis (Baron & Schembri-Wismayer, 2011; Bouwman et al., 2017; Cohn & Weaver, 2006; Galvani & Novembre, 2005; Galvani & Slatkin, 2003; Hummel et al., 2005; Kremeyer, Hummel, & Herrmann, 2005; Mecsas et al., 2004; Styer, Click, Hopkins, Frothingham, & Abalay, 2007). Of note, CCR5−/− mice are not resistant to Y. pestis infection (Mecsas et al.,
2.1 | Brucellosis

Brucellosis, also known as Malta fever, is a common zoonosis caused by bacteria of the *Brucella* genus. Classically, three main species are responsible for infection in humans: *Brucella melitensis*, *Brucella abortus* and *Brucella suis* (Boschirol, Foulongne, & O’Callaghan, 2001; Franco, Mulder, Gilman, & Smits, 2007), although *Brucella canis* can also infect humans (Bukhari, 2018). Monocytes and macrophages are the main replication sites of *Brucella* spp., being also their cellular reservoirs (Wang, Li, et al., 2017). Brucellosis is a febrile disease that, in some cases, is severe and debilitating (Boschirol, et al., 2001; Franco et al., 2007). This disease has an incubation time of 2–4 weeks and triggers a broad spectrum of manifestations, including fever, headache, chills, arthralgia, fatigue and osteoarticular infection (Bukhari, 2018; Harrison & Posada, 2018). Approximately 500,000 new cases are identified annually worldwide (Harrison & Posada, 2018; Pappas, Papadimitriou, Akritidis, Christou, & Tsianos, 2006).

*Brucella* spp. is commonly transmitted by the ingestion of contaminated/unpasteurized milk of sheep, cow, goat and camel. In addition, other forms of transmission have also been reported, such as congenital, sexual and breastfeeding (Harrison & Posada, 2018). *Brucella* spp. infection can also occur via inhalation, damaged skin and conjunctiva (Franco et al., 2007). Cases of paediatric infection are common, mainly in endemic countries. In low-income countries, paediatric infection is associated with contact of children with animals and ingestion of unpasteurized milk (Alshaalan et al., 2014; Bukhari, 2018).

Pronounced inflammation is a key feature of *Brucella*-infected tissues. One interesting characteristic of brucellosis is the apparent milder inflammatory response in the affected organism, but the long-term presence of the pathogen leads to tissue damage through the production of cytokine and chemokines (Baldi & Giambartolomei, 2013; Krishnan, Kaplin, Graber, Darman, & Kerr, 2005; Seidel, Pardo, Newman-Toker, Olivi, & Eberhart, 2003). Considering the potential role of CCR5 in the immune response against *Brucella* infection and interactions of the pathogen with CCR5+ cells, Skendros, Boura, Tsantas, Debre, and Theodorou (2002) evaluated the influence of CCR5Δ32 in both susceptibility and outcome of human brucellosis. Of note, it was observed a deviation from the Hardy–Weinberg equilibrium within the brucellosis group due to the proportion of CCR5Δ32 homozygous patients (2 out of 185 individuals). Although the authors have suggested that this result may indicate an association of CCR5Δ32 with the disease, no statistically significant difference in the CCR5Δ32 allele frequency between patients with brucellosis and controls was detected. Also, no difference was found between patients with acute brucellosis and those with chronic/relapsing brucellosis (Skendros et al., 2002). In general terms, the available data do not support a pivotal influence of CCR5Δ32 on *Brucella* spp. infection. However, to the best of our knowledge, only the study of Skendros et al. (2002) evaluated the CCR5Δ32 in the context of brucellosis so far.

2.2 | Chlamydia trachomatis infection

*Chlamydia trachomatis* infection is registered worldwide, with an overall prevalence of 1%–6% (Rawre, Juyal, & Dhawan, 2017). It was estimated that approximately 90 million people are infected by *C. trachomatis* each year (Starnbach & Roan, 2008). This infection is sexually transmitted and is a common cause of nonnongonococcal...
urethritis (Rawre et al., 2017). Infection by C. trachomatis is generally an asymptomatic and nonfatal disease, but untreated infection can lead to chronic production of pro-inflammatory cytokines, resulting in tissue damage and inflammation-related diseases, including pelvic inflammatory disease. In the long term, this condition in women can cause ectopic pregnancy and tubal factor infertility. Other consequences of long-term infection are the development of epididymitis and proctitis in men (Brunham & Rey-Ladino, 2005; Rawre et al., 2017; Starnbach & Roan, 2008). Moreover, one of the possible complications after infection is the emergence of postvaginal reactive arthritis, a form of inflammatory arthritis (Carter & Hudson, 2009).

The chemokines CXCL9, CXCL10 and the CCR5 ligand CCL5 are upregulated in cells from the upper genital tract after C. trachomatis infection (Maxion & Kelly, 2002). Also, two studies performed with mice have shown that CCR5 has a fundamental role in T cell-mediated clearance of C. trachomatis in genital mucosa (Barr et al., 2005; Olive, Gondek, & Starnbach, 2011). In humans, the presence of CCR5Δ32 was associated with increased C. trachomatis burden, based on the measurement of bacterial chromosome copies in synovial biopsies (Gérard et al., 2010). Taking into consideration that CCR5Δ32 may affect the activity of inflammatory cells involved in C. trachomatis-associated diseases, the potential impacts of this polymorphism on C. trachomatis infection was assessed in a few studies.

Barr et al. (2005) evaluated the effect of CCR5Δ32 on the risk of developing tubal pathology in Caucasian subfertile women seropositive for C. trachomatis infection. Although no statistically significant differences in the CCR5Δ32 frequency between subfertile women and controls were found, a higher frequency of CCR5Δ32 was observed in women seropositive for C. trachomatis without tubal pathology as compared to women with tubal pathology (Barr et al., 2005). This result suggests that, in the context of C. trachomatis infection, the CCR5Δ32 could protect against tubal pathology. However, the sample size used in this specific analysis was limited (n = 41 in total), and this result must be considered with prudence. Moreover, the CCR5Δ32 was not a protective factor of tubal pathology development in C. trachomatis-infected women in a subsequent study that evaluated 174 women with reproductive problems (99 positive for C. trachomatis) and 126 fertile women (42 positive for C. trachomatis), both groups from India (Mania-Pramanik, Kerkar, Vallabhadas, Mehta, & Salvi, 2011).

Finally, Carter et al. (2013) investigated the effect of CCR5Δ32 on the susceptibility to C. trachomatis-associated reactive arthritis in a sample of the North American population, but no association between the polymorphism and the disease was found. Taking together, the results mentioned above do not support a critical role of CCR5Δ32 in the development of C. trachomatis-associated diseases.

2.3 | Osteomyelitis

Osteomyelitis is a bone inflammation associated to infections (mainly Staphylococcus aureus). Healthy bones have high resistance to infections. Thus, osteomyelitis is more likely to occur among patients presenting conditions such as decubitus ulcers, surgery, traumas, intravenous drug use and diabetes (Chihara & Segreti, 2010). Diabetic foot ulcers and diabetic foot infections often trigger osteomyelitis (Malhotra, Chan, & Nather, 2014). The disease causes destruction of the bone and can occur in different clinical forms: secondary to a contiguous focus of infection, secondary to vascular insufficiency, or from haematogenous origin. Osteomyelitis may develop acutely or chronically (Lew & Waldvogel, 2004). Furthermore, osteomyelitis can be classified into 12 different clinical stages, combining the anatomical type affected by the disease (medullary, superficial, localized or diffuse) with the patient’s physiological state (Birt, Anderson, Bruce Toby, & Wang, 2017). The disease encompasses a wide range of symptoms: chills, fever, fatigue, irritability, pain, local swelling, lethargy and malaise (Chihara & Segreti, 2010; Lew & Waldvogel, 2004). Due to physiological and anatomical characteristics of bones, osteomyelitis is a difficult-to-treat condition (Lew & Waldvogel, 2004).

It was suggested that CCR5 is important for S. aureus pathogenesis (Alonzo et al., 2013; Alonzo & Torres, 2013; De Souza et al., 2015). Specifically, Alonzo et al. (2013) have shown that CCR5 acts as a receptor for S. aureus leukotoxin ED (LukED), a toxin that promotes cell death, and that CCR5-deficient mice are strongly protected from lethal S. aureus infection.

De Souza et al. (2015) performed a cohort study in a sample of the Northeast Brazilian population, aiming to assess the influence of the CCR5Δ32 polymorphism on the risk of developing osteomyelitis after bone traumas. As expected, S. aureus was the main pathogen responsible for osteomyelitis in the studied patients. Interestingly, most of Δ32 allele carriers were found in the group of patients who did not develop osteomyelitis. This result suggests a protective effect of the CCR5Δ32 against osteomyelitis, but no statistically significant results were found (De Souza et al., 2015).

Although the influence of CCR5 and CCR5Δ32 on osteomyelitis has been sparsely studied, when considered together, the results obtained in mice (Alonzo et al., 2013) and humans (De Souza et al., 2015) indicate that CCR5 and the CCR5Δ32 may play essential roles on the development of S. aureus-associated osteomyelitis. These topics should be studied more intensely, mainly because the use of CCR5 blockers, such as maraviroc, may have a beneficial effect in the treatment of S. aureus infection (Alonzo et al., 2013; Alonzo & Torres, 2013).

2.4 | Mycoplasma pneumoniae infection

Mycoplasmas are the smallest self-replicating bacteria with the capacity of cell-free existence. Some mycoplasmas are causative agents of human diseases. Among them, Mycoplasma pneumoniae is responsible for 20%–40% of community-acquired bacterial pneumonia cases during epidemics (Waites & Talkington, 2004; Waites, Xiao, Liu, Balish, & Atkinson, 2017), although other authors mention variable percentages (Parrott, Kinjo, & Fujita, 2016). China, Russia,
Mexico and Brazil are among the countries with the highest number of *M. pneumoniae* cases per 100,000 people (Parrott et al., 2016).

*Mycoplasma pneumoniae* is a human-specific obligate parasite that inhabits epithelial tissues, such as those of the urogenital and respiratory tracts (Waites & Talkington, 2004; Waites et al., 2017). When the pathogen reaches the respiratory tract, it invades epithelial cells, causing cilia destruction and compromising the respiratory capacity. Such events are accompanied by an important inflammatory reaction in the lungs (Waites & Talkington, 2004). *M. pneumoniae* pneumonia occurs in adults and children but is generally more harmful to the second group (Parrott et al., 2016). The severity of the infection ranges from mild to life-threatening. Of note, *M. pneumoniae* can cause asthma and persistent cough, and even promote extrapulmonary manifestations located mainly in brain, skin, but also other organs (Parrott et al., 2016; Waites et al., 2017).

A set of evidence points to a role of CCR5 in the pathophysiology of distinct respiratory diseases (Bracke, Demedts, Joos, & Brusselle, 2007; Capelli, Stefano, Gnemmi, & Donner, 2005; Dawson, Beck, Kuziel, Henderson, & Maeda, 2000). Host immune factors affect the response against *M. pneumoniae* infection and modify the course of lung disease (Waites et al., 2017). In this context, Ungvári et al. (2007) assessed the possible associations of *M. pneumoniae* infection and the allele distribution of CCR5Δ32 in Hungarian children with asthma. The authors described an association between CCR5Δ32 and chronic *M. pneumoniae* infection. Also, they found that *M. pneumoniae*-infected children with the Δ32 allele have a reduced risk of developing asthma as compared to Δ32 allele noncarriers (Ungvári et al., 2007). These findings, as well the data presented in some of the next topics here discussed, indicate that, although the role of CCR5 in respiratory infections is still a neglected topic, it should be explored in greater detail.

### 2.5 | *Streptococcus pneumoniae* infection

*S. pneumoniae* can cause respiratory diseases in humans, including community-acquired pneumonia. Infection by this bacterium affects mainly children, elderly people, and individuals with a deficient immune function. In some cases, the disease can be fatal (Brooks & Mias, 2018). As expected, different cell receptors, chemokines and host cell pathways are involved in the immune responses against *S. pneumoniae*. The inflammatory profile of each individual can significantly influence such responses, affecting bacterial pathogenesis and transmission (Brooks & Mias, 2018). In this context, there is evidence that CCR5 and its ligand CCL5 have some influence on the interactions between *S. pneumoniae* and the host (Palaniappan et al., 2006).

Evaluating Russian individuals, Salnikova, Smelaya, Moroz, Golubev, and Rubanovich (2013) investigated the influence of CCR5Δ32 on the susceptibility to community-acquired pneumonia. *S. pneumoniae* (alone or together with other infectious agents) was detected as the causative agent of most cases of pneumonia in the evaluated patients. In their study using multiple SNP analysis, the wild-type genotype of CCR5 was a risk factor for community-acquired pneumonia. Therefore, the Δ32 allele is a potentially protective factor against the disease (Salnikova et al., 2013). However, it is essential to consider that this is a population-specific finding. This study should be replicated in other populations so that broader conclusions are possible.

### 2.6 | Tuberculosis

Tuberculosis is an infection caused by bacterial species belonging to the *Mycobacterium tuberculosis* complex. The infection affects mainly the lungs but may also occur in other organs (Pai et al., 2016). Of note, individuals exposed to *Mycobacterium tuberculosis* can eliminate the pathogen without clinical manifestations. If elimination does not occur, the individual may develop latent or active infection. The disease will manifest depending on the immunological conditions and comorbidities of the host (Pai et al., 2016). Tuberculosis is the leading cause of death among human infectious diseases, being considered one of the main public health concerns nowadays (Azad, Sadee, & Schlesinger, 2012; Furin, Cox, & Pai, 2019). Drug-resistant tuberculosis is a growing problem, making the epidemiological situation of this disease even more worrying. It is estimated that each year more than 10 million new cases of tuberculosis occur worldwide (Furin et al., 2019).

Historically, humans and *M. tuberculosis* have a long and strong host-parasite interaction. This interaction left marks on the genome of both organisms. As a consequence, the susceptibility to tuberculosis varies in different human populations (Azad et al., 2012). Variants of immune system-related genes play a prominent role in the differential susceptibility to this infection, including polymorphisms of CCL5, the gene encoding one of the major ligands of CCR5 (Azad et al., 2012; Mhmoud, Fahal, & Wendy van de Sande, 2013; Mishra, Poojary, Raj, & Tiwari, 2012).

Different lines of evidence point to the existence of a relationship between CCR5 and tuberculosis. Infection with *M. tuberculosis* was associated with increased CCR5 expression (Juffermans et al., 2001). A study using mice and in vitro experiments suggested that the pathogen may stimulate CCR5 expression and consequent CCR5 downstream signalling as a mechanism to subvert the immune response (Das et al., 2014). Thus, based on evidence showing a functional interaction between CCR5 and *M. tuberculosis*, CCR5Δ32 could also have some effect on the pathogenesis of tuberculosis.

Mamtani et al. (2011) evaluated the effects of CCR5 haplotypes (including CCR5Δ32 and eight other CCR5 variants) on tuberculosis in Colombian individuals (Mamtani et al., 2011; Mummidji et al., 2000). The haplotype CCR5-HHD (in which CCR5Δ32 wild-type allele is present; see Table 1 for complete haplotype description) was associated with increased CCR5 expression and was considered a risk factor for tuberculosis (Mamtani et al., 2011). Therefore, in accordance with studies mentioned above (Das et al., 2014; Juffermans et al., 2001), increased CCR5 expression may contribute to greater susceptibility to tuberculosis, as well as to disease pathogenesis.
(Mamtani et al., 2011). Unfortunately, studies evaluating the effect of CCR5Δ32 as an individual factor in the context of tuberculosis were not available. Thus, although haplotypic analyses (Mamtani et al., 2011) suggest that the wild-type genotype of CCR5 is a risk factor for disease development, this approach needs to be explored in further studies.

3 | CCR5 AND CCR5Δ32 IN PARASITIC INFECTIONS

3.1 | Toxoplasmosis

Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii*, an intracellular protozoan. Humans are infected by handling/ingestion of undercooked or raw meat (particularly pork and lamb meat) containing *T. gondii* cysts or water/food contaminated with parasite oocysts. Cats are definitive hosts of *T. gondii* and can participate in the disease transmission cycle by eliminating parasite oocysts through faeces, contaminating drinking water. Transmission of *T. gondii* by organ transplantation or during pregnancy may also occur (Montoya & Liesenfeld, 2004). Around 30% of the world’s population has serological evidence of *T. gondii* infection, a particularly important problem in HIV-infected individuals (Wang, Wang, et al., 2017). In most human cases (~90%), the primary infection is asymptomatic. However, some infected individuals can develop cervical lymphadenopathy, heart problems or ocular manifestations (chorioretinitis). Latent infection is generally asymptomatic, but reactivation can occur in immunocompromised patients, leading to toxoplasmic encephalitis. Infection during pregnancy is associated with birth defects, including blindness, microcephaly and intracranial calcifications (Montoya & Liesenfeld, 2004).

Host cell lysis, hypersensitivity and inflammatory responses triggered by *T. gondii* infection are the main responsible factors for the health problems observed in immunocompetent and immunocompromised patients. Therefore, cytokines and chemokines are essential regulators of toxoplasmosis immunopathology (Gaddi & Yap, 2007). In this context, several studies have shown that CCR5 signalling has different and fundamental roles in *T. gondii* infection. CCR5 participates in processes that contribute to parasite persistence as well as in the host immune response against the parasite (Bonfá et al., 2014; Denkers, 2003; Diana et al., 2005; Golding et al., 2003; Ibrahim, Bannai, Xuan, & Nishikawa, 2009; Khan et al., 2006; Kikumura, Ishikawa, & Norose, 2012; Luangsay et al., 2003; Nishimura, Umeda, Suwa, Furuoka, & Nishikawa, 2017; Scanga et al., 2002). For example, *T. gondii* can secrete cyclophilin-18, a chemokine mimic that binds to CCR5, promoting IL-12 production, which is one of the molecules used by the parasite to modulate the host immune response (Denkers, 2003). CCR5 promotes control of *T. gondii* infection and is important to maintain the metabolic, hepatic and intestinal integrity of the host (Bonfá et al., 2014). Also, CCR5 absence can increase susceptibility to *T. gondii* (Bonfá et al., 2014; Khan et al., 2006). Finally, a recent study suggested that CCR5 participates in the regulation of inflammatory response, tissue injury and elimination of *T. gondii* infection in the brain (Kobayashi et al., 2019).

Human genetic traits, especially variants in HLA, TLR and cytokine genes, have a fundamental involvement in the development of ocular toxoplasmosis (Fernández, Jaimes, Ortiz, & Ramírez, 2016). Polymorphisms of the CCR5 gene could impact ocular toxoplasmosis (De Faria Junior et al., 2018). Also, there is a body of evidence supporting an involvement of the CCR5Δ32 variant in toxoplasmosis. Meyer et al. (1997) evaluated the effect of CCR5Δ32 on HIV disease progression in a sample of Caucasian individuals. Looking at results regarding CCR5Δ32 and toxoplasmosis, this infection was observed only in wild-type individuals, suggesting that the heterozygote genotype could have a protective effect on *T. gondii* infection (Meyer et al., 1997). The protective effect of the Δ32 allele on toxoplasmosis development in HIV-infected individuals was confirmed in later studies (Ashton et al., 2002; Meyer et al., 1999). However, these results should be interpreted with caution, as the scenario of treatment and prevention of HIV infection has changed immensely since they were conducted.

In a brief description, Vallochi et al. (2008) reported no association between the CCR5Δ32 variant and ocular toxoplasmosis in Brazilian individuals. Subsequently, De Faria Junior et al. (2018) investigated the polymorphism in patients with ocular toxoplasmosis and healthy controls from Brazil. The study found no statistically significant differences regarding CCR5Δ32 allelic and genotypic frequencies between cases and controls, considering the polymorphism as an individual factor in the analysis. However, individuals with CCR5 wild-type genotype (normal CCR5 expression) plus AA or AG genotypes from CCR5-59029 A/G variant (rs1799987) showed a higher risk of ocular toxoplasmosis development (De Faria Junior et al., 2018).

3.2 | Leishmaniasis

Leishmaniasis is a tropical vector-borne infection caused by parasites from *Leishmania* genus. The transmission of leishmaniasis between mammalian species occurs through the bite of sandflies (Burza, Croft, & Boelaert, 2018; Pace, 2014). Although several species can cause leishmaniasis, the main ones are *Leishmania infantum*, *Leishmania donovani*, *Leishmania tropica*, *Leishmania major*, *Leishmania braziliensis*, *Leishmania mexicana*, *Leishmania amazonensis*, *Leishmania guyanensis* and *Leishmania aethiopica* (Burza et al., 2018). After malaria, leishmaniasis is the deadliest parasitic disease in humans, with a mortality rate of 10%–20% in low-income countries (Pace, 2014). Leishmaniasis is endemic in approximately 100 countries (Alvar et al., 2012; Burza et al., 2018). However, few countries (Bangladesh, Brazil, India, Ethiopia, Kenya, Somalia, South Sudan and Sudan) encompass more than 90% of worldwide cases of visceral leishmaniasis, and therefore, the disease is considered an important public health issue in these countries (Alvar et al., 2012; Burza et al., 2018; Pace, 2014). Noteworthy, the rise of international travelling has been
facilitated the number of new leishmaniasis cases in nonendemic countries (Pace, 2014).

Leishmania spp. infection can be asymptomatic or cause cutaneous, mucocutaneous, or visceral disease (Burza et al., 2018; Pace, 2014). The clinical outcome of this disease depends on the infecting species, vector biology and the host immune response (Burza et al., 2018). The levels of CCR5+ cells and CCR5 expression are increased in HIV/Leishmania co-infected individuals (Nigro et al., 2007; Vallejo et al., 2015). Interestingly, CCR5 facilitates parasite persistence by modulating the migration of regulatory T cells in the host in an animal model of L. major infection (Yurchenko et al., 2006). In a preliminary analysis, these findings suggest that CCR5∆32 could reduce this phenomenon and even promote some protection against leishmaniasis. However, studies with humans do not point in this direction. Brájão de Oliveira et al. (2007) assessed the influence of CCR5∆32 in the progression from cutaneous to mucocutaneous leishmaniasis in a Brazilian population sample (from Paraná State). The allele frequencies were not statistically different between leishmaniasis patients and healthy controls. Regarding disease progression/severity, the ∆32 allele was related to a protective effect on these aspects, but also without statistical significance. The small sample number used in this study (100 individuals in each group) probably influenced these results (Brájão de Oliveira et al., 2007). Subsequently, another study evaluating the effect of CCR5∆32 on the cutaneous leishmaniasis pathogenesis was performed with individuals from Paraná State, Brazil (Ribas et al., 2013). This study found no statistically significant difference when genotypes were compared between leishmaniasis patients and controls. On the other hand, the CCR5∆32 heterozygous genotype was associated with disease recurrence, suggesting that the ∆32 allele may be a risk factor for the pathogenesis of the disease (Ribas et al., 2013). However, this result should be interpreted with caution due to the very small sample size employed in this specific analysis.

Finally, Sophie et al. (2016) analysed the frequency of the CCR5∆32 in Pakistani individuals with cutaneous leishmaniasis. However, CCR5∆32 was not associated with protection or susceptibility to leishmaniasis when patients were compared to controls. Taken together, the three studies reviewed here (Brájão de Oliveira et al., 2007; Ribas et al., 2013; Sophie et al., 2016) suggest that CCR5∆32 has no major effect on leishmaniasis development.

3.3 | Chagas disease

Chagas disease (American trypanosomiasis) is caused by Trypanosoma cruzi infection and is one of the most important public health problems in Latin America. Of note, T. cruzi infection is a neglected tropical disease with critical social and economic impacts. Triatominine bugs are the main vectors of T. cruzi (Ayo et al., 2013; Pérez-Molina & Molina, 2018). In brief, an individual becomes infected when metacyclic trypomastigotes of T. cruzi, found in faeces of an infected triatominine bug, penetrate the skin through lesions produced by the bug’s oral apparatus following a blood meal on human skin. The parasite can also penetrate the host through mucosal membranes (Pérez-Molina & Molina, 2018). Humans can also be infected by T. cruzi in other ways, including the ingestion of contaminated food and by congenital or sexual transmission (Ayo et al., 2013).

The clinical manifestations of Chagas disease are divided into acute and chronic phases. The acute phase is usually short (4–8 weeks) and asymptomatic, but high parasitemia is present. In most cases, the acute infection resolves spontaneously, but a portion of individuals may develop chronic infection, especially if untreated. Chronic infection is asymptomatic in most cases (Ayo et al., 2013; Pérez-Molina & Molina, 2018). On the other hand, it is estimated that ~40% of chronically infected patients develop specific organ diseases 10–30 years after acute infection. Such diseases are cardiomyopathy (Chagas heart disease) or megaviscera, including megaesophagus and megacolon. Heart disease is the most frequent and severe manifestation observed in chronically infected individuals (Pérez-Molina & Molina, 2018).

The occurrence and progression of heart disease in Chagas disease patients is influenced by the effect of host immune responses (mainly the inflammatory profile) on the persistence of infection. Although inflammation is important to limit parasite action on the host, in general, an inflammatory environment facilitates the establishment and progression of Chagas heart disease. In addition, Trypanosoma-related factors and human genetics also have a critical impact on the different manifestations of Chagas disease (Ayo et al., 2013; Oliveira et al., 2016; Pérez-Molina & Molina, 2018; Vasconcelos, Montenegro, Azevedo, Gomes, & Morais, 2012). Looking at host genetics, HLA alleles and variants in cytokine genes impact both resistance and susceptibility to Chagas diseases and the associated health problems (Ayo et al., 2013; Vasconcelos et al., 2012).

Moreover, a body of evidence supports the involvement of the CCR5 protein (Batista et al., 2018; Dutra, Rocha, & Teixeira, 2005; Hardison et al., 2006; Kroll-Palhares et al., 2008; Machado et al., 2005; Marino et al., 2005; Medeiros et al., 2009; Roffe et al., 2019; Roffé et al., 2010; Silva et al., 2007), as well as gene variants of CCR5 and CCR5 ligands (Batista et al., 2018; Calzada et al., 2001; Flórez et al., 2012; Machuca et al., 2014; Oliveira et al., 2015, 2016) on varied aspects of Chagas disease, mainly associated to the development of Chagas heart disease. For example, animal-based evidence pointed to a protective role of CCR5 in controlling T. cruzi replication and maintaining a protective immune response in acute infection (Hardison et al., 2006). On the other hand, CCR5 may participate in the inflammation and heart damage observed in Chagas heart disease (Batista et al., 2018; Roffe et al., 2019), suggesting that CCR5 deficiency might play a protective role against Chagas-associated cardiomyopathy. Therefore, CCR5 has two basic conflicting effects on Chagas disease: it is protective in the acute phase and acts as a facilitator of disease-related inflammation in chronic infection (Oliveira et al., 2016). Interestingly, the potential use of pharmacological CCR5 modulators to treat Chagas disease has already been suggested by different authors (Machado et al., 2005; Marino et al., 2005; Medeiros et al., 2009; Roffe et al., 2019). In the opposite
Schistosomiasis has three basic clinical stages: acute, established active and late chronic infection. Feverish syndrome characterizes the acute schistosomiasis’ stage. The presence of parasite eggs in the host liver, intestine and bladder ultimately causes intense inflammation and obstructive disease, leading to intestinal, hepatosplenic or urogenital complications. These manifestations are more severe in the established active and late chronic stages of the infection (Gryseels, Polman, Clerinx, & Kestens, 2006; McManus et al., 2018).

After frequent exposure to parasite antigens, in some individuals, the host immune response can develop resistance to reinfection (McManus et al., 2018). However, reinfection is very frequent in schistosomiasis patients, especially among those living in endemic areas (Dejon-Agobé et al., 2019; Gazzinelli et al., 2017; Woldegerima, Bayih, Tegegne, Aemero, & Jejaw Zeleke, 2019). The development of resistance or susceptibility to reinfection is influenced by age, pretreatment infection intensity, host immune characteristics, the occurrence of “heavy” infection at baseline, among other factors (Gazzinelli et al., 2017; Mbanefo et al., 2014).

An exacerbated inflammatory response against Schistosoma eggs may contribute to schistosomiasis pathogenesis (McManus et al., 2018). According to Souza, Sousa-Pereira, Teixeira, Lambertucci, and Teixeira (2006), the chemokines CCL3 and CCL5 along with the chemokine receptors CCR1 and CCR5 modulate the clinical course of S. mansoni infection. Thus, chemokines and chemokine receptors are key modulators of the granulomatous inflammation process during Schistosoma infection (Souza et al., 2011; Souza, Souza, Negrão-Correa, Teixeira, & Teixeira, 2008). Also, by combining pieces of evidence, it was hypothesized that a predominant CCL5/CCR5-associated immune response is linked to the mildest form of schistosomiasis whereas a predominant CCL3/CCR1-associated immune response would be linked to more severe forms of the disease (Souza et al., 2006). Other chemokine receptors, such as CCR2 and CCR4, apparently act similarly to CCR1 (Souza et al., 2008). In brief, these receptors may be important drivers for granuloma formation and fibrosis development in response to antigens from Schistosoma eggs. On the other hand, the CCL5/CCR5 pathway decreases disease severity by controlling inflammation, fibrosis and collagen deposition in addition to the recruitment of T regulatory cells (FoxP3+ cells) to the granulomatous lesions (Souza et al., 2008, 2011).

Therefore, the classical link “lack of CCR5 – less inflammation” seems not to be true in schistosomiasis. The role of CCR5 in this infection is regulatory (Souza et al., 2008, 2011). As will be briefly discussed in the section “Role of CCR5 on T regulatory cells,” the regulatory action of CCR5 is still a little-explored field, but it may answer important questions related to CCR5 functions.

Animal and in vitro studies suggest an involvement of CCR5 in different aspects of schistosomiasis pathogenesis (Liang et al., 2012; Richardson et al., 2014; Souza et al., 2011). CCR5-deficient mice show more severe Schistosoma infection and mortality rate than CCR5 wild-type mice, suggesting a protective role of CCR5 against aggressive granuloma formation during the course of infection (Souza et al., 2011). Studies with humans linked Schistosoma infection to increased CCR5 expression or CCR5+ cell frequencies (Kleppa
| Disease/pathogen                     | Population | Sample size                                                                 | Main findings                                                                                      | Reference                |
|-------------------------------------|------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------|
| **Brucellosis/Brucella infection**   | Greek      | 185 infected individuals vs 141 healthy controls                             | No statistically significant difference regarding CCR5Δ32 was found between cases and controls    | Skendros et al. (2002)   |
| **Chlamydia trachomatis infection**  | Dutch      | 256 subfertile women vs 145 healthy controls                                | No statistically significant difference regarding CCR5Δ32 was found between cases and controls    | Barr et al. (2005)       |
|                                     | Indian     | 174 women with reproductive problems (99 positive for C. trachomatis) vs 42 fertile women (42 positive for C. trachomatis) | No impact of CCR5Δ32 on tubal pathology                                                             | Mania-Pramanik et al. (2011) |
|                                     | North American | 365 subjects tested positive for C. trachomatis vs - | No impact of CCR5Δ32 on C. trachomatis-induced reactive arthritis | Carter et al. (2013)     |
| **Osteomyelitis/Staphylococcus aureus infection** | Brazilian | 39 patients with trauma who developed osteomyelitis vs 114 patients with trauma who did not develop osteomyelitis | CCR5Δ32 was suggested as a protective factor against osteomyelitis (without statistical significance) | De Souza et al. (2015)   |
| **Mycoplasma pneumonia infection**   | Hungarian  | 254 asthmatic children positive and negative for M. pneumoniae infection vs 260 healthy controls | CCR5Δ32 was associated with chronic M. pneumoniae infection; M. pneumoniae-infected children with Δ32 allele have reduced risk of asthma development | Ungvári et al. (2007)    |
| **Streptococcus pneumoniae infection** | Russian   | 319 patients with community-acquired pneumonia vs 141 exposed but noninfected individuals; 313 healthy controls | CCR5Δ32 (wild-type genotype) was a risk factor for community-acquired pneumonia | Salnikova et al. (2013)  |
| **Tuberculosis/Mycobacterium tuberculosis** | Colombian | 114 patients with tuberculosis vs 184 healthy controls | CCR5 haplotypic analyses (including CCR5Δ32) found CCR5-HHD as a risk factor for tuberculosis | Mantani et al. (2011)    |
| Disease/pathogen | Population | Sample size | Controls<sup>a</sup> | Main findings | Reference |
|------------------|------------|-------------|----------------------|---------------|-----------|
| Toxoplasmosis/Toxoplasma gondii | Caucasians | 412 HIV-infected patients | - | Toxoplasmosis was associated with CCR5Δ32 wild-type genotype, suggesting a protective effect of Δ32 allele on such infection. A small sample size was considered | Meyer et al. (1997) |
| | Caucasians | 1657 HIV-infected patients | - | The Δ32 allele was associated with protection against toxoplasma infection. | Meyer et al. (1999) |
| | Australian | 117 HIV-infected patients | - | The Δ32 allele was associated with protection against a set of infections (including toxoplasmosis) | Ashton et al. (2002) |
| | Brazilian | 160 patients with ocular toxoplasmosis and 160 patients without ocular toxoplasmosis | 160 seronegative controls | CCR5Δ32 wild-type genotype plus CCR5 −59029 (rs1799987) AA or AG genotypes was associated with ocular toxoplasmosis | De Faria Junior et al. (2018) |
| Leishmaniasis/genus Leishmania | Brazilian | 100 cutaneous leishmaniasis patients | 100 healthy controls | No statistically significant difference regarding CCR5Δ32 was found between patients and controls | Brajão De Oliveira et al. (2007) |
| | Brazilian | 111 cutaneous leishmaniasis patients | 218 healthy controls | No statistically significant difference regarding CCR5Δ32 was found between patients and controls. The heterozygous genotype was associated with disease recurrence (a small sample size was used in this specific analysis) | Ribas et al. (2013) |
| | Pakistani | 276 cutaneous leishmaniasis patients | 119 healthy controls | No statistically significant difference regarding CCR5Δ32 was found between patients and controls | Sophie et al. (2016) |
| Chagas disease/Trypanosoma cruzi | Peruvian | 85 seropositive patients (32 patients with cardiac symptoms and 53 asymptomatic patients) | 87 seronegative healthy controls | The frequency of Δ32 allele was too low to assess its potential influence on Chagas disease | Calzada et al. (2001) |
| | Venezuelan | 107 seropositive patients (34 asymptomatic, 38 arrhythmic and 35 cardiomyopathic patients) | - | No statistically significant result was found regarding CCR5Δ32 | Fernández-Mestre et al. (2004) |
| | Colombian | 260 seropositive individuals (130 asymptomatic and 130 cardiomyopathic patients) | - | The frequency of Δ32 allele was too low to assess its potential influence on Chagas heart disease | Flórez et al. (2012) |
| | Brazilian | 168 seropositive patients divided into three groups: normal left ventricular systolic function (n = 85), mild-to-moderate left ventricular systolic dysfunction (n = 43) and severe left ventricular systolic dysfunction (n = 40) | - | No statistically significant result was found | Oliveira et al. (2014) |
| | Brazilian | 109 patients with digestive form of chronic Chagas disease and 131 patients with cardiac form of chronic Chagas disease | 172 healthy controls | No statistically significant result was found regarding CCR5Δ32 | Oliveira et al. (2015) |
| Schistosomiasis/Schistosoma mansoni | Egyptian | 220 S. mansoni mono-infected patients and 190 HCV/ S. mansoni co-infected patients | - | CCR5Δ32 was associated with spontaneous HCV clearance in co-infected patients. Nonsignificant association between CCR5Δ32 and less severe hepatic fibrosis | El-Moamly et al. (2013) |

<sup>a</sup>Considering healthy individuals.
et al., 2014; Secor et al., 2003; Silveira-Lemos, Teixeira-Carvalho, Martins-Filho, Oliveira, & Corrêa-Oliveira, 2006). Importantly, since CCR5 is the main HIV co-receptor, such an increase in the number of receptors on the surface of immune cells enhances the susceptibility to HIV infection in Schistosoma-infected patients. The increase in CCR5+ cells/CCR5 expression seems indeed to be a consequence of Schistosoma infection since parasite treatment decreases these CCR5-related parameters (Kleppa et al., 2014; Secor et al., 2003).

The hepatitis C virus (HCV) co-infection in S. mansoni-infected individuals is a significant problem, particularly in some countries such as Egypt and Brazil (Van-Lume et al., 2013). In order to understand the factors involved in the association between schistosomiasis and HCV infection, El-Moamly et al. (2013) evaluated the variant CCR5Δ32 in S. mansoni-infected and in S. mansoni/HCV co-infected Egyptian patients. The study revealed an association between the presence of CCR5Δ32 and higher rates of spontaneous HCV clearance among co-infected patients. Of note, CCR5Δ32 was not associated with susceptibility to HCV infection in S. mansoni-infected individuals, a result in accordance with other studies (Ellwanger, Leal, et al., 2018; Glas et al., 2003; Toelen et al., 2005). Although lower frequencies of severe liver fibrosis have been observed in patients carrying the Δ32 allele, no statistically significant results were found regarding this finding or potential associations between CCR5Δ32 and viral RNA or ALT levels (El-Moamly et al., 2013). This study did not include a group of S. mansoni-uninfected individuals, making it impossible to evaluate the effect of CCR5Δ32 on susceptibility to this parasitic infection, which represents an interesting aspect of being addressed in future studies.

4.1 | Summarizing what we know

Details of the studies investigating the impacts of the genetic variant CCR5Δ32 on bacterial and parasitic infections are summarized in Tables 2 and 3, respectively. Before discussing open questions and emerging issues regarding CCR5 research, it is fundamental to summarize the well-established impacts of CCR5Δ32 on different infectious diseases (Figure 2). CCR5 is a key regulator of leucocyte migration, thus modulating inflammatory responses. Reduction or absence of CCR5 expression due to CCR5Δ32 may have distinct effects in the course or establishment of infections:

1. Reduced CCR5-mediated inflammation. On the one hand, this may impair the protective inflammatory response, thereby facilitating disease progression. On the other hand, decreased inflammatory response during infection may reduce inflammation-related problems, contributing to a better prognosis;
2. Reduced susceptibility to infection by CCR5-tropic pathogens. Although the most classic and important example is HIV infection, it should not be ruled out that CCR5Δ32 also significantly impacts other infections. Studies investigating the use of CCR5 as an entry receptor for other intracellular pathogens will help to elucidate this aspect;
3. Deficient CCR5-mediated immune response (due to CCR5Δ32) against a particular pathogen during host invasion may increase susceptibility to infection.

4.2 | CCR5 in fungal diseases

Studies are showing the involvement of CCR5 in some fungal diseases, including Aspergillus fumigatus-induced asthma in mice (Schuh, Blease, Brühl, Mack, & Hogaboam, 2003; Schuh, Blease, & Hogaboam, 2002), and infections by Candida albicans (Kim et al., 2005), Paracoccidioides brasiliensis (Moreira et al., 2008), Histoplasma capsulatum in mice (Kroetz & Deepe, 2010, 2011, 2012) and Coccioidioides (Davini et al., 2018). Due to the limited number of studies that have addressed CCR5 in the context of human fungal infections, it is not yet possible to establish the real importance of this receptor in the clinical course of these diseases. However, taking into account the studies carried out so far, together with the known impacts of CCR5 on infections caused by other pathogens, we speculate that CCR5 could play important but little-explored roles in fungal diseases.

The potential effect of CCR5 blockers on fungal infections is another overlooked topic. It is unlikely that pharmacological CCR5 blockage affects susceptibility to fungal infections. However, this is a topic that should be further investigated, particularly in immunosuppressed patients (Merchant, Reichman, & Koval, 2007).

4.3 | Role of CCR5 on regulatory T cells

Pieces of evidence point to a role of CCR5 in the mediation of recruitment and action of regulatory T (Treg) cells in fungal (Davini et al., 2018; Kroetz & Deepe, 2010), bacterial (Ahmed et al., 2018), parasitic (Romano et al., 2016; Souza et al., 2011; Yurchenko et al., 2006) and viral (Kim et al., 2016) infections. CCR5+ Treg cells have immunosuppressive activity (Soler et al., 2013) and CCR5 signalling mediates the recruitment of Treg cells to inflammation sites, thus modulating inflammatory responses by inducing a Treg-mediated immunosuppressive environment (Dobaczewski, Xia, Bujak, Gonzalez-Quesada, & Frangogiannis, 2010; Doodes et al., 2009; Li et al., 2017; Velasco-Velázquez, Xolalpa, & Pestell, 2014; Wildenberg et al., 2008). Therefore, lack or reduced expression of CCR5 due to CCR5Δ32 may contribute to exacerbated inflammation and be associated with a worse prognosis in infection-related inflammatory states (Figure 3). For example, in schistosomiasis, the recruitment of Tregs cells via CCR5 towards granulomatous lesions has important impacts on disease outcomes (Souza et al., 2008, 2011). These aspects are quite interesting and can shed light on the mechanisms involved in the pathogenesis of different diseases. Moreover, the
**FIGURE 2** Impacts of CCR5Δ32 on different infectious diseases. “Reduced expression” is a phenotype observed in CCR5Δ32 heterozygotes. In CCR5Δ32 homozygotes, the CCR5 expression on the cell surface is absent. For more details, see the topic “4.1. Summarizing what we know.”

**FIGURE 3** CCR5 regulatory action on infection-related inflammation. Inflammation induced by *Schistosoma* spp. eggs are illustrated in the figure. The CCR5 molecule mediates the migration of regulatory T cells to inflammation sites, thus modulating inflammation. Reduced or absent CCR5 expression (due to CCR5Δ32 heterozygosity and homozygosity, respectively) can impair the migration of regulatory T cells to inflammation sites. This figure was created using Servier Medical Art illustrations (available at https://smart.servier.com, under a Creative Commons Attribution 3.0 Unported License)
regulatory action resulting from the CCR5-Treg cells interaction may be a promising therapeutic target. However, the regulatory action of CCR5 is a still neglected topic that also needs further investigation. Future studies may help explain the multiple and often contradictory effects of CCR5 on different infections.

5 | CONCLUSIONS

Based on the infections discussed in this review, it is clear that the influence of CCR5 and CCR5∆32 in different diseases should not be generalized. The role of these two factors is quite variable in different conditions and may also vary in distinct clinical times of the same disease. For example, both CCR5 and CCR5∆32 impact the development of osteomyelitis, although in Chagas disease, CCR5 is involved in the disease pathogenesis, and the CCR5∆32 variant has little influence. In schistosomiasis, on the other hand, the action of CCR5 seems to be based on regulatory mechanisms. Also due to the different roles in distinct pathological conditions, the use of CCR5 blockers would be beneficial in some clinical situations, such as HIV infection. However, their effects on the inflammatory response in the context of other infections can be quite variable and even harmful. Therefore, the clinical use of CCR5 blockers must be investigated in detail in each clinical scenario rather than being regarded as a general rule.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Joel Henrique Ellwanger involved in conceptualization, investigation, writing and editing; Valéria de Lima Kaminski, Andressa Gonçalves Rodrigues and Bruna Kulmann-Leal involved in investigation, writing and editing; José Artur Bogo Chies involved in investigation, writing, editing and supervision.

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