Ticks and Tick-borne Diseases 10 (2019) 729–741

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Review Article

# Host immunogenetics in tick-borne encephalitis virus infection—The CCR5 crossroad

Joel Henrique Ellwanger, José Artur Bogo Chies*

*Laboratory of Immunobiology and Immunogenetics, Department of Genetics, Universidade Federal do Rio Grande do Sul – UFRGS, Porto Alegre, Brazil*

ARTICLE INFO

*Keywords:*
TBEV
Tick-borne encephalitis
Tick
CCR5
CCR5Δ32
Genetics
Inflammation

ABSTRACT

The human *Tick-borne encephalitis virus* (TBEV) infection is a complex event encompassing factors derived from the virus itself, the vectors, the final host, and the environment as well. Classically, genetic traits stand out among the human factors that modify the susceptibility and progression of infectious diseases. However, and although this is a changing scenario, studies evaluating the genetic factors that affect the susceptibility specifically to TBEV infection and TBEV-related diseases are still scarce. There are already some interesting pieces of evidence showing that some genes and polymorphisms have a real impact on TBEV infection. Also, the inflammatory processes involving tick-human interactions began to be understood in greater detail. This review focuses on the immunogenetic and inflammatory aspects concerning tick-host interactions, TBEV infections, and tick-borne encephalitis. Of note, it has been described that polymorphisms in *CD209*, *GSTM1*, *IL-10*, *IL-28B*, *MMP9*, *OAS2*, *OAS3,* and *TLR3* have a statistically significant impact on TBEV infection. Besides, CCR5, its ligands, and the CCR5Δ32 genetic variant seem to have a very important influence on the infection and its immune responses. Taking this information into consideration, a special discussion regarding the effects of CCR5 on TBEV infection and tick-borne encephalitis will be presented. Emerging topics (such as exosomes, evasins, and CCR5 blockers) involving immunological and inflammatory aspects of TBEV-human interactions will also be addressed. Lastly, the current picture of TBEV infection and the importance to address the TBEV-associated problems through the One Health perspective will be discussed.

## 1. Introduction – basic aspects of TBEV infection

*Tick-borne encephalitis virus* (TBEV) is an RNA virus that belongs to the *Flaviviridae* family, *Flavivirus* genus (Gritsun et al., 2003). Of note, modifications in the TBEV sub-type classification have already been proposed (Zlobin et al., 2001; Demina et al., 2012). This virus species is traditionally divided into three sub-types: Far Eastern, Siberian, and European viruses (Süss, 2011), although a new TBEV sub-type was proposed by Kovalev and Mukhacheva (2017), the Baikalian-TBEV. More recently, the Himalayan virus was described in China, potentially representing an additional TBEV sub-type (Dai et al., 2018). Moreover, the Siberian virus is the most genetically diverse TBEV sub-type, and the classification of their lineages are under frequent review (Kovalev and Mukhacheva, 2013, 2017). Tick-borne viral diseases represent critical veterinary and human medical problems in many countries. At least 17 tick-borne diseases affect humans (Dantas-Torres et al., 2012) and the TBEV has a prominent role among the etiological agents of such conditions.

TBEV is the causative agent of the tick-borne encephalitis (TBE), an infectious disease that affects people mostly in countries of Europe and Asia, being this virus considered a public health problem in such areas (Gritsun et al., 2003; Mansfield et al., 2009; Süss, 2011). TBEV has been known since 1937 when the Soviet virologist Lev Alexandrovich Zilber and a team of other scientists discovered the virus and characterized its link with TBE (Zlobin et al., 2017). Between 1990 and 2009, ~170,000 clinical cases of TBE were reported in Russia and some European countries (Süss, 2011). In addition to TBEV, *Louping ill virus*, *Langat virus*, and *Powassan virus* can also cause TBE (Gritsun et al., 2003), but this review will mainly highlight studies focused on TBEV-related TBE.

In general, humans are infected by TBEV through the bite of a TBEV-infected tick (Gritsun et al., 2003; Süss, 2011). Less commonly the infection can be caused by human contact with aerosol or through ingestion of food products contaminated with the pathogen (Dörrbecker et al., 2010). *Ixodes ricinus* and *I. persulcatus* are the most important tick vectors of TBEV (Gritsun et al., 2003; Süss, 2011; Kazimírová et al., 2017). Wild rodents play a pivotal role in the ticks' life cycle and the

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* Corresponding author at: Laboratório de Imunobiologia e Imunogenética (Prédio 43323, Laboratório 212), Departamento de Genética, Instituto de Biociências, Universidade Federal do Rio Grande do Sul – UFRGS. Av. Bento Gonçalves, 9500, Campus do Vale, 91501-970, Porto Alegre, RS, Brazil.

*E-mail address:* jabchies@terra.com.br (J.A.B. Chies).

https://doi.org/10.1016/j.ttbdis.2019.03.005
Received 3 October 2018; Received in revised form 18 February 2019; Accepted 10 March 2019

TBEV maintenance in wild animals (Mansfield et al., 2009), probably being the main reservoirs of tick-borne pathogens (Vayssier-Taussat et al., 2015).

Due to the inexistence of curative treatment for the disease, the currently TBE therapy available is only supportive (Mansfield et al., 2009). Nevertheless, vaccination against TBEV infection is effective and recommended for people living on, or visiting, regions where the pathogen circulates (Süss, 2011). Although vaccination is highly recommended for populations in countries at high risk for TBEV infection, each country in endemic TBEV regions applies vaccination strategies based on their epidemiological situation and vaccination policies (Zavadska et al., 2013). There are different TBEV vaccines, including FSME-Immun (Baxter Vaccines, Austria), Encepur (Novartis Vaccines and Diagnostics, Germany), EnceVir (Virion Corporation, Russia), and TBE-Moscow (Chumakov Institute for Poliomyelitis and Viral Encephalitides, Russia) (Lehrer and Holbrook, 2011). In general, TBEV vaccines are well tolerated. Systemic and local adverse effects may occur in some individuals following vaccination, especially in children. The adverse effects are mild and transient, such as fever and pain at the site of vaccination. However, neurological manifestations may occur in a small portion of the vaccinated individuals. When they happen, neuritis and headache are the main manifestations. However, there is no strong association of TBEV vaccines with neurological adverse effects, and the vaccines are generally safe (Grzeszczuk et al., 1998; Kunz, 2003; Lindquist and Vapalahti, 2008; Rendi-Wagner, 2008; Demicheli et al., 2009; Šmit and Postma, 2015; Bogovic and Strle, 2015; Galgani et al., 2017). Ecotourism, camping, and adventure tourism facilitate the transmission of tick-borne diseases once such activities put humans in close contact with nature and wildlife. Thus, as mentioned above, tourists visiting endemic TBEV regions may receive TBEV vaccine (Jensenius et al., 2006).

The clinical manifestations and outcome of TBE can be quite particular. The following forms of TBE are known: febrile, meningeal (the most common), meningoencephalitic, poliomyelitic, polyradiculoneuritic, and chronic (Gritsun et al., 2003). In brief, fever, nausea, vomiting, muscular pain, and meningeal disorders are classic TBE symptoms (Gritsun et al., 2003). These non-specific symptoms make TBE diagnosis a clinical challenge (Zavadska et al., 2013). Such infection can initially cause only a febrile syndrome, which may or may not progress and then affect the CNS and promote neurological disorders (Mansfield et al., 2009). In general, clinical TBE is characterized by a biphasic disease, in which the patient shows flu-like symptoms in the first stage of the illness and CNS/neurologic symptoms in the second stage. These stages are intercalated by an asymptomatic period (Süss et al., 2010; Süss, 2011). In general, ˜20% of TBE patients have some sequel, being age and protein concentration in CSF important risk factors for sequels development (Czupryna et al., 2018). The TBE progression pattern may vary according to the particular TBEV sub-type which is infecting the host (Mansfield et al., 2009). Other viral factors, such as virus tropism, and specific host characteristics are determining factors of TBEV infection outcome (Süss, 2011). Among host factors, age, immune status, and some genetic features have a meaningful impact on the susceptibility and progression of TBEV infection (Süss, 2011). In this context, recent results obtained by Vora et al. (2017) suggested that host immunological background influences the tick-associated fibrinogenolytic activity. Together, the information mentioned above demonstrates that human-tick interactions are quite complex, being affected by factors derived from human and tick.

The cysteine-cysteine chemokine receptor 5 (CCR5) modulates the immune response against different human infectious diseases. In some infections, CCR5 can act as a "protective molecule," helping the host mitigate the infection. On other occasions, nevertheless, CCR5 can mediate post-infection inflammatory responses which can be harmful to the host (Klein, 2008). Considering the scenario mentioned above, in this review we will address the genetic factors involved in the susceptibility to TBEV infection and disease progression, focusing on studies evaluating the CCR5 and its ligands. Before that, we will briefly describe the fundamental aspects of the host immune response in the context of the human-tick interaction. Lastly, we will bring emerging topics regarding human-tick interactions in the context of the One Health concept.

## 2. Immune responses during human-tick interactions and TBEV infection

As blood-feeding arthropods, ticks need to circumvent the host immune defenses to obtain their bloodmeals adequately. The interaction between tick and host skin can last for days, and this will correspond to the blood feeding period. Host inflammatory responses at the tick biting site would hamper the feeding process. Thus, ticks developed the ability to disrupt the host chemokine-mediated immune response. Such disruption enables these parasites to feed on host blood "free" of a local inflammatory response at the site of interaction between the tick mouthparts and the host damaged skin (Ribeiro et al., 1985; Hajnická et al., 2005; Vančová et al., 2007; Hovius, 2009; Vančová et al., 2010; Wikel, 2013; Mason et al., 2014; Kotál et al., 2015; Chmelař et al., 2016; Bonnet et al., 2018). For example, different studies have shown that tick saliva suppresses the activity of a number of cytokines and chemokines, including IL-2, IL-4, IL-6, CXCL8/IL-8, IL-12, TNF-α, CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, CCL11/eotaxin, and CCL5/RANTES (Ribeiro et al., 1985; Gillespie et al., 2001; Hajnická et al., 2001, 2005; Frauenschuh et al., 2007; Vančová et al., 2007; Déruaz et al., 2008; Oliveira et al., 2008; Peterková et al., 2008; Hovius, 2009; Vančová et al., 2010; Marchal et al., 2011; Poole et al., 2013; Mason et al., 2014; Hayward et al., 2017). It is possible that such a simultaneous disruption of the activity of multiple chemokines results from the complex interactions and robustness of the chemokine-receptor system network (Mantovani, 1999). In other words, ticks need to disrupt the entire cytokine/chemokine network at a local level to obtain blood from the host (Hajnická et al., 2005). Besides, tick saliva could also modulate the host immune system at a systemic level (Kazimírová et al., 2017). Importantly, tick species, developmental stage, the amount of saliva used by the tick, and the duration of the feeding process (number of days) are influencing factors of the tick-derived anti-chemokine activity (Vančová et al., 2010). Prostaglandin $E_2$ (Poole et al., 2013) and the chemokine-binding proteins known as evasins (Bonvin et al., 2016; Hayward et al., 2017) are some molecules that regulate the chemokine-mediated local immune response triggered by ticks saliva. However, a wide variety of molecules present in the tick saliva account for the immune regulation (Beaufays et al., 2008; Oliveira et al., 2011; Hidano et al., 2014; Kazimírová et al., 2017; Šimo et al., 2017). On the other hand, some reports point to a tick saliva-induced increase in the production of different chemokines (Langhansová et al., 2015). Nevertheless, it appears that tick saliva contains immune-regulatory molecules and that it induces the secretion of such molecules as well (Poole et al., 2013).

It was shown recently in an animal model that, in the very early stage of the tick feeding process, the CCR5 is up-regulated, potentially due to the initial inflammatory response observed when the tick damages the skin (Thangamani et al., 2017). In general, in the first 3 h of the tick feeding process, the bite site can be considered an inflammatory environment (Thangamani et al., 2017). Interestingly, TBEV-infected ticks trigger higher recruitment of inflammatory cells to the bite site in comparison to non-infected ticks (Thangamani et al., 2017). In this context, tick-mediated TBEV infection in early stages of tick bite occurs in an "inflammatory" environment, which in turn, could favor the host infection (Thangamani et al., 2017). In humans, the early stages of ticks-induced skin lesions activate the innate immune system (Glatz et al., 2017). In the presence of pathogens, such immune response will depend on the pathogens transmitted by the tick (Pulendran et al., 2001; Akira et al., 2006; de la Fuente et al., 2017). After a tick bite, macrophages, neutrophils, and dendritic cells are recruited to the skin

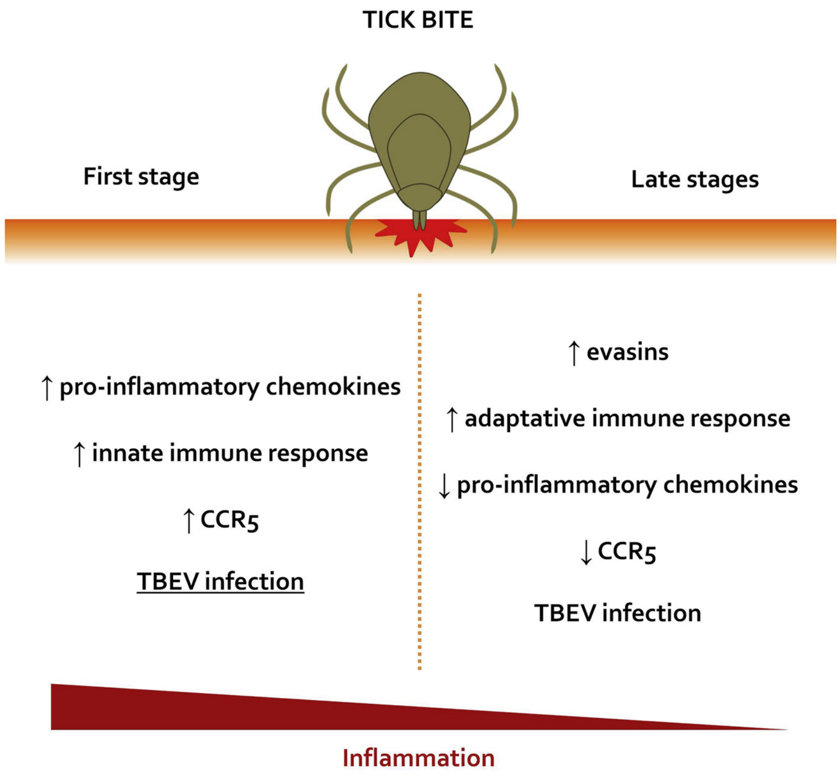

**Fig. 1. Inflammatory events that probably occur in the human skin in the first and late stages of a tick bite.** In the first stage of the tick bite, there is an increase of the local host inflammatory response, with activation of the innate immune system associated with an increase of pro-inflammatory chemokines and expression of inflammatory receptors such as CCR5. TBEV infection is likely to happen more easily in this early stage of the tick bite, although it may also occur in other stages. During the late stages of the tick bite occurs the development of an adaptive immune response. Concomitantly, an increased release of tick saliva-derived immune-suppressive molecules (mainly evasins) associated with a decreased pro-inflammatory chemokines production and expression of inflammatory receptors (including CCR5) by the host cells is observed. See text for references.

lesion (Glatz et al., 2017). After the first 24 h of tick-skin interaction/bite, the inflammatory context is reduced due to the anti-inflammatory action of the tick saliva; this event is accompanied by the development of an adaptive immune response (Glatz et al., 2017). Fig. 1 summarizes the potential inflammatory events that occur during the first and late stages of a tick bite. The dual effect of tick saliva on the host inflammatory response demonstrates that ticks have sophisticated mechanisms to control the action of inflammatory cells. Finally, it is also important to mention that the dual inflammatory/anti-inflammatory effect of tick saliva on host cells also depends on the cell type exposed to tick saliva (Scholl et al., 2016).

The immune response of the mammalian host against the TBEV infection is quite complex. In the first place, it will depend on the route of infection by the pathogen: tick bite, ingestion (TBEV-contaminated milk products), or inhalation (aerosol containing TBEV) (Dörrbecker et al., 2010). Depending on the transmission route of the pathogen to the host, different tissues and organs will participate in the immune response (skin, stomach, and olfactory tract, among others). How and how easily the TBEV will overcome the blood-brain barrier (BBB) will also depend on the entry route of the virus into CNS. For example, the TBEV entry by the olfactory tract probably facilitates its passage through the BBB, which eventually allows the virus to reach the brain directly (Dörrbecker et al., 2010).

Furthermore, TBEV-infected cells can mediate the pathogen passage through the BBB (Dörrbecker et al., 2010). TBEV-infected human brain microvascular endothelial cells promote brain infection without causing substantial disruptions to BBB (Palus et al., 2017). Of note, Zhou et al. (2018) reported that exosomes support TBEV transmission through the BBB. These processes occur in a microenvironment where the host attempts to regulate BBB integrity to avoid infection or mitigate it through the action of inflammatory cells and orchestration of chemokine release (Miner and Diamond, 2016). Lastly, the impact of the virus on the CNS as well as the infection-related tissue-specific response will depend on the pattern and types of inflammatory cells, humoral response, as well as the cellular components and chemokines/cytokines engaged by the host (Dörrbecker et al., 2010).

In general, infection by tick-borne flaviviruses has a significant impact on the release of many cytokines and chemokines. Also, which cytokines or chemokines will be released and in which tissue this release occurs will depend on the viral species by which the host was infected (Tigabu et al., 2010). We suggest that this differential pattern of immune response can also occur in infections with different TBEV sub-types. As described in the introduction of this review, such different modes of immune response will vary according to the characteristics of each patient, including age, immune status, and genetic features (Süss, 2011). In the next section, we will address the influence of human genetic factors on the immune response during TBEV infection and TBE pathogenesis.

## 3. Host immunogenetics in the TBEV infection context

Different genetic factors from both the pathogen and the host influence the susceptibility to an infectious disease as well as the disease outcome (Powell et al., 2000; Toan et al., 2006; Janssen et al., 2007; Jayadev and Garden, 2009; Chapman and Hill, 2012; Moore et al., 2013; da Silva et al., 2014; Rajoriya et al., 2017; Valverde-Villegas et al., 2017). For example, and as recently reviewed, microRNAs-related polymorphisms have significant impacts on the susceptibility and progression of several human viral infections (Ellwanger et al., 2018a). Looking specifically at TBEV-host interactions, Barkhash et al. (2016b) argued that in the Central Asian Mongoloid populations the susceptibility to TBEV infection is modulated by various genes and polymorphisms. Moreover, a study using mice models with different genetic patterns of susceptibility to TBEV infection indicated that the genetic background has a meaningful impact on the clinical course of TBE (Palus et al., 2013). Such data points to the existence of genes that control TBEV infection susceptibility.

Recently, a system biology analysis performed by Ignatieva et al. (2017) have pointed to *IL-10*, *IFNL3/IL-28B*, *ARID1B*, *IFNAR1*, and *CCR5* as important genes of the immune response against TBEV. Based on the number of genes/proteins interactions, *IFNAR1* and *CCR5* were assumed as the most relevant amongst all candidate genes. These

**Table 1**
Studies that evaluated the impact of gene variants on TBEV infection/TBE.

| Study | Gene | Variants evaluated | Population | Sample size ($n$)[a] | | Main findings |
|---|---|---|---|---|---|---|
| | | | | Cases | Controls | |
| Barkhash et al. (2010) | *OAS1* | rs1131454, **rs10774671**, rs1131476, rs1051042, rs2660, rs6489865 | Russian | 142 | 302 | No evident influence of the polymorphisms on TBE/TBEV infection. |
| | *OAS2* | rs2384075, rs2072138, rs1293762, rs2240185, rs929291, rs2240184, rs15895, rs1732778 | | | | rs1293762, rs15895, and rs1732778 have an impact on TBE outcome. |
| | *OAS3* | rs7967461, rs1156361, rs2285932, rs2072136, rs2240187, rs1557866, rs2010549 | | | | rs2285932 and rs2072136 have an impact on TBE outcome. |
| | *OASL* | rs3213545, rs12819210 | | | | No evident influence of both gene variants on TBE/TBEV infection. |
| Kindberg et al. (2011) | *OAS1* | **rs10774671** | Lithuanian | 128 | 135 | No impact of this SNP on TBE/TBEV infection. |
| | *TLR3* | rs5743305, **rs3775291** | | | | rs3775291 (wild-type genotype/allele) was a risk-factor for TBE/TBEV infection; No impacto of rs5743305 on TBE/TBEV infection. |
| Barkhash et al. (2012) | *CD209* | **rs4804803**, **rs2287886** | Russian | 136 | 263 | rs2287886 (A allele and AA genotype) was linked to a higher predisposition to severe forms of TBE; No statistically significant differences regarding rs4804803 genotype/allele frequencies between TBE and control groups. |
| Barkhash et al. (2013) | *TLR3* | **rs3775291** | Russian | 137 | 269 | GG genotype and G allele (wild-type genotype/allele) were linked to higher predisposition to TBE. |
| Mickienė et al. (2014) | *TLR3* | **rs3775291** | Lithuanian | 348 | 212 | Wild-type allele was higher in TBE patients than in controls; The SNP influenced the TBE severity in adults; Dual effect of *TLR3* on TBEV infection. |
| Grygorczuk et al. (2015) | *IFNL4/IL-28B* | **rs12979860** | Polish | 15 | [b] | rs12979860 influenced the IFN λ3 concentrations in cerebrospinal fluid. |
| | *IL-10* | **rs1800872**, **rs1800896** | | | | No effect of both gene variants on TBE was detected. |
| | *CD209* | **rs287886**, **rs4804803** | | | | rs287886 influenced the IL-10 concentrations in cerebrospinal fluid. No effect of rs4804803 on TBE was detected. |
| Barkhash et al. (2016a) | *IL28B* | rs8103142, rs12980275 | Russian | 132 | 221 | rs8103142 TT genotype and T allele were linked to higher TBE predisposition; rs12980275 AA genotype and A allele were linked to higher TBE predisposition. |
| | *IL-10* | **rs1800872**, rs3021094, rs3024498 | | | | rs1800872 AA genotype was linked to higher TBE predisposition. No influence of other two SNPs on TBE was observed. |
| Czupryna et al. (2017) | *CD209* | **rs2287886, rs4804803** | Polish | 59 | 57 | rs2287886 AG genotype was linked to higher susceptibility to TBE; No important impact of rs4804803 on severe forms of TBE. |
| | *IL-10* | **rs1800872, rs1800896** | | | | No important impact of both SNPs on severe forms of TBE. |
| | *IFNL4/IL-28B* | **rs12979860** | | | | No important impact of this SNP on severe forms of TBE. |
| Ilyinskikh and Ilyinskikh, (2017) | *GSTM1*<br>*GSTT1* | *GSTM1* deletion<br>*GSTT1* deletion | Russian | 120 | 124 | The inactive form of both genes was linked to increased TBEV-associated cytogenetic aberrations in young patients. |
| Barkhash et al. (2018) | *SCRIB* | rs6558394 | Russian | 150 | 228 | No influence of this SNP on TBE at population level. |
| | *MMP9* | rs17576 | | | | rs17576 G allele was linked to severe TBE. |

TBE: Tick-borne encephalitis; TBEV: Tick-borne encephalitis virus.

[a] See the original studies for the exact number of subjects genotyped for each polymorphisms.

[b] No controls were included in the genetic analysis (patients were stratified according to clinical criteria); Gene variants evaluated in more than one study are highlighted in bold; Gene variants that had a significant impact on TBEV infection/TBE are pointed in "main findings" column and summarized in Fig. 2.

findings are of great importance, but functional and population-based studies are needed to confirm the effects of such genes and proteins on TBEV infection. In an interesting initiative, Ignatieva et al. (2017) developed an online platform which provides a variety of information on the genes (140 so far) linked to the immune response against TBEV infection, the "TBEVHostDB" (http://icg.nsc.ru/TBEVHostDB/).

The genes and polymorphisms that may be involved in the susceptibility to TBEV infection and TBE development are summarized in Table 1. Studies involving the *CCR5* will be addressed separately in the next sections of this review.

Barkhash et al. (2010) evaluated 23 SNPs in genes of the 2′-5′-oligoadenylate synthetase (2′-5′-OAS) proteins family. Such proteins show antiviral activity and, in brief, five SNPs showed important influences on TBE outcome: rs1293762, rs15895, rs1732778 (located on *OAS2*), rs2285932, and rs2072136 (located on *OAS3*). These results suggest that the *OAS* family plays a prominent role in the clinical course of TBEV infection. However, functional studies associated with population-based studies are not yet available, being quite essential to confirm these findings.

Looking at *TLR3* rs3775291, Kindberg et al. (2011) found that the wild-type genotype/allele of this polymorphism was a risk-factor for TBE/TBEV infection. A disrupted TLR3-mediated immune response associated with gene variants could decrease the deleterious effects of the exacerbated inflammation/immune response during TBEV infection (Kindberg et al., 2011). In this case, the variant allele would act as a protective factor against TBEV-related diseases. In concordance, this association first observed in the Lithuanian population was corroborated in the Russian population. In the later study, the wild-type genotype/allele of *TLR3* rs3775291 was also a risk factor for TBE (Barkhash et al., 2013). On the other hand, partial results reported in a study performed by Mickienė et al. (2014) challenged the scenario mentioned above regarding the role of *TLR3* rs3775291 on TBE. The functional TLR3 can indeed promote the pathogenesis of TBE. However, TLR3 can also be necessary for the anti-TBEV response when the virus is in the brain. Moreover, the role of *TLR3* rs3775291 on TBEV infection can differ between adults and children (Mickienė et al., 2014), data that together with those previously mentioned, suggest a dual effect of TLR3 during TBEV infection.

Besides the genes mentioned in Table 1, other candidate genes have potential importance in the context of TBEV infection. For example, based on gene expression data obtained from an *in vitro* model of tick-borne flavivirus (TBFV) infection, relevant effects on the TBFV persistence were assigned to genes such as *CXCL10, INF-β1*, and *TNF-α* (Mlera et al., 2016). An interesting table including various other genes observed up- or down-regulated post-infection can be found in the original study (Mlera et al., 2016). Furthermore, recent studies in mice suggest that *CD33*, *KLK1B22*, *SIGLECE*, *KLK1B16*, *FUT2*, *GRWD1*, *ABCC6*, *OTOG*, and *MKRN3* (all located on chromosome 7) may also be important in the context of susceptibility and progression of the TBEV infection and should be better studied, also considering their ortholog human genes (Palus et al., 2018). According to Barkhash et al. (2012), studies focused on genetic variants that influence the predisposition to TBEV-related diseases may be useful to understand the pathogenesis of TBEV. Furthermore, such studies may provide insights into the development of therapies for the treatment of TBEV-related diseases (Barkhash et al., 2012). Once the influence of genes on human-TBEV interactions is well established, genetic markers could be used as predictors of the clinical progression of TBEV infection (Ignatieva et al., 2017). Finally, Fig. 2 shows the genes and polymorphisms that have already been statistically linked to some effect on TBEV infection and disease progression. The proportion of genetic factors involved in "protection" and "susceptibility", gene-gene interactions (Phillips, 2008), gene penetrance (Alcaïs et al., 2009), and gene-environment interactions (Hunter, 2005) may affect the influence of genes and polymorphisms on TBEV infections and therefore all such situations are mentioned in Fig. 2. Furthermore, it is important to highlight that a statistically significant association sometimes does not represent a critical biological effect and therefore must be interpreted with prudence (Cordell, 2009; EFSA Scientific Committee, 2011; Lovell, 2011).

## 4. The CCR5, CCR5Δ32, and CCR5 ligands in TBEV infection and TBE outcome

The pattern of the immune response against TBEV has a pivotal role in the course of infection in humans since sometimes the immune response *per se* is responsible for the damage associated to the infection (Dörrbecker et al., 2010). Similarly, individual genetic factors play a remarkable role in the susceptibility to TBEV infection and clinical course of TBE, as demonstrated by studies focusing on single nucleotide polymorphisms (Table 1; as discussed in the previous section). In this context, we would like to draw attention to the potential role of the CCR5 and the CCR5Δ32 genetic variant in TBEV infection.

CCR5 is a cell-surface receptor (Raport et al., 1996; Signoret et al., 2000) expressed in macrophages (Raport et al., 1996; Rottman et al., 1997), lymphocytes (Raport et al., 1996; Rottman et al., 1997; Wu et al., 1997), and monocytes (Rottman et al., 1997; Wu et al., 1997), being observed also in non-blood cells (Rottman et al., 1997). CCR5 regulates a variety of immune functions, mainly leukocyte migration to sites of inflammation (Lederman et al., 2006). The main CCR5 ligands are CCL3 (Samson et al., 1996a; Mueller et al., 2006), CCL4 (Samson et al., 1996a; Bondue et al., 2002), and CCL5 (Samson et al., 1996a; Mbemba et al., 2001; Lin et al., 2008). Fig. 3 shows a schematic representation of CCR5.

The interaction of type 1 human immunodeficiency virus (HIV-1) with surface CCR5 in CD4$^+$ T cells allows the virus entry into the cell (Proudfoot, 2002; Brelot and Chakrabarti, 2018). The cellular susceptibility to HIV infection correlates with the levels of CCR5 expression (Wu et al., 1997; Fear et al., 1998; Zella et al., 1998). CCR5 is expressed by the gene of the same name, located on chromosome 3 (Raport et al., 1996). CCR5Δ32 (rs333) is a 32-base pair deletion in *CCR5*. In general, CCR5Δ32 homozygous individuals are not infected by HIV-1, due to the absence of CCR5 on the cell surface, although heterozygous individuals for CCR5Δ32 present a slower progression to AIDS mainly due to reduced expression of functional CCR5 (Dean et al., 1996; Liu et al., 1996; Wu et al., 1997; Proudfoot, 2002; Venkatesan et al., 2002; Brelot and Chakrabarti, 2018). The CCR5Δ32 allelic frequency can reach ˜16% in some Euro-derived populations (Solloch et al., 2017), being rare in Afro-derived individuals (Martinson et al., 1997; Solloch et al., 2017). In admixed populations, such as the Brazilian, the allelic frequency is 3–6% (Silva-Carvalho et al., 2016; Ellwanger et al., 2018b). The protection against HIV infection attributed by CCR5Δ32 was described in 1996 (Dean et al., 1996; Liu et al., 1996; Samson et al., 1996b). Since then such discovery has led to significant advances in HIV therapy once CCR5Δ32 implications have provided support for the development and use of CCR5 blockers. Currently, Aplaviroc, Cenicriviroc, Maraviroc, and Vicriviroc are examples of CCR5 antagonists under study in humans (Vangelista and Vento, 2018). Among them, Maraviroc is considered effective and safe, already being used in the clinical practice (CONITEC, 2012; Brites et al., 2015). Besides HIV infection, CCR5 and CCR5Δ32 also play a relevant role in some inflammatory-associated diseases (Kohem et al., 2007; Martin-Blondel et al., 2016; Schauren et al., 2013; Scheibel et al., 2008) and different viral infections (Glass et al., 2006; Marques et al., 2015; Rustemoglu et al., 2017).

### 4.1. CCR5 and CCR5Δ32

The studies approaching the role of the CCR5 and the CCR5Δ32 polymorphism in TBVE infection are summarized in Table 2, suggesting altogether that CCR5 plays a prominent role in TBE infection. This view is mainly supported by data from Kindberg et al. (2008), Mickienė et al. (2014), Michlmayr et al. (2016), Ignatieva et al. (2017), and

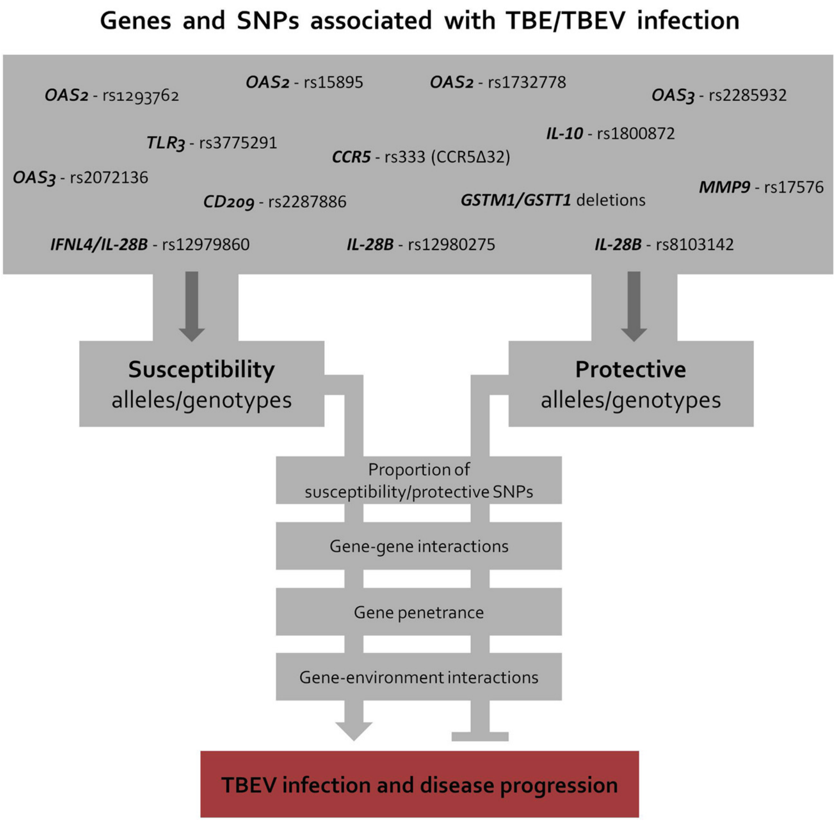

**Fig. 2. Genes and polymorphisms associated with TBEV infection and TBEV-related disease progression.** The proportion of "protective" and "susceptibility" genetic factors, gene-gene interactions, and gene penetrance may affect the impact of genes and polymorphisms on TBEV infection. Of note, non-human factors and gene-environment interactions should also be taken into account when interpreting the effect of a particular gene or polymorphism on TBEV infection. The effect of each polymorphism shown in this figure is detailed in Table 1. See text and Table 1 for references.

Thangamani et al. (2017). Specifically, functional CCR5$^+$ cells seem to be important in the immune response against the TBEV infection and its effects in the brain. CCR5Δ32 disrupts CCR5 and potentially affects the CCR5$^+$ cell function, thus favoring TBEV pathogenesis and TBE progression (Kindberg et al., 2008; Mickienė et al., 2014), although part of the data presented by Grygorczuk et al. (2016) challenge this view. Interesting, using a mouse model, Michlmayr et al. (2016) suggested that CCR5 deficiency is a contributing factor to symptomatic TBEV infection. In line with a potential role of the CCR5 in the TBEV pathogenesis, it has been demonstrated that CCR5Δ32 is an important risk factor for symptomatic West Nile virus infection (Glass et al., 2006), a condition that also affects the central nervous system. Nevertheless,

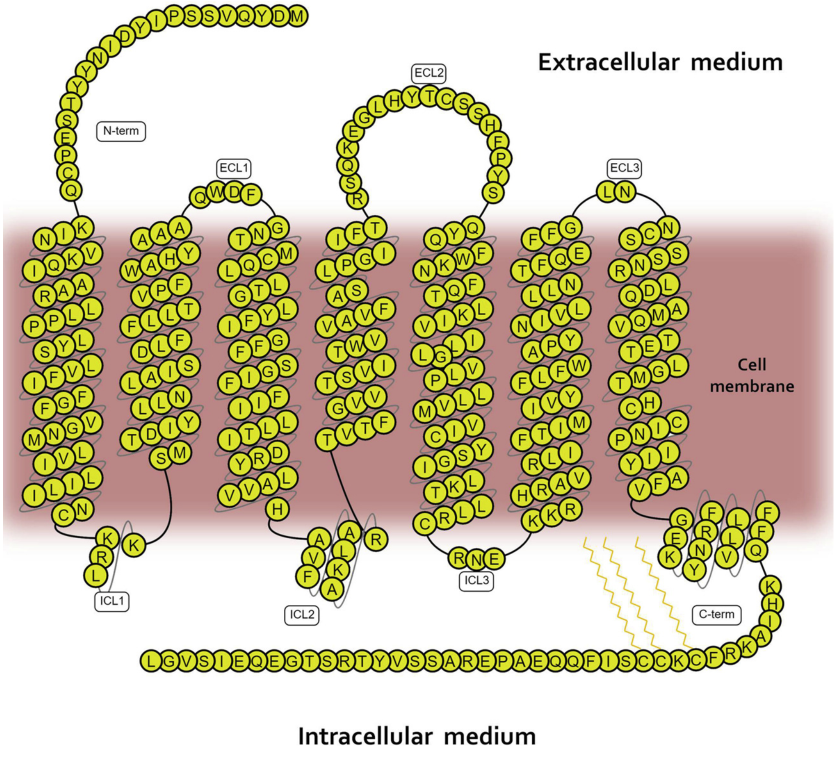

**Fig. 3. CCR5 structure.** Schematic representation (2D, linear) of CCR5 structure. The figure shows seven transmembrane domains, extracellular loops (ECL1, ECL2, ECL3), intracellular loops (ICL1, ICL2, ICL3), N-terminus (N-term), and C-terminus (C-term). Three palmitoylated cysteines (that interact with the cell membrane) are indicated in the figure. Capital letters indicate amino acids. Basic CCR5 structure was created using the GPCR database: http://gpcrdb.org/ (Pándy-Szekeres et al., 2018) and then edited based on information obtained in previous studies (Oppermann, 2004; Lederman et al., 2006; Parmentier, 2015; Brelot and Chakrabarti, 2018).

**Table 2**
Impacts of CCR5 and CCR5Δ32 on TBEV infection/TBE.

| Reference | Population evaluated or study model | Sample size (*n*) | | Main findings |
|---|---|---|---|---|
| | | Cases | Controls | |
| Kindberg et al. (2008) | Lithuanian | $n = 129$ | $n = 134$ | CCR5Δ32 homozygous frequency was higher ($p < 0.05$) in TBE patients than in controls; CCR5Δ32 allele frequency was higher in TBE patients than in controls and in TBE patients with moderate/severe disease than in patients with mild symptoms (but not significantly). |
| Engman et al. (2012) | Swedish | $n = 8$ | $n = 15$ | No influence of CCR5Δ32 on TBE susceptibility. |
| Barkhash et al. (2013) | Russian | $n = 137$ | $n = 268$ | No influence of CCR5Δ32 on TBE susceptibility or clinical manifestations. |
| Mickienė et al. (2014) | Lithuanian | $n = 349$ | $n = 213$ | CCR5Δ32 homozygous frequency was higher ($p < 0.05$) in TBE patients than in controls; Δ32 allele was a risk factor for clinical TBEV infection ($p < 0.05$, using subgroups data); No influence of CCR5Δ32 on TBE severity. |
| Grygorczuk et al. (2015) | Polish | $n = 15$ | [a] | No influence of CCR5Δ32 on cytokine concentrations of TBE patients. |
| Grygorczuk et al. (2016) | Polish | $n = 79$ | $n = 18$ | CCR5 plays a role in the pathogenesis of TBEV infection (neurologic phase); CCR5 may act in the early response to TBEV infection; No influence of low CCR5 expression in peripheral blood lymphocytes on TBE susceptibility; No significant impact of CCR5Δ32 on TBE clinical manifestations. |
| Michlmayr et al. (2016) | Mouse model | | | CCR5 plays a pivotal role in the immune response against TBEV infection in the central nervous system; CCR5 deficiency may promote symptomatic TBEV infection. |
| Czupryna et al. (2017) | Polish | $n = 59$ | $n = 57$ | No influence of CCR5Δ32 on TBE susceptibility or clinical manifestations. |
| Ignatieva et al. (2017) | Systems biology | | | *CCR5* gene is suggested as having remarkable participation in the immune response to TBEV infection. |
| Thangamani et al. (2017) | Mice model | | | *CCR5* gene is up-regulated after TBEV-infected tick feeding. |

TBE: Tick-borne encephalitis; TBEV: Tick-borne encephalitis virus.
[a] No controls were included (patients were stratified according to clinical criteria).

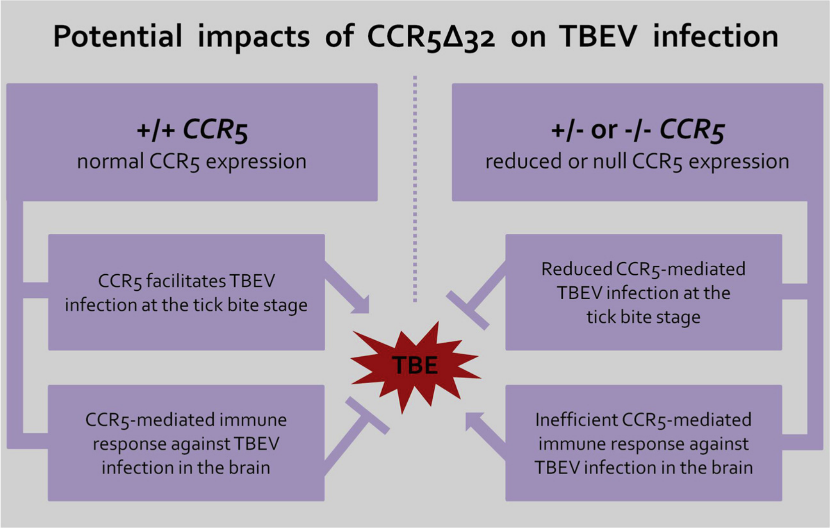

**Fig. 4. Potential impacts of CCR5Δ32 on TBEV infection.** Functional CCR5 is important in the immune response against TBEV infection and its effects in the brain, but CCR5 can facilitate the infection during the early stages of the tick bite. CCR5Δ32 disrupts CCR5 expression, potentially favoring TBEV pathogenesis and TBE progression. On the other hand, CCR5Δ32-derived low or null expression probably protects against TBEV-infection at the biting stage. See text for references.

some of the studies mentioned here evaluated CCR5Δ32 (Barkhash et al., 2013; Czupryna et al., 2017; Engman et al., 2012; Grygorczuk et al., 2015, 2016) and fail to describe a direct influence of this genetic variant on TBE susceptibility or clinical parameters. However, the studies of Czupryna et al. (2017), Engman et al. (2012), Grygorczuk et al. (2015), and Grygorczuk et al. (2016) were performed on small samples, which may have influenced their results. Considering the findings, investigations on the frequency of CCR5Δ32 in different non-vaccinated populations from geographical locations where the TBEV circulates are needed. When evaluated together, the data obtained from these studies will give us a better understanding of the possible influence of CCR5Δ32 on susceptibility to TBEV infection and disease progression. Based on the studies mentioned here, we have schematized in Fig. 4 the potential impacts of CCR5Δ32 on TBEV infection.

The analysis of gene interaction networks points to *CCR5* as a player in the TBEV-derived host immune response (Ignatieva et al., 2017). Further functional studies allied with bioinformatics analyses focusing on the role of CCR5 in the immune response against TBEV infection are of great relevance. This approach is fundamental, especially taking into account the increasing amount of studies assessing the potential clinical implications of CCR5 blockade in different contexts (Vangelista and Vento, 2018). Actually, a better comprehension of the CCR5 roles in TBEV infection may be quite relevant for the development of CCR5-based TBE therapies since we are facing a potential challenging crossroad: CCR5 agonists/modulators could be useful for treating TBE, but simultaneously we should be aware of the unknown impacts of CCR5 blockade on TBEV infection susceptibility. Such hypotheses should be evaluated.

### 4.2. *CCR5 ligands*

It is important to remember that CCL3, CCL4, and CCL5 are the main CCR5 agonists, regulating the action of different CCR5$^+$ leukocytes (Samson et al., 1996a; Jones et al., 2011). Oliveira et al. (2008) demonstrated that *in vitro* chemotaxis of immature dendritic cells (DCs) is inhibited by tick saliva. Specifically, such inhibition is mediated by down-regulation of CCR5 expression on the cell surface. In line with these findings, the study also has shown that tick saliva disrupts CCL3 chemotactic function (Oliveira et al., 2008). Evasin-1 is a candidate molecule in this pathway, since it binds to CCL3, besides binding to CCL4 and CCL18/PARC (Frauenschuh et al., 2007). A study by Carvalho-Costa et al. (2015) also showed that tick saliva decreased the CCR5 expression in DCs and reduced the migration of these cells, reinforcing and complementing the findings reported by Oliveira et al. (2008). Carvalho-Costa et al. (2015) also showed that tick saliva has a suppressive action on DCs differentiation. Prostaglandin $E_2$ must be responsible at least in part by the results found in the study (Carvalho-Costa et al., 2015).

Prostaglandin $E_2$ from tick saliva decreases the CCL5 levels released by macrophages (Poole et al., 2013). This tick saliva-induced CCL5 reduction potentially prevents a pro-inflammatory response at the site of the tick bite (Poole et al., 2013). Evasin-4 also binds to CCL5 (Déruaz et al., 2008; Bonvin et al., 2014), inhibiting its function (Déruaz et al., 2013). Nevertheless, the inhibitory activity of evasin-4 is not exclusive upon CCL5. Other chemokines are also inhibited by evasin-4 (Déruaz et al., 2013), and some data suggests that other evasins also bind to CCL5 (Singh et al., 2017).

Besides viruses, ticks are hosts of different microorganisms (Asman et al., 2015; Beltrame et al., 2018; Johnson et al., 2018; Karasartova et al., 2018). Therefore, the immunomodulatory effects of tick saliva can be influenced by the presence of these microorganisms. The incubation of THP-1 cells (a human monocytic cell line) with tick saliva in the presence of *Borrelia burgdorferi* inhibited the production of CCL3, CCL4, and CCL5, compared to THP-1 cells exposed only to *B. burgdorferi*, as evaluated by a cytokine bead array (Scholl et al., 2016). Although these results suggest that the observed immunomodulatory effect was derived from tick saliva components and not evoked by *B. burgdorferi*, such data draw attention to the need of considering that the immunomodulatory effects of tick saliva can occur concomitantly with the host inflammatory response against different tick-derived microorganisms, such as bacteria and protozoa.

Increased production of pro-inflammatory chemokines, including CCL5, CCL3, and CCL4, was observed in the brain of mice infected with TBEV (Palus et al., 2013). A similar phenomenon seems to occur in humans since Palus et al. (2015) have observed increased levels of some inflammatory markers in TBE compared to controls; however, the levels of the CCR5 agonists CCL3, CCL4, and CCL5 were not statistically different between the groups (Palus et al., 2015). No difference of CCL3 and CCL4 levels between TBE patients and controls were also reported in another study (Grygorczuk et al., 2016). On the other hand, using a Langat virus-induced TBE rat model, Maffioli et al. (2014) observed higher CCL5 levels in the cerebrospinal fluid of infected rats in comparison to controls, in accordance with data from TBEV-infected humans evaluated in the same study (Maffioli et al., 2014). Other studies also described higher levels of CCL3 (Grygorczuk et al., 2006) and CCL5 (Grygorczuk et al., 2016) in TBE patients compared to controls. In line with these findings, an *in vitro* study performed by Palus et al. (2014) showed that TBEV infection in human astrocytes induced an increased expression of CCL4 and other pro-inflammatory cytokines and chemokines. According to the same study, astrocytes are the potential source of the pro-inflammatory chemokines found in the brain during TBEV infection. Thus, such TBEV-infected astrocytes would mediate the inflammation-related neurodegenerative events found in TBEV infection (Palus et al., 2014).

In an overall perspective, CCL5 should be considered as an important mediator of the inflammatory response related to TBEV infection (Zhang et al., 2016). Up-regulation of *CCL5* expression was observed in an *in vitro* model of tick-borne flavivirus infection (Mlera et al., 2016). In line with this finding, Zhang et al. (2016) have shown that intracerebral TBEV infection induces CCL5 expression in brain tissue of BALB/c mice. Also in the context of TBEV infection using the BALB/c mice model, CCL5 inhibition was linked to extended survival and reduced brain inflammation (Zhang et al., 2016). Furthermore, the CCL5 up-regulation was confirmed using human brain-derived cell lines, and such up-regulation seems to be mediated by the interferon regulatory factor 3 (IRF-3) activation (Zhang et al., 2016). Finally, a recent study suggested the TBEV nonstructural protein NS5 as the viral activation factor of the IRF-3-associated CCL5 up-regulation in the context of TBEV infection (Zheng et al., 2018). Taking together, data from TBEV-infected humans, animal models, and *in vitro* studies reinforce the involvement of CCR5 agonists in the pathogenesis of TBEV infection.

## 5. Perspectives and emerging topics

### 5.1. Exosomes and TBEV infection

It is quite evident that tick-borne viruses exploit tick-saliva components and their immune regulation properties to evade the host immune system and to promote infection (Kazimírová et al., 2017). Recently, it has been suggested that TBEV infection from ticks to humans can be facilitated by tick-derived exosomes (Zhou et al., 2018). Exosomes are nanovesicles released in the extracellular medium by different cell types. Such vesicles enable the communication and transport of molecules between cells (Properzi et al., 2013; Ellwanger et al., 2017a; Samanta et al., 2018; de la Torre Gomez et al., 2018). Also, it is likely that host-derived exosomes may affect the TBEV infection of neuronal cells (Zhou et al., 2018). In concordance, it is already known that exosomes and other extracellular vesicles influence human-virus interactions and the course of different viral infections (Chahar et al., 2015; Ellwanger et al., 2018c; Liu et al., 2017; Anderson et al., 2018; Hackenberg and Kotsyfakis, 2018; Martelli et al., 2018; Vora et al., 2018; Wang et al., 2018; Wu et al., 2018; Yao et al., 2018). Interestingly, it is possible that some viruses explore the budding and transport machinery of exosomes to evade the immune system and promote infection (Gould et al., 2003). Taking these points into consideration, the role of exosomes in TBEV infection is an interesting topic that deserves to be explored in detail. Finally, we speculate that the exosomes participate, at least in part, in the regulation of the anti-inflammatory microenvironment induced by ticks during their bloodmeal at the bite site.

### 5.2. Modulating the immune response and TBEV infection: Evasins and CCR5 blockade

The therapeutic potential of inflammatory modulators based on evasins activity has been addressed in different studies (Déruaz et al., 2008; Bonvin et al., 2016). Indeed, several evasins may be used for therapeutic strategies (Hayward et al., 2017). Interestingly, it is possible that evasins and other tick saliva-derived anti-inflammatory molecules are not (or are scarcely) immunogenic (Déruaz et al., 2008), which makes the use of these molecules for the treatment of inflammatory diseases even more promising.

Also looking at the pharmacological modulation of the immune response, the use of CCR5 blockers stands out in the current literature. The effects of CCR5 blockers may be different on cells of the central nervous system as compared to cells of peripheral organs. Besides, the CCR5 blockers administered in the central nervous system may have different effects from those caused by the systemic CCR5 deficiency due to the CCR5Δ32 allele (Zhang et al., 2016). Currently, there is a growing use of CCR5 blockers to treat HIV infection and in strategies of Pre-exposure prophylaxis (PrEp) to prevent new cases of infection (Luz et al., 2018; Riddell et al., 2018). However, the impacts of population-scale use of CCR5 blockers (due to HIV treatment or prevention) on TBEV infection are unknown. Immunization against TBEV has been suggested before initiating the use of CCR5 blockers in HIV-infected patients (Klein, 2008).

### *5.3. Current status of TBEV infection: look at pathogen, ticks, human factors, and the environment in an integrated way*

Currently, there are phylogenetic data pointing to the existence of at least five TBEV sub-types (Kovalev and Mukhacheva, 2017; Dai et al., 2018). However, the public health importance of the newly discovered Himalayan-TBEV (Dai et al., 2018) and Baikalian-TBEV (Kovalev and Mukhacheva, 2017) is unknown and therefore need to be investigated. In this sense, a better understanding of the biological and pathogenic particularities of each TBEV sub-type will allow the establishment of therapies and vaccines specific for each type of virus. In addition, mapping the circulation of each TBEV sub-type is essential to develop actions focused on pathogen control at a population level.

In essence, TBEV infection is an emerging zoonosis (Mansfield et al., 2009) that represents not only a medical problem but also an ecological challenge. Contradictorily, compared to other infectious diseases, tick-borne viral diseases are considered of little importance on a global epidemiological scale (Kazimírová et al., 2017). The lack of implementation of prevention and control measures is a contributing factor to the spread of tick-borne viral diseases (Kazimírová et al., 2017).

Climate change, alterations in ticks ecology, and social factors (urbanization, international travels, human migration, outdoor activities, among others) are involved in the increase/decrease of TBEV-related problems (Süss et al., 2010; Süss, 2011), but such factors are still poorly understood and subject of debate (Süss, 2011). However, there is no doubt that unbalances between human, animal, and environmental factors are involved in the emergence of infectious diseases (Mwangi et al., 2016; Ellwanger et al., 2017b; Destoumieux-Garzón et al., 2018), including tick-borne diseases (Vayssier-Taussat et al., 2015). Moreover, looking specifically at the human factor, individual genetic features have a pivotal role in the susceptibility and progression of viral diseases (Chapman and Hill, 2012; Ellwanger et al., 2018a). This role is evidenced in this review through different studies involving TBEV infection.

Considering the number of factors that influence different aspects of TBEV ecology and human-TBEV interactions, the risk of TBEV infection should be assessed both at the individual as well as at the population levels (Süss et al., 2010). Understanding the immunological processes that permeate the relationships between ticks, humans, and tick-borne viruses is essential for the development of new control strategies targeting tick-borne infections (Wikel, 2013; Kazimírová et al., 2017). The challenge is to identify what are these factors and how to control them to contain the pathogen and disease emergence. At a population level, tick-borne viral diseases may be faced within the One Health perspective, in which the characteristics of the pathogens are considered together with human, animal, and environmental factors in the application of broad-spectrum disease control strategies (Vayssier-Taussat et al., 2015; de la Fuente, 2018). For such approaches to be effectively implemented, professionals from different areas, such as microbiology, veterinary, epidemiology, human health, and sociology should be involved (Vayssier-Taussat et al., 2015).

The points discussed above in association with characteristics from ticks and humans may represent barriers or bridges that TBEV must overcome to infect humans. For example, viral genetic factors can serve as bridges or barriers, increasing or decreasing viral pathogenesis according to TBEV sub-types (Mansfield et al., 2009; Robertson et al., 2009). Similarly, it is possible that viral factors also influence the TBEV infectivity. In addition, protective or susceptibility human genetic factors (see some examples in Table 1 and Fig. 2) may represent barriers or bridges to TBEV infection. Finally, Fig. 5 puts together all the factors that should be taken into consideration when TBEV infection control is sought at the individual and population levels.

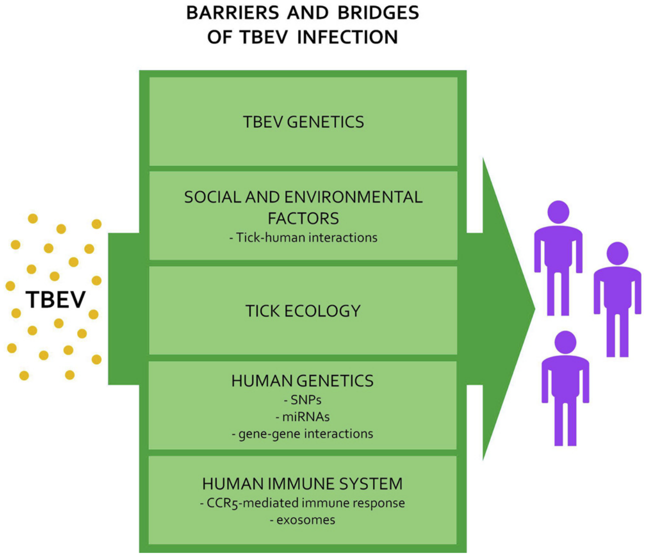

**Fig. 5. Barriers and bridges of TBEV infection.** Several factors separate TBEV from humans. Some of these factors can be compared to "bridges" that facilitate infection processes in humans (for example, viral genetic factors that increase virulence or outdoor activities that put humans in close contact with ticks). On the other hand, some factors can be considered as "barriers" that make TBEV infection difficult (for example, host protective immunogenetic factors). All these barriers and bridges should be taken into consideration in control and mitigation measures of TBEV infection. The approach that integrates animal, human, and environmental factors for the control and prevention of infectious disease is in line with the One Health perspective. See text for references.

## 6. Conclusions

TBEV infection is a complex zoonosis. Therefore, prevention of human TBEV infection should be performed through vaccination initiatives especially in populations in endemic areas. In association, actions focused on the One Health perspective can contribute to the control of the tick populations. Looking at human factors, it is clear that the host genetic polymorphisms (as highlighted in Fig. 2) have a critical impact on the susceptibility to TBEV infection and disease progression. In this context, *CCR5* plays a prominent role, both at the gene level as well as at the protein level. The CCR5 is important in the immune response against TBEV infection and its effects in the brain, although it may facilitate the infection in the early stages of the tick bite. Furthermore, it seems that the CCR5Δ32-associated disruption of the CCR5 function favors TBEV pathogenesis and TBE progression. On the other hand, CCR5 down-regulation due to CCR5Δ32 would protect against TBEV infection. Complementing these findings, different types of evidence have shown that host-derived CCR5 agonists CCL3, CCL4, and CCL5 have a significant influence on the clinical outcome of TBEV infection. Studies addressing tick-human interactions point to the potential pharmacological use of immunomodulatory proteins present in the tick saliva. Finally, the use of CCR5 blockers to treat HIV infection can interfere with TBEV infection in HIV/TBEV co-infected individuals.

## Conflict of interest

No conflict of interest to declare.

## Acknowledgments

JHE receives a doctoral scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil). JABC receives a research fellowship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil).

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