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Human host genetics and susceptibility to ZIKV infection

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ABSTRACT

Managing emerging infectious diseases is a current challenge in the fields of microbiology and epidemiology. Indeed, among other environmental and human-related factors, climate change and global warming favor the emergence of new pathogens. The recent Zika virus (ZIKV) epidemic, of which the large and rapid spread surprised the scientific community, is a reminder of the importance to study viruses currently responsible for sporadic infections. Increasing our knowledge of key factors involved in emerging infections is essential to implement specific monitoring that can be oriented according to the pathogen, targeted population, or at-risk environment. Recent technological developments, such as high-throughput sequencing, genome-wide association studies and CRISPR screenings have allowed the identification of human single nucleotide polymorphisms (SNPs) involved in infectious disease outcome. This review focuses on the human genetic host factors that have been identified and shown to be associated with the pathogenesis of ZIKV infection and candidate SNP targets.

1. Introduction

ZIKV is an emerging arthropod-born virus (Arbovirus) belonging to the genus *Flavivirus* of the *Flaviviridae* family that was not considered to be a public-health priority due to only sporadic cases being reported until 2007. At that time, a large epidemic was reported on Yap Island, in which nearly 75% of the population was infected with the virus (Duffy et al., 2009), followed by several outbreaks reported in French Polynesia, New Caledonia, Easter Island, and the Cook Islands in 2012, indicating rapid spreading of the virus in the Pacific until 2014 (Musso et al., 2014). These outbreaks were also associated with more severe ZIKV infection-related symptoms such as neurological disorders like Guillain Barré syndrome, which incidence unexpectedly increased by 20 fold (Oehler et al., 2014).

In 2015, the ZIKV epidemic was declared a public-health emergency when it reached the American continent, where an estimated 400,000–1.5 million cases of autochthonous transmission of the virus was reported in Brazil. It has since been associated with imported cases of ZIKV infection, notably in Europe, indicating rapid spreading of the virus worldwide (Zammarchi et al., 2015). This outbreak raised major concerns about the pathogenicity of ZIKV, as severe neurological complications in fetuses, neonates, and adults have been shown to be

associated with the infection (Cao-Lormeau et al., 2016; Mlakar et al., 2016; Baud et al., 2017; Ferraris et al., 2019b).

An exceptional effort has been made by the scientific community to characterize the interaction between this virus and its target cells, in particular, to better understand the viral pathogenicity to aid healthcare systems in managing the epidemic (Hamel et al., 2015; Baud et al., 2017; Morris et al., 2017; Christian et al., 2019; Ferraris et al., 2019b). ZIKV possesses a positive single-stranded RNA that encodes a polyprotein precursor that is processed by cellular and viral proteases to yield the three structural proteins: the capsid (C), the precursor of membrane (prM), and the envelop (E), followed by seven nonstructural proteins: NS1 to NS5. The African and Asian ZIKV strains have been extensively studied (Wichit et al., 2021). Due to their genetic difference, it has been shown that the two ZIKV lineages differentially infect and lyse human placental trophoblast (Sheridan et al., 2018). The prM protein is involved in ZIKV-mediated neuro-pathogenicity (Nambala and Su, 2018). In fact, it has been demonstrated that the higher neurovirulence of African strains could be linked to differences in ten amino acid residues in the prM proteins of the two ZIKV strains (Nakayama et al., 2021). African strains also display higher transmissibility and fetal pathogenicity than Asian strains (Aubry et al., 2021). The antiviral response elicited against the two strains upon infection of human neural

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progenitors and astrocytes could also contribute to the higher neurovirulence of the African strains (Simonin et al., 2016; Hamel et al., 2017).

Many species of *Aedes* mosquito can transmit ZIKV, including *Ae. aegypti* and *albopictus*, which can be found in south of Europe. The *Aedes* genus is dispersed across three continents (Asia, Africa, and the Americas) in predominantly tropical areas, but has been increasingly spreading, particularly in the Northern regions of the Americas, Europe, and China (Kraemer et al., 2015). Several studies have been performed to evaluate the ability of *Aedes* mosquitoes to transmit ZIKV. A total of 13 *Aedes* species have been identified as ZIKV potential vectors including *Aedes* (Epelboin et al., 2017; Zhou et al., 2020).

The threat posed by ZIKV can be expected to be the same as that of Chikungunya and Dengue virus due to similar clinical symptoms and a similar distribution (Musso et al., 2015). ZIKV infection is characterized by fever, rash, arthralgia, and conjunctivitis in infected individuals. However, the biggest concern about ZIKV infection is the development of neurological disorders, such as microcephaly and congenital Zika syndrome (CZS), in newborns (Mlakar et al., 2016).

A better understanding of the cellular mechanisms involved in ZIKV pathogenesis is crucial for the identification of potential single nucleotide polymorphisms (SNPs) as susceptibility factors for the infection. Many studies have identified key anthropic factors in the emergence of viruses, such as ecological modifications and human societal behavior. However, due to the diversity of human genetics no one has been able thus far to determine whether human genetic polymorphisms may be involved in susceptibility to ZIKV infection. Since the large outbreak of ZIKV infection in Brazil, the scientific community has unraveled much about the cellular and molecular mechanisms involved in the infection (Baud et al., 2017; Ferraris et al., 2019b). Moreover, recent advances in human genome sequencing have led to improvements in genome-wide association studies (GWAS) over the last 10 years. These studies attempt to correlate human genetic variants (SNPs) with phenotypic features (symptoms, treatment efficacy, disease, etc.). Thus, the identification of key cellular factors and GWAS results should allow us to determine potential genetic factors involved in the susceptibility of humans to ZIKV infection. In the current review, we focus on the human genetic factors that may be associated with susceptibility to ZIKV infection.

2. Cellular susceptibility: cell entry and nervous system tropism

Several studies have determined the cell types that can be infected by ZIKV and the cellular mechanisms involved (Agreli et al., 2019). Many cell types can be infected by ZIKV, but the main concern in human ZIKV infection is those that are associated with the nervous system, reproductive tract, and maternofetal barrier and their role in the pathogenicity and/or transmission of the virus. Like many other flaviviruses, ZIKV uses a member of the C-type lectin receptor family (DC-SIGN), cellular lipid receptors (TIM, TAM), clathrin-mediated endocytosis, GAG, NMR, and endosome-lysosome processes to enter cells (Agreli et al., 2019). Thus, all genes involved in these mechanisms can affect ZIKV infectivity and their activity may be influenced by human genetic polymorphisms. Although AXL has been shown to be an essential ZIKV entry factor (Hamel et al., 2015; Meertens et al., 2017), genetic alteration of this gene appears to have no effect on ZIKV infection in mice (Wang et al., 2017; Wells et al., 2016). These results highlight the diversity of ZIKV entry mechanisms according to cell type. A recent genome-wide CRISPR screen study identified two V-ATPase component genes (ATP6V1F, ATP6V1C1) involved in endosome-lysosome pathways, of which their mutation led to reduced ZIKV infection in human neural progenitor cells (hNPCs) (Li et al., 2019). These results however are yet to be validated in animal models to evaluate the importance of these gene mutations in global ZIKV infection. Another study used human neuroprecursor cells (hNPC) cells from dizygotic twins exposed to ZIKV during their mother's pregnancy where one child developed CZS

while the other did not (Amaral et al., 2020). This case-control sample represented a rare opportunity to test the genetic contribution to the outcome of ZIKV infection by comparing in vitro gene expression of ZIKV infected hNPCs (generated by the induced-pluripotent cell technology) (Caires-Júnior et al., 2018). They first showed that hNPCs from the CZS-affected child were more susceptible to ZIKV infection than those from the non-affected child. Then, they showed differential expression of genes involved in the mTOR inhibition pathway (DDIT4L), Wnt signaling (LHX2, EGR2, SFRP2, WNT7A), and FOXO1G1 to be particularly involved in numerous cellular processes, such as cell growth, proliferation, survival, and embryonic development, all associated with microcephaly syndrome (Caires-Júnior et al., 2018). However, it is not known whether these genes are directly or indirectly linked to the pathogenicity. It will be informative to compare the sequences of these genes between the twins (dizygotic and monozygotic) to potentially identify key mutations. The same groups also investigated differential gene expression in infected trophoblasts of the dizygotic twins under the same conditions (Amaral et al., 2020). They did not observe significant differences in gene expression related to candidate attachment factors. Most flaviviruses, such as Dengue virus (DENV), West Nile virus (WNV), and ZIKV, share similar tropism and a similar replication cycle. Therefore, GWAS studies performed on other flaviviruses could help to identify potential polymorphisms associated with susceptibility to ZIKV infection. GWAS studies of DENV infection have identified several human genetic factors associated with the severity of infection (Khor et al., 2011; Sierra et al., 2017; Xavier-Carvalho et al., 2017a, 2017b), which may also affect ZIKV infection. For example, SNPs have been identified in the promoter sequence of the DC-SIGN gene (CD209) that have been shown to be associated with a predisposition to Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS) (Wang et al., 2011). As ZIKV also uses the DC-SIGN receptor to enter cells, this polymorphism may also lead to a predisposition to ZIKV susceptibility.

3. Innate immunity

Innate immunity is a key cellular mechanism in the control of the outcome of viral infections, as it represents the first barrier. Although controlled moderate activation of innate immunity can quickly control the infection, a stronger immune response can lead to pathogenic effects. Indeed, when the virus enters the cells it is recognized by various pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs). These activate the expression of molecules, such as interferon (IFN), which also leads to the expression of interferon-stimulated genes (ISGs). Thus, any functional mutation in one of these genes could affect the immune response and, thus, the infection outcome and pathogenicity. The specific innate immune response to ZIKV has been investigated in many studies and the IFN type I and III pathways appear to be crucial for the early steps of controlling the infection (Hamel et al., 2015; Lazear et al., 2016; Bayer et al., 2016; Grant et al., 2016; Jagger et al., 2017; Baud et al., 2017; Ferraris et al., 2019a, 2019b). A recent study involving ZIKV-infected pregnant women and newborn babies showed that the rs3775291 SNP in the mother's TLR3 gene, activated by viral RNA, is associated with the occurrence of CZS (Santos et al., 2019). This SNP was already shown to be associated with other viral infections (Verma and Bharti, 2017). They also identified the rs1799964 SNP in the newborn's gene for TNF α , a cytokine involved in inflammation, that also appears to be associated with severe microcephaly (Santos et al., 2019). IFN molecules belong to the cytokine class and are released in response to the presence of pathogens. Each IFN type (I, II and III) can differentially activate the JAK/STAT pathway by interacting with their specific receptors, leading to the expression of many genes involved in antiviral responses. Several mouse genetics studies have also highlighted roles for specific genes involved in the IFN pathway (STAT proteins, IFN receptors, ISGs, etc.) and associated with susceptibility or resistance to ZIKV infection (Manet et al., 2018). It is now important to identify the polymorphisms of these genes that are related to ZIKV pathogenicity.

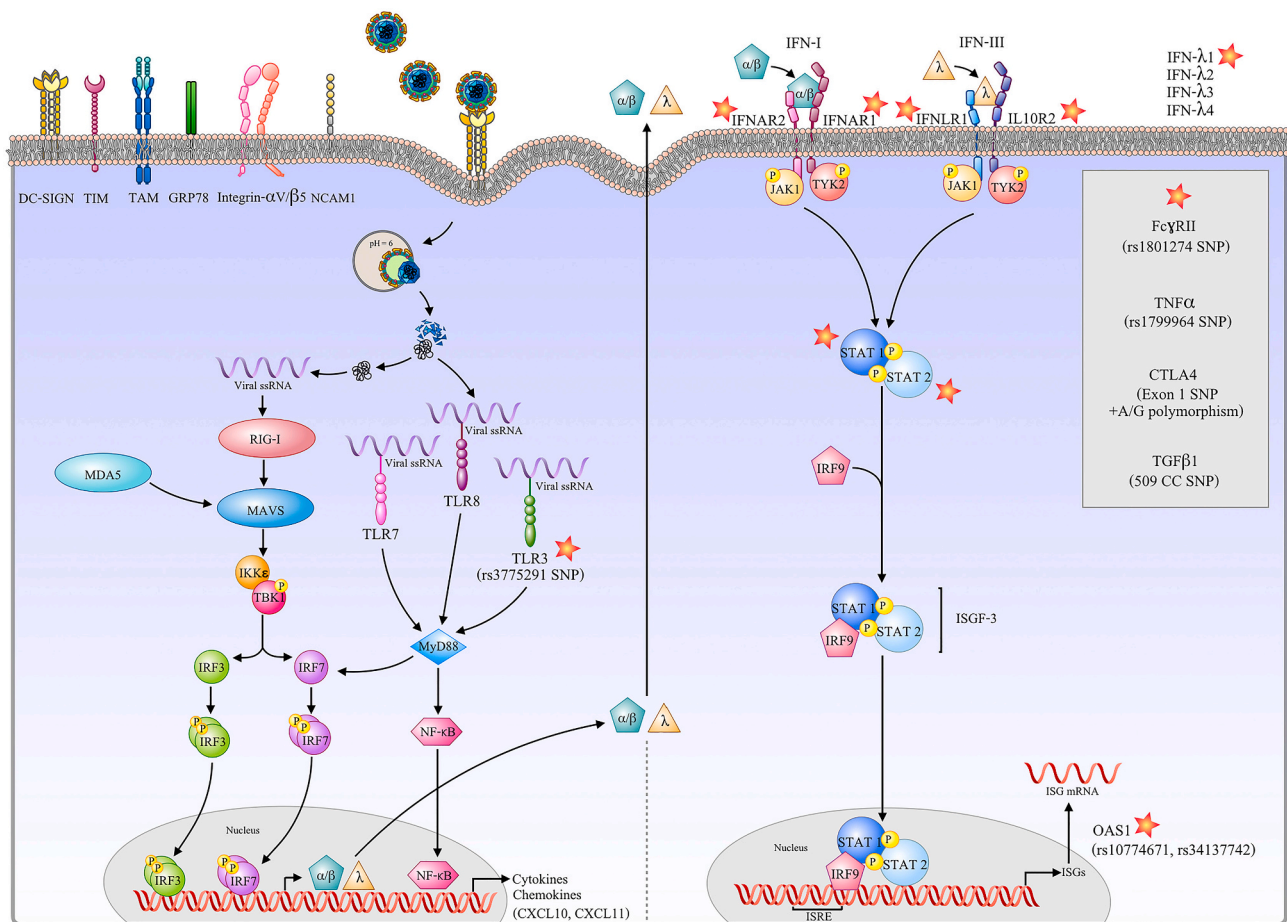


Fig. 1. Summary of susceptible genes and SNP targets associated with pathogenicity and transmission of Zika virus infection in innate and adaptive immunity of humans. Star: susceptible gene and its SNP target (Modified from Wichit et al., 2021).

Several polymorphisms in genes known to be part of the response against other members of the *Flaviviridae* family have been identified. Indeed, polymorphisms have been described for several genes, such as CLEC5A (rs1285933), inducing expression of the proinflammatory cytokine; OAS1 (rs10774671, rs 34137742), involved in viral RNA degradation; and TNF α (rs1800629) for WNV and DENV infections (Mashimo et al., 2002; Manet et al., 2018; Xavier-Carvalho et al., 2017b). Type III IFNs (IFN- λ 1 (IL29), IFN- λ 2 (IL28A), IFN- λ 3 (IL28B), and more recently IFN- λ 4), appear to play a determinant role in the innate immune response against RNA viruses. The recently discovered IFN- λ 3 (rs12979860 C/T) and IFN- λ 4 (rs368234815 TT/-G) polymorphisms have been shown to affect the outcome of hepatitis C virus (HCV) infection (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009; Prokunina-Olsson et al., 2013; Bibert et al., 2013). Although the expression of IFN- λ 4 is very low during viral infection, this protein appears to play a crucial role in HCV clearance and the resistance to IFN- α treatment, showing a strong phenotype associated with the polymorphism (Prokunina-Olsson et al., 2013; Ferraris et al., 2016). Several studies have also suggested an association between this polymorphism and tick-borne viruses (Barkhash et al., 2016) and Coronavirus (Hamming et al., 2013) infection, but its impact on other RNA viral infections has been dispraised. HCV belongs to the *Flaviviridae* family, which also include arbovirus such as ZIKV, DENV, yellow fever virus (YFV), and WNV. Therefore, it is possible that this polymorphism could affect other viruses of this family as well. Indeed, IFN- λ 4 appears to act as a negative regulator of type I IFN activation, which could improve or decrease the efficiency of the immune response, depending on the pathogen (Ferraris et al., 2016; Obajemu et al., 2017). The loss of IFN- λ 4 expression confers

protection against HCV infection, probably due to virus/host adaptation. However, the expression of IFN- λ 4 could have different effects in the context of other RNA viral infections, which is yet to be investigated (Prokunina-Olsson et al., 2013; Booth and George, 2013; Ferraris et al., 2016). This polymorphism is specifically distributed throughout the world according to country and ethnicity, more particularly between Africa and Asia. The loss of IFN- λ 4 expression appears to have been associated with selection pressure during human and viral evolution (Wack et al., 2015; Ansari et al., 2017). The ethnic distribution of polymorphisms in southern countries and the speared of arboviruses suggest that the polymorphism of IL28B involved in innate immunity could be a cellular host factor associated with viral outbreaks, such as that of ZIKV.

4. Adaptive immunity

An effective and specific adaptative immune response is also primordial for the control of viral infection. However, a dysfunctional or over/under-activated response can lead to symptoms associated with the infection. Thus far, no SNPs associated with the adaptative immune response against ZIKV have been identified. Several human genetic polymorphisms have already been characterized for other flaviviruses and need to be investigated in the context of ZIKV infection. A major concern of ZIKV infection is the possibility that the infection can lead to antibody-dependent enhancement (ADE), as observed for DENV, or be enhanced by ADE from a prior DENV infection. ADE is caused by non-neutralizing antibodies that are produced during the infection. They form an immunocomplex with the virus that can be internalized by Fc-

Table 1
SNP genes associated with ZIKV and Flaviviridae infection pathogenicity.

Cell susceptibility				Innate immunity			Adaptative immunity		
Zika				TLR3	rs3775291	Verma and Bharti (2017)			
Candidate SNP from other Flaviviridae	PLCE1	rs3740360	Dang et al. (2014), Khor et al. (2011), Whitehorn et al. (2013)	TNFA	rs1799964	Santos et al. (2019)	FcγRII	rs1801274	Loke et al. (2002), García et al. (2011b)
		rs3765524		CLEC5A	rs1285933	Xavier-Carvalho et al. (2017b)			
	MICB	rs3132468	Dang et al. (2014), Khor et al. (2011), Whitehorn et al. (2013)	OAS1	rs10774671; rs34137742	Lim et al. (2009)	CTLA4	Exon 1 + A/G	Fang et al. (2012), Fernández-Mestre et al. (2009)
	DC-SIGN CD209	rs4804803	Sakuntabhai et al. (2005), Wang et al. (2011), Xavier-Carvalho et al. (2017a)	OASL	rs3213545	Yakub et al. (2005)	TGFB1	509 CC	Chen et al. (2009)
				TNFA	rs1800629	Fernández-Mestre et al. (2004)			

receptor-bearing cells (Bournazos et al., 2020; Littau et al., 1990). Despite the fact that ZIKV infection appears to not lead to the production of such antibodies, it appears that prior DENV infection and DENV-ADE production can enhance ZIKV infection (Castanha et al., 2016; Khandia et al., 2018). The relationship between ADE production and the outcome of ZIKV infection is still debated due to contradictory results and likely multifactorial mechanisms. For example, DENV serotypes appear to play a key role in the production of ADE (Guzman et al., 2013; Khandia et al., 2018) and human genetic factors may be involved in the pathogenic effects of ADE in second infections. For example, several FcγRII gene polymorphisms have been identified, in particular, the SNP rs1801274, which has been shown to be associated with the severity of DENV symptoms (Loke et al., 2002; Sánchez et al., 2010; García et al., 2011b; Fang et al., 2012; Dettogni et al., 2015) depending on the ethnicity of the population (Noecker et al., 2014). Thus, rs1801274 could be a determinant factor for the outcome of ZIKV infection for those who had a prior DENV infection or vice versa. In addition, studies of GBS patients and the use of meta-analysis, have reported that CD1E and FcγRIIA genes polymorphism are associated with susceptibility to GBS and ZIKV infection-related symptoms (van der Pol et al., 2000; Wu et al., 2012; Zhang et al., 2018). When a virus infects a cell, it is degraded into small peptides that are presented on the cell surface through major histocompatibility complex (MHC) receptors to be recognized by lymphocytes. The locus for MHC receptors is highly polymorphic, especially that for MHC class II. MHC class II genes have been shown to be associated with the outcome of many viral infections, such as WNV disease and its severity (Lanteri et al., 2011). Several studies have explored the potential genetic contribution of the MHC genes and revealed several significant SNPs associated with the symptoms of WNV infection and neuroinvasion (Lanteri et al., 2011; Manet et al., 2018; Sarri et al., 2016). Such studies also identified MHC class I and II SNPs closely associated with the severity of DENV infections (DHF/DSS) (Stephens, 2010; García et al., 2011a; Fang et al., 2012). These studies thus represent an interesting means to also determine potential MHC polymorphisms associated with the outcome of ZIKV infection. In addition, another polymorphism in the CTLA4 lymphocyte receptor has been shown to be associated with DENV disease (Fang et al., 2012). This receptor is expressed on activated lymphocyte T cells to downregulate the immune response through the transmission of an inhibitory signal. Indeed, the SNP Exon 1 + A/G polymorphism in CTLA4 genes appears to enhance DENV-associated symptoms (Fernández-Mestre et al., 2009). Moreover, a study showed that the combination of this SNP with the TGFB1 (which controls immune cell growth, proliferation, and differentiation) SNP - 509 CC is associated with DHF in the Taiwanese population (Chen et al., 2009). Further studies are needed to evaluate the impact of CTLA4 and TGFB1 polymorphisms in other flavivirus

infections, such as ZIKV, and on other populations.

5. Conclusion

Viral propagation and pathogenicity depend on multiple pathways. The identification of key cellular factors and their polymorphisms will allow to define a panel of genes strongly involved in pathogenicity and transmission, making it possible to better prevent infection and improve patient outcome. Studies have revealed a strong disequilibrium between ethnicity and population for susceptibility to flavivirus infection. This review summarizes susceptible genes and SNP targets associated with the innate and adaptive immune responses against ZIKV as shown in Fig. 1 and Table 1. It is therefore crucial to investigate these polymorphisms in various populations. These results could at least partially explain the emergence and propagation of ZIKV and other flaviviruses. Because the virus also shows genetic variability, it is important to take into account such factor in association with human genetic polymorphisms and identify possible combinations of mutations that play a role in the symptoms of ZIKV infection. The worldwide propagation of ZIKV has been highlighted by the occurrence of severe symptoms, revealing perhaps just the tip of the iceberg. There is clearly an urgent need to understand both the overall spatial and temporal pattern of intercontinental transmission of ZIKV, which should be integrated with new knowledge on the evolution of epidemic lineages.

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