Mol Neurobiol (2018) 55:4160–4184
DOI 10.1007/s12035-017-0635-y

Zika Virus as an Emerging Neuropathogen: Mechanisms of Neurovirulence and Neuro-Immune Interactions

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Received: 5 January 2017 / Accepted: 23 May 2017 / Published online: 11 June 2017

Abstract Zika virus (ZIKV) is an emerging arbovirus of the genus Flaviviridae, which causes a febrile illness and has spread from across the Pacific to the Americas in a short timeframe. Convincing evidence has implicated the ZIKV to incident cases of neonatal microcephaly and a set of neurodevelopmental abnormalities referred to as the congenital Zika virus syndrome. In addition, emerging data points to an association with the ZIKV and the development of the so-called Guillain-Barre syndrome, an acute autoimmune polyneuropathy. Accumulating knowledge suggests that neurovirulent strains of the ZIKV have evolved from less pathogenic lineages of the virus. Nevertheless, mechanisms of neurovirulence and host-pathogen neuro-immune interactions remain incompletely elucidated. This review provides a critical discussion of genetic and structural alterations in the ZIKV which could have contributed to the emergence of neurovirulent strains. In addition, a mechanistic framework of neuro-immune mechanisms related to the emergence of neuropathology after ZIKV infection is discussed. Recent advances in knowledge point to avenues for the development of a putative vaccine as well as novel therapeutic strategies. Nevertheless, there are unique unmet challenges that need to be addressed in this regard. Finally, a research agenda is proposed.

Keywords Zika virus · Neurodevelopment · Microcephaly · Guillain-Barre syndrome · Perinatal infection · Neurology · Psychiatry · Autoimmunity · Cytokines

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Introduction

In April 1947, the Zika virus (ZIKV) was first isolated from the serum of a pyrexial Rhesus monkey caged in the canopy of Zika forest in Uganda. The second isolation occurred in 1948 from *Aedes africanus* in the same forest [1, 2]. The ZIKV is an arthropod-borne member of the *Flaviviridae* family of positive-strand RNA viruses [3]. The capacity of the virus to infect humans was established a few months later and an association between ZIKV infection and the development of a 'Dengue-like febrile illness' was demonstrated in 1953 by a medical team led by Dr. W. Searle [4]. The virus was subsequently isolated in several countries in Southeast Asia at approximately the same latitude as Nigeria and Uganda [5, 6]. By the end of the twentieth century, the ZIKV had been detected in India, Malaysia, the Philippines, Vietnam, Indonesia, Thailand and Pakistan [7, 8]. However, despite such a wide geographical distribution, reports of human diseases attributed to ZIKV infection were extremely rare until 2007 with only approximately 14 cases documented in medical literature at that time [6, 9]. Therefore, a ZIKV epidemic affecting several islands in the State of Yap, Federated States of Micronesia, in that year infecting approximately 70% of the total population emerged as an unexpected public health concern [10]. A subsequent epidemic in French Polynesia occurred in 2013 and 2014, and affected approximately 32,000 people with confirmed or suspected ZIKV infection [11, 12]. Notwithstanding most people infected with the ZIKV presented with a similar pattern of symptoms to those displayed during the epidemic in Micronesia namely fever, rash, conjunctivitis and arthralgia [10], a 20-fold increase in the incidence of the Guillain-Barre syndrome (GBS) which was related to ZIKV infection was observed [11, 13, 14]. It is noteworthy that subsequent ZIKV outbreaks have occurred in other Pacific islands, such as New Caledonia, Easter Island, the Cook Islands (2014), Samoa (2015) and American Samoa (2016) [8]. Furthermore, Brazil has reported an estimated 500,000 to 1,500,000 new cases of ZIKV infection in 2015 [3, 15], and ZIKV cases have recently been reported in Europe [16], in the USA [17, 18] and in Singapore [19]. The ZIKV is transmitted primarily by mosquitoes of the *Aedes* genus, notably *Aedes aegypti* and *Aedes albolpictus* with the latter being able to hibernate and thrive in temperate climates and may well be the culprit behind spread of the ZIKV into Southern Europe [20, 21]. Figure 1 provides a wide-angle lens view of the worldwide spread and distribution of the ZIKV infection. Evidence of human-to-human transmission has been recently documented; sexual and maternal transmission comprise possible routes, although evidence remains inconclusive [22–25]. Prenatal infection by the ZIKV represents a significant public health concern worldwide due to accumulating evidence demonstrating an association with the development of microcephaly and other neurodevelopmental abnormalities [26, 27]. Several comprehensive reviews have recently appraised the amount and quality of available evidence that points to an association between ZIKV infection and increased rates of microcephaly [8, 28, 29]. In brief, convincing evidence supports a causal association between prenatal infection by the ZIKV and microcephaly [29]. However, tentative neuro-pathogenetic models for ZIKV related to microcephaly and GBS have not been proposed.

Therefore, this paper aims to propose mechanistic models based on available clinical and experimental data, and also to critically review possible factors which might have contributed to the emergence of neuro-pathogenic strains of ZIKV in a relatively short period of time. We initially overview an ever-increasing body of evidence on the structure and genomic organisation of the ZIKV, and in particular unique features as well as similarities with other established pathogenic mosquito-borne flaviviruses (MBV) namely yellow fever virus (YFV), dengue virus (DENV), West Nile virus (WNV), St. Louis encephalitis virus (SLEV), Japanese encephalitis virus (JEV) and the tick-borne encephalitis virus (TBEV). Finally, a research agenda towards the development of preventative (e.g. vaccine development) and therapeutic approaches is discussed.

Genomic and Protein Organisation of ZIKV

Virion Organisation and Structure

Early investigations examining ZIKV particles in the central nervous system (CNS) of mice adduced evidence that virions were spherical with an envelope of approximately 43 nm in diameter surrounded by a central core of 28 to 30 nm in diameter [30]. Hamel and fellow workers in a more recent study examining various parameters following ZIKV infection of cultured human skin fibroblasts broadly confirmed those initial findings [9]. Examination of ZIKV-infected cells revealed that the virions were spherical particles with an overall diameter of 40 to 43 nm and a central electron dense core of 28 to 30 nm in diameter. Recently, published cryo-electron microscopy studies have revealed that the viral particles are ~50 nm in diameter consistent with values reported for other flaviviruses [31] with a surface envelope structure composed of four domains with significant similarities to DENV types 3 and 4, while also resembling WNV to a certain extent [32, 33]. These electron microscopy studies have also confirmed that ZIKV is primarily composed of a central core containing the capsid protein intimately associated with genomic RNA incorporated into lipid bilayer presumably derived from host cell. The membrane (M) and envelope (E) proteins, which form the outer shell of the ZIKV virion, are also anchored into the lipid envelope. These latter proteins are comprised of 180 copies comprised of 90 homodimers similarly to other flaviviruses [32–35]. A difference at a particular glycosylation site in the E protein and in nature of the attached glycan residue was observed in the ZIKV strain derived from the 2007

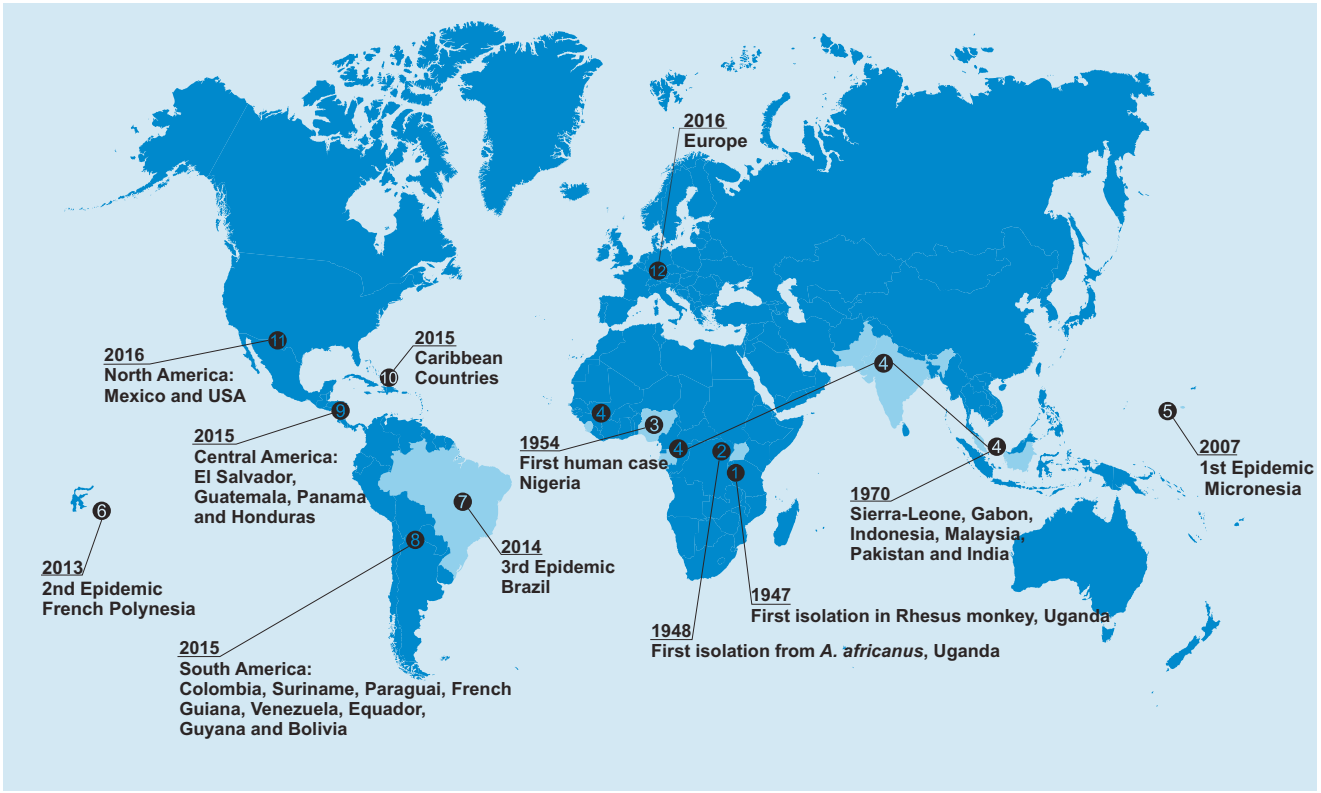

Fig. 1 Spread of the ZIKV in the world from 1947 to 2016. *1* First isolation of the ZIKV in Rhesus monkeys in Uganda; *2* first isolation of the ZIKV from *A. africanus* in Uganda; *3* first human case reported in Nigeria; *4* human cases in Sierra-Leone, Gabon, Indonesia, Malaysia, Pakistan and India; *5* first epidemic in Micronesia; *6* second epidemic in French Polynesia; *7* third epidemic in Brazil; *8* increase in cases across South America; *9* human cases across Central America; *10* cases in Caribbean; *11* human cases in North America human cases; and *12* 'Imported' human cases in Europe. Zika virus (ZIKV)

outbreak compared to other exemplars of the *Flaviviridae* family [33]; these distinct morphological aspects may have significant pathogenic implications, and may also influence the tropism of the ZIKV (vide infra). In addition, some evidence suggests that ZIKV could be more heat-stable than other flaviviruses, which may increase its ability to survive in a wider range of body compartments (and environments), e.g. blood, semen and urine [32]. These properties may aid in the transmission, while also offering evolutionary advantage for the perpetuation of this pathogen.

Genomic Organisation of the Zika Virus

The genomic organisation of the ZIKV is similar in many aspects to other flaviviruses, with a positively polarised single-stranded RNA of approximately 10.794 nucleotides containing a single open reading frame (ORF) encoding a single polypeptide with a methylated cap structure at its 5′ end [36, 37]. The sole ORF is flanked at the 3′ and 5′ ends by two untranslated regions (UTR) [37]. However, it is worthy to note that some significant differences in nucleotide sequence and genomic length between and within different ZIKV strains have been reported [38, 39]. The UTR of the ZIKV genome contains three highly conserved base sequences (CSs) and a complex pattern of secondary RNA structures which seem to play a pivotal role in the cyclisation of the genome, which is a prerequisite for viral replication. The genomic cyclization of different flaviviruses is mediated by the physical interaction between two CSs RNA structures [22, 37]. The UTR regions of flaviviruses also contain a highly variable domain directly proximate to the stop codon, and a moderately conserved region containing a hairpin stem loop (SL) and dumbbell (DB) structures [37]. However, there is some evidence indicating that the organisation of the CS at the 3′ end of the ZIKV RNA differs from that of other mosquito-borne flaviviruses [37]. In addition, there are significant differences between the 3′-UTR sequence of African and the 2007 epidemic ZIKV strains [40]. A detailed review of the various replication strategies utilised by flaviviruses is beyond the scope of this review. We refer the reader to some excellent reviews on this topic [41, 42]. The UTRs are also a source of a unique form of sub-genomic RNA (sf RNA) shared by several flaviviruses thus far investigated [43].This sf RNA is generated by the incomplete cleavage of the 3′ UTR of the ZIKV RNA by the cellular 5–3′ exoribonuclease [44]. This sub-genomic viral RNA seems to modulate host cellular activity in many aspects, e.g. mRNA stability, suppression of the RNA interference (RNAi) pathway and inhibition of interferon

production, and hence may play a major role in converting host cells into 'virus-producing factories' [44, 45].

Zika Virus Polyprotein Cleavage and Non-structural Proteins

The viral polyprotein of flaviviruses is cleaved by a combination of cellular and viral proteases into three structural proteins referred to as the capsid (C), premembrane/membrane (prM) and envelope (E), as well as seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) [32].

These non-structural proteins have been a focus of intensive research which is unsurprising as they influence many pathways of viral replication as well as host immune responses [46]. For example, the ZIKV NS-1 protein modulates host antibody responses and may contribute to several immune evasion strategies [47, 48]. In addition, NS2B, NS4A and NS4B are known to inhibit the production of interferon by host immune cells [49, 50]. Furthermore, the NS2B protein in combination with NS3 may cleave and inactivate the mitochondrial bound sensor of cytosolic nucleic acid STING [51]. Evidence indicates that STING plays a significant role in mounting an interferon response to invading bacteria and DNA viruses [52]. However, STING also has a pivotal role in facilitating the detection and immune response to RNA viruses albeit via mechanisms which remain to be elucidated [52]. The structural proteins of flaviviruses are modified at post-translational levels via the incorporation of oligosaccharides, which may have a profound effect on virus infectivity, replication, tropism and neurovirulence [53–55]. Unsurprisingly, variations in base sequences leading to amino acid changes appear to have played a major evolutionary role in the emergence of highly pathogenic strains of ZIKV as we will now discuss.

Potential Mechanisms Underpinning the Emergence of Pathogenic Zika Virus Strains

Amino Acid Substitutions in Non-structural Proteins

Few sporadic cases of human ZIKV infections were reported in Asia and Africa prior to 2007 when large-scale outbreaks started to appear in the Pacific islands as aforementioned in this review. Furthermore, ZIKV infection have been related to different neurological disturbances, such as the GBS [56], neonatal microcephaly [29] and a congenital syndrome which may encompass several neurodevelopmental abnormalities (e.g. epilepsy) beyond microcephaly [57]. Therefore, changes in the viral genome/polypeptide sequences could have contributed to the emergence of highly pathogenic ZIKV strains. A comprehensive assessment of the genome and polypeptide sequences of all pre-epidemic and epidemic strains of the ZIKV which have been deposited in the GENBANK was recently performed by Zhu et al. [58].

These authors noted that 25 amino acid (aa) substitutions emerged between the Malaysia 1966 pre-epidemic strain and the 2007 epidemic stain, with most significant changes occurring at NS proteins, with 7 and 8 aa substitutions occurring in NS4 and NS5 proteins, respectively [58]. Conversely, no aa substitutions in NS2 were observed when those two ZIKV strains were compared. Interestingly, marked changes in polypeptide sequence were observed when a representative African strain was compared to an epidemic Asian strain, with a total of 75 aa substitutions once again concentrated in the NS5 and NS4 proteins, respectively [58]. However, in this instance, a significant number of aa substitutions were also detected in the prM and E structural proteins [58]. Interestingly, most of these aa substitutions were evident in the pre-epidemic and epidemic Asian strains but 15 were unique to the 2007 strain. Most of these unique aa substitutions were observed in the NS5 and E proteins, with five aa substitutions in NS5 and three in the E [58]. It is also noteworthy that two aa substitutions were observed in all epidemic Asian strains but in none of the pre-epidemic strains (Fig. 2).

The NS1 glycoprotein contains numerous disulphide bonds and potential glycosylation sites which seem to influence the viability and virulence of a number of flaviviruses [53, 59, 60]. In addition, it is interesting to note that recent evidence strongly suggests that significant NS1 codon adaptations in epidemic Asian ZIKV strains may be a driver of increased viral tires and rates of replication and thus have played a major role in the spread of the virus in the human population [61]. It is also noteworthy that thus far, no NS1 glycosylation sites have been detected in any of the lodged ZIKV genomes and there are five aa substitutions between the African and epidemic Asian strains which could be an additional source of increased replication and virulence in the latter lineages [58]. Given the preponderance of aa substitutions at NS5 between African, pre-epidemic Asian strains and epidemic strains, their significance in terms of increased pathogenicity appears to be worthy of particular comment [62].

The Flavivirus NS-5 facilitates the cleavage of STING and STAT-2 [63] and also seems to play a major role in enabling the blockade of type 1 interferon signalling [49, 64], hence structural and functional variations in this protein could provide a mechanism which could clearly enhance the capability of the ZIKV to evade immune responses potentially leading to increased titres. It should also be noted that NS-5 plays an essential role in initiating and propagating flavivirus replication by facilitating the formation and stability of the replication complex in tandem with other NSPs [65] and highly conserved secondary RNA structures [66]. The interaction between these players could be of particular relevance given recent data revealing major differences between the secondary RNA structures of the representative African strain and the

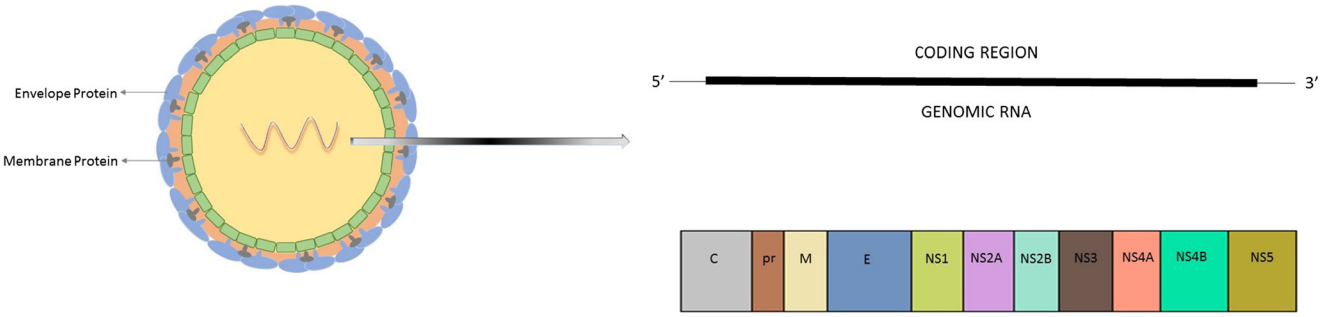

Fig. 2 The structure and genomic organisation of the Zika virus. The ZIKV comprise envelope (*E*), membrane (*M*) and capsid (*C*) proteins which surround the genome. The ZIKV RNA encodes a polyprotein with three structural proteins (capsid, premembrane/membrane and envelope), and seven non-structural proteins referred to as NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5

epidemic Asian strain with a large nine-base bulge in the representative Asian epidemic strain replacing the external loop on SL-1 at the 3′-UTR immediately distal to the NS5 stop codon found in the representative African strain [58]. The significance of this observation remains to be ascertained but increased virulence and or changes in tropism of the virus are possibilities.

Envelope Glycosylation and the Emergence of Neurovirulence

Another source of increased pathogenicity in the epidemic Asian strains may be the acquisition, or perhaps re-acquisition, of a N-linked glycosylation site at Arg-154 (N-154) in the E protein, which several experts suggest is absent in at least some African strains [23, 38]. Several research teams have detected a probable Asn-X-Thr motif located among E protein sequences from a number of epidemic ZIKV strains thus pointing to the presence of a N-linked glycosylation site in residue Asn-154 [38, 67]. These computational predictions have been recently confirmed by Sirohi et al. [33] who studies the 2007 epidemic ZIKV strain through cryo-electron microscopy at a resolution of 3.8 Å. A large body of evidence suggests that some African strains lack this glycosylation site, and therefore it might confer pathogenicity to the virus [22, 23]. Importantly, the E-154 appears to play a major role in the assembly and infectivity of flaviviruses [55, 68]. *N*-glycosylation also appears to play a major role in host and cellular tropism [69]. For example, the presence of an E *N*-glycosylation in the dengue virus decreases its infectivity but otherwise enhance virion release [68]. Other lines of evidence indicate that the absence of a *N*-glycosylation site may increase the replication of dengue virus in mosquito cells, but may also decrease infectivity to mammalian cells, at least in part by reducing binding to DC-SIGN receptors in immature dendritic cells [55, 69]. In this context, it is worthy to note that preliminary evidence suggests that a loss of the ZIKV N-154 site could be induced by serial passage through mice brains [38]. On the other hand, Faye et al. [70] have adduced data to indicate that the ZIKV has lost or gained this site at periodic intervals throughout its evolutionary history, and the loss of the N-154 site in African strains could aid in the adaptation to the *Aedes daliezi* vector [70]. Finally, a sequence of ten aa substitutions surrounding the Arg-X-Thr region not seen has not been observed non-pathogenic ZIKV strains or in other flaviviruses, thus suggesting a putative role for this region in the pathogenicity of the epidemic Asian lineage [33].

Although the exact role of the N-154 glycosylation site for the emergence of neuro-pathogenic ZIKV strains is still a matter of debate, we now drive our attention to another mechanism which is a recognised source of rapid genetic evolution namely recombination, which has been reported for ZIKV [58, 70]. Nevertheless, recombination seems to be a rare event among flaviviruses [71], and hence these data have also been met with some scepticism.

Recombination as a Source of Genetic Variability in ZIKV Strains

Faye et al. [70] provided a synthesis of efforts to investigate the phylogeny of several mainly African strains of ZIKV supplied by the CRORA Dacca Institute Pasteur; the existence of up to 13 possible recombination events were identified in some isolates. In addition, further analysis revealed the existence of breakpoints in the E and NS-5 genomic fragments with five recombination events being identified in E and three in the NS-5 [70]. However, no information about possible recombination partners was provided. However, Zhu et al. [58] characterised the genomes of 24 ZIKV strains originating from Africa, Asia, the Pacific Islands and Latin America whose complete genomic or polyprotein sequences were lodged in the GENBANK repository. Their phylogenetic analysis using the maximum likelihood approach with the MEGA software pointed to a recombination between the ZIKV and the closely related flavivirus SPOV in the NS2B gene [58]. These findings contrast with another study that investigated genome sequences of ZIKV strains derived from Brazil, and no evidence of recombination events was observed [72]. Nevertheless, the SPOV flavivirus was not included in their analysis [72], which is a shortcoming because both the ZIKV

and SPOV belong to the Sponweli clade, which does not encompass other flaviviruses, such as DENV and WNV [73]. Therefore, SPOV could more likely be a recombination partner than other flaviviruses included in the analysis of Calvet et al. [72]. The evidence above indicates that recombination events could have contributed to the evolutionary 'journey to pathogenicity' of ZIKV either from the African or more benign Asian strains, although these data do not provide a proof thereof.

Notwithstanding the field has witnessed significant advances, the precise mechanisms by which the ZIKV infection could induce serious neuropathology are not well understood, and hence the remainder of this paper is devoted to propose a mechanistic framework which might guide future research efforts or otherwise provoke more discussion in this area. Initially, we provide a background on the clinical aspects and factors known to be involved in the pathogenesis of microcephaly and GBS and illustrate how specific properties of ZIKV and other flaviviruses could lead to development of highly specific phenotypes of both conditions.

ZIKV and Microcephaly

Microcephaly: Clinical Background and Pathogenesis

Microcephaly is a condition rather than a disease entity itself and there is ongoing debate about its correct definition remains. Nonetheless, this condition is commonly referred to as 'an occipitofrontal circumference measurement of less than the third percentile or below two standard deviations of the mean measurement for age, gender and ethnicity' [74, 75]. Microcephaly is described as primary when the small size of the brain is due to suboptimal embryonic development due to malformations and or genetic factors [74], whereas secondary microcephaly ensues when embryonic development is normal but the brain suffers subsequent damage impeding or arresting further development, e.g. perinatal and post-natal diseases or various vascular processes [76]. Microcephaly could be challenging to diagnose as exemplified by the results of a relatively recent German study where authors reported that approximately half of the study population with confirmed microcephaly had not received a prior diagnosis [77]. Up to 90% of infants diagnosed with microcephaly develop a wide range of neurocognitive abnormalities and a general pattern of mental retardation of variable severity. However, children whose condition is of familial origin often display normal cognitive development [74]. Importantly, appropriate treatment at the earliest years of life can significantly enhance cephalic parameters and thereby enhance or even normalise cognitive development and thus play a major role in improving the patients' quality of life [78, 79]. The pathogenesis of microcephaly is heterogeneous, involving genetic factors such as polymorphisms in the tyrosine phosphorylation-regulated kinase 1A (DYRK1A) that is located within the Down syndrome (DS) critical region of chromosome 21, and RAD-3 related genes [75, 80], as well as epigenetic factors such as dysregulated expression of miRNAs. Other causes include intrauterine growth restriction and environmental factors, which can influence the development and size of the brain [78, 81]. Evidence also point to an epidemiological link between microcephaly and diarrhoea and malnutrition [82]. Perinatal infections are also well known causes of microcephaly, and cytomegalovirus [83], rubella virus infection [84, 85], *Toxoplasma gondii* and the herpes simplex virus are recognised culprits [86].

Microcephaly may also occur due to a phenomenon referred to as the 'foetal brain disruption sequence', where the collapse of the foetal skull due to the destruction of brain tissue during pregnancy is followed by a pattern of virtually normal brain development [87, 88]. Interestingly, some evidence suggests that the foetal brain disruption sequence may be due to viral infections in utero [88]. Moreover, the presence of ZIKV nucleic acid in the amniotic fluid and brain tissue of foetuses with microcephaly together with abnormally high rates of microcephaly among babies and infants born to mothers with a proven history of acute ZIKV infection [89] provides persuasive evidence linking perinatal ZIKV infection to the development of microcephaly [8, 28]. Furthermore, many infants whose microcephaly appears related to ZIKV infection exhibit a phenotype that resembles the foetal brain disruption sequence [90–92]. Microcephaly is a very rare consequence of maternal infection by other members of the Flaviviridae family such as DENV and WNV, even though the latter virus is a firmly established neuropathogen [93, 94]. Hence any explanation of possible routes whereby the ZIKV could induce microcephaly must consider the dramatic increase in the incidence of microcephaly following ZIKV outbreaks compared to other Flaviviruses. Before addressing this controversial issue, an overview of the evidence purporting to demonstrate an association is provided below.

ZIKV Infection and the Development of Microcephaly

Several well-conducted epidemiological and ecological studies have provided strong, but not yet conclusive evidence of a causal association between exposure to ZIKV and the development of microcephaly, and other adverse neurodevelopmental sequelae [26, 27, 89, 95–97]. Brasil et al. [89] conducted a prospective evaluation of 88 pregnant women in Rio de Janeiro between September 2015 and February 2016 for the presence of the ZIKV RNA via RT-PCR and foetal abnormalities via ultrasound. These authors examined 42 ZIKV positive females and all ZIKV negative females using ultrasonography. There was a dramatic and highly significant difference in the incidence of microcephaly in foetuses of ZIKV positive females compared to those of

ZIKV negative females with the condition observed in 42% of ZIKV positive participants but not in any of the ZIKV negative females [89].

Cauchemez et al. [98] retrospectively reviewed serology and medical records of assumed or confirmed cases of microcephaly following ZIKV infection during the epidemic in French Polynesia between 2013 and 2014. Briefly, these authors estimated that the baseline incidence of microcephaly was approximately 2 cases per 10,000 infants but the risk of developing microcephaly following ZIKV infection in the first trimester was 95 cases per 10,000 infants, which is some 50 times higher. It is also noteworthy that the association between ZIKV infection in the other pregnancy trimesters and increased risk of developing microcephaly was nebulous and a precise estimation of increased risk was impossible to calculate with the model used [98]. These findings are consistent with a Brazilian study, which found no association between ZIKV infection and the development microcephaly in pregnant females infected with ZIKV in the third trimester [99]. The study by Cauchemez et al. [98] could be criticised due to the small sample and the wide confidence intervals of the association. However, another research team reported similar findings, i.e. a 20-fold increase in the development of microcephaly in a retrospective review of 333 medical records from a Brazilian health registry [100]. This association has been further reinforced by a recently published case-control epidemiological study conducted between January and May 2016 in eight state hospitals in the city of Recife (Brazil) [101]. Briefly, 32 serum and CSF samples derived from 32 microcephaly cases and 64 controls were tested for the presence of ZIKV-specific IgM and the presence of ZIKV RNA via QRT-PCR [101]. The authors reported that 80% of the mothers of microcephaly cases and 64% of mothers of unaffected offspring tested positive for ZIKV. However, while 41% of neonates with microcephaly tested positive for ZIKV infection, all unaffected neonates tested negative [101]. It should also be noted that this was a preliminary report of a much larger study involving 200 microcephaly cases and 400 controls prospectively examined over the same time period in the same region. The results of the whole study are awaited with interest.

It is also becoming increasingly clear that there are a broad range of birth defects associated with ZIKV infection during pregnancy with several research teams reporting intracranial calcifications, redundant scalp skin, clubfoot and arthrogryposis in addition to severe microcephaly [26, 27, 95]. Hence, this typical constellation of neurodevelopmental abnormalities is being increasingly recognised as a 'congenital ZIKV syndrome' [27, 96, 97].

Many infants with confirmed or presumed congenital ZIKV infection display features consistent with the foetal brain disruption sequence as discussed above [87, 102]. This phenotype is associated with severe neurological impairment, overlapping cranial sutures, severe microcephaly, prominent occipital bones and redundant scalp skin [27, 90]. The former team of researchers reported that a third of infants diagnosed with microcephaly following ZIKV infection reported to a Brazilian health registry had redundant scalp skin indicative of foetal brain disruption sequence. This phenomenon was previously acknowledged as a very rare feature of microcephaly with only some 20 cases being reported in published literature worldwide [102]. Thus, the question arises as to why the ZIKV infection is associated with such a rare abnormality and perhaps just as importantly why are other mosquito-borne flavivirus infections rarely associated with microcephaly or other neurodevelopmental disorders as discussed above. Another relevant research question is why the Asian lineage is associated with the development of microcephaly whereas the African strain is not? We now consider these intriguing questions and propose a mechanistic framework based on the acknowledged capacity of ZIKV to infect neural progenitor cells (NPCs).

ZIKV Invasion of NPCs in Utero

Several authors using a range of in vitro techniques have demonstrated the capability of ZIKV to infect human NPCs [24, 103–105]. Furthermore, recent rodent studies have demonstrated that the infection of NPCs by the ZIKV may cause a range of developmental abnormalities, such as developmental delays, ocular defects and severe microcephaly [106, 107]. Another team of authors reported infection of NPCs and a significantly reduced cortical thickness and microcephaly following direct ZIKV injections directly into the lateral ventricle of embryonic mice brains [108]. The works of Tang et al. [103] and Rolfe et al. [109] appear worthy of particular emphasis as both research teams examined cellular and/or transcriptional responses within NPCs following ZIKV infection.

Tang et al. [103] demonstrated that the MR766 serotype infected human NPCs leading to the release of infectious ZIKV particles, and this infection increased cellular apoptosis and led to transcriptional dysregulation of cell-cycle genes, leading to attenuated NPC growth [103]. Similarly, Rolfe et al. [109] analysed changes in gene expression patterns in NPCs exposed to an Asian strain of ZIKV or to cytomegalovirus. These authors observed that the abnormal patterns of gene expression induced by ZIKV were consistent with aberration that were previously related to the development of congenital neurodevelopmental conditions such as microcephaly [109]. The ZIKV infection also provoked robust antiviral responses and activation of inflammatory pathways involved in innate and humoral immune responses, whereas these immune responses were either greatly attenuated or absent in CMV-infected NPCs [109]. Furthermore, ZIKV infection was found to deplete NPCs in human cerebral organoids via activation of toll-like receptor (TLR)-3 [105]. Likewise, ZIKV infection also activates TLR-3 in human fibroblasts [9]. Activation of the TLR-3 after ZIKV infection may provide a

route whereby the virus may cause microcephaly. Consistent with this hypothesis, animal studies have shown that the activation of TLR-3-mediated immunity during gestation inhibits cortical neurogenesis [110]. Prenatal activation of TLR-3 by RNA viruses could mimic effects of polyinosinic-polycytidylic Poly (I:C), which inhibits the expression of the GluN1 subunit of the NDMA receptors [111, 112]. In addition, the adverse effects of Poly (I:C) on embryonic neural stem/progenitor cells (NPC) proliferation is abrogated in TLR-3 knockout mice [110].

The Role of TLR-3

Neurogenesis occurs predominantly during embryogenesis, and decreases during early post-natal development and remains at a basal level into adulthood [113]. Importantly, defective and dysregulated neurogenesis results in the development of severe brain abnormalities in the foetus (e.g. microcephaly) [114, 115].

TLRs exhibit differential expression patterns in the brain and perform diverse and indispensable functions within the developing central nervous system (CNS) [112, 116]. In particular, this family of receptors regulate a plethora of functions intimately associated with neurogenesis and general post-natal neural development such as cell migration [117], cell cycle [118] and neural plasticity [119] (see ref. [120] for a review).

Importantly, while expression of TLRs in the brain was once thought to be confined to astrocytes and microglia [121, 122], there is now copious evidence demonstrating their expression on neurons and NPCs [123–125]. In particular, the weight of evidence suggests that neurons and NPCs express a range of TLRs, which may be readily activated in response viral RNAs or bacterial antigens, including but not limited to TLR-2, TLR-3 and TLR-4 [123, 125, 126].

TLR-3 expression is normally at highest levels during early cortical development when NPCs are at their most proliferative capacity before decreasing to low basal levels when neurogenesis (and gliogenesis) predominates [127, 128]. The weight of the evidence suggests that this TLR inhibits the proliferation of embryonic NPCs but appears to have no such effect on NPCs of adult mammals [127, 129]. A possible mechanism underpinning this inhibition could be the modulation of the sonic hedgehog pathway [130], which plays a pivotal role in governing many aspects of early brain development [131]. Embryonic neurogenesis is also regulated by the nuclear factor kappa beta (NF-κB) signalling pathway [132, 133]. This may explain data obtained by in vivo and in vitro experimentation demonstrating that induction of TLR-3-mediated immunity during gestation inhibits cortical neurogenesis [110], and, in particular, prenatal activation of TLR-3 by the RNA virus mimetic poly(I:C) changes the expression of the GluN1 subunit of the NDMA receptor leading to impaired neural development and an abnormal arrangement of synaptic proteins [111]. Therefore, the long-lasting activation of TLR-3 by ZIKV virus infection of NPCs may provide a plausible model by which ZIKV could induce microcephaly in some neonates. Another hypothesis is that when cranial neural crests cells exhibit limited apoptosis once infected by ZIKV, but otherwise may secrete cytokines that may promote cell death and drive abnormal differentiation of NPCs. However, this phenomenon does not consistently occur after dengue virus infection (Fig. 3) [134]. Finally, the NS4 and NS5 proteins of the ZIKV may inhibit the mammalian target of rapamycin protein (mTOR) pathway after activation by receptor tyrosine kinases [135]. The mTOR pathway has been widely implicated in neurogenesis, and thus this mechanism can further hamper neurodevelopment. Hence, defective mTOR signalling has been implicated in a range of autophagy-related neurodevelopmental disorders (vide infra) [136].

The Role of the Unfolded Protein Response

While chronic or prolonged TLR-3 activation provides a plausible model to explain the development of microcephaly in some infants, another more general effect of flavivirus infection could also impact neurogenesis by activating the unfolded protein response (UPR) leading to endoplasmic reticulum (ER) stress and thus provide another possible route whereby ZIKV infection could lead to the congenital ZIKV syndrome.

The endoplasmic reticulum acts as a highly dynamic calcium storage system and a unique protein processing and folding centre. Unsurprisingly, this cellular organelle is exquisitely sensitive to cellular dyshomeostasis, which lead to the accumulation of aggregated and or misfolded proteins ultimately triggering multiple pathways governing the induction of programmed cell death [137]. There are several drivers of ER stress, e.g. the overproduction of reactive oxygen species, increased intracellular calcium ion concentration, nutrient or glucose deprivation, expression of mutant proteins, increased demand for protein folding [137]. In addition, ER stress may contribute to brain damage in the perinatal period [138]. The ER has evolved highly specific and sophisticated signalling pathways collectively described as the UPR, which inhibit or otherwise alter intracellular transcriptional and translational machinery with the aim of reducing the accumulation of unfolded or misfolded proteins, thus increasing luminal folding capability and enhancing misfolded protein degradation via the ER-associated protein degradation (ERAD) or by promoting increased autophagy [139–141]. The complex network of the UPR to ER stress is mediated by a few ER transmembrane proteins: PERK (PKR-like ER kinase), IRE1 (inositol-requiring enzyme 1), and ATF6 (activating transcription factor 6) [142, 143].

Flaviviruses provoke structural and compositional changes to host cell membranes to create organelle-like structures described as replication complexes in the cytoplasm aimed at establishing the optimal environment for their replication [144]. The ER is a main source of these structures, and the accumulation of viral structural and non-structural proteins

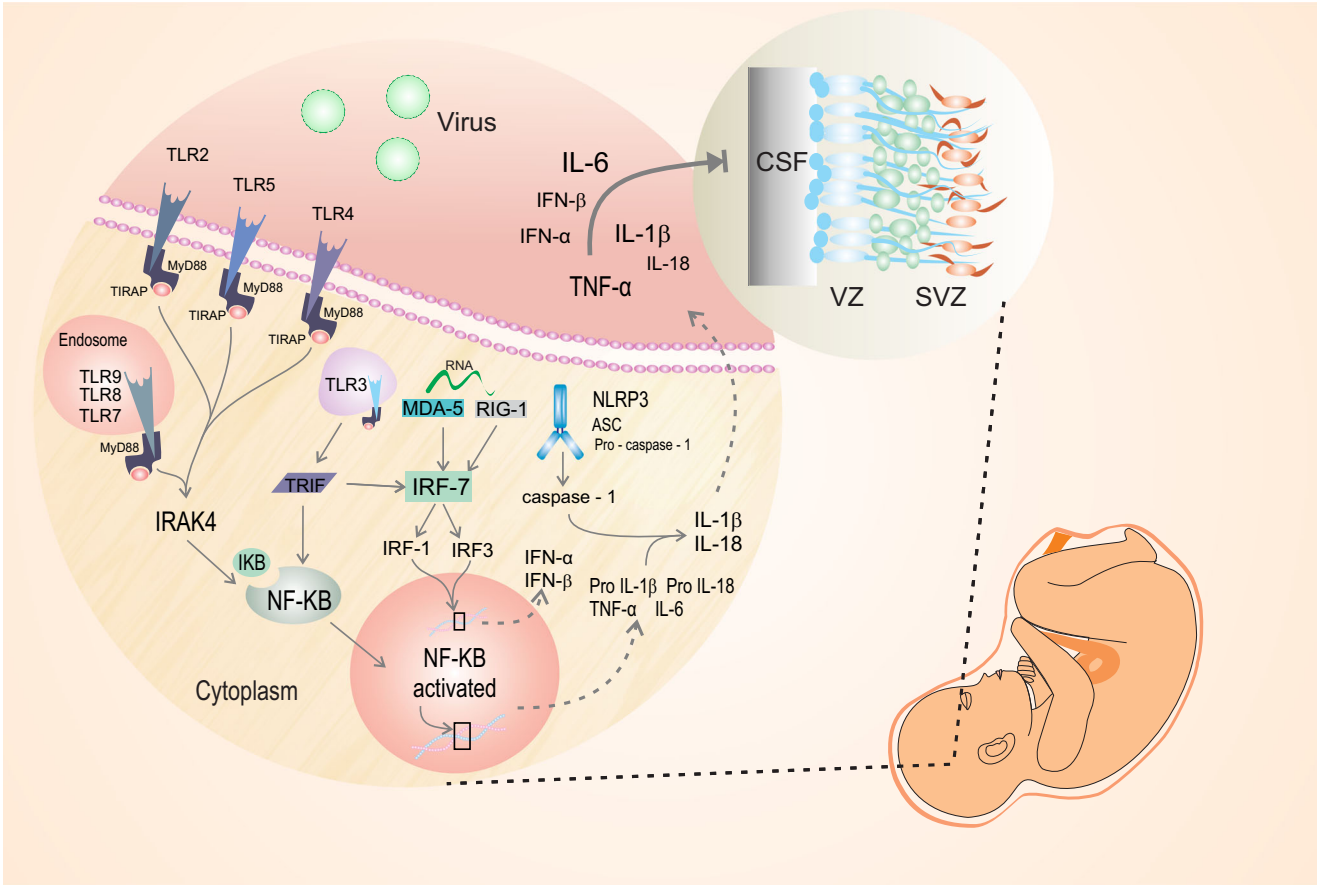

Fig. 3 Association between ZIKV infection and the development of microcephaly. Toll-like receptors (TLRs), melanoma differentiation-associated gene 5 (MDA-5) and retinoic acid-induced gene-1 (RIG-1) like receptor are pattern recognition receptors involved in the detection of pathogens (e.g. ZIKV). TLR-3, RIG-1 and MDA-5 promote the expression of type I and type III interferons (IFNs), and the NF-kappa B-dependent expression of pro-inflammatory cytokines. Maternal immune activation increases the levels of cytokines in the serum as well as in amniotic fluid, placenta and foetal brain. IL-6, TNF-α and IL-1β may adversely impact the developing foetal brain. Another hypothesis is that the ZIKV infection may induce cranial neural crest cells to produce high levels of cytokines affecting the formation of cranial bone and cartilage as well impairing CNS development. Zika virus (*ZIKV*), ventricular zone (*VZ*), subventricular zone (*SVZ*), cerebrospinal fluid (*CSF*)

may be a source of stress within this organelle [145–147]. Unsurprisingly, all flaviviruses activate at least one arm of the UPR but pathways may vary with different viruses, strains and stage of the replication cycle. In particular, an accumulating body of evidence suggests that activation of autophagy via drug interventions may protect against in vivo flavivirus infections (see ref. [148] for a review). Hence, should the involvement of the UPR in the pathogenesis of ZIKV congenital syndrome be confirmed, there is some promise for the development of novel prophylactic or even therapeutic targets provided that concerns regarding teratogenicity can be addressed.

The UPR is activated in the developing brain and multiple lines of evidence indicates that temporal and spatial changes in the intensity of UPR signalling plays an indispensable role in regulating processes connected to membrane development and vascularisation during direct and indirect neurogenesis [149–151]. Importantly, neural development is highly sensitive to longitudinal abnormalities in the levels of UPR signalling, which can lead to substantial neurodevelopmental pathology [152, 153]. In particular, progressive downregulation of UPR activity is required to regulate the transition between direct and indirect neurogenesis and in the regulation of multiple aspects of neural development thereafter [149, 154]. In the absence of such downregulation, constantly exacerbated UPS activity results in the inhibition of indirect neurogenesis and the development of microcephaly in rodents [154, 155] and in humans [156–158]. Chronic activation of the UPR is also a driver of severe neuropathology in adults, and has been implicated in the pathophysiology of several neurodegenerative conditions, e.g. Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis and Parkinson's disease [140, 141, 159].

When evidence is considered as a whole, it seems clear that mechanisms exist whereby ZIKV could induce neurodevelopmental abnormalities notwithstanding outstanding questions remain. Two such questions are why is ZIKV associated with a high incidence of microcephaly and why are post 2007 Asian strains associated with

the development of microcephaly while African strains are not? We will now consider the work of Zhang et al. [160] and Braul et al. [107], which may provide some clues to these questions.

Brault et al. [107] infected cultured murine embryonic brain segments with the 2013 French Polynesian strain of ZIKV and detected productive infection of ZIKV in neocortical tissue, with a distribution pattern showing ZIKV replications predominantly being confined to the ventricular zone. Perhaps most importantly, these authors reported that ZIKV preferentially infected radial glial progenitor cells, which are the precursors of NPCs and hence of all neurons and glia [107]. Hence given the established role of NPCs in neurogenesis the preferential capacity of ZIKV to infect these cells could at least partly explain the higher incidence of microcephaly following ZIKV outbreaks compared to other flaviviruses.

It is also of interest that the molecular biosignature within NPCs following infection with African and Asian strains of ZIKV appear to be markedly different. Zhang et al. [160] directly infected NPCs with the African MR766 strain or the FSS13025 Cambodian of ZIKV and thereafter examined the changes in the transcriptome of these cells. Infection by the Asian strain of ZIKV led to the downregulation of genes involved in DNA replication and repair [160]. Furthermore, the Asian strain of ZIKV upregulated the expression of genes involved in the regulation and instigation of apoptosis, notably p53, as well as genes involved in the antiviral response, whereas the African strain did not [160]. Hence, the African strain does not seem to induce deleterious effects in NPCs, which are characteristic of the Asian strain and is unlikely to disturb neurogenesis to the same extent if at all. Therefore, differences in gene expression induced within NPCs could account, at least in part, for the markedly different rates of microcephaly associated with the Asian compared to the African lineages.

ZIKV and Guillain-Barre Syndrome

Clinical Background and Pathogenesis

Guillain-Barre syndrome (GBS) is the most common acquired flaccid paralysis in the world and may be defined as an acute immune-mediated post-infectious peripheral neuropathy with highly variable clinical presentation, patterns of pathology and prognosis [161, 162].

Infectious and non-infectious triggers of GBS have been documented [163], but the role of antecedent infections appear to predominate as slightly over two-thirds of cases are preceded by symptoms of gastrointestinal or upper respiratory tract infection [163]. *Clostridium jejuni* is the most common pathogen involved with the development of GBS with some 30% of cases being associated with infection by this organism [164]. A number of *C. jejuni* strains contains lipooligosaccharides (LOS), a carbohydrate structure located on its outer membrane. The oligosaccharide core of LOS molecules expressed by *C. jejuni* structurally resemble the oligosaccharide core of certain molecules expressed in neural tissue [165, 166]. The most common class of molecules are gangliosides, which are glycolipids containing sialic acid—primarily found in the nervous system [167].

The exact pathogenesis of GBS is not fully understood; however, molecular mimicry between *Campylobacter* sp. LOS and gangliosides in nervous tissue induces a cross-reactive antibody response [168, 169], and these ganglioside targeting autoantibodies play a pivotal role in the pathogenesis of the syndrome [170, 171]. It is also noteworthy that the dominant type of autoantibody produced may predict to some extent the clinical presentation of the illness. For example, antibody reactivity against GM1, GM1b and GalNAc-GD1a are associated with pure motor GBS [172], whereas anti-GQ1b antibody reactivity has a stronger association with oculomotor symptoms and ataxia [173].

However, only one in 1000 to 5000 patients suffering from *Campylobacter enteritis* ultimately develop GBS [174, 175], and those infected with the same organism can display quite different clinical manifestations. The weight of evidence suggests that genetic or epigenetic factors within host and pathogen determine the susceptibility of an individual to develop GBS [176]. While the activation of the complement cascade by autoantibodies targeting glycosides is a cardinal step in the genesis of GBS, numerous pathways and players within the immune system seem to be involved [177]. For example, systemically and locally released cytokines seem to contribute to immune-mediated axonal damage and demyelination of peripheral nerves in the context of GBS. Activated TLRs appear to be the prime source of these cytokines and polymorphisms in TLRs appear to be a risk factor for the development of GBS [178]. Abnormal patterns of macrophage activity, T cell activation and a Th17/T reg imbalance also appear to play a major role in the pathogenesis of the illness [179, 180].

In addition, accumulating evidence points to the involvement of innate and humoral immune activity against epitopes of myelin Schwann cells and/or axon-expressed antigens [170]. It is also of interest that a role for infection in the emergence of autoimmunity has been repeatedly demonstrated [181].

Flaviviruses and Molecular Mimicry

Molecular mimicry appears to be a major driver of autoimmune pathology observed in many individuals following infections with flaviviruses. For example, ample evidence indicated that the potentially life-threatening dengue haemorrhagic fever may be caused by molecular mimicry between viral proteins, endothelial cells, thrombin and plasminogen, which ultimately may elicit the production of autoantibodies with antithrombotic and pro-

fibrinolytic activities, thus dysregulating the coagulation cascade and as a consequence haemostasis [182, 183]. In addition, the production of these cross-reactive autoantibodies stems from amino acid sequence homology between various coagulation models, structural proteins and enzymes, notably protein disulphide isomerase, in platelets and endothelial cells and the viral core Prm and E proteins as well as the C-terminal region of NS-1 [184]. For example, one source of autoantibody production is sequence homology between plasminogen, tissue plasminogen activator, factors XI, X, IX, VII, II (thrombin) and sequence 101–106 of the E protein, while antibodies targeting the C-terminal region of NS1 can damage platelets and endothelial cells leading to a loss of function and interfering with formation of fibrin leading to increased thrombin time [182, 183, 185]. Molecular mimicry towards acetylcholine receptors is also thought to play a role in the onset of myasthenia gravis seen in some individuals following WNV infection [186, 187]. Leis et al. [186] reported on patients who had developed MG in the context of otherwise stable neurological defects, 3 to 7 months following WNV infection; all had had elevated titres of acetylcholine receptor (AChR) antibodies. Another study has found that 17% of patients with MG and elevated AChR autoantibodies but without obvious signs of previous WNV infection displayed anti-WNV IgG [187].

Notwithstanding isolated cases of GBS have been reported following DENV and WNV infections, such cases are very rare [13, 188, 189], and thus any explanatory model purporting to explain the involvement of ZIKV in the pathogenesis of GBS must consider that the risk of developing GBS following infection by this virus seem to be far higher. Likewise, one would also need to consider mechanisms which might explain the relative rare incidence of GBS following infection with the African strain compared to the relatively common development of this illness following infection with the neuro-pathogenic Asian strain.

Links Between ZIKV Infection and GBS

dos Santos et al. [190] presented the results of a case series of 7 countries involving a total of 164,237 confirmed and suspected cases of ZIKV infection and 1474 cases of the GBS in Colombia, the Dominican Republic, Brazil, El Salvador, Honduras, Venezuela and Suriname from April 1st, 2015 to March 31st, 2016.

These authors noted that the reported increase in incidence of ZIKV infection in this time frame was clearly associated with an increased incidence of GBS [190]. During that time period, there were dramatic increases in the incidence of GBS compared to pre-ZIKV baseline rates with a 211% increase in Colombia, a 150% increase in the Dominican Republic and a 172% increase in the State of Bahia (Brazil). Furthermore, increases in incidence in El Salvador, Honduras, Venezuela and Suriname were equally alarming with respective rates of increased GBS incidence of 100, 877 and 400% [190]. Importantly, the peaks of ZIKV infections also corresponded with peaks in the number of GBS cases. Moreover, in countries that reported decreases in the incidence of ZIKV infections, the incidence of GBS also declined [190].

Several research teams have adduced laboratory evidence supporting a causative role for ZIKV in the pathogenesis of some cases of GBS [191–195]. Arguably, the strongest evidence has been provided by Cao-Lormeau et al. [194] and Parra et al. [195], and these studies provide complimentary information. It should be noted at the outset, that virtually all patients enrolled in both studies manifested symptoms consistent with a ZIKV infection, e.g. fever, rash, myalgia and a history of such an infection was confirmed by the presence of cross-reacting IgM or IgG antibodies directed against flavivirus antigens. Furthermore, these antibodies were observed in a significantly higher proportion of patients with GBS compared to unaffected controls [194]. Parra et al. [195] reported that 40% of patients tested using RT-PCR on blood urine or CSF were positive for the nucleic acid of ZIKV but no patients tested positive for DENV RNA, while Cao-Lormeau et al. [194] also found antibodies directed towards GM1 in approximately 50% of patients. Interestingly, both research teams reported that the time between the first symptoms of ZIKV and the development of neurological symptoms was extremely short (i.e. 6 to 7 days). This timescale is more consistent with a parainfectious trigger rather than a post-infectious profile [196], such as cases triggered by pathogens such as *C. jejuni* [161, 196]. It should also be noted that the subtypes of GBS were different in the two studies, with 78% of GBS patients presenting with acute inflammatory demyelinating polyneuropathy (AIDP) in Colombia [195], whereas acute motor axonal neuropathy (AMAN) prevailed in French Polynesia [194]. Furthermore, the development of GBS was almost entirely confined to ethnic Polynesians in the study conducted by Cao-Lormeau et al. [194], a finding that was later confirmed by Watrin et al. [14]. Conversely, there was no apparent ethnic stratification of cases in the Colombian study [195]. In addition, serological examination of Colombian GBS patients revealed evidence of prior DENV infection, whereas no serological evidence of prior DENV infection was detected in French Polynesia [194, 195].

Whilst it is possible that the rapid onset of GBS following ZIKV infection could be driven by molecular mimicry prior to the onset of symptoms, profound immune dysregulation as a result of direct neuro-invasiveness and prolonged infection as evidenced by the presence of replicating ZIKV in the CSF of GBS sufferers extending well beyond the symptomatic and viremic phases [67, 193, 195] could also play a pathophysiological role. In addition, some evidence indicates that immune responses evoked by acute ZIKV infection particularly in terms of the type 1 interferon response differs to that of other mosquito-borne viruses, which may contribute to the emergence of GBS.

Flaviviruses and Subversion of the Type 1 Interferon Response

Flaviviruses have evolved a number of mechanisms aimed at avoiding detection by membrane and cytosolic pattern recognition receptors (PRRs), such as TLR-3 or RIG-1 receptors or the inhibition of interferon signalling via the downregulation of interferon-α/β receptor (INFARs) and or key effectors in the JAK-STAT signalling cascade such as ak-1 and tyrosine kinase-2 [197–199]. These immune evasion strategies are mainly facilitated by a range of non-structural proteins, such as NS2A, NS4A and NS4B, and, in particular, WNV NS5 proteins inhibit STAT1 phosphorylation and nuclear translocation as well as inhibiting the surface expression of INFR1 via direct physical interaction with the cellular dipeptidase prolidase [200, 201].

Similarly, while type 1 interferons may play a pivotal role in the clearance of viral pathogens, these cytokines also exert a range of immune-modulatory influences notably on dendritic cell function, particularly on the efficiency of antigen presentation and type of cytokine production, B cell activity and T cell activation, differentiation and stability [202–204]. From the perspective of this review, it is particularly important to note that type 1 interferons, notably interferon-beta, enhances apoptosis of TH17 T cells [205], inhibits the differentiation of naive CD4 T cells into the Th17 phenotype [206, 207] and suppresses the secretion of Th17 polarising cytokines from various antigen presentation cells, most notably plasmacytoid dendritic cells [204, 207]. Importantly, the in vivo inhibition of endogenous IFN-β signalling leads to increased synthesis and secretion of IL-17A, IL-17F, IL-9, IL-21 and IL-22 by activated but anergic T cells extracted from patients with relapsing-remitting multiple sclerosis (RRMS) [208]. In keeping with this view, mounting evidence indicates that a deficient or subnormal type 1 interferon signalling plays a pivotal role in the pathophysiology of a range of neurological disorders, e.g. Parkinson's disease and multiple sclerosis [209–213]. Furthermore, accumulating evidence indicates that the inhibition of the differentiation of Th17 T lymphocytes and IL-17A secretion by the administration of IFN-β therapy underpins the efficacy of this treatment in many patients with multiple sclerosis by modifying the autoimmune processes and cytokine secretion patterns associated with the pathogenesis of this illness [206, 214, 215]. This is consistent with a wealth of data supporting a pathogenic role for Th17 T cells and IL-17 in RRMS at least in the early phases of the disease [216, 217]. From the perspective of this paper, it is important to reiterate that accumulating evidence indicates that Th17 cells and their biosignature cytokines play a major role in the pathogenesis and persistence of GBS [179, 218]. In addition, drugs demonstrating some success in alleviating the clinical signs of the illness (e.g. immunoglobulins) may act at least in part by decreasing the differentiation and/or propagation of Th17 cells and/or the activity of IL-17A [179, 219]. Thus, a mechanism through which the suppression of interferon signalling by flaviviruses could bias the immune response towards Th17 T cell production could be involved in the emergence of GBS, a mechanism which we will now discuss in further details.

Flaviviruses and the Treg/Th17 Balance: Differences Between DENV, WNV and ZIKV

A higher population of Treg cells is a characteristic feature in acute WNV and DENV infections, which tends to normalise in convalescent individuals [220]. Moreover, some evidence suggests that levels of these lymphocytes correlate with a reduction in the severity of disease, and protect against the development of neurological sequelae [220–222]. The reasons for such an increase in Tregs during acute infection remain incompletely elucidated. However, in dengue, one possible explanation is the recruitment of the E3 ligase UBR4 by NS5 to increase the degradation of STAT-2 as part of the viral anti-interferon strategy. E3 ligase exerts several modulatory effects on an activated immune system, especially T cell activation and differentiation and is involved in the induction of T cell anergy and the production of Tregs [223, 224]. Hence, the recruitment of this ligase could provide an explanation for the elevated numbers of Tregs during acute DENV infection [222, 223]. The ZIKV also inhibits interferon but via an unexplained mechanism which differs from that employed by DENV and WNV [225]. The host immune response to acute ZIKV infection is characterised by poly-functional T cell activation with elevated production of Th1, Th17, Th9 and even Th2-derived cytokines followed by normalisation or significant decreases in their levels during convalescence [226]. This finding is consistent with a biased pro-inflammatory immune response provoked by ZIKV infection of NPCs in vitro with an increased production of 'Th17' cytokines and chemokines such as tumour necrosis factor (TNF)-α, IL-1β and IL-8 [109, 227]. It seems reasonable to conclude that the Th17 bias of the immune response to ZIKV infection compared to an increased Treg/Th17 ratio in the immune response to WNV and DENV could plausibly explain the increased incidence of GBS following ZIKV notwithstanding some pertinent questions remain unanswered. Particularly, why were the subtypes of GBS different in French Polynesia and Colombia and why was the development of GBS confined to ethnic Polynesians in the study reported by Cao-Lormeau et al. [194].

ZIKV and Genetic Susceptibility in the Pathogenesis of GBS

The importance of genetic factors in the development of GBS is well documented and many research teams have reported a relationship between FcγR human leucocyte HLA complex

CD1 and TNF alpha gene polymorphisms, and increased predisposition to the development of GBS [228–231]. These associations have been supported by the conclusions of well-conducted meta-analyses [232, 233]. In addition, these findings seem to be associated with the severity and subtype of illness one develops [234–237] (see refs. [177, 238] for reviews on this topic). Magira et al. [239] reported a significant association between class II HLA gene polymorphisms and the risk of developing the ADIP form of GBS but no such association was found with an increased risk of developing the AMAN form of the illness. This finding provided support to earlier data reported by Monos et al. [236]. Therefore, different immunological mechanisms may drive the pathogenesis of the two forms of GBS [236, 239]. Further support for this viewpoint may be obtained from the work of Jiao et al. [230], who reported a significant associations of a range of TNF-α polymorphisms and the AMAN form of the illness, whereas no associations between TNF alpha gene polymorphisms and ADIP were observed. Therefore, the frequency of common variants in HLA genes in the genomes of ethnic Polynesians could account to their increased susceptibility to the develop ADIP compared to other ethnic groups.

In the study by Parra et al. [240] conducted in Colombia, there was evidence that the patients who had developed GBS had also experienced historical infection by DENV [240]. Thus, it is conceivable that antibody-dependent enhancement (ADE) of ZIKV infection could have resulted in high viral titres and hence an unusually vigorous immune response based on high levels of pro-inflammatory cytokines [241], which could trigger the emergence of GBS in some people even with lower of genetic susceptibility to the illness. The phenomenon of ADE has been demonstrated in experiments involving the ZIKV [94, 242]. Paul et al. [242] reported that DENV immune sera cross-react with ZIKV without neutralising the virions. Actually, this response enhanced the replication of the ZIKV [242]. The use of a panel of anti-DENV monoclonal antibodies revealed that the vast majority also reacted with the ZIKV [242]. These finding have been replicated by others [94]. It is noteworthy that over 85% of GBS cases had evidence of prior dengue infection in the study conducted by Parra et al. [195], which makes the phenomenon of ADE a prime suspect as far as the development of GBS in these patients is concerned.

However, the above does not fully explain the apparent capacity of Asian lineages of ZIKV to trigger GBS in some patients, which appears to be lacking or greatly attenuated in the African strains. In order to propose such an explanation, we will revisit the phenomenon of NS1 codon adaptation initially described by Freire et al. [61]. Hence, codon preferences of the Asian and African lineages are distinct, and codon usage adaptation in the NSI gene for human host housekeeping genes was detected [61]. This finding was replicated by Butt et al. [243], and may result from genomic variation produced by a combination of mutations and natural selection processes [243]. These are highly significant findings as codon preferences and codon adaptation to the host transcriptional and translational machinery can strongly affect gene transcription and increase the efficiency of translation leading to higher viral titres [244, 245]. Furthermore, the interplay between viral codon usage may increase viral fitness and survival, and may also aid in immune evasions [246, 247]. Studies of codon usage have identified several factors that can influence codon usage patterns, including natural or translational selection, mutation pressure, replication, secondary protein structure, selective transcription, the external environment and hydrophobicity and hydrophilicity of the protein [243]. Hence, the capacity to cause GBS in some patients apparently displayed by the Asian lineage of ZIKV but not by the African lineage could be due to codon usage adaptation by the former and in this context it is noteworthy that NSI levels correlate with disease severity and viremia in other flaviviruses [248]. Intriguingly, NSI has the capacity to interact with STAT-3 [249] whose upregulation is a driver of activated T cell differentiation along the Th17 pathway [250, 251].

There is also evidence that STAT-3 acts as a negative regulator of type I interferon signalling [252] and hence activation of STAT-3 by ZIKV's NS1 could explain the different cytokine signatures following acute infection and alternative interferon suppressing strategies used by ZIKV compared to DENV and WNV [225]. New findings indicate that the 1.9-Å-resolution EM structure of the complete NSI protein extracted from the original Uganda and current Brazilian strains of ZIKV [253] demonstrated significant differences in the surface electrostatic potential of ZIKV's NS1 compared to DENV and WNV which could enable a different pattern of interactions with host proteins, which could provide an indirect explanation to the aforementioned preposition, i.e. the NSI of distinct ZIKV strains may interact differently with STAT-3 and not STAT-2, whereas the NSI of DENV and WNV seem to display the opposite pattern. Interestingly, these authors also noted significant differences between the surface structures of full-length NS1 proteins obtained from the Ugandan and Brazilian ZIKV strains which would change the 'visibility' of the proteins as far as the immune system is concerned [253], which may be another factor in the acquisition of pathogenicity by the South American strains of the virus. Asian strains of the ZIKV were not directly examined in this study.

In this context, it should also be noted that the structure of NSI influences the neuro-invasiveness of flaviviruses [248], and hence the observed structural differences in the NSI proteins obtained from the African and South American strains of ZIKV may be another element in explaining the increased rates of microcephaly and GBS following infection with the South American, and possibly, the Asian strains compared to the African strains. In addition, EM imaging of NSI in its

secreted heteromeric form (NSI') has revealed the existence of distinct domains involved in interaction with immune system players [254]. Such interactions involve the upregulation of TLR-4 in macrophages and PMBCs leading to a surge in the production of pro-inflammatory cytokines shortly after infection [255], as well as an activation and exacerbation of the classical compliment cascade [256]. NSI' also engages with other proteins in the complement system such as C4 and glycoprotein factor H to inhibit viral recognition and lysis of infected cells respectively [257, 258]. Moreover, there is accumulating evidence that interaction between NSI and C1q plays a major enabling role in ADE [248].

Given the preceding data targeting the production and or inhibiting the activity of ZIKV NS1 is clearly an attractive proposition as far as developing therapeutic options for ZIKV prophylaxis or treatment is concerned. Indeed, methods for inhibiting the production and activity of ZIKV NS1 as well as mitigating against its pathological effects form the basis of our research recommendations outlined in the following and final section of this paper. Targeting this protein is not without its risks, however, and ultimately our recommendation is based on mitigating these risks as well as a consideration of resources and the urgent need for effective interventions in the face of the rapid geographical spread of this virus, which according to the WHO appears to be beyond the capacity of emergency measures to control.

Research Implications: Possible Preventative and Therapeutic Strategies

Subunit or DNA Vaccines

The efficacy of several NSI subunit or DNA vaccines have been trailed in several animal studies (reviewed in ref. [248]) and while there have been partial success [259, 260], thus far only one chimeric anti-NSI vaccine has entered human phase III trials [260]. There are several issues limiting the effectiveness of anti-NSI vaccines such as the pre-existence of anti-NS1 antibodies [260] and the coexistence of NS1 and NS1', which leads to a reduced expression of NS1 on membrane surfaces [261]. DENV NS1 antibodies have a pathogenic role in increasing disease severity [185, 262–264]. DENV and ZIKV NSI share many B cell epitopes [61], hence the enterprise of producing antibodies against ZIKV which do not cross-react with possible untoward consequences following a subsequent ZIKV or DENV infection is challenging. This could also be an issue with a vaccine raising antibodies towards ZIKV envelope proteins are the surface composition of DENV and ZIKV are virtually identical [265] and hence ZKV E specific antibodies could in theory exacerbate ZIKV or otherwise DENV infections, with detrimental consequences via the phenomenon of ADE [266, 267].

Passive Immunisation

Technology for harvesting human monoclonal antibodies has improved immeasurably in recent years and several research teams have adduced evidence demonstrating that passive immunisation utilising human neutralising anti-DENV monoclonal or polyclonal antibodies can against DENV infection in mice [268–270] and primates [271]. However, therapeutic use of monoclonal antibodies and delivery into humans has until recently proved to be prohibitively expensive [272]. Nevertheless, this team of authors has recently demonstrated that simple and low-cost intramuscular delivery into mice accomplished by electroporation of DNA plasmids engineered to produce modified human neutralising monoclonal antibodies directed towards multiple DENV serotypes conferred a high degree of protection against DENV disease and, crucially, prevented ADE [272]. This latter finding is supported by other evidence suggesting that modified human monoclonal antibodies can be effective while mitigating against or avoiding the phenomenon of ADE [273]. It is also worthy of note that unlike viral vectors, this method would appear to have no additional serological consequences and hence would be a suitable vehicle for administrating repeated treatments [274, 275]. Passive transfer of monoclonal and polyclonal antibodies also offers a very rapid treatment [276], which is very important in the context of data suggesting that GBS may develop in some people in as little as 7 days following initial infection [192, 193]. There is also a considerable body of evidence alluding to the safety of passive antibody therapy during pregnancy [277, 278] which is important in the context of a pregnant female affected with ZIKV. However, there is also data indicating that monoclonal antibodies do not cross the placenta until the second trimester [275, 276] and hence this approach cannot reasonably be expected to confer protection to the foetus.

Interferon Therapy

There is evidence indicating that ZIKV is sensitive to the antiviral activity of type 1 interferons [9] and hence interferon therapy could be a reasonable option. Interferon-beta also inhibits Th17 T cell differentiation in vivo [279, 280] and hence the use of interferon-beta may target the virus and the pathogenic immune sequelae of virus infection which is important in the context of GBS development. There is also replicated data demonstrating that interferon-beta stabilises the blood brain barrier [281, 282], which is important because a disrupted BBB may play a pivotal role in the pathogenesis of the disease in approximately 50% of patients [283]. Whilst interferon-beta may well be an attractive option for ZIKV infection in adults, there is a question mark regarding its safety in pregnant women infected with ZIKV or otherwise. However, Romero et al. [284] reviewed a total of 423 pregnancies where mothers had been exposed to interferon-beta throughout the course of their pregnancy and reported that the

rate spontaneous abortions as well as major and minor birth defects were no higher than the population norms in the USA and the EU [284], although it would seem appropriate to seek mechanisms which could limit the use of interferon-beta in this vulnerable patient for the shortest time possible.

In this scenario, there is a rationale for a trial involving interferon-beta in combination with vitamin D. There is evidence of synergy between the two molecules in inhibiting Th17 T cell differentiation in vivo [285, 286] and recent data indicate that vitamin D can enhance the effectiveness of interferon-beta [287]. It is also noteworthy that vitamin D can enhance the synthesis of interferon-alpha, which also has a major role in the antiviral defences of the human immune system [288]. There is also evidence that vitamin D at 4000 IU daily for 6 months appears to be safe and well tolerated in pregnancy [289], which is almost exactly the dose which has displayed therapeutic efficacy when used in conjunction with interferon-beta [286]. It should also be noted that several research teams have reported that vitamin D supplementation alone reduces the differentiation and expansion of Th17 T cells and inhibits their cytokine production in children and adults [290, 291], although the maximum effect appears to take place at a dose of 10,400 IU per day [292], which clearly limits its potential as a potential treatment in pregnant women.

Conclusion

Evidence that Asian and South American ZIKV strains cause microcephaly and GBS in some adults and infants, respectively, has accumulated in quantity and quality. The 'journey to pathogenicity' of the Asian strains of ZIKV indicates that a combination of factors such as genetic variation in the NS5 gene as a result of mutations or recombination events and the reacquisition of a E-154 glycosylation motif could contribute to neurovirulence. Both elements could account in part for differences in the replication efficiency, neuro-invasiveness and neurotropism of the Asian ZIKV strains compared to native African ones. Codon usage adaptation to human hosts displayed by the NS1 gene of the Asian strains also seems to be an important factor as this phenomenon is known to increase translational efficiency leading to increased fitness survival and higher titres as well as enhancing immune evasion strategies. Changes in NSI structure between the African and Asian strains may also contribute to increased neuro-invasiveness and a distinct pattern of host gene activation. Our model proposes that Asian and South American strains of ZIKV induce microcephaly in some infants via the infection of NPCs and upregulating TLR thereafter inducing the expression of a range of genes regulating immune-inflammatory and apoptotic pathways not seen following infection of the same cells by African strains, thus leading to increased apoptosis and decreased growth of NPCs and compromised TLR3 regulated neurogenesis. Alternatively or otherwise additionally, ZIKV infection of NPCs may lead to chronic upregulation of the UPR which further compromises normal neurodevelopment. We propose that ZIKV induces the development of GBS by provoking a Th17-biased immune response as a consequence of an alternative strategy for suppressing type 1 interferon production in the context of genetic predisposition or very high viral titres. Vaccine development although obviously desirable will likely encounter the same issues of inherently pathogenic antibodies and ADE which have bedevilled the development of vaccines towards WNV, and particularly DENV. New methods of delivery and relative freedom from ADE make the development of passive immunisation based on modified monoclonal antibodies a low cost and attractive proposition with the potential for rapid benefit, which may be an attractive preventative approach to the development of GBS but would not offer direct protection to a developing foetus. Trials of interferon-beta in combination with vitamin D are encouraged as there is a potential for eradicating ZIKV while also mitigating against the sequelae of ZIKV infection and hence directly preventing or mitigating the development of microcephaly and GBS.

Compliance with Ethical Standards We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Authors AFC and MM contributed equally as senior authors of this review article.

Author's Contributions All authors had contributed to the design and writing of this manuscript. Its final version was read and approved by all authors.

Conflict of Interest The authors declare that they have no conflict of interest.

Funding There was no specific funding for this specific study.

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