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Review Article

Cross-Reactivity of Non-Neutralizing Antibodies to Dengue and Zika Viruses: Implications for Vaccination

Abstract

Dengue is the leading vector-borne viral disease of humans and poses a major international public health concern in tropical and subtropical regions in which it is endemic. Cross-reactivity among the different serotypes of dengue virus promotes antibody-dependent enhancement of secondary infection, an immunopathological response that is thought to amplify viral replication and thereby to increase disease severity. The previously relatively neglected fellow flavivirus Zika has now emerged strikingly in countries where dengue virus is endemic, notably across Latin America. Recent reports suggest that anti-dengue virus antibody can potentiate Zika virus replication. Conversely, it appears that anti-Zika virus antibody may exacerbate dengue infection. Such pre-existing immunity against one flavivirus may not only confuse the diagnosis of disease produced by infection with a heterologous flavivirus, but conceivably affect the clinical outcome. The existence of non-neutralizing antibodies to a prior dengue or Zika infection can result in worse disease manifestations upon infection with a secondary, heterologous flavivirus. This has important implications for the administration of vaccines currently in development, immunization with which will promote the generation of homotypic flavivirus antibodies but that may have an unintended adverse effect of raising susceptibility to heterologous infection of either dengue or Zika.

Introduction

The arthropod-borne (arbo)viruses dengue (DENV) and Zika (ZIKV) are two of the major human pathogens that comprise the family Flaviviridae, which also notably includes the aetiological agents of yellow fever, Japanese encephalitis and West Nile encephalitis [1]. They are closely related members of the *Flavivirus* genus of enveloped, positive sense, single-stranded RNA viruses [2,3], furthermore, each is transmitted between human hosts by female mosquitoes of the genus *Aedes*, principally *Ae. aegypti* and *Ae. albopictus* [4]. Due to the widespread geographical distribution of their shared vectors, co-circulation of DENV and ZIKV is a common occurrence in many areas of the world [5,6]. A prophylactic vaccine or therapeutic drug with which to treat infection caused by each virus is currently neither available nor affordable to inhabitants of developing countries [7,8].

Dengue incidence and epidemiology

At present, dengue is the most rapidly spreading vector-transmitted disease globally [9,10]. While dengue is a historically important disease that was likely first documented in Chinese medical records in 992 AD [11], it emerged as a significant threat to public health only in the second half of the twentieth century. Between 1960 and 2010 the incidence of infection escalated 30-fold [12,13]. Today, in excess of 2.5 billion people in tropical and subtropical regions that are co-inhabited by vector mosquitoes are placed at risk of infection; this includes South and Central America [5]. Despite the implementation of vector control measures in most affected countries, such a mass level of exposure results in an estimated 390 million dengue infections annually in close to 130 nations and territories [14]. Estimates of the annual global incidence range between 200-400 million clinical cases [13].

Zika incidence and epidemiology

In contrast to dengue, Zika was originally identified as recently as 1947 in Uganda, East Africa, where it was isolated from rhesus macaques [15]. For nearly 70 years the prevalence of Zika infection was very low, or at least underreported due to symptoms similar to other acute febrile illnesses, such that it attracted only the interest of tropical medicine specialists. Since early 2015, however, this scenario has changed dramatically consequent to a major Zika epidemic in over 35 countries in Latin America and the Caribbean [6]. This includes an estimated 1,400,000 clinical cases in Brazil, from where the outbreak arose [16], although the accuracy of reporting has been queried [17]. Moreover, the World Health

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Organization (WHO) predicted that by the end of 2016 as many as 4 million people across the Americas may become infected with the Zika virus [18]. Sexual transmission of Zika has been proposed [19], which may provide a minor auxiliary route to enable viral persistence in locations that are not endemic for *Aedes* mosquitoes.

Clinical manifestations of dengue infection

Dengue infections can be asymptomatic or may develop into one of three traditionally recognized clinical manifestations; dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) [20,21]. DF is due to primary infection of any one of the five serotypes, is generally mild and self-limited, from which recovery is complete. It is characterized by a fever for 2-10 days, headache, retro-orbital pain, myalgia, arthralgia and rash. DHF is due to secondary infection with a serotype different to that which caused primary infection, and is characterized by plasma leakage, thrombocytopenia and haemorrhagic sequelae along with symptoms of primary infection [22]. DSS, another form of secondary infection, occurs when fluid and protein leak into the intestinal spaces and results in systemic shock. Both DHF and DSS are serious, often fatal, complications that are marked by problems of capillary permeability and disordered blood clotting [22]. In recent years the WHO and the Special Programme for Research and Training in Tropical Diseases revised the guidelines for dengue case classification. Clinical infection is categorized as: mild self-limiting illness; dengue with a wide range of warning signs; or severe dengue [23].

Clinical manifestations of Zika infection

Compared to dengue, infection with which can be severely incapacitating for a human of any age, around 80% of adults infected with Zika show no clinical manifestations [24]. Hence, for several days after the bite of an infectious mosquito they may serve as asymptomatic carriers of infection. If a person is ill, the principal symptoms last for up to one week and are similar to, but less severe than, other related febrile diseases – mild headache, fever, myalgia, arthralgia, conjunctivitis and maculopapular rash [25]. The main possible consequence of infection, for which there is now a causal link [26,27], occurs via congenital transmission from a pregnant woman to her foetus *in utero* or newborn baby [25,28], the effects of which can be profoundly debilitating and long-lasting [29]. In Brazil alone, Zika virus has been associated with over 4,000 cases of microcephaly [6], a hitherto uncommon condition that as a consequence of abnormal brain development babies are born with aberrantly small heads and usually neurological impairment. Rarely, Zika is also associated as a trigger of Guillain-Barré syndrome in adults, a neural demyelination syndrome that is considered to be an autoimmune sequela of infectious disease [27,28].

Dengue virus serotypes, immunity and immunopathology

There are four closely related, antigenically distinct serotypes (DENV-1 to DENV-4) of the aetiological agent that causes dengue infections [20,21,30]. The existence of a fifth, phylogenetically more distant, virus serotype was mooted recently, although its recognition remains to be ratified [31]. Infection with one serotype induces production of neutralizing homotypic immunoglobulin (Ig)G antibodies that confer life-long immunity to the exposed serotype but provide only transient protection against others [32-34]. Importantly, secondary (or higher level) infection with a heterologous serotype elicits cross-reactive non-neutralizing antibodies, the presence of which in the peripheral circulation increases the potential risk of antibody-dependent enhancement (ADE) of infection, a type of immunopathology. Circulating antibodies raised against a primary DENV challenge recognize but fail to neutralize a subsequent, heterologous DENV serotype, instead binding to the virion and enabling the so-formed virus-antibody complex to enter Fcγ receptor-expressing antigen-presenting cells, leading to elevated levels of viraemia and thus to a worsening of disease [35]. Different dengue serotypes vary in their capacity to cause severe illness, but there is no expert consensus as to the extent of a causal association [36]. Multiple serotypes are in circulation in many regions of dengue endemicity, including the highly populated Indian subcontinent [37].

Zika virus immunity and immunopathology

As for dengue, the human immune response to a Zika primary infection is characterized by generation of virus-specific IgG [38]. Unlike for DENV, however, there is currently only a single known serotype of ZIKV [39]. An individual who experiences secondary or multiple exposures to ZIKV mounts an effective anamnestic response to homologous challenge, such that infection will very likely be at a subclinical level. Prior to its recent global emergence Zika was a neglected tropical disease, so precise details of host immunity to infection remain incomplete. However, further to the considerable investment of resources to support research into Zika vaccine development over the last year [40], the knowledge gap with respect to immunity and immunopathogenesis is closing rapidly [41].

Dengue vaccine development

As efficacious vaccines have been prepared against the fellow flaviviruses that cause yellow fever and Japanese encephalitis, it is anticipated that a similar therapeutic is feasible for both dengue and Zika [42]. For the former in particular the challenge to vaccinologists is to achieve pan-serotype immunity without triggering associated pathology [43,44]. A number of tetravalent vaccines which aim to produce balanced immunity against DENV 1-4 are being tested in field trials [7]. However, as circulating antibody titres diminish with time after vaccination the spectre of ADE becoming problematic is raised. Hence, recurrent infection is the major risk factor for the serious, often fatal, complications of DHF and DSS. Infants who are immunized passively via receipt of maternal antibodies from a dengue pre-immune mother are at high risk of severe dengue infection [35,44]. The positive news is that the latest clinical trial of an experimental dengue vaccine, TV003, has proved 100% effective, albeit a small-scale volunteer challenge study of only the DENV-2 serotype performed under highly controlled conditions [45]. This has

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led very recently to the first licensure for commercial use of any dengue vaccine, a DENV 1-4 chimera constructed on a yellow fever 17D backbone, recombinant, live attenuated, tetravalent virus (CYD-TDV; Dengvaxia®, Sanofi Pasteur) [46]. However, due to concerns regarding the effects of ADE major challenges remain in respect of vaccine effectiveness and long-term safety in the administered population.

Zika vaccine development

As an offshoot of the success of the Dengvaxia® vaccine it is hoped that a modified version of the live attenuated construct may be developed in order to treat the related ZIKV. This head start may accelerate production of a candidate Zika vaccine for which prior to the present outbreak there had been no pressing demand. However, as for any infectious disease the vaccine development pathway from candidate design, via preclinical screening, through phase I-III clinical trials to final approval for administration to the public is long, demanding and expensive [47]. While this has now been prioritized by international funding agencies for Zika [40], it may take several years for a vaccine to come to commercial fruition [48,49]. Although to gain ethical approval for, and to conduct, tests of vaccine safety and efficacy in humans necessitates diligence and caution at all times, the due process for any candidate vaccine that is dispensed to pregnant women is naturally subject to extremely exacting analysis [50,51]. This would relate especially to ZIKV since the gravest manifestation of infection, microcephaly, affects pregnancy. It is in this context that vaccine researchers, project managers and public health administrators should be mindful not to add to the wealth of 'false news' surrounding Zika by suggesting, however guardedly or inadvertently, that a vaccine is imminent [52,53].

Pre-existing heterologous antigens trigger antibody-dependent enhancement of infection

DENV and ZIKV share approximately 60% nucleotide identity [3]. Since the two viruses are so closely related, there is considerable homology in the antigenicity of their surface epitopes [3,54]. As explained above, through ADE anti-DENV antibodies to one serotype can enhance the subsequent infectivity of other DENV serotypes for certain classes of immune cells, principally monocytes and macrophages, causing increased virus production that correlates with severe disease outcomes [35]. Similarly, *in vitro* ZIKV has been shown to trigger ADE in response to sub-neutralizing concentrations of homotypic antiserum and, importantly, heterotypic antisera generated in response to other flaviviruses, including DENV [38,55]. To date, however, *in vivo* ADE that promotes more severe disease has been described only for dengue and heterotypic DENV antibody [35,54]. These observations highlight the need to use animal models and epidemiological studies in order to substantiate the role of ADE in the development of congenital and neurological complications associated with ZIKV infections.

Dengue virus antibodies enhance Zika virus infection

The protective and infection-enhancing potential of well-characterized broadly neutralizing human anti-DENV monoclonal antibodies and human DENV immune sera against ZIKV was tested recently using, respectively, neutralization and ADE assays [56,57]. This demonstrated that anti-DENV monoclonal antibodies cross-react, do not neutralize, and boost considerably Zika infection of a FcγRII-expressing cell line *in vitro*. DENV immune sera exhibited varying degrees of neutralizing capacity against ZIKV and similarly elevated ZIKV infection. Such pre-existing immunity to DENV *in vitro* may, it is supposed, enhance ZIKV infection *in vivo* and thus lead to increased disease severity [54,57]. In a separate contemporaneous study serum samples from Brazilian dengue-immune pregnant women enhanced ZIKV infection of a different target phagocyte cell line *in vitro* [58]. Of note, ADE of ZIKV infection was not observed in samples collected from dengue patients during the febrile and acute phases (i.e. before serum conversion) of primary infection but only during convalescence or recovery, but especially after secondary infection [58].

Zika virus antibodies enhance dengue virus infection

Now that reports indicate that anti-DENV antibodies enhance ZIKV replication, is the opposite also true – does a ZIKV-induced antibody response enhance dengue infection? Perhaps not surprisingly given the substantially overlapping antigenicity of the genetically similar viruses [3,53], this appears to be the case. Thus far, it has been demonstrated that antibodies to ZIKV possess the capacity to enhance DENV-2 replication *in vitro* [59]. Furthermore, mice exposed to ZIKV produced homotypic antibodies that enhance DENV replication. Polyclonal serum elicited a strong ZIKV-neutralizing effect but showed a DENV-sub-neutralizing capacity and thereby the potential to increase dengue severity [59].

Implications of non-neutralizing antibody cross-reactivity

In the majority of countries to which ZIKV has spread DENV is already well-established [5,6], so co-circulation now occurs. Indeed, conditions that facilitate DENV transmission also support that of ZIKV as they share primary vectors, *Ae. aegypti* and *Ae. albopictus* [4]. It is thus probable that many patients who contract ZIKV have had previous exposure to one, if not more, DENV serotypes. For instance, due to the high rate of DENV transmission in Brazil, more than 90% of the adult population has been exposed to DENV, especially in the north east region that was the epicentre of the recent microcephaly epidemic [60]. Likewise, many individuals who are exposed to at least one of the DENV serotypes will, presently and in future, be exposed to ZIKV [61]. It may be reasonably anticipated that the distribution of ZIKV will eventually extend to all global regions where competent *Aedes* mosquito vectors are found. While for most people in these areas DENV will remain the predominant flavivirus infection, ZIKV may represent the primary flavivirus infection for a significant minority of the population. This means that those persons will mount an antibody response to DENV and to ZIKV, respectively, in the absence of a history of exposure to other flaviviruses.

Conclusion

In regions where DENV and ZIKV co-circulate an understanding of how primary infection with one virus affects

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susceptibility to secondary exposure to the other critically informs implementation of measures for disease prevention, control and therapy. A compounding factor is that due to the intense circulation of DENV and ZIKV in endemic areas, it is likely that some individuals will be boosted naturally by multiple exposure to the same serotype, resulting in an altered antibody profile. Since anti-flavivirus IgGs are highly cross-reactive this may affect not only the specificity of antibody, such as its cross-neutralization capacity, but also the spectrum of susceptibility. There is potential either to protect or, via the ADE mechanism, to escalate infection. Dissecting the dynamics of these antibody interactions will improve public health responses, notably the ability to make correct diagnoses, predict accurately clinical outcomes, and better inform vaccine design and delivery. As the first DENV vaccine is set to become commercially available [46], and a new ZIKV vaccine candidate has recently shown promise [62], consideration should be given to the potential for immunization to exacerbate flaviviral disease due to a person's known or unknown pre-existing heterologous DENV or ZIKV exposure. The possible clinical ramifications of an ill-founded vaccination strategy are both apparent and profound.

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