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# The importance of B cells in the development of preventive and therapeutical approaches against Dengue, Zika and Chikungunya viral infections

Among the deadliest animals on the planet, mosquitoes occupy the number 1 in the ranking. They are capable of transmitting several diseases caused by parasitic, bacterial or viral pathogens. The prevalence of mosquito borne-diseases is higher in tropical areas where high humidity and temperature as well as unplanned urbanization are found. In the context of viral diseases, a particular mosquito vector, *Aedes aegypti*, has been in the spotlight. It transmits Yellow Fever (YFV), Dengue (DENV), Zika (ZIKV) (all Flaviviruses) and Chikungunya (CHIKV) viruses (alphavirus) to humans. Recently, DENV, ZIKV and CHIKV infection outbreaks have been detected simultaneously in the same locations, such as French Polynesia (Musso *et al*., 2015) or Brazil (Brazilian Ministry of Health, 2016 -http://portalsaude.saude.gov.br/images/pdf/2016/maio/17/2016-016---Dengue-SE16-publica----o.pdf), raising global concerns. There is evidence that ZIKV transmission occurs through mosquito bite, blood or sexual contact (Foy *et al*., 2011; Musso *et al*., 2015; McCarthy, 2016). Generally, its symptoms are mild and similar to DENV and CHIKV infections. Nevertheless, some ZIKV-infected patients showed development of neurological alterations such as Guillain-Barré syndrome (Brasil *et al*., 2016), microcephaly, macula atrophy and others (Li *et al*., 2016; Mlakar *et al*., 2016; Ventura *et al.*, 2016; Cugola *et al*., 2016; Garcez *et al*., 2016). Currently, Brazil is a major hotspot for DENV, ZIKV and CHIKV infections, which have been detected in almost all regions of the country (Cardoso *et al.*, 2016). Unfortunately, Brazilians have struggled with government slow actions in response to those epidemics. Consequently, it delays their diagnostics and the start of a treatment, raising awareness that those viral infections may spread out quickly in the Americas and other parts of the world where *Aedes* mosquitoes reside.

Regarding the immune responses against those three viral infections, they usually induce antibodies with neutralizing abilities (Dejnirattisai *et al*., 2015; Clapham *et al*., 2016; Dai *et al.,* 2016; Smith *et al*., 2015). However, DENV-specific responses are more complex because there are four different viral serotypes and the antibody response induced by one serotype does not protect against the other (reviewed by Whitehead *et al*., 2007). Instead of virus neutralization, the elicited process is antibody-dependent enhancement of infection (ADE) on Fc receptor-bearing cells (Dejnirattisai *et al.*, 2010). Considering that ZIKV has about 43% identity with the DENV polyprotein or the envelope ectodomain (Lazear, Diamond, 2016), it requests further analyses whether ZIKV-specific antibodies derived from a previous infection can induce DENV ADE. Apparently, DENV-specific antibodies not only bind ZIKV, but also trigger ZIKV ADE (Cardoso *et al*., 2015). Interestingly, most of the confirmed ZIKV infection cases in the Brazilian Northeast states were of DENV-exposed individuals.

In terms of antibody-secreting cell responses, there is a massive antigen-specific plasmablast response during the acute phase of DENV infection, accounting for more than 50% of all IgG-secreting cells (Wrammert *et al*., 2012; Garcia-Bates *et al*., 2013). Similarly, an Asian ZIKV strain elicited an increased plasmablast frequency seven days after challenge in rhesus macaques. However, that evaluation did not verify what percentage of cells was antigen-specific (Dudley *et al.*, 2016). On the other hand, there is not much data available about the plasmablast response in the context of CHIKV infection, but only antibody titers and their neutralisation capacities in the serum (Yoon *et al*., 2015).

Although the YFV-specific vaccine (YF-17D strain) is one of the most effective formulations developed so far, there are no protective vaccines against the other viruses transmitted by *Aedes aegypti.* Recombinant YF-17D constructs containing genes from different pathogens have been able to elicit substantial degrees of protection (Tao *et al*., 2005; Guy *et al*., 2010; Nogueira *et al*., 2011). DENV-specific YF-17D vectors were already made (Guy *et al*., 2010, 2011) and recently tested in clinical trials (Capeding *et al*., 2014; Villar *et al*., 2015). That type of recombinant construct greatly stimulates T cell and humoral responses (Monath *et al*., 2003; reviewed by Guy *et al*., 2010). Considering the pivotal role of antibodies in preventing viral infections post-vaccination as well as therapeutic tools (Caskey *et al*., 2015; Fibriansah, Lok, 2016; Pal *et al*., 2013), it is crucial that any vaccine candidates for DENV, ZIKV and CHIKV infections are able to promote extensive B cell responses. To study vaccine- or viral infection-derived B cell responses, different cell subsets could be assessed, such as memory B cells or plasmablasts. Although both cell types have been successfully used to produce antigen-specific monoclonal antibodies (mAbs) with neutralizing abilities, plasmablasts at the peak of response represent a more accessible source of material to produce antigen-specific mAbs (reviewed by Silveira *et al*., 2015). The knowledge of vaccine- or viral infection-derived mAb repertoire and their functional characteristics would certainly improve the development of preventive and therapeutic approaches against DENV (Silveira, 2015), ZIKV or CHIKV infections.

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