EBioMedicine 12 (2016) 12–13

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

The Chosen Few: Only a Subset of Memory B Cells Responds to Secondary Dengue Virus Infections

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ARTICLE INFO

Article history:
Received 30 September 2016
Accepted 30 September 2016
Available online 11 October 2016

Keywords:
Dengue virus
Memory B cells

Dengue virus (DENV) is a mosquito-borne flavivirus that infects an estimated 400 million people each year, with one-third of the world's population at risk (WHO, 2009). Dengue infections can be caused by any one of four stereotypically distinct viruses: DENV1–4. A primary infection by one DENV serotype provides lifelong immunity to that serotype, but only short-term immunity to the other serotypes (Sabin, 1952). Moreover, in contrast to a primary DENV infection, secondary heterologous DENV infection increases the risk of hemorrhagic fever (Nimmannitya et al., 1969). This increased risk is thought to be due to antibody-dependent enhancement of infection and original antigenic sin. Antibody-dependent enhancement occurs when sub-neutralizing antibodies bind to surface Fc receptors that facilitate enhanced viral uptake (Halstead and O'Rourke, 1977). Original antigenic sin occurs when memory lymphocytes generated during a primary infection weakly recognize non-neutralizing epitopes yet preferentially expand during secondary infections by related but distinct viruses (Halstead et al., 1983). This leads to an antibody response that preferentially recognizes the original, rather than the secondary virus. A major challenge is thus to develop vaccines that avoid these problems and provide protection against all four DENV serotypes. For this purpose, an understanding of the epitope-specificities of responding B cells during pathogenic secondary DENV infections is needed. This information in turn may help develop epitopes for subunit vaccines that elicit neutralizing, rather than infection-enhancing antibody responses.

During recall responses, memory B cells can differentiate into antibody-secreting plasmablasts and plasma cells, re-initiate germinal centers for affinity maturation towards the new pathogen, and undergo self-renewing divisions. Distinct subsets of human memory B cells prefer one of these fates vs. the others. These functional traits largely segregate with the isotype of the B cell receptor. IgM-expressing memory B cells tend to re-initiate germinal centers, while IgG isotype-switched memory B cells yield plasmablasts and plasma cells (Seifert et al., 2015). Yet in the context of secondary DENV infections in humans, it is unclear how pre-existing memory B cells behave. Are all Dengue-specific memory B cells recruited into the response? Or do only certain subsets respond? In this issue, Appanna et al. demonstrate that IgG memory B cell-derived plasmablasts formed during the acute phase of secondary infection have a non-overlapping clonal repertoire compared with that of memory B cells at convalescence (Appanna et al., 2016). These data agree with and extend upon similar studies by other groups (Priyamvada et al., 2016).

Antibodies following DENV infection can be directed at envelope (E), pre-membrane (prM), and capsid proteins, and non-structural proteins 1, 3, and 5. Appanna and colleagues show that antibodies derived from plasmablasts are almost exclusively specific to the E protein whereas antibodies derived from DENV-specific memory B cells can recognize E, prM or non-structural proteins. A few plasmablast clones were specific for the primary, rather than the secondary virus, indicative of original antigenic sin. Yet the overwhelming majority of these plasmablasts were cross-reactive across multiple different DENV serotypes. Though numbers were somewhat limited, monoclonal antibodies from plasmablasts tended to be more potent neutralizers relative to antibodies derived from memory B cells. In addition to differences in antigen specificity between the plasmablasts and memory B cells, Appanna et al. also found minimal immunoglobulin gene overlap through repertoire sequencing. Thus, it appears that not all DENV-specific memory B cells respond to generate circulating plasmablasts during secondary infections. This suggests that there are at least two "types" of memory B cells: a subset that is predisposed to becoming plasmablasts during secondary DENV infections, and another subset that either fails to respond or is biased towards maintaining memory B cell identity.

The observation that B cell subsets possess different antigen specificities following subunit vaccination or flavivirus infection is not new (Lavinder et al., 2014; Purtha et al., 2011), but given the issues of antibody-dependent enhancement and original antigenic sin, human responses to DENV warrant deeper exploration. Appanna et al. thus address an important aspect in DENV immunity: how can effective and efficient antibody responses be evaluated? The authors' data suggest that

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.09.003.
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http://dx.doi.org/10.1016/j.ebiom.2016.09.032
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analysis of plasmablasts and their antibodies is likely insufficient as a correlate of one component of long-term immunity against DENV: diversity of the memory B cell compartment. The extent to which these antibodies may instead continue to be produced by bone marrow-resident long-lived plasma cells or enhance infections remains unknown. It also remains unknown why only a subset of memory B cells is recruited into the circulating plasmablast pool. Are the pre-existing antibody affinities of memory B cells different between E vs. prM or non-structural proteins? Or are other subsets of plasmablasts in fact formed but retained in secondary lymphoid organs? How can the desired specificities of memory B cells be preferentially recruited into the response by vaccination? These questions will be important to address as the basic biology of responses to DENV infections continues to instruct future vaccine design.

Disclosure

The authors declare no competing interests. D.B. is a New York Stem Cell Foundation-Robertson Investigator and is supported by grants from the National Institutes of Health (R01AI099108), the American Cancer Society (125091-RSG-13-252-01-LIB), and the New York Stem Cell Foundation (NYSCF-R-I14). R.W. is supported by a predoctoral fellowship from the National Science Foundation (DGE-1143954). The funding sources had no role in the writing of this manuscript or decision to submit. The authors were not paid to write this manuscript by pharmaceutical companies or any other agencies.

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