Review of: "Christ Bearing the Cross: the original antigenic sin of the immune system and its potential role in emerging diseases"

William Murphy[1]

1 University of California, Davis

Potential competing interests: No potential competing interests to declare.

This article describes the potential contribution of cross-reactive secondary immune responses in the context of current CoV2 responses. For obvious reasons, the term “Original Antigenic Sin” connotates religious ideas and some within the scientific community discourage use of it. I feel it is appropriate though on the context of immune responses. The review is fairly balanced and there have been considerable research publications demonstrating cross-reactive T and B cell responses do indeed exist and preclinical models indicating potential inhibition of primary CoV2 immune responses as a result. The paradigm could have been a bit more clearly explained as how both positive (these rapidly induced secondary responses can provide instant protection from acute infection) and negative (how lower affinity secondary responses could outcompete and inhibit productive new high affinity responses) resulting in a “short-term gain, long-term loss” scenario. These are some of the most complex immunological concepts and for the most part the authors have done a laudable job. Explanation on how affinity as a concept is relative and diverse in antibody/antigen reactions would help given the popular view that everything fits like a “lock and key” where there are huge ranges in binding capability. Also, the concept that secondary responses by their nature are faster and need less for activation giving any cross-reactive memory responses a huge “edge” would help. It would also be better to explain ADE as a process though since most will not be familiar with it at all (it could be an article by itself). Another important caveat in their interpretation on activation of cross-reactive responses to the other hCoVs, is that all immune responses are polyclonal and thus only the cross-reactive secondary responses/clones would be expected to be activated with CoV2, not all hCoVs responses. Secondly, naive B cells are produced throughout life and thus, there will always be a ready supply for responses. The issue are the T cells needed for appropriate T cell “help” for the B cells and isotype-switching (ie- IgG) for high affinity responses. Thymic involution throughout life limits naive T cell production and causes a huge reliance on pre-existing and long-lived memory T cells. Thus, in the eldery, one would expect an increased reliance on these cells and more effects of the OAS in vaccine responses and infection. This then can be a problem depending on how immune-evasive the pathogen is by mutation (which in CoV2, could be significant which is why newer vaccine formulations are recommened now). Some more citations on literature demonstrating existence of cross-reactive Abs to CoV2 in sera from patients prior to the pandemic as well as data demonstrating the converse (sera from CoV2 patients binding hCoVs) along with studies attempting to correlate with outcome, provide some context. Nonetheless, this is an interesting article bringing forth an older immune concept that may be very pertinent to the current CoV2 situation.