Review of: "Revisiting Immunology Textbooks: Considering Potential Insights Based on the Role of RNA-Guided Antiviral Defense"

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Potential competing interests: No potential competing interests to declare.

First of all, I don't think there are any serious or professional immunologists left on earth who still believe in the rigid dichotomy of innate and adaptive immunity, cellular and humoral immunity in 2024. With the discovery of innate type B cells, B1a cells, MZ B cells, gd T cells, NKT cells, and iNKT cells, even textbooks of immunology printed in this decade would not suggest such a rigid dichotomy, but the structure might have been left in many textbooks as a historical reference to how the idea of the complex immune system evolved as a branch of biology.

Authors have only briefly mentioned interferons as auxiliary antiviral defense, yet interferon-alpha and beta are significant contributors to antiviral defense and maintain a tight link to other components of the immune system, including but not exclusively to the inflammatory response.

Authors have proposed the role of RNA interference but did not explain exactly how it can act in virus-specific or strain-specific immunity and immunological memory essential for the development of vaccines . MicroRNAs, on the other hand, can exert control not just through RNA interference but through post-translational regulation, activation, and promoter regulation, thus providing a very big scope that can influence the plasticity of immune cells themselves. The role of microRNAs can theoretically extend to class switching, somatic hypermutation, enhancement of epitope specificity, TCR rearrangement, cytokine production, switching MHC expression levels, and more, but the exhaustive study of the microRNA landscape during the progression of the immune response, different immune cells, and different disorders is yet to be determined as there are far more microRNAs than functional genes, the variety and pleiotropic effects of these microRNAs, and the technical challenges, so to put it simply, it's not the fault of the writers of immunology textbooks, but the knowledge base is still developing and a coherent, clear picture is not available that can serve as textbook material. Textbooks serve the purpose of introduction of concrete ideas, not all possible speculations and possibilities.

Antibodies are not considered by immunologists as the chief driver of anti-viral immunity; T cell memory and NK cell contributions are deemed essential, and any vaccine that is specifically designed to invoke only an antibody response and not T cell memory (T helper as well as CTL) is not going to be very successful in the ‘long run,’ barring a select few pathogens. Antibodies do play a vital role in neutralization and as antagonists that prevent binding, attachment, and delivery of viral genetic material inside the cell.

There is a very sophisticated receptor mechanism to deal with both DNA and RNA viruses that involves a number of

Cytoplasmic TLRs (TLR family proteins are remarkably conserved, and even the downstream signaling pathways in most metazoans), in addition to that, there are NODs, NLRs, and RIG and RIG-like receptors that are also linked to many components of the immune system, including, again, inflammation. These are textbook knowledge now because the pathway has been substantiated on the basis of numerous studies. The authors did mention RLR but ever so briefly.

There are many editing mistakes; lines are repeated. A few more subheadings and a more structured manuscript would be helpful for readers.

Overall, the authors initiated some much-needed conversation that needs to start between clinicians, protein biologists, molecular biologists, classical immunologists, and vaccinologists, as each of these fields remained esoteric, yet when observed properly, these fields are entangled beyond separation, and a real working vaccine strategy for combating threats of pandemics like COVID-19 (which is likely to become more frequent) is needed urgently. So from that point of view, authors have prepared a timely manuscript for a discussion platform, but as far as interpretation is concerned, it's not as ‘new’ as the authors suggest. Most of these ideas, pathways, and molecules are very well known to most immunologists, even those who have just started working in this field. This manuscript can provide a crash course on antiviral defense mechanisms to undergraduate students.