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Systems immunology: Beyond antibody titers

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Summary Despite the evident success of currently available vaccines to prevent infectious diseases, we still lack a full understanding of the mechanisms by which vaccines induce protective immune responses. Systems immunology applies multifaceted analytical tools to better understand the immune responses to vaccines by deep characterization of the cellular components, regulatory pathways, antibody responses and immune gene profiles with the ultimate goal of identifying the complex cellular, genetic and regulatory factors and mechanisms that contribute to effective and protective immune responses.

Vaccines are considered the most effective medical intervention to reduce the morbidity and mortality caused by infectious diseases in the last century. Vaccination has been responsible for the eradication of smallpox, near eradication of polio, and drastically reducing many other diseases, such as mumps, rubella, measles and *Haemophilus influenza* type b.[1,2] Efforts are in place to continue to improve existing vaccines and to develop new ones against more complex infections, such as malaria, dengue, HIV or RSV.[3–5] Nevertheless, despite the evident success of currently available vaccines to prevent infectious diseases, we still lack a full understanding of the mechanisms by which vaccines induce protective immune responses.

Vaccination confers protection against diseases mainly by inducing neutralizing antibodies.[6,7] Hemagglutination inhibition and neutralization assays are widely used to assess vaccine responses, since they allow measurement of functional antibody activity. These serological parameters, however, may over- or underestimate real vaccine immunogenicity as they do not completely control for pre-vaccination antibody titers.[8,9] Taking as an example the influenza vaccine, which is universally used and it is known to protect against epidemics and pandemics, the induced protection and effectiveness depends on many factors. These include the quality of the vaccine and the match between the vaccine strains and the virus circulating that season, as well as the previous exposures to influenza either via previous vaccination or natural infection.[10]

Systems biology has been used to study the complex interactions within the host in response to acute infections and to identify biomarkers of disease severity, among others.[11–13] One of the tools that has been used as part of this multifaceted approach is host transcriptomics. Using gene expression profiles, studies have identified pathogen-specific biosignatures, since each microbe stimulates specific host immune responses that can be used as a potential diagnostic instrument.[14,15] Each pathogen interacts in a specific manner with pattern-recognition receptors

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expressed on leukocytes, which ultimately carry information on the pathogens transcriptional signatures and thus allows differentiating viral from bacterial infections. Investigators showed that blood immune cells display discriminative transcriptional signatures from viral and bacterial infections, assisting the differential diagnosis of infectious diseases.[16] Zaas *et al* were able to identify and validate an acute respiratory viral signature based on an experimental human viral challenge with respiratory syncytial virus (RSV), human rhinovirus (RV) or influenza A. They first identified a signature for influenza A infection that distinguished subjects infected with influenza A and healthy controls. In addition, discrimination of individuals with symptomatic acute respiratory infections from uninfected individuals was performed with 95% accuracy and viral from bacterial infections with 93% accuracy.[14] These studies demonstrated the successful use of gene expression profiles to differentiate patients with acute viral and bacterial infections and the ability to derive pathogen specific gene signatures obtained by blood analysis.

Whole blood gene expression has been used to distinguish patients with acute viral infections and to assess disease severity in infants with RSV infection.[12] Children less than 2 years old hospitalized with lower respiratory tract infection caused by RSV, RV or influenza were compared with age matched healthy controls. A total of 2317 transcripts were found to be significantly differentially expressed between children infected with RSV and healthy controls, with overexpression of genes related to interferon (IFN) and neutrophil function and underexpression of T- and B cell-related genes. This transcriptional profile accurately distinguished infants infected with RSV from those infected with RV or influenza virus, and more importantly the authors identified a genomic score in RSV infected infants that significantly correlated with clinical outcomes.[12]

In addition to study the response to infection by different pathogens, systems immunology has been used to study immune responses to vaccines. Examples are the yellow fever, influenza, meningococcal and pneumococcal vaccines.[17–21] The goal of this approach is to identify biomarkers that can predict protective immune responses and possible adverse effects arising from the administration of different vaccines. Protective biomarkers could be identified by assessing the relationship between early patterns of gene expression and the magnitude of antibody responses. Obermoser *et al* demonstrated that vaccines against influenza and pneumococcus elicit different transcriptional responses in the blood of adults. Both showed a spike in transcriptional activity within 24 h of immunization, suggesting activation of the innate immune responses. However, while pneumococcal vaccine induced an increase in myeloid and inflammation-related genes, the influenza vaccine induced an IFN-inducible transcriptional signature at day 1 post-immunization. Regardless of the initial response, both vaccines induced over-expression of B cell genes at day 7 post-immunization.[21]

Li *et al* reported the distinct transcriptional signatures associated with antibody responses after administration of different vaccines targeting viruses and bacteria, by analyzing public human blood transcriptomes datasets. They identified gene signatures shared by the different vaccines through differential expressed genes. Genes associated with innate immunity and IFN responses were found to be upregulated 3 days post-vaccination with live attenuated virus vaccines, such as the yellow fever and the live attenuated influenza vaccine (LAIV). B cell genes were upregulated in individuals vaccinated with quadrivalent conjugated meningococcal vaccine and the trivalent inactivated influenza vaccine (TIV). These included TNFRSF17, a B cell differentiation gene that is predictive of antibody responses to the yellow fever and TIV vaccines.[18] The study conducted by Cao *et al* showed that two formulations of influenza vaccine, TIV and LAIV, elicited overexpression of IFN-related genes, but with distinct kinetics. IFN-related genes were upregulated 1 day post-vaccination with TIV, while the same genes were found upregulated 7 days post-vaccination with LAIV, the latter only in children less than 5 years of age, which demonstrated the influence of age in the immune

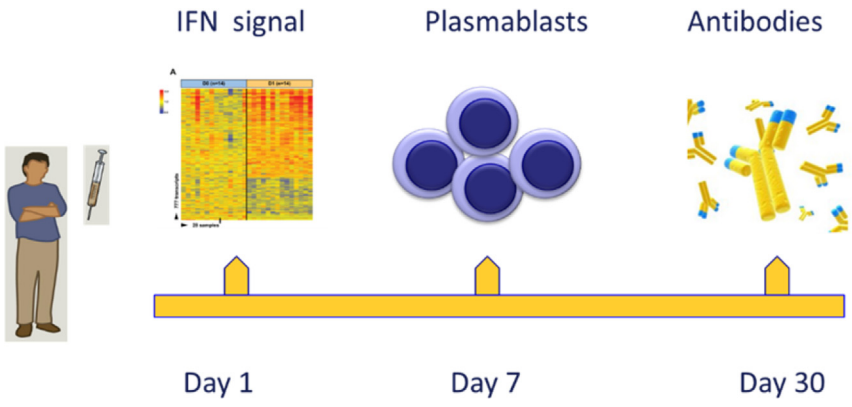

Figure 1 System analysis reveals dynamics of the immune response to influenza vaccine. Administration of the intramuscular formulation of influenza vaccine (TIV) is characterized by activation of interferon (IFN) 1 day post-vaccination. At the cellular level, increase in number of plasmablasts occurred 7 days post-vaccination. In addition, there is a significant correlation between the number of plasmablasts (day 7) and antibody titers measured 30 days post-vaccination, as well as between expression of IFN-inducible genes (day 1) and antibody titers.