Vaccine-induced responses

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Immune signature atlas of vaccines: learning from the good responders

Isabela Pedroza-Pacheco & Andrew J. McMichael

Understanding immune determinants of vaccine-mediated immunogenicity could further provide rational vaccine design. Two research groups revealed pre-existing and early innate immune signatures associated with better vaccine-mediated antibody responses.

Vaccines are among the most successful interventions for preventing infection-induced morbidity and mortality. However, a thorough systematic molecular dissection to understand why some individuals mount better antibody responses than others is still lacking. For the most part, this is due to the limited availability of large centralized and batch-corrected multiscale databases representing the wide demographic and biological diversity of individuals worldwide. In this issue of *Nature Immunology*, the groups of Kleinstein, Sekaly and Pulendran used systems-based approaches to address this challenge.

By integrating transcriptional data from different platforms of over 3,000 peripheral blood samples from 820 adults across 28 studies of 13 vaccines, the authors dissected pre-existing and early transcriptional signatures associated with high antibody titers. This outstanding compendium included data related to vaccines against influenza, hepatitis B, yellow fever, varicella zoster, malaria, meningococcus, Ebola, tuberculosis, HIV-1 and smallpox, providing an unprecedented resource for immunologists. The dataset includes different types of vaccines ranging from subunits to live attenuated viruses, and the analysis considers them all together as well as revealing differences between them (Fig. 1). The dataset, which is freely available, opens up exciting opportunities for its use as a reference to improve our understanding of the complex genetic and immune mechanisms involved in the induction of antibody responses following vaccination.

Using unsupervised clustering analysis of blood transcriptional modules previously coupled to immunological function[1], Fourati et al. classified pre-vaccination transcriptional profiles into three main endotypes[2]. Contributing to 12% of the variance observed in healthy participants, these endotypes were differentially defined by the expression of blood modules associated with innate immune responses, including Toll-like receptor (TLR) genes, interferon-mediated genes and genes associated with metabolic alterations downstream of the transcription factor NF-κB, that were critical for antiviral responses, antigen presentation and B cell activation. Notably, individuals with a 'high' pro-inflammatory endotype, highly expressed in classical monocytes and myeloid dendritic cells (mDCs), had slightly greater serum antibody responses a month after vaccination. These data suggest that individuals with higher overall innate immune activation may have 'ready-to-go' monocytes and DCs that favor the elicitation of vaccine-specific antibodies by facilitating the presentation of vaccine peptides to $CD4^+$ T cells and exerting pro-inflammatory cytokines to promote B cell differentiation into plasmablasts and plasma cells, crucial for high-affinity antibodies. Interestingly, the authors attributed this 'primed' innate immune environment to subclinical bacterial infections at the time of vaccination, as measured by the transcriptional expression of a gene bacterial meta-score (*HK3*, *TNIP1*, *GPAA1* and *CTSB*) previously identified in patients with acute bacterial infections (*Streptococcus pneumoniae, Neisseria meningitidis* and *Escherichia coli*, among others)[3]. This suggests that individuals living in geographical regions with higher burdens of bacterial infections — as in low- and middle-income countries — could benefit from better antibody responses upon vaccination. The future incorporation of subjects from other ethnicities and geographical locations raises an exciting opportunity among the vaccine scientific community to significantly aid rational design of adjuvants to improve vaccination in low-responder groups.

Hagan et al. applied the same approach to find common and unique features associated with antibody responses across vaccines in the early post-vaccination period[4]. Unsupervised analysis of gene profiles revealed four temporal expression patterns: on days 1–3, innate responses (predominant in live viral vectors) and lower natural killer cell (NK cell) responses; and on day 7, expansion of plasmablasts and stimulation of $CD4^+$ T cells. NK cells have been reported to control $CD4^+$ T cells, and their dysfunction has been associated with increased broadly neutralizing antibodies in the context of HIV-1 infection[5]. This analysis supports the hypothesis that an immune-regulatory environment with strong $CD4^+$ T cell responses and reduced NK cell regulation promotes B cells to produce higher antibody titers. The design of adjuvants to favor these responses could improve vaccine efficacy, especially in those vaccines for which antibody development is challenging to achieve, such as HIV-1.

A compelling connection observed between the individuals with a high inflammatory endotype before vaccination and those with early innate responses 3 days after vaccination is the expression of five shared blood modules associated with monocytes, antigen presentation and B cell development and activation, reinforcing the idea that early innate immune responses are critical for $CD4^+$ T cell and plasmablast responses on day 7 that lead to higher antibody titers on day 28. Another important outcome of this systematic approach is the observation of marked heterogenicity of the immune response of participants vaccinated with live attenuated yellow fever virus compared to the other vaccines (Fig. 1). Strikingly, yellow fever vaccines produced a delayed innate immune response, especially in antiviral and interferon pathways (day 7 post vaccination), with genes such as *CXCL10* and *OAS1* upregulated as late as 21 days after vaccination. One potential mechanistic explanation for these unique immune responses could be provided by previous in vitro observations that yellow fever — and other flaviviruses — control antiviral responses by inhibiting the

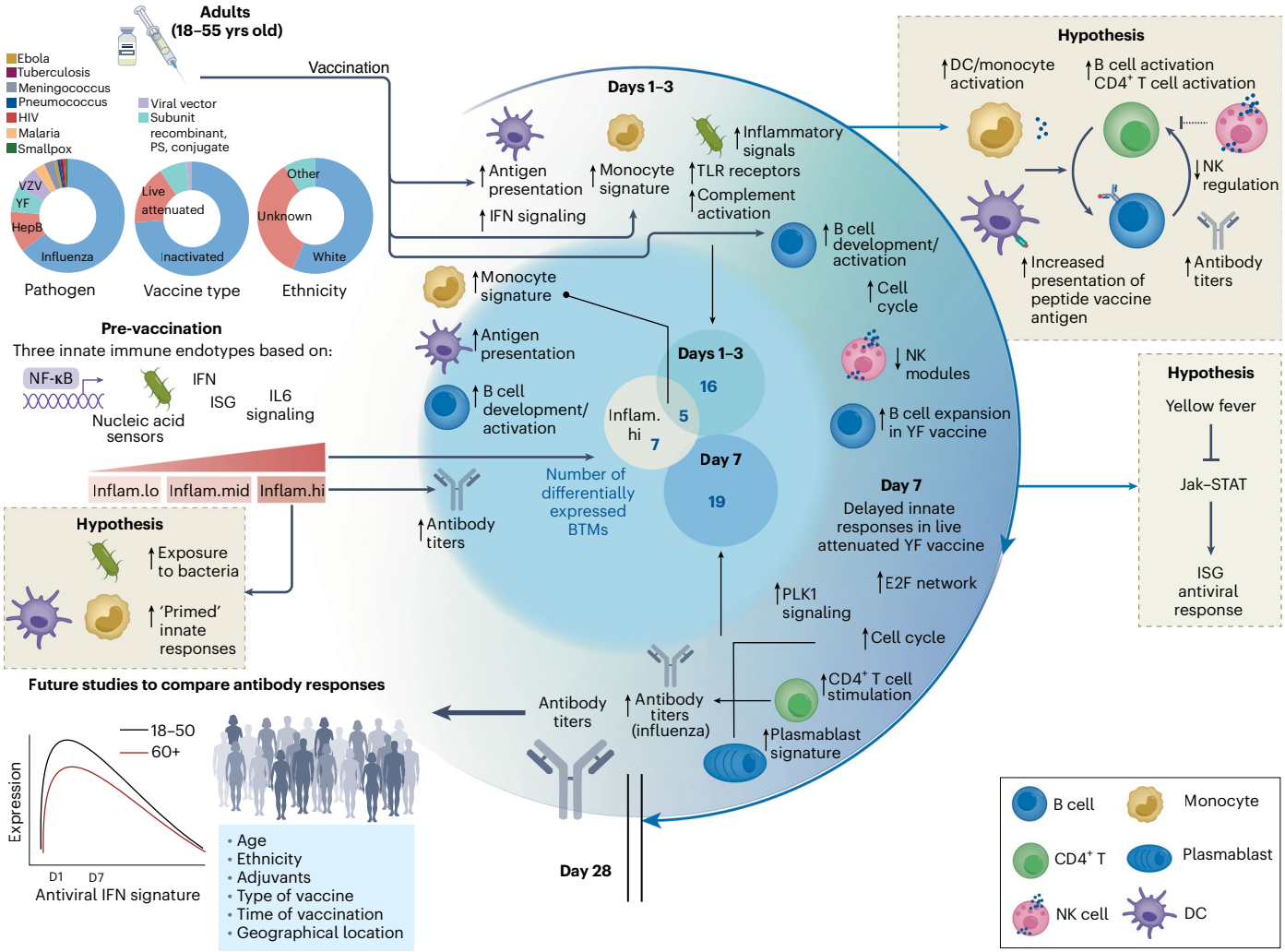

Fig. 1 | Pre-existing and early immune responses associated with vaccine-mediated antibody responsiveness. Transcriptional profiling from whole blood or peripheral blood mononuclear cells from adults 18–55 years (yrs) of age was obtained by microarray or RNA-sequencing assays before vaccination and on days 1, 3 and 7 after vaccination. Pie charts at left indicate an estimated proportion of samples obtained from different vaccine types, pathogens and demographics. Enriched blood transcriptional modules (BTMs) from individuals with high pre-vaccination pre-inflammatory innate responses (Inflam.hi) were obtained through unsupervised clustering analysis. BTMs differentially expressed at the post-vaccination relative to the pre-vaccination time point (shared across four or more vaccines) were obtained by unsupervised clustering (for all time points) and by supervised analysis in a subset of participants with high and low antibody responses to influenza vaccines (day 7 post vaccination). Venn diagrams indicate the number of differentially expressed BTMs (in red) at each time point. Antibody titers were determined as maximum fold change on day 28 (±2 days) relative to the pre-vaccination timepoint. Gray arrows indicate whether BTMs are upregulated or downregulated. E2F1, E2 transcription factor; IFN, interferon; IL, interleukin; ISG, interferon-stimulated genes; PLK1, polo-like kinase 1; PS, polysaccharide; VZV, varicella-zoster virus; YF, yellow fever.

Jak–STAT signaling pathway as a mechanism of immune evasion[6]. A direct comparison of blood modules in vaccinated individuals with natural infection could provide insight into the mechanisms by which yellow fever and the attenuated strain YF-17D evade the immune system; this could aid researchers in improving the next generation of vaccines against other flaviviruses, such as dengue and Zika, a public health concern in parts of the tropical and subtropical regions of Asia, Africa and Latin America.

Together, the two papers demonstrate the use of large, multicenter datasets to delve deeper into the complexity of biological processes that influence antibody responses. By controlling for sex and age, the authors were able to dissect the critical role of the innate immune system in priming humoral responses. A limitation of using transcriptional gene profiles from blood or peripheral blood mononuclear cells as a readout to study immune responses to vaccination is that they might not fully reflect the environment supporting humoral responses in lymphoid tissues. The use of lymph node fine-needle aspiration could address this challenge, albeit being difficult to achieve in human studies. Also, bulk analysis of cells is limited by lack of single-cell resolution. Although the authors carefully corrected for potential differences in cell frequencies and utilized cell deconvolution algorithms to determine the potential cellular source of the main signal, it is plausible

that some cell subsets may have been missed due to their low cell numbers. Despite these limitations, the analysis of whole transcriptional profiles from blood still offers unparalleled insight into the early post-vaccination cellular immune environment, providing an exciting opportunity for the generation and validation of data-driven hypotheses to follow up with further cellular and functional assays.

Another important consideration about the datasets used by the two groups is the uneven representation of ethnicity: most subjects were of European descent or unknown origin, resulting in a low variance in ethnicity in the studies. It is increasingly known that sex, age, previous or subclinical infections, and environmental factors including nutrition status and microbiome composition can shape the immune system throughout life and influence vaccine-mediated antibody responses[7]. Best studied is the effect of age on antibody responsiveness, with elderly individuals known to have lower antibody titers than younger people after vaccination[8]. Although Fourati et al. did not address how age contributed to the primed endotype before vaccination[2] — possibly due to data scarcity in the datasets — Hagan et al. used their dataset to compare blood modules after vaccination[4]. Consistent with previous results[8], they found that elderly individuals had reduced transcriptional expression in modules associated with interferon responses and plasmablasts, but the kinetics of responses remained the same. Designing novel vaccines with adjuvants to overcome the diminished interferon responses could significantly improve antibody titers.

Overall, Fourati et al.[2] and Hagan et al.[4] have demonstrated the use of this compendium as a highly valuable tool to gain insight into the variation in antibody response observed between individuals, which provides an excellent resource for immunologists and vaccinologists to use in comparative studies to obtain further mechanistic insight into the effect of genetic factors (age, sex, ethnicity) and environmental factors (nutrition, geographical location, time of vaccination) that shape cellular and molecular mechanisms and underpin antibody responsiveness. Growing evidence points to adult females having better protective immune responses[9], possibly due to increased innate immune responses; to pregnant women responding better to vaccination in the first and third trimesters;[10] to novel mRNA vaccines inducing a more potent monocyte response;[11] and to greater effectiveness of vaccination in the morning because of circadian rhythms[12]. Learning from individuals with high antibody responses will enable the rational selection of adjuvants (e.g., emulsion, lipid nanoparticles, innate potentiators such as TLR agonists) and vaccine types (e.g., subunit versus live virus, novel mRNA vaccines) to emulate a permissive immune environment favorable for the optimal elicitation of vaccine antibody responses and provide more efficient and safer vaccines to the community.

Isabela Pedroza-Pacheco & Andrew J. McMichael ✉
Nuffield Department of Clinical Medicine, Oxford University, Oxford, UK.
✉e-mail: andrew.mcmichael@ndm.ox.ac.uk

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Competing interests

A.J.M. is a consultant to and SAB member of Osivax and of Oxford Vacmedix.