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Variability in the Immune System: of Vaccine Responses and Immune States

Shai S. Shen-Orr[a,*] and **David Furman**[b]

[a]Rappaport Institute of Medical Research, Faculty of Medicine and Faculty of Biology, Technion-Israel Institute of Technology, Haifa, 31096, Israel

[b]Department of Microbiology & Immunology, Stanford University School of Medicine, Stanford, CA 94305, USA

Abstract

System-wide approaches are now being applied to study vaccine responses, whose mechanisms of action, and failure, are not well understood. These works have repeatedly shown vaccine response to be an orchestrated process involving multiple arms of immunity most noticeable sensing and innate components. Prediction of vaccine responses based on system-wide measures is achievable, but challenges remain for robust population wide predictions based only on pre-vaccination measures, especially in partially efficacious vaccines such as influenza. This is especially true in older adults, who are often less responsive to vaccination and exhibit high level of variation compared to young in many components of immunity. Despite this increase in variation, most of the studies on aging use group averages of immune phenotypes to model immune system behavior. Using systems approaches, it is possible to exploit this variation to form distinguishable clusters of phenotypes within and across individuals to discover underlying immune states.

Introduction

Despite the widespread use of vaccines and success of vaccination in eradicating devastating infectious diseases, how vaccines work and why they fail, remains a mystery. Thus, understanding mechanisms of vaccine response is an important goal for both fundamental immunology and public health. This is particularly true in the context of aging where the immune responses to vaccination are often defective[1-4]. Recently, integrated measurements of an individual's immune profile has become a feasible reality, as technological advances have enabled accurate, rapid and relatively low cost enumeration of multiple components of immune system determinants and in a broad manner, including: 35 parameter cell subset phenotypes and responses by mass cytometry, multiplex (currently 51) serum cytokine abundances, comprehensive affordable sequencing of HLAs, Ig repertoires and antigen specificity, as well as more established technologies such as whole-genome gene expression[5-8]. Each such individual measurement may be considered as a new dimension on which the immune system may be probed. This system-wide approach to immunology has recently been used in vaccination as a means of exploring the immune

*Corresponding Authors: Shen-Orr, Shai S, shenorr@technion.ac.il, Telephone:+972-4-829-5210, Fax: +972-4-851-4702, Furman, David, furmand@stanford.edu, Telephone: +1-650-725-4755.

response in an unbiased manner in humans and it is starting to yield insights involving multiple components of immunity.

Learning the ropes – Application of Systems-wide measurement to highly effective vaccines

Initial work from Gaucher *et al.*[9] monitored a group of volunteers over a period of a year following their administration of a live attenuated yellow fever vaccine (YF17D). Multiple immune parameters and expression of genes from whole blood were measured at different time points. This unbiased approach identified for the first time, a gene signature induced early after vaccination (days 3 and 7) composed of several transcription factors with functionality spanning multiple arms of immunity. Most prominently these included genes associated with a number of pathways from the innate immune response such as the molecular sensor for single-stranded RNA, Toll-like receptor 7 (TLR7) and its downstream adaptor molecule MyD88, as well as other several molecules with direct antiviral activity such as ISG20 and OAS1, 2, and 3. Genes controlling important innate responses such as type I IFNs, inflammasome, complement system and cytokine signaling, such as IRF7, STAT1, C_1QA and C_1QB were also significantly induced by the YF17D. A similar time series analysis of YF17D administration, conducted by Querec *et al.*[10], showed many overlapping genes signatures to those observed by Gaucher *et al.* and used computational models of an individual's gene expression measurement from early time points (up to day 7), to predict the subsequent magnitude of neutralizing antibody titers and antigen specific CD8+ T cell responses to YF17D. Importantly, as YF17D yields strong immune responses in the wide majority (90%) of individuals[11] and it is logistically easy to recruit study subjects with no prior exposure, its choice as the first vaccine in which to apply an integrative system-wide approach was sensible, and offered good grounds for learning. From the perspective of this review, the strength of response is such that the variation observed between individuals is relatively small compared with other cohorts, for example in aging, where one can expect a much larger variation. Nonetheless, a recent re-analysis by gender of yellow fever vaccination data[9], highlighted the fact that the identified gene signatures induced by YF17D, occurred almost exclusively in females[12], which are known clinically to have a stronger response to vaccination in general[12-15]. This indicates that the factors determining the variation in the immune responses and phenotypes must be taken into account especially in studies conducted in humans where a significant variation is often observed.

Getting complex - Systems-wide vaccination responses in vaccines with variable response and partial efficacy

In more challenging applications, several groups and large consortia [16,17] have been using such integrative system-wide measurement approaches to understanding molecular mechanisms predictive of seasonal influenza vaccine response[18,19,20,21], HIV vaccines[22] and others[20,23-25]. Interestingly, these unbiased profiling analyses are enabling the discovery of new molecules involved in vaccine response, and are generating hypotheses for mechanisms of action that may be tested in animal models. For example, Pulendran and colleagues studied influenza vaccine response[18] in a study design parallel to their initial efforts in yellow fever[10], and showed that the gene expression of the calcium-calmodulin-dependent protein kinase IV (CaMKIV) is predictive at day 3 post-vaccination of end outcome influenza specific antibody titers. CaMKIV was known to have a role in T cell development, inflammatory responses and hematopoietic stem cell maintenance[26-29], but not in the B-cell response. Returning to animal models, they showed that vaccination of CaMKIV-deficient (*Camk4*-/-) mice with TIV, induced enhanced

antigen-specific antibody titers, demonstrating an unappreciated role for CaMKIV in the regulation of antibody responses.

More recently, we have adopted an integrative system-wide approach to find baseline (i.e. prevaccination) correlates of vaccine responsiveness in older adults (>60 years). Results of these studies, which also included young controls, yielded new age-dependent and age-independent predictors of vaccine response encompassing several ‘layers’ of the immune system including the proportion of various cell subsets, levels of serum cytokines, the functional status of immune cells, and expression of genes known to regulate apoptosis. Integration of such different aspects of immunity supported a critical role for apoptosis in the response to the influenza vaccine such that the presence of soluble anti-apoptotic molecules from blood (e.g. sFasL) and sets of genes with pro-apoptotic function such as GSTP1, FCGR2A, ZPB89, and others were positive predictors of the antibody response against influenza vaccination. This new role of the apoptosis machinery in vaccine response was confirmed in apoptosis-deficient animal models. From such studies, we suggested that the observed deficits in apoptosis can cause accumulation of memory cells (also known as memory inflation[30]) that are specific for diverse chronic infectious agents[31]. Due to the limited niche availability, such accumulation may restrict the number of cells able to respond to novel antigenic challenges and vaccination.

Our studies also show that prediction of vaccine response is less accurate and more sensitive in the elderly than in young individuals, indicating that we have not yet exhausted examining the variation across human populations. Moreover, as shown above, the immune predictors of vaccine responsiveness differ depending on the vaccine formulation (live-attenuated versus inactivated vaccines), cohort demographics (age, gender, race, others), exposure history (to the same or other antigens), etc. These findings also mesh with results from Chaussabel and colleagues, who performed a detailed time course investigating immune responses to influenza and pneumococcal vaccines, in a set of adults aged 18-64, and identified both shared and differing gene expression signatures for the different vaccines. Thus, we are experiencing the early days for the application of system-wide approaches for the identification of immunological features involved in the response to vaccination, and more generally, to the understanding of immune variation in humans,

Increased Variation in Older Adults and the Possibility of Immune System States

From a predictive point of view, our studies were challenging given the increased variation observed in the elderly as compared with young adults in many of the features (gene, cytokine, cell subset abundance or response) assayed. For example, we observed CD8 Naïve relative cell subset whose mean proportion in blood declines with age, show age dependent increase in coefficient of variation. This is likely the underlying reason why finding predictive models that explain vaccine responsiveness based on immunological features seems to be more difficult in older adults[19]. Indeed, a detailed inspection of the literature reveals that the variation in immune phenotypes in humans increases with aging (measureable as increased CV), such that the elderly exhibit a higher degree of diversity than is seen in young individuals [3,32-38]. Yet, most studies modeling immune behavior and clinical phenotypes with age have reported group mean dysregulations (Fig. 1). This increase in variance observed in older adults, is likely due to an individual's life-history (i.e. footprints of prior exposure and disease), with younger adults starting off from more similar ‘initial conditions’. A notable outlier to test may be the exceptionally old who are a select group of individuals who have buffered the effects of aging and thus may be expected to show lower variance [39]. Importantly though, even in young individuals, the immune system does not start off identical, heritability studies (performed mostly in twins) have

pointed towards genetic determinants influencing various leukocyte cell-frequencies[40], abundance of pro-inflammatory cytokines in plasma[41], and gene expression transcripts levels [42] and methylation patterns[43] from blood derived cells.

This raises the question as to whether sets of events (e.g. a low frequency of a certain cell-type in peripheral blood or a high abundance of a certain cytokine in serum) occur independently of one another or co-occur within the same individual. If the latter is the case, it implies the existence of 'immune states', likely the result of the 'network' nature of the immune system and detectable by analyzing groups of individuals sharing related traits, and/or by following single individuals over time. What would such states look like? They would be a combination of immune factors that co-vary, more so than would be expected in a loosely coupled system where each factor is independently, or close to independently, varying. Implicitly, experienced clinical immunologists have knowledge of such immune system states, stemming from having observed multiple laboratory tests performed on the same patient and for hundreds of patients; they learn to expect to observe abnormalities in a test assaying one factor of the immune system, when abnormal values are observed in another test; assaying a different immune system factor. Such behavior is indicative of a network connection between the two factors. However, the complexity of the immune system is so high that the ability to make such observations quickly decays the more factors are involved, and knowledge is limited primarily to extreme conditions of disease.

We explicitly make a distinction between immune states inferred from individuals with clinically described disease (from hereon: disease immune states) and those derived from those who are considered clinically healthy (or non-diseased) by today's clinical criteria (from hereon: healthy immune states). The distinction between disease and healthy immune states are blurred to some degree by the definition of what exactly is considered a 'healthy immune system', a definition likely to shift with time. As a working definition we would propose that healthy immune states are those detected in a healthy population and capturing much of the underlying variation due to differing life history events or genetics, whereas, disease immune states, sit 'on top' of healthy immune states, and represent a breakaway from an individual natural immune system alterations. We note, that by this definition the identification and clinical implications of disease immune states are relatively straight forward (for the identification of disease sub-group subsets, progression and treatment, discussion of which we leave for others) whereas the clinical significance of healthy immune states rests in how they affect disease susceptibility and trajectory, and is likely harder to detect. Hence, evidence as to the existence of differing immune states in those we currently consider healthy is scarce, as is the ability to distinguish those that are of good immune health versus those that are at risk within them.

First glimpse of Immune States Inferred from those Considered "Clinically Healthy"

A prime example of what could be considered a healthy immune state with clinical implications is the 'immune risk profile' (IRP) established from longitudinal studies of very elderly Swedish cohorts and characterized by an inverted CD4/CD8 ratio (<1), increase in late-differentiated CD8 T cells, as well as low B cells and CMV seropositivity[44-48]. This cluster of measures has been associated with mortality in 85 year-olds, with 2, 4 and 6 year follow-up, and more recent studies suggest that it can be applied to subjects over 65 years of age. We note that the IRP did not investigate any correlations of immune parameters with response to vaccination, and it is important to define whether it can also be applied to other cases and populations. Yet, it is an example that highlights the importance of standardized multi-parameter measurements for the discovery of immune states with clinical implications.

At a more detailed level, system-wide studies of vaccines, such as influenza, where immune response is highly variable and efficacy partial, are identifying segregated populations of responders and non-responders. Beyond their direct usefulness to understanding the conditions in which vaccines fail, these studies are informative for identifying immune states present in what is generally considered a healthy population. For example, in the work of Furman et al., the age-related decay in apoptosis function may well represent a cluster of measurements including genes, serum cytokines, etc. that identify individuals at risk of a weak vaccine response and maybe to other immune responses[19]. Similarly, Pulendran and colleagues were able to identify in young individuals gene signatures early after vaccination that could allow for early identification of subjects at risk of having poor responses to influenza vaccination[18]. Of note, of the 133 genes used to predict the antibody response to the seasonal influenza vaccine, 7 were also predictors of the antibody response to vaccination with the YF-17D vaccine[10,18]. Key genes in the predictive signatures were *TNFRSF17*, which encodes BCMA, (known to have a key role in B cell differentiation), and *CD38*, which encodes a surface protein important in lymphocyte development. Interestingly, BCMA belongs to a family of molecules (BAFF, APRIL, BAFF-R and TACI) that regulate plasma cell differentiation and the authors found strong correlations between the expression of genes encoding APRIL, BAFF-R and TACI and the response to both influenza and YF-17D vaccines. These results strongly suggest that the players involved in this network regulating the antibody responses to different vaccines could be also used to identify immune states representing poor versus good immune health.

Systems-wide approaches can identify underlying immune states and their trajectories with age

Immunologists may learn from other scientific fields where complex system theory ideas have taken hold and system level approaches have shown utility in revealing underlying complex system organization. These range from relatively close fields such as cancer genomics, to far flung ones such as gut microbiome interactions and complex ecosystems. A commonality to the approaches taken in probing these systems is the harnessing of the variance exhibited in the system towards an improved understanding. Yet, the view for much of ongoing research in immunology is that high variance is abhorred, considered as anywhere between a necessary nuisance to a reason to stop an experiment short. The identification of immune states necessitates a high level of variation between samples needed to detect coherent co-variation of multiple immune system components. System-wide studies of older adults, where the data generated is both of high dimensionality and highly variant between samples, notwithstanding controlling for confounding factors, may offer an ideal discovery ground for immune states while simultaneously answering clinically relevant questions regarding the variation in immune response.

A dynamic system with many components exerting regulation on one another is expected to gravitate towards a stable state[49,50]. Immune system homeostasis is considered as such a stable condition. Yet both the long term alterations in the immune compartments with aging and the large variation in measures observed between individuals would suggest that more than one stable state exists, both within an individual over time and between individuals. If so, this brings about fascinating and important questions: Within an individual we may ask when did these multiple states appear? Were they present at the onset of an individual's development or appeared as ‘sink holes’ later in life? The low variance observed in the young, compared to the old, would suggest that they are life history dictated, yet minor differences present in ‘initial conditions’ may grow in magnitude to be detectable with age. If the latter is the case, the increase in the variance of immunological parameters could therefore be considered as different immune trajectories of aging. Whichever is the case, sudden events or long term trajectories, it would be important to identify the possible system

states, the biological mechanisms which drive an individual's immune system towards a specific state and the clinical implication of different immune system states to disease.

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Highlights

- System-wide approaches are now applied to study vaccine response in healthy adults.
- Vaccine response involves multiple arms of immunity and can be predicted.
- Robust prediction of response from pre-vaccination measures remains a challenge.
- Phenotypic variance rises with age; suggest use of individual data over group means.
- Variation within and between individuals, may reveal underlying immune states.

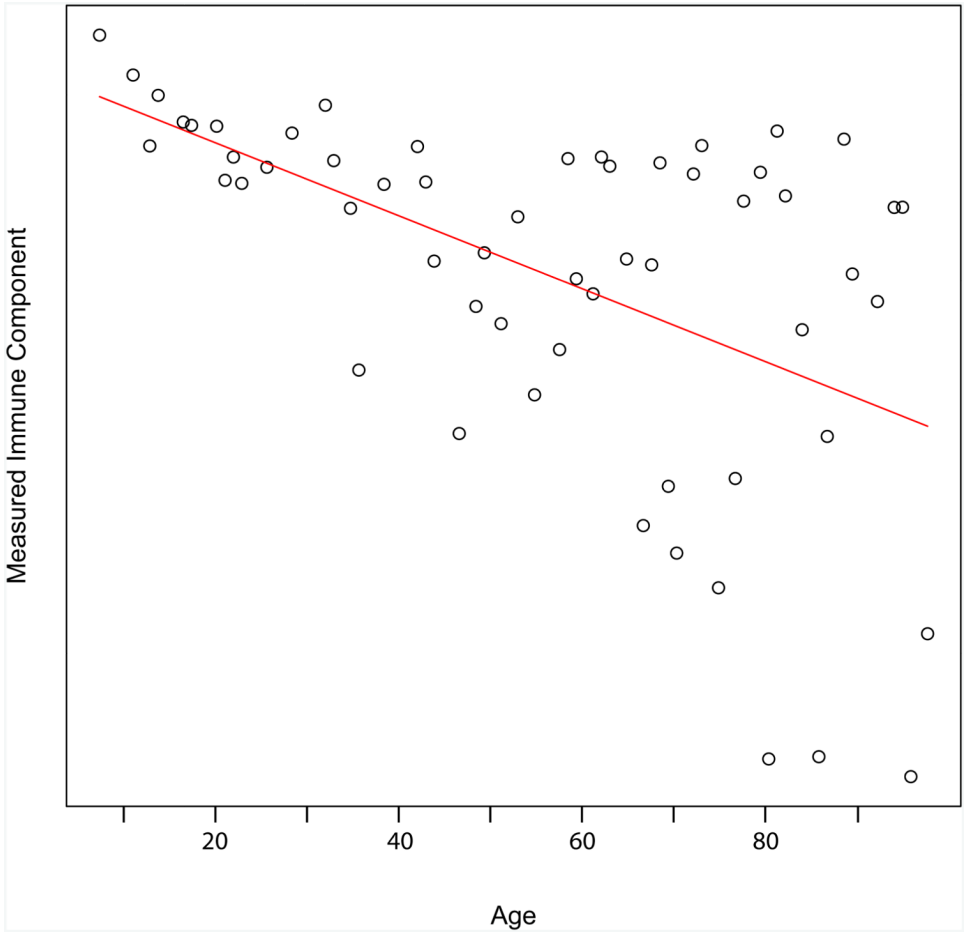

Figure 1. A characteristic plot of showing the measurement of an immune component as a function of age

Quiet commonly, especially in humans, the variation in phenotypes increases with age, such that older adults exhibit a higher degree of diversity (increased CV) than is seen in young individuals[3,32-3732-37]. Yet, most studies modeling immune behavior and clinical phenotypes with age have reported group mean dysregulations. Shown in red is a least square regression of the plotted simulated data, the ages on the x-axis vary by immune component assayed.