# Understanding immune variation for improved translational medicine

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## Abstract

The goal of translational medicine is to use an improved understanding of human biology to develop new clinical approaches. Immune responses are highly variable from one person to another, with this variability strongly impacting clinical outcome. Variable immunity can determine differential risks for infection, for development of autoimmunity, and for response to therapeutic interventions. Therefore, a better understanding of the causes of such differences has huge potential to improve patient management through precision medicine strategies. Variability in immunity is determined by intrinsic (e.g. age, sex), extrinsic (e.g. environment, diet), and genetic factors. There is a growing consensus that genetics factors account for 20-40% of immune variability between individuals. The remaining unexplained variability is likely due to direct environmental influences, as well as specific gene-environmental interactions, which are more challenging to quantify and study. However, population based cohort studies with systems immunology approaches are now providing new understanding into these associations.

## The contribution of genetics to immune variability

With the exception of a few specific traits (i.e. certain cell populations and plasma proteins) between 20-40% of variation in immune traits can be explained by heritable factors [1]. Recent studies have reported that genetics has relatively stronger effects on the innate immune arm, as compared to the adaptive [2,3]. One possible explanation for this, is that innate immune cells have shorter half-lives than adaptive cells, and therefore potential genetic effects are more detectable before the environment can assert its influence. In turn environmental effects have more time to influence, and therefore a greater effect, on adaptive cells. This is supported by clinical observations of the age of onset of certain diseases. For example, pathologies with a stronger genetic component, such as systemic lupus erythematosus (SLE), occur earlier in life than those with less of a genetic component such as rheumatoid arthritis [4]. While studies of in-born errors of immunity have revealed much new knowledge about critical immune pathways, they are more limited for understanding population level genetic variability. Outside of primary immunodeficiencies, genetic variation acts in more subtle ways, resulting

in differential levels of transcription or translation of key immune mediators. This can be revealed by the response to microbial stimulation in expression quantitative trait loci studies [5,6] (and reviewed elsewhere in this issue). Therefore, teasing apart how such small, but significant, effects on immune responses are influenced by environmental triggers to affect clinical outcome requires large sample sizes, longitudinal studies and integrative analysis including both genetic and epigenetic approaches [7].

## Impact of age and sex on immune variability

Recent population-based studies have demonstrated and quantified the strong and widespread effects of sex and age on immune variability [2,8,9]. This is recognized clinically with a general increased incidence of autoimmunity [10] and lower susceptibility to infection in females, as compared to males [11], and increased risk of infection with old age [12]. This may also be complicated by sex differences at different stages of life, for instance urinary tract infection (UTI) which has significantly greater incidence in females, yet, infection in males is more persistent with greater associated morbidity in young adults, but not in children or the elderly [13]. More challenging to understand are the interactions between age and sex, often due to hormonal changes, as well as differences caused by gender influences, that is, sociocultural (rather than biological) differences between men and women that can also impact clinical outcomes. For example, females respond better to influenza vaccine, and this difference is more pronounced in older (≥50 years) than in younger (<20 years) individuals [14]. However, women are also more likely to report severe effects from acute infection [15]. Aside from hormonal changes, sex related immune differences may also be a result of sexual dimorphism [10], pregnancy [16,17], breast feeding, or differential sex chromosome gene expression [18].

A recent transcriptomic meta-analysis identified a robust sex-associated immune gene signature that was consistent across studies and populations [19]. Although 85-95% of genes that show a species-conserved sex bias are reported to be autosomal [20], sex chromosomes contribute a significant fraction of gene expression sex differences, in particular for important immune related genes. An interesting example recently described how a substantial number of immune cells from both women, and Klinefelter syndrome males, express TLR7 on both X chromosomes. This results in higher protein expression and preferential proliferation of these biallelic B cells which may lead to higher SLE risk [21]. Within the 8 healthy donors studied, TLR7 biallelic cell frequency ranged from 20-50% across B cells, monocytes, and pDCs suggesting further high inter-individual variability. On the other hand, the Y chromosome is frequently lost in the leukocytes of ageing men which is linked to numerous disease outcomes

including all-cause mortality [22]. A recent study highlighted how altered immune cell function though loss of the Y chromosome could be directly implicated in disease, as important immune genes affected include *IL1R2*, *LY6E*, and *LAG3* among many others [23]. Future population-based studies with single cell resolution will help to identify the causes of variability behind these sex-gene associated phenotypes.

Diminished immunity with old age has long been a feature of clinical medicine, however recent longitudinal studies are revealing how this age-associated decline is also highly variable and likely impacted by environmental effects. The Stanford-Ellison longitudinal aging study profiled healthy individuals (aged 20-96) with cellular and molecular immunomonitoring tools [24]. This revealed that healthy individuals vary highly for age-related changes of immune cells, and a gene signature of immune aging derived from immune cells was significantly associated with all-cause mortality in a large independent cohort [24]. This observation was further supported by a more recent longitudinal study of donors from the Swedish SCAPIS cohort, where intra-individual variability at the immune cell level was associated with markers of poor metabolic health [25]. Understanding whether these associations are causative or merely correlative will greatly support future novel diagnostic and therapeutic strategies.

**Acute, chronic and latent infection differentially impact immune variability**

Differential encounters with microbes throughout life is another compounding variable when trying to understand direct versus indirect effects of age on immunity. For example, the measles virus, primarily encountered in childhood (in the absence of vaccination), can have a major impact on broad immunity. Acute measles infection was recently shown to cause elimination of 11-73% of the pre-existing antibody response in unvaccinated children [26]. While this antibody response could gradually be restored, it resulted in increased risk of clinical complications due to infection. This study was enabled by advances in unbiased antibody profiling and unfortunate vaccine hesitancy resulting in widespread measles infection, however it is challenging to study the direct impact of acute infection on immune variability outside of pandemic situations. One study showed that acute gastroenteritis had no discernable impact on immune phenotypes suggesting an inherent elasticity to short infectious perturbations. Our understanding of variable human immunity during acute infection will undoubtedly be deepened through ongoing studies of Covid-19 patients, with the hope that it will contribute to new therapeutic and vaccination strategies against SARS-CoV-2 but also potentially other viral infections.

In contrast to acute infection, the impact of chronic infections (e.g. HIV, TB, HCV) on immune responses has been well described to result in multiple co-morbidities. While these are often well-known impacts of the microbe on immune cells such as in HIV infection, there are also cases of less well-described indirect effects, such as a bystander effect of HCV on the naïve T cell repertoire [27]. Interestingly this broad effect of microbes on immune responses, is being exploited clinically in a positive way through BCG vaccination. This is based on a growing body of epidemiological studies supporting the concept that BCG, a vaccine for tuberculosis, provides heterologous immunity against many non-related pathogens [28], and is associated with lower incidence of certain cancers [29]. The proposed mechanism are through induction of innate immune memory and heterologous lymphocyte activation, with ongoing placebo controlled randomized trials currently being implemented for clinical validation [28].

Latent infection, in particular cytomegalovirus (CMV), is consistently reported to shape NK and T cell populations [2,3]. However, despite this clear impact on immune cells, the clinical consequences remain to be fully defined. CMV was also recently identified as a risk factor for development of TB disease, perhaps acting through T cell activation or NK cell modulation [30], and $CMV^+$ persons show higher all-cause mortality, which may or may not be immune-mediated [31]. In contrast, an intriguing study reported a beneficial impact of CMV seropositivity on influenza vaccination[32], but this finding was not replicated in a larger meta-analysis [33].

## Additional environmental effects

The strong impact of broad environmental effects on immune diversity has been nicely demonstrated in studies of twins [2] and co-habiting couples with children [34]. Indeed, the degree of immune variation was shown to be 50% lower between opposite-sex couples living with a child, and the general public. Interestingly the immune similarity in each couple was unique, suggesting the combined effect of multiple factors that made baseline immune phenotypes more similar [34]. Unfortunately, microbiome analysis was not performed in this study, as the challenge now remains to determine whether environmental effects are impacting immune diversity either directly or indirectly through microbiome modulation [35] . The ability of the microbiome to directly impact immunity has been demonstrated in a vaccine study with antibiotic treatment [36] and a study of neonates born in different environments [37]. The impact of the microbiome is also likely to be of different degrees depending on age and stage of immune system development as suggested by a recent neonatal study [38]. Additional factors that have been shown to have direct (and potentially indirect) effects on immune variability in

humans include diet [39], BMI/obesity [40], smoking [41], pollutants [42], season [43] and socio-economic factors [44,45]. Many of the mechanisms behind these associations remain to be understand and will likely require animal models and/or experimental medicine studies. An example was a recent mouse study showing how humidity levels had a striking impact on host anti-viral immune response with major impacts on survival to influenza challenge [46], which may explain some of the seasonal or geographical impacts on variable immunity.

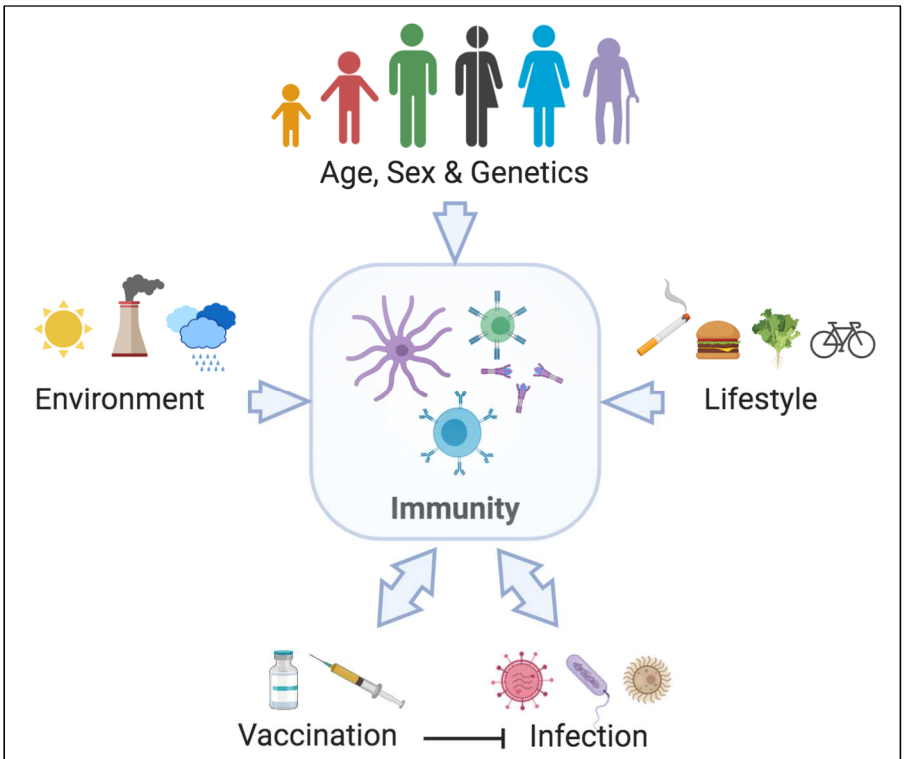


Figure 1. Major sources of variability in immune responses.

## Clinical impact of variability for immunotherapy

Preventive and treatment strategies that target immune responses have been in clinical use for hundreds of years, with a recent renaissance inspired by the success of checkpoint blockade inhibition for cancer immunotherapy. Immunotherapies can be broadly categorized into strategies that either boost immune responses (e.g. vaccination, cytokine therapy, CAR T cells), target inhibitors of immunity (e.g. immune checkpoint blockade molecules), or dampen immune responses (e.g. anti-cytokine monoclonal therapy). However, all such approaches show highly variable efficacy and/or toxicity, likely reflecting underlying high inter-individual immune variability and posing challenges for broad clinical application.

Cytokines, which may be considered as the “hormones” of immune and inflammatory responses offer great potential for therapeutic intervention, but this has yet to be fully realized

[47]. Type I interferon, the first cytokine to be discovered, is crucial for host responses to viruses and is also strongly implicated in many autoimmune diseases. Reflecting diversity within the human immune response, there are 18 subtypes that exhibit marked evolutionary differences in terms of selective conservation, suggesting different immunological relevance [48]. IFNα2 is clinically approved for treatment of chronic infection with hepatitis B (HBV) and C (HCV) viruses and for certain cancers, and IFNβ for multiple sclerosis (MS). Other cytokines used with mixed clinical success include IL-2 and IL-11 for cancer, and IFNγ for chronic granulomatous disease and osteopetrosis [47]. GM-CSF, C-CSF, BMP, and EPO are also cytokine therapies utilized for their cell growth promoting capabilities in conditions such as anemia and neutropenia [47]. However, response rates to cytokine therapies are highly variable, for example IFNα treatment for HCV is effective in about 50% of patients. As a result, more effective antivirals that directly target the virus have been developed and approved with widespread success, making the use of IFNα in HCV redundant. Nevertheless, the study of clinical non-response to IFN therapy may provide a strategy for applying to other diseases. Multiple GWASs identified polymorphisms in type III interferons (IL-28B) [49], and protein biomarker based studies characterized circulating levels of CXCL10 (an ISG chemokine)[50], as two independent biomarkers which when combined could predict non-response to IFN treatment [51]. Indeed, the IL-28B SNP is one of the rare FDA approved pharmacogenomic biomarkers for an infectious disease, even if now redundant. A recent interesting approach that may improve clinical success rates involves re-engineered cytokines, that recapitulate the binding sites of natural cytokines, but are unrelated in topology or amino acid sequence [52]. So called neoleukin-2/15 (mimics IL-2 and IL-15) binds to the IL-2 receptor βγc heterodimer (IL-2Rβγc), but not IL-2Rα (CD25) or IL-15Rα (CD215), and showed superior therapeutic activity to conventional IL-2 in mouse models of melanoma and colon cancer with reduced toxicity [52].

An alternative approach to cytokine therapy with greater clinical success is the blocking of cytokine responses with monoclonal antibodies or other anti-cytokine agents. Anti-IL-1β treatments show good efficacy in diseases that are classified as auto-inflammatory [47]. For other disorders that have both an auto-inflammatory and autoimmune component (e.g. RA) anti-TNF and anti-IL-6R treatments are more successful [47]. However, the major risk factor for these therapies is the increased risk of opportunistic infection, or reactivation of latent infections such as tuberculosis, illustrating the internal balance required to maintain healthy immune homeostasis. Interestingly, monoclonal antibodies against TNFα and IL-1

receptors were initial failures for the treatment of sepsis but are major success stories for autoimmune and autoinflammatory diseases [47]. This highlights the added complexity often present in host responses to infection, where variability in the pathogen also plays a role [53], as compared to dysregulated responses in auto-immunity.

Recent success in the treatment of cancer have reinvigorated translational research in cancer immunotherapy strategies, initiated by William Coley in the 1890s. The most successful approaches so far are mAbs that block CTLA4 (cytotoxic T-lymphocyte-associated protein 4), PD1 (programmed death 1), or PD-L1 (programmed death-ligand 1) and leverage pre-existing immunity by targeting molecular inhibitors on tumor specific T cells or the APC (antigen-presenting cell) [54]. Used as single agents, such immune checkpoint blockade inhibitors have clinical response rates ranging from 10-35% with tumor type, stage and underlying host immunity all widely contributing to this variability [54]. In addition, despite their success, such therapies have a risk of autoimmune disease as they disrupt the balance between tolerance and immunity. It is therefore hoped that an improved understanding of factors underlying natural variability in immunity will help to increase efficacy rates, while reducing adverse reactions, of current and future cancer immunotherapy strategies.

Vaccination against infectious disease is undoubtedly one of the success stories of translational research. The list of vaccine-preventable diseases through routine childhood vaccination includes diphtheria, tetanus, pertussis, pneumococcus, rotavirus, poliovirus, and *Haemophilus influenzae* type b [55]. Because of their high efficacy, sufficient herd immunity can be generated if widely applied in the general population, that vulnerable immunocompromised individuals also benefit from greatly reduced risk of infection. Indeed vaccination strategies may be considered the most positive "environmental" effect on immune variability given the widespread protection they provide to many previously widespread diseases. However effective vaccines for tuberculosis, HIV, HCV, malaria, and many cancers remain to be developed. Furthermore, licensed vaccines with variable efficacy rates include influenza [56] and HBV [57], which have been studied with systems vaccinology approaches to understand variable response rates [58]. A recent influenza vaccination study identified a baseline inflammatory gene signature that was associated with better antibody responses to vaccination in young individuals (<35 years), but with worse responses in older individuals (>60 years) [59]. Independent studies examining either H1N1 vaccination responses [60], or *ex vivo* transcriptomic response to influenza stimulation [9], reported similar differential age effects in donors <35 years. Additional longitudinal studies will be required to dissect

whether such effects are due to age-associated immune decline, or original antigenic sin, the concept that an individual's first infection with influenza determines future encounters [61].

## Conclusions

Our current understanding of human immune variability has mostly come from well curated population-based cohort studies. To further this understanding we need to extend these approaches to populations of different backgrounds, life stages, and environments as pioneered by the Framingham Cohort [62] and more recently the UK biobank [63]. In addition, longitudinal study designs should be considered if possible, as well as experimental interventions such as vaccination or antibiotic treatments where ethically possible. Such experimental medicine studies will allow specific hypotheses to be tested in controlled settings. There also remains a need for unbiased discovery-based approaches, though findings should be replicated where possible in independent studies. The increasing number of cohort studies around the world and open sharing of data sets makes this increasingly feasible. At the discovery stage efforts can be made to minimize technical variability as much as possible through the use of standardized sampling and biological assays [64]. This will help to reduce technical noise and maximize statistical power [65], especially important when integrating diverse data sets to identify novel interactions. However as biological systems are inherently noisy we should not expect to explain and account for all variability [66]. For this reason, when moving from discovery studies to replication, validation, and eventually clinical translation, real world data sets should be included as much as possible. This so called "dirty data" approach can ensure resilience of any biomarker-based strategy through testing and validation in diverse data sets [67]. This better reflects the reality of heterogenous clinical settings, as compared to well controlled experimental studies, and will be of increasing importance for machine learning approaches. All of these approaches will help to maximize efforts to translate an improved basic understanding of immune variability into new clinical tools.

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