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The causes and consequences of variation in human cytokine production in health

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Cytokines are important cell-signaling molecules that activate and modulate immune responses. Major factors influencing cytokine variation in healthy individuals are host genetics, non-heritable factors and the microbiome. Genetic variation accounts for a significant part of heterogeneity in cytokine production by peripheral blood mononuclear cells. Variation in cytokines such as IL-6 and IL-6Ra is strongly influenced by heritability, suggesting an evolutionarily pressure for their genetic regulation that potentially contributes to differences in immune responsiveness between human populations. Non-heritable factors, including age, body weight and environmental variables such as seasonality, drive variation in baseline cytokine levels. Age further affects pathogen-induced lymphocyte-derived cytokine responses, whereas seasonality affects monocyte-derived cytokine production in response to influenza virus, *Coxiella burnetti* or *Cryptococcus neoformans*. Another influential factor that shapes the immune system is the human microbiome. Microbes and microbial products (e.g. short-chain fatty acids and tryptophan metabolites) possess strong immunomodulatory effects, induce regulatory T cells and lead to the diversification of B cells and the production of specific antibodies. In particular, differential TNFα and IFNγ production is associated with the gut microbiome. Understanding causes of variation in the healthy human immune system can reveal factors that lead to aberrant cytokine production in immune-related disorders.

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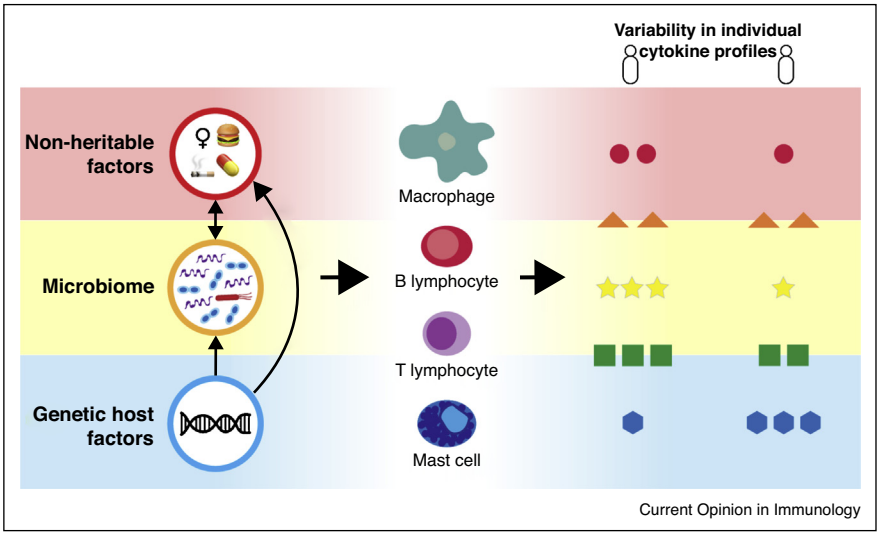
Introduction

Cytokines are small proteins produced by many cell types, especially immune cells, that mediate inter-cellular communication and initiate, modulate and attenuate immune responses, including inflammation. Cytokines include chemokines, interferons (IFNα, IFNβ, IFNγ), interleukins (IL-1 to IL-39), and tumor necrosis factors (among which TNFα and TNFβ/LTα are the best known). Produced by a range of immune cells such as macrophages, B lymphocytes, T lymphocytes and mast cells, cytokines are also released by endothelial cells, fibroblasts, and various stromal cells. Their immunomodulatory effects can be systemic (endocrine signaling) or local and tissue-specific (autocrine and paracrine signaling), and their biological functions can be redundant, complementary (several cytokines required together), pleiotropic (different effects on different cells) or in certain situations antagonistic. Defective or inappropriate cytokine production influences pathophysiology of autoimmune and inflammatory diseases, infections and cancer. A number of host and environmental factors are implicated in human cytokine production variability among individuals, including genetic factors, non-heritable factors and the microbiome (Figure 1). A better understanding of the causes and consequences of cytokine variation will greatly improve our understanding of and further our ability to treat immune-related diseases.

Variability in cytokine production

It is widely accepted that a broad range of factors contributes to human immune system variation. Using high-throughput '*omics*' technologies and large population-based cohorts, recent studies simultaneously profiled various molecular entities, such as circulating

Figure 1



Non-heritable factors, the microbiome and host genetic factors affect cytokine production capacity. Genetic factors impact the human microbiome and non-heritable factors, such as medication efficacy. Further, the microbiome can affect non-heritable factors and vice versa; for example, diet shapes microbial community composition and microbial metabolism affects medication efficacy. All of these factors interact with the immune system and influence an individual's cytokine production capacity.

immune cell counts and cytokine levels. Detailed phenotypic information such as age, sex, microbiome and specific environmental factors were tested to clearly distinguish between genetic and non-heritable influences on cytokine production variation and human immune diseases.

Cytokine production in studies is commonly induced with *Escherichia coli* lipopolysaccharides (LPS), which is a part of most Gram-negative bacterial outer membranes. Importantly, differential effects of various LPS structures from different bacterial species on innate immune responses were recently identified (Figure 2) [1,2••]. Specifically, structural changes in lipid A impact recognition by the TLR4 complex, and the removal of a single phosphate group from bacterial LPS determined whether the host maintained or removed commensal bacteria in response to inflammation.

Large-scale studies made two important observations: the relative contribution of genetic and non-heritable host factors to cytokine variability is significantly different for different cytokines, and cytokine production greatly depends on the context in which immune cells function and the cell or tissue type that produced the cytokines. For example, host genetic variation explains an important part of cytokine production variability by peripheral blood mononuclear cells (PBMCs) upon pathogen stimulation [3••,4], while non-heritable factors largely drive variation in baseline immune parameters [5,6••]. In the following review, we discuss recent insights obtained from cohort-based, systems-immunology studies.

Effects of non-heritable factors on cytokine production capacity

Humans display differential susceptibility to infections and immune-related diseases depending on their age, sex and lifestyle [7–13]. By measuring 204 immune parameters in 210 healthy twins in a recent cohort-based study, Brodin *et al.* argued that variation in over 77% of these parameters was largely determined by non-heritable factors [5]. The effects of non-heritable and genetic factors on circulating cytokine concentrations, however, depend on the specific cytokines and their functions. For example, the impact on the anti-inflammatory cytokine IL-10 was mainly independent of genetic factors, while genetics played an important role for IL-12p40. The study also assessed twin–twin correlations for all immune measurements between the oldest and youngest monozygous pairs. Interestingly, reduced correlations were observed in older compared to younger twins for cytokines such as IL-17, IL-15, chemokine CXCL10/IL-10 and others, indicating that age and other non-heritable factors drive immune function variation in genetically identical twins. Another population-based cohort study of over 1000 individuals assessed the roles of non-heritable factors on 77 serum proteins [14], finding that age and body weight were strongly associated with multiple proteins but medication and smoking affected only a few.

These studies mainly assessed circulating cytokine production, but another important question is how non-heritable factors influence cytokine production capacity stimulated by invading pathogens and pathogen-associated molecular patterns (PAMPs) during infection. In a