

Decoding the body language of immunity: Tackling the immune system at the organism level

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Abstract

The immune system is a dynamic mesh of molecules, cells, and tissues spanning the entire organism. Despite a wealth of knowledge about the components of the immune system, little is known about the general rules governing the organismal circuitry of immunity. Deciphering the immune system at the scale of the whole organism is crucial to understanding fundamental problems in immunobiology and physiology, and to manipulate immunity for maintaining health and preventing disease. Here I discuss the emerging principles of interorgan communications during immune responses by focusing on three common themes: the regulation of the (i) composition, (ii) condition, and (iii) coordination of communicating organs by molecular and cellular factors. Based on these common principles, I emphasize fundamental gaps in our knowledge of organismal immune processes and the outlook to tackle immunity at the scale of the whole organism.

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Current Opinion in Systems Biology 2019, 18:19–26

This review comes from a themed issue on **Systems immunology & host-pathogen interaction**

Edited by **Thomas Höfer** and **Grégoire Altan-Bonne**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 6 November 2019

<https://doi.org/10.1016/j.coisb.2019.10.010>

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Keywords

Inter-organ communications, Organismal physiology and immunology, Whole-body analysis, Cytokines, Immune cells.

Introduction

Organs exchange information. For example, organs sensing food, light, or stress send signals to other organ systems, allowing the organism to maintain homeostasis [1,2]. Mammalian immunity is one of the most striking examples of such interorgan communications (Figure 1). The immune system evolved to cope with pathogens

anywhere in the body—may it be a parasite residing in the gut or a virus spreading to multiple organs. As a result, molecules, cells, and tissues with immunological functions are ubiquitously and dynamically distributed across the organism.

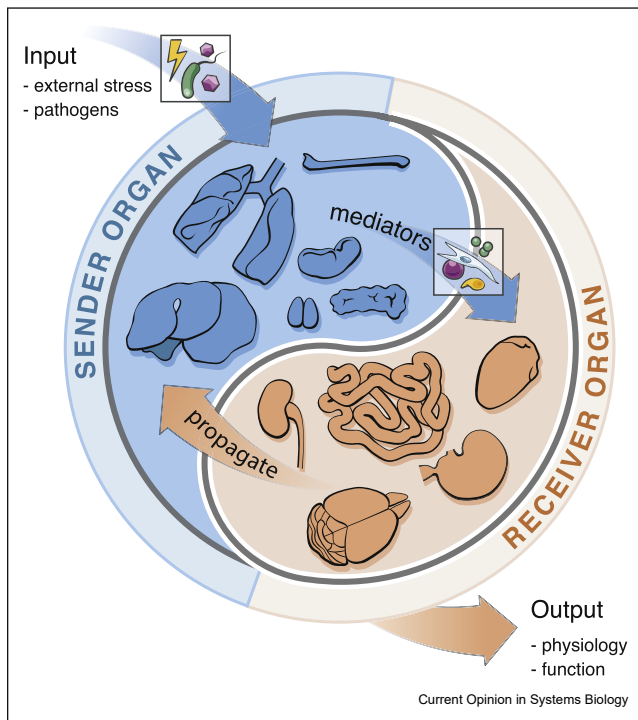
However, although the systemic property of immunity is obvious, remarkably little is known about the general rules guiding immune processes across organs. For example, when the concentration of a cytokine varies in the blood as a result of host defense, homeostasis, or disease, we most often lack a clear picture of the sender and receiver organs and cells that are involved. Another example is the migration dynamics of immune cells across the body, which remains to be elucidated for most cell types.

Thus, a fundamental challenge in immunology today is to develop new ways to study the structure, regulation, and function of the immunological events that cross organ boundaries. Deciphering the design principles of interorgan immune signaling will yield insights into the functions and malfunctions of immunity at an unprecedented scale, that of the whole organism. Here I discuss examples of interorgan communications in immunology by focusing on three common themes: the regulation of the (i) composition, (ii) condition, and (iii) coordination of communicating organs by molecular and cellular factors. I also emphasize fundamental questions in this emerging field and the outlook to answer them.

Molecular and cellular immune factors involved in interorgan communications

All tissues in the body can secrete factors with local or systemic effects. A survey of 32 human tissues estimated that 10–20% of the transcripts found in any given tissue produce secreted proteins [3]. In some cases, the percentage of transcripts encoding secreted proteins can be much higher because of tissue specialization, including 70 and 40% for the pancreas and liver, respectively [3]. Although many factors have key roles in interorgan communications, including metabolites, growth factors, or extracellular vesicles, I focus here on cytokines which *sensu stricto* include interleukins, chemokines, and other overlapping families of secreted immune factors. Although the concepts discussed here apply to other molecular species with immune

Figure 1



Interorgan communications in the mammalian immune system. Simplified schematic of the communication events taking place between organs during organismal immunological processes. A sender organ processes input signals such as pathogens, injury, or stress and releases molecular or cellular mediators. Mediators reach one or more distant, receiver organs via blood and/or lymph. The receiver organ modifies its immunological and/or physiological states and, in cases of complex interorgan circuits, may further propagate information to other organs.

functions, I primarily discuss cytokines for simplicity and because (1) they can be secreted by most, if not all, nucleated cells; (2) they can act as autocrine, paracrine, and endocrine messengers; and (3) their primary function is the regulation of the immune system.

Many aspects of cytokine biology have been under investigation for decades, including their structural and signaling properties, their impact on cell proliferation, differentiation or death, and their association with human diseases [4–17]. In addition, recent work has begun to reveal key properties of the intercellular communications mediated by cytokines. For example, quantitative models helped explain the dynamics of cytokine production and consumption in cell ensembles [18], or the integration of multiple cytokine signals by T lymphocytes [19,20].

In response to local or systemic cues such as cytokines, immune cells relocate across the body as they mature and guard the host against pathogens. For example, the T cell life cycle starts in the bone marrow, continues in the thymus and, for naïve T cells, throughout the body

until encountering a cognate antigen [21]. However, despite this wealth of knowledge about immune cells and cytokines, we know surprisingly little about the organismal circuitry of the cytokine system and its systemic impact on cells. We also lack dynamic models that help to explain interorgan molecular and cellular exchanges during immune processes.

Although the roles of cytokines and immune cells are seemingly countless in health and disease, I argue here that common themes can be found in interorgan signaling and can be useful as a conceptual guide for the much-needed exploration of the immune system at the scale of the whole body. To illustrate this point, I examine the following examples of interorgan crosstalk which fall into three categories on the basis of the ability of immune cells and cytokines to regulate the (i) composition, (ii) condition, and (iii) coordination of organ systems.

Regulating the cellular composition of organs

The first category of interorgan crosstalk reflects the role that cytokines and immune cells can play in regulating the cellular composition of distant organs. For example, the composition of the hematopoietic compartment of the bone marrow can be dramatically remodeled during the switch from steady state to so-called emergency hematopoiesis during systemic bacterial infection [22]. Endothelial cells from multiple tissues, including the heart, liver, kidney, spleen, and bone marrow, can detect lipopolysaccharide (LPS) via Toll-like receptor (TLR) 4 and release granulocyte colony-stimulating factor (G-CSF) into the blood circulation. G-CSF then acts on myeloid-restricted progenitors in the bone marrow to increase granulopoiesis [23]. Interestingly, this concept of the remote regulation of hematopoiesis has been observed in other contexts, including in lung adenocarcinoma where the release of a soluble receptor in the blood triggers an increase in neutrophil maturation and recruitment to the tumor [24].

As demonstrated with hematopoiesis, the efflux and afflux of immune cells can modify the cellular composition of an organ. Such changes in composition can be temporary during an acute response or long term as seen, for example, with the seeding of macrophages throughout the body during embryonic development [25]. Another example of this paradigm is the memory T cell compartment. Pioneering work revealed that memory T cells can distribute to most lymphoid and nonlymphoid organs in the body upon systemic challenge [26,27]. Recently, changes in immune cell composition were observed in mice during cycles of fasting or caloric restrictions as a result of interorgan signals involving bone marrow, liver, and lymphoid

tissues. The numbers of monocytes and lymphocytes in blood and peripheral organs were strongly reduced, whereas in the bone marrow, lymphocyte numbers increased and monocyte egress decreased [28–30], which highlights the complex regulation of various immune cell compartments across organs.

Conditioning the functional state of organs

Cytokines may condition a tissue to perform a specific task related to a physiologic or defense need for the host. For instance, type I interferons (IFNs) produced in one organ can trigger an antiviral state in distant tissues. Respiratory viral infection can lead to the activation of antiviral genes in the bone marrow [31], whereas skin infection with a live attenuated strain of Vaccinia virus triggers a whole-body antiviral state through interorgan IFN signaling [32]. Perhaps systemic IFN signaling evolved to arm distant tissues with antiviral defenses as a means for the host to prevent the spread of a virus across the body [32].

Similar to cytokines, immune cells modify the state of tissues as part of various interorgan circuits. For example, neutrophils contribute to liver tissue repair before migrating to the lungs and subsequently the bone marrow, where they die by apoptosis [33]. Another example comes from memory T cells that reside in tissues, so-called T_{RM} cells [34–36], which have been shown to trigger organ-wide antimicrobial states [32,37]. Furthermore, upon skin injection of a live attenuated strain of Vaccinia virus, $CD8^+$ T_{RM} cells have been shown to distribute broadly across distant organs, such as the lung and liver, and to establish intercellular circuits that are tissue-specific and important for protection. The resulting multiorgan web of T_{RM} cells can trigger organ-wide, antiviral states in tissues targeted by the virus as a means to limit viral spread [32].

Physiologic and immune coordination across organs

Cytokines may act by coordinating the physiological pathways of multiple organs either in parallel or serially. For example, TNF- α , IL-1 β , and IL-6 have been much studied for their roles in the interorgan communications regulating metabolism [38]. Another example is TGF- β 2 that is released by subcutaneous adipose tissue after exercise, leading to increased glucose uptake by muscle, heart, and brown adipose tissue and beneficial metabolic effects across the body [39]. In addition, secreted factors may affect distant organs indirectly via, for example, a nervous system relay [40]. For example, IL-1 β produced in the gut [41] or GDF15 in the liver or kidney [42] can act on the brain to, respectively, modify host anorexic behavior or hepatic triglyceride fluxes that are key for heart function during sepsis. Together, these examples highlight the power of cytokines in coordinating the activities of multiple organs either directly,

through sensing of a given cytokine by multiple tissues, or indirectly, by acting on nonimmune relays to communicate between organs such as neurons.

Furthermore, a variety of immune cell types migrate between organs to coordinate immunosurveillance and protective responses across the body. For example, progenitor and mature innate and adaptive immune cells share similarities in their recirculation patterns across organs. Hematopoietic progenitor cells originating in the bone marrow traffic to multiple nonlymphoid tissues where they temporarily reside before returning to the blood via the lymph, similarly to naïve T cells [43]. Innate lymphoid cells (ILCs) were recently found to also follow interorgan paths. Group 2 ILCs migrate from the gut to peripheral tissues such as lungs to protect the host from helminth infection [44].

Open questions about interorgan immune crosstalk

Several fundamental questions arise from the observations reported in the case studies discussed earlier. Indeed, although it is clear that cytokines and immune cells cross organ boundaries to coordinate host protection and physiology, little is known about the design principles of these interorgan circuits.

First, we lack a clear picture of the scope of these organismal communications. For cytokines, we often do not know which ones are released from which organs to affect which distant tissues, in what biological contexts do these cytokinic communications occur, and what are the temporal and spatial parameters at play during intertissue crosstalk? For cells, the organismal migration patterns of circulating immune cell types and subsets are not well understood and difficult to track experimentally. In addition, the full complement of the immune cell types that are involved in such interorgan pathways is likely unknown. For example, recent work has shown that cells thought to be largely tissue resident were in fact able to recirculate and reach distant tissues in some conditions, including both innate [44] and adaptive [45,46] cells.

Second, in the context of cytokines whose organismal effects have been documented, we often lack information about the sender and receiver cells involved and that may be hematopoietic or not. For example, cytokines such as IL-22 are secreted by hematopoietic cells and target nonhematopoietic cells [47]. One corollary to this lack of knowledge about the sender and receiver cells for any given cytokine is that, in most cases, the cytokine signaling relays that are responsible for the mobilization, migration (influx and efflux), positioning, and adaptation of immune cells within a tissue remain unclear.

Third, what are the combinatorial effects of cytokines and other signals on cells and tissues? Many diseases are

associated with increased levels of multiple cytokines in the blood. Presumably, each receiver cell and organ for those endocrine signals could respond to more than one cytokine at the same time. For example, at the level of T cells, the strength of a response is equal to the sum of its parts, including cytokine signals [19,20]. Whether such a simplifying principle holds true in other cases remains to be tested and is worth considering for the study of interorgan signaling.

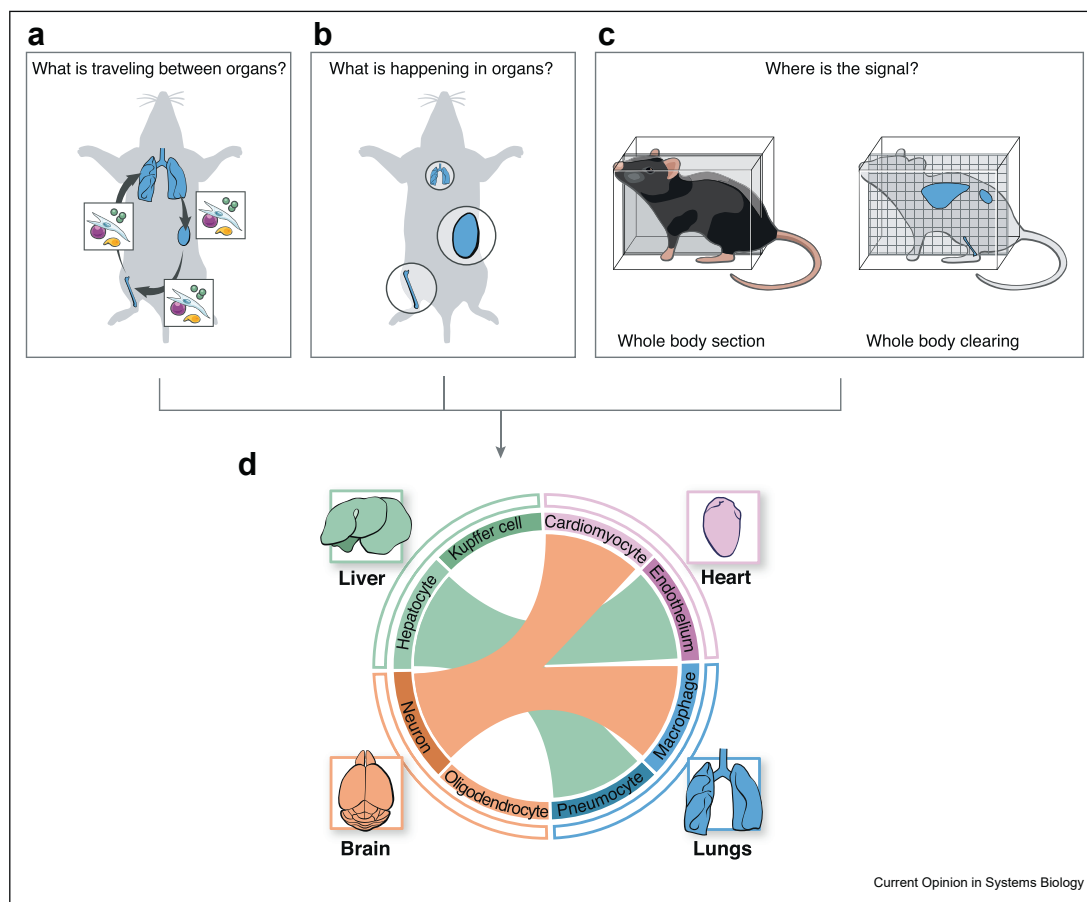
Overall, addressing the questions highlighted earlier will help to identify the common rules governing the interorgan circuitry of immunity. Furthermore, although I focused on cytokines, similar points can be raised for other interorgan factors, including metabolites, hormones, antibodies, microbial components, or even self-antigens, which can cross organ boundaries in type 1 diabetes [48].

Outlook on studying interorgan communications

I discussed examples of interorgan crosstalk and their impact on the composition, condition, and coordination of organs during immune processes, as well as fundamental questions for the future. What is the outlook to answer those questions and tackle the challenges posed by the ubiquitous nature of immune factors across the body? The central challenge is twofold: organism-wide sampling and connecting the dynamic events involved in interorgan signaling, which will require the development of new tools and approaches (Figure 2).

First, to identify the mediators that carry information across organs, it is critical to improve methods to profile cells and molecules in the circulatory systems of the body (*i.e.*, blood, lymph). For example, sampling the

Figure 2



Studying immunological processes at the scale of the whole body. (a–c) Schematics illustrating the fundamental challenges associated with studying interorgan signaling. The three upper panels illustrate how to identify the mediators of interorgan communications and their impacts on organ states. In **a**, the boxes illustrate the molecular and cellular mediators of interorgan communications—using lungs, bone, and kidney as a hypothetical network of communicating organs. In **b**, organs involved in a systemic communication circuit are shown in circles whose size is proportional to a given activity or effector mechanism. In **c**, organism-wide imaging is illustrated using as examples whole-body sectioning or clearing. (d) Toward organism-level analyses of immune circuitry and its integration with host physiology. Data obtained through the approaches listed here (a–c) are integrated as a hypothetical interorgan network, which is represented as a circular plot with links between communicating organs (outer circle) and cell types (inner circle) within each organ. The color of the lines linking organs depicts the sender organ.

influx and efflux of molecules and cells from multiple organs across the body will help to inform the identity of interorgan signals and their fluxes in individual organs (Figure 2a). Such methods have long been used to study the fluxes of substrates across organs and were successfully used to measure changes in arteriovenous metabolomic profiles across most organs in pigs [49]. Sampling of immune cells in the lymph has also revealed key properties for memory T cells [50]. Thus, combining large-scale sampling of bodily fluids and measurements of various molecular and cellular entities will be a powerful means to identify interorgan messengers.

Second, interorgan signaling affects the states of the communicating organs. Thus, experimental methods are needed to characterize the dynamic changes occurring across communicating organs (Figure 2b). For example, multitissue gene expression studies have started to contribute to addressing this challenge by identifying shared and tissue-specific expression patterns that vary in health and disease [51–59]. In addition, organ-level expression can detect immunological changes driven by cell composition or direct gene regulation, even in rare cells [32,37,60,61]. Multitissue profiling approaches will further help to decipher interorgan circuits when combined with, for example, (1) ongoing efforts to map the cellular composition of organs at large [62–64], or by focusing on immune cells [65,66], (2) single-cell measurement tools that are becoming increasingly multiparametric [67], (3) methods to locate molecules and cells in tissue sections or whole tissues [68–75], and (4) computational deconvolution methods, whereby cellular composition and contribution are inferred from bulk expression or epigenomic measurements [76,77].

Third, and perhaps most difficult, how can we establish causal relationships between systemic mediators and the regulation of multiorgan processes (Figure 2d)? First, chemical, genetic, or other perturbations will help to understand interorgan pathways as long as such perturbations are applied to a sender organ specifically while monitoring the impact on putative receiver organs. Modifying molecular and cellular mediators through engineering can broaden the range of perturbations available to tease apart interorgan signaling. For example, recent advances in engineering proteins [78] and cytokines [79] will be invaluable tools, with key applications including the targeting of a given cytokine to a tissue of interest [80]. In addition, the ability to recreate multitissue systems *in vitro* is likely to generate useful toy models that are easy to manipulate to tease apart interorgan signaling [81–83].

Next, computational approaches that can be applied to the study interorgan signaling are emerging. For example, a simple example comes from the mining of the expression patterns of secreted proteins and their cognate receptors across nine organs upon infection,

which helped to infer putative interorgan connectivity maps that can then be used as starting points for in-depth studies [32]. In addition, methods such as systems genetics that leverages the analysis of multitissue data sets across individuals from various genetic backgrounds [84] and large-scale text mining of the PubMed database [85] also provide powerful tools to decipher interorgan signaling. Complementing these approaches with quantitative models built for interorgan timescales and processes will be crucial to understand the emerging principles of systemic communications in immunology. The development of such models will benefit from the acquisition of time series data at the scale of the whole body, which is becoming increasingly feasible using whole-tissue gene expression [32].

Last, recent developments in imaging modalities across the organism will be valuable to observe and quantify the dynamics of molecules and cells across multiple organs in parallel, including, for example, immuno-PET [86], whole-body sectioning [27,87,88], or clearing methods [89] (Figure 2c). Combining whole-body imaging with reporters of various cellular activities or recent advances in cellular barcoding approaches for lineage tracing [90–92] is likely to yield important insights for our understanding of whole-body immunity.

Conclusions

Using examples of the regulation of organ composition, condition, and coordination by the immune system, I have emphasized how little we know about organismal immunity. Deciphering the immune system at the scale of the whole organism is crucial to understanding fundamental problems in immunobiology and physiology, and to manipulate immunity for maintaining health and preventing disease. Although studying interorgan immune signaling is a daunting challenge, I highlighted several paths forward based on recent advances in immunology and beyond. Approaches likely to help us in this endeavor include (1) finding a minimal set of models to focus on for the comparative analysis of interorgan circuits; (2) mapping organism-wide communications by developing molecular and cellular measurement, imaging and perturbation tools; and (3) creating synthetic assemblies of tissues and organs that mimic key features of interorgan processes.

Conflict of interest statement

Nothing declared.

Acknowledgements

I am grateful to many colleagues in the field and members of the lab for critical discussions. I thank the editors of this issue and anonymous reviewers for helpful comments and Sigrid Knemeyer for help with figures. This work was kindly supported by a National Institutes of Health Director's New Innovator Award (DP2 AI145100) and the Elliot and Ruth Sigal Melanoma Research Alliance Young Investigator Award (571146).

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