HHS Public Access

Author manuscript

Curr Opin Syst Biol. Author manuscript; available in PMC 2020 June 02.

Published in final edited form as:

Curr Opin Syst Biol. 2019 December ; 18: 19–26. doi:10.1016/j.coisb.2019.10.010.

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 inter-organ communications during immune responses by focusing on three common themes that are 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.

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 inter-organ communications (Figure 1). The immune system evolved to cope with pathogens anywhere in the body – may it be a parasite residing 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, while 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 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 inter-organ immune signaling will yield insights into

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the functions and malfunctions of immunity at an unprecedented scale, that of the whole organism. Here I discuss examples of inter-organ communications in immunology by focusing on three common themes that are 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 inter-organ 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 due to tissue specialization, including 70 and 40% for the pancreas and liver respectively [3]. While many factors have key roles in inter-organ 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 below apply to other molecular species with immune 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 inter-cellular 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 naive 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 inter-organ molecular and cellular exchanges during immune processes.

Though the roles of cytokines and immune cells are seemingly countless in health and disease, I argue that common themes can be found in inter-organ 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 below examples of inter-organ crosstalk which fall into three categories based on 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 inter-organ 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 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 non-lymphoid 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 inter-organ signals involving bone marrow, liver and lymphoid tissues. The numbers of monocytes and lymphocytes in blood and peripheral organs were strongly reduced, while 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], while skin infection with a live attenuated strain of Vaccinia virus triggers a whole-body antiviral state through inter-organ 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 inter-organ circuits. For example, neutrophils contribute to liver tissue repair prior to 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 anti-microbial states [32,37]. Further, 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 lung and liver, and to establish

intercellular circuits that are tissue-specific and important for protection. The resulting multi-organ 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-1β and IL-6 have been much studied for their roles in the inter-organ communications regulating metabolism [38]. Another example is TGF-β2 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 impact distant organs indirectly via, for example, a nervous system relay [40]. For example, IL-1β 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 non-immune 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 prior to returning to the blood via the lymph, similarly to naive T cells [43]. Innate lymphoid cells (ILCs) were recently found to also follow inter-organ 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 inter-organ immune crosstalk

Several fundamental questions arise from the observations reported in the case studies discussed above. Indeed, while 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 inter-organ 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 impact which distant tissues, in what biological contexts do these cytokinic communications occur, and what are the temporal and spatial parameters at play during inter-tissue 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 inter-organ 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 non-hematopoietic 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 simplifying principle will hold true in other cases remains to be tested but it is worth considering for the study of inter-organ signaling.

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

Outlook on studying inter-organ communications

I discussed examples of inter-organ 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 inter-organ 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 profiles cells and molecules in the circulatory systems of the body (*i.e.*, blood, lymph). For example, sampling the influx and efflux of molecules and cells from multiple organs across the body will help to inform the identity of inter-organ signals and their fluxes in individual organs (Figure 2A). Such methods have long been employed to study the fluxes of substrates across organs and were successfully employed 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 inter-organ messengers.

Second, inter-organ signaling impacts the states of the communicating organs. Thus, experimental methods are needed to characterize the dynamic changes occurring across communicating organs (Figure 2B). For example, multi-tissue 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]. Multi-tissue 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 multi-organ processes (Figure 2D)? First, chemical, genetic or other perturbations will help to understand inter-organ 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 inter-organ signaling. For example, recent advances in engineering proteins [78] and cytokines [79] will be invaluable tools, with application including the targeting of a given cytokine to a tissue of interest [80]. In addition, the ability to recreate multi-tissue systems *in vitro* is likely to generate useful toy models that are easy to manipulate to tease apart inter-organ signaling [81-83].

Next, computational approaches that can be applied to the study inter-organ 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 inter-organ 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 multi-tissue datasets across individuals from various genetic backgrounds [84] and large-scale text mining of the PubMed database [85] also provide powerful tools to decipher inter-organ signaling. Complementing these approaches with quantitative models built for inter-organ 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 inter-organ immune signaling is a daunting challenge, I highlighted several paths forward based upon 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 inter-organ 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.

Acknowledgments

I am grateful to many colleagues in the field and members of the lab for critical discussions. I thank 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 (1DP2AI145100-01) and the Elliot and Ruth Sigal Melanoma Research Alliance Young Investigator Award.

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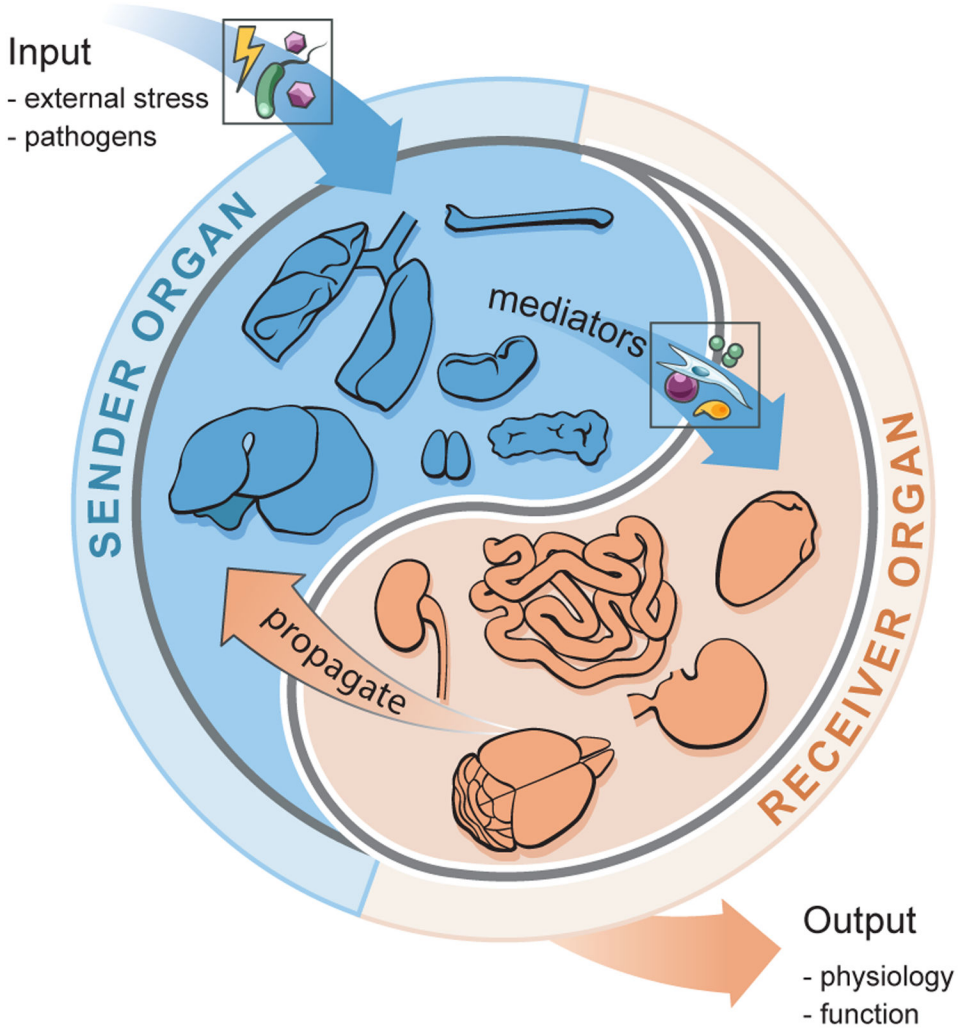

Figure 1. Inter-organ communications in the mammalian immune system.

Simplified schematic of the communications 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 inter-organ circuits, may further propagates information to other organs.

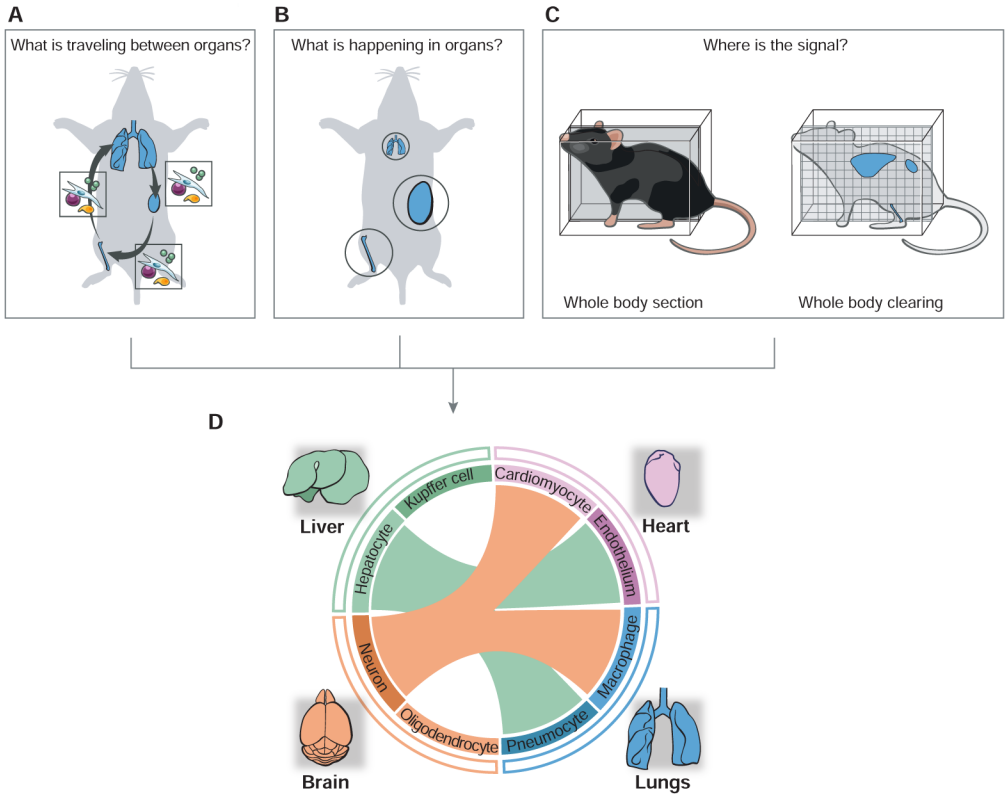

Figure 2. Studying immunological processes at the scale of the whole body.

(A-C) Schematics illustrating the fundamental challenges associated with studying inter-organ signaling. The three upper panels illustrate how to identify the mediators of inter-organ communications and their impacts on organ states. In A, the boxes illustrate the molecular and cellular mediators of inter-organ 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) Towards organism-level analyses of immune circuitry and its integration with host physiology. Data obtained through the approaches listed above (A-C) are integrated as a hypothetical inter-organ network, which is represented as a circular plot with links (colored lines) between communicating organs (outer circle) and cell types (inner circle) within each organ. The color of the lines linking organs depicts the sender organ.