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Systemic responses during local viral infections: Type I IFNs sound the alarm

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Abstract

Type I IFNs are well known for their role in controlling virus replication and spread. Type I IFNs produced by the infected tissue also signal beyond the boundaries of the infection to regulate different elements of the anti-viral immune response. Recent reports show that type I IFNs directly condition naive monocytes residing in the distal bone marrow and induce the expression of effector molecules in memory T cells, prior to their recruitment to the infected site. In addition, hematopoietic stem cells were shown to enter the cell cycle in response to systemic type I IFNs. These discoveries expand our understanding of the pleiotropic effects of type I IFNs during infection and highlight the involvement of the whole organism in the development of an effective response to a localized viral infection.

Introduction

Systemic manifestations of virus infections have been recognized for a long time. Fever, fatigue, malaise, myalgia and headache are normally the first evidence of the organism's reaction to the presence of the invading pathogen (**Fig. 1**). These symptoms are manifested upon infection with a broad array of infections including those contained in a single organ, such as the lung, liver, or gut. At the site of infection, the production of pro-inflammatory molecules and the massive recruitment of cells from the periphery are hallmarks of inflammation and indicate that the hematopoietic system is actively engaged in combating the pathogen. The mechanisms by which distinct systems are engaged in the response to distal infection, discern the type of response required, and support the development of immunity, are subjects of vigorous investigation. New evidence indicates that type I interferons (IFNs) generated at the site of infection act as primary systemic alarm signals that promote the development of effective innate and adaptive responses. Here, we discuss the current models for the study of systemic responses to virus infection and the data supporting a critical role for type I IFNs in shaping these responses.

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Localized versus systemic models of virus infections

Evidence of systemic involvement in the response to viruses is observed during infections that spread to multiple body compartments, as well as during infections that are limited to a particular organ. Viruses that spread through the organism, such as Epstein-Barr virus (EBV), lymphocytic choriomeningitis virus (LCMV), human immunodeficiency virus (HIV), vaccinia virus (VV), and mouse hepatitis virus (MHV) are complex systems for studying the mechanism that drive the systemic response to the infection as it is difficult to isolate the effect of direct infection from that of signals that originate in distal sites [1-8]. Viruses that do not disseminate systemically from the site of infection provide a superior model for studying the systemic events that take place in response to tissue signals generated after infection. These models, while allowing the examination of *in vivo* responses, are not compromised by the direct recognition of viral products in tissues that respond to systemic signals. Among these viruses are those that replicate mostly exclusively in the respiratory tract, including human parainfluenza virus, and its mouse homologue Sendai virus (SeV), respiratory syncytial virus, human metapneumovirus and certain strains of influenza virus [9-11]. It is important to keep in mind that the ability of the virus to infect multiple organs may change in different virus strains or due to the host's immunological condition.

Systemic signals of virus infections: Virus detection and production of pro-inflammatory molecules

In mammals, viruses are detected at the site of infection by a panel of cellular proteins that include members of the Toll-like receptor (TLR) family (TLRs 3, 7, 8 and 9), the retinoic-inducible gene-I (RIG-I)-like family of receptors (RLR), which includes RIG-I and melanoma differentiation-associated gene 5 (MDA5), and the DNA-dependent activator of interferon-regulatory factors (DAI) [12,13]. Viral sensors recognize conserved pathogen associated molecular patterns including viral DNA (TLR9 and DAI) and RNA (TLR 3, 7, 8, RIG-I and MDA5) leading to transcription of pro-inflammatory genes involved in the anti-viral response. Among these molecules are cytokines such as type I interferons (IFNα and IFNβ), type III IFN (IL-28, IL-29 or IFNλs), interleukin 6 (IL-6), IL-12, IL-1β, tumor necrosis factor α (TNFα), as well as many chemokines and growth factors [9,14]. At the infected site, type I and III IFNs act in concert with other pro-inflammatory molecules to impede the replication and spread of the virus and to recruit and activate innate immune cells. Simultaneously, these early cytokines enter the blood stream and act on multiple organs outside the infected site as systemic alarms of the presence of a pathogen. For example, IL-1β, IL-6 and TNFα drive the production of prostaglandin E2 in the brain triggering the hypothalamus to induce fever, a systemic manifestation of the host response to infection [15,16].

Viral antagonism and its effect on anti-viral immunity

Successful pathogenic viruses encode antagonists that obstruct the function of the intracellular pathways of virus sensing allowing the virus to replicate to high titers before it is counteracted by the immune system (recently reviewed in [17]). Through the inhibition of cytokine production, virus antagonists not only inhibit local virus clearance but also obstruct the cytokine-mediated mechanisms of systemic alertness and response to the infection. A well studied viral antagonist is the influenza virus protein NS1 that has been shown to inhibit the induction of type I IFN and other pro-inflammatory cytokines in the lung for up to two days after infection *in vivo* [18]. During this period, there is no detectable manifestation of immune response at the local or systemic levels.

Sensing of distal infections by bone marrow (BM) leukocytes: Type I IFN and HSC cycling

The BM is the primary hematopoietic organ in adult mammals and provides many of the cellular components of the immune response to infection. Hematopoietic stem cells (HSCs) that give rise to virtually all leukocytes in the adult organism reside in the BM. It has been recently shown that dormant HSCs enter the cell cycle after intravenous injection of type I IFNs [19,20], during systemic infection with VV, and in response to IFNγ induced by infection with the bacterium *mycobacterium avium* [21]. Although the activity of BM HSCs during a distal and localized virus infection has not been tested, it is likely that BM HSCs increase the production of hematopoietic cells in response to type I IFNs produced by the infected tissue, playing an important role in the development of the anti-viral response.

Type I IFNs in the instruction of BM monocytes

Evidence of the plasticity of hematopoietic cells in response to tissue signals and the importance of the specific conditioning of BM leukocytes for an optimized anti-viral response has been accumulating in recent years. Human monocyte-derived DCs primed *in vitro* with type I IFN show resistance to virus infection, enhanced anti-viral response once challenged with virus, and display superior ability to activate T cells [22-24]. Importantly, during the days immediately following respiratory infection with influenza or SeV, monocytes residing in the BM become resistant to a wide variety of viruses and more responsive to viral cues [9]. This acquired phenotype, which results from the signaling of type I IFNs produced in the infected lung and then transported through the blood to the BM, is essential for the anti-viral activity of monocytes once recruited to the lung during infection and leads to the efficient clearance of the virus [9]. Notably, most cell types in the BM respond to type I IFNs with the upregulation of anti-viral genes, indicating that the impact of the anti-viral conditioning of hematopoietic cells in the regulation of innate cellular responses is just beginning to be appreciated.

Type I IFNs in the regulation of immunity

A role for type I IFNs in regulating elements of the adaptive immune response has long been recognized. Type I IFNs influence T cells by enhancing clonal survival *in vivo* in response to infection [25-27] and by directing the quality and magnitude of B cell responses [28-30]. Interestingly, it has been shown recently that during viral infections type I IFNs systemically regulate the expression of the T cell activation markers CD69 [31,32] and the cytolytic activity of recall responses by promoting the antigen-independent expression of granzyme B in memory T cells [33]. Type I IFNs, therefore, act as an alarm system during both primary and recall anti-viral responses by alerting and instructing different immune components to combat the invading pathogen effectively. Paradoxically, type I IFNs also have anti-inflammatory effects and it has been recently shown that they inhibit the production of IL-1 thereby increasing the host susceptibility to superinfections [34] highlighting the complexity of the type I IFN regulatory network.

Other systemic signals of infection

In addition to type I IFNs, a large variety of cytokines are produced at the site of virus infection. Many of these molecules are known to influence leukocytes residing in the BM but only a few of them have been demonstrated to act distally during virus infections (**Table 1**). TNF-α and lymphotoxin-α (LTα) were shown to induce apoptosis of early B cell precursors in the BM [35], but their effect in the development of lung anti-viral immunity is unknown. Growth factors capable of affecting HSCs differentiation and mobilization from

the BM are also produced at high levels in the lung infected with influenza or SeV [9,14,36]. These growth factors include granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF). The effect of these factors in viral infections is also not fully understood, however we have observed a critical role of G-CSF in sustaining mice survival upon infection with influenza or SeV as G-CSF deficient mice succumbed to normally sub-lethal infectious doses of these viruses (unpublished results). Chemokines, such as the CCR2 ligands CCL-2 and CCL-7, have been shown to mobilize monocytes from the BM during infection and in their absence monocytes fail to egress from the BM and virus clearance is delayed [9,37,38] and they might also play a role in the mobilization of HSCs to the site of infection [39]. Interestingly, the expression of CCL-2 is regulated by type I IFNs demonstrating that that these cytokines indirectly regulate the mobilization of matured cells from the BM [40,41].

Concluding remarks

The type I IFN-mediated interaction between the infected tissue and cells residing in distal and sterile organs has revealed an underappreciated mechanism for the systemic regulation of immunity during localized virus infections. The effect of the anti-viral conditioning of many BM cell types in the resolution of primary or secondary infections and in the regulation of viral pathogenesis remains to be investigated. It is evident that the infected tissue interacts with a number of organs beside the BM during the course of an infection. New interactions between the infected site and the Central Nervous System impacting the host's immune competence are beginning to be characterized [42], and evidence for the need of priming of memory cells before reaching the infected site during recall responses is accumulating [33]. The crosstalk between infected and non-infected tissues may regulate the outcome of the infection at multiple levels: a) suboptimal anti-viral priming in patients with underlying health conditions could lead to weak or inappropriate innate anti-viral responses, b) on the flip side, conditioning in response to highly virulent viruses could lead to an excessive inflammatory response at the infected site leading to tissue damage and disease, or c) anti-viral conditioning could bias the host immune response augmenting their susceptibility to non-viral pathogens. This later mechanism could contribute to the enhanced pathology observed during secondary bacterial infections.

The origin of the systemic type I IFN remains to be determined. Particularly intriguing is the role of plasmacytoid dendritic cells (pDCs) in disseminating these cytokines from the site of infection as pDCs are circulating cells that are highly specialized in producing type I IFNs through mechanisms that scape viral antagonism. It was recently shown that pDCs are required for the production of type I IFNs during the early stages of viral infection [43] but not at later stages, suggesting that other sources of type I IFNs participate on the *in vivo* response to infection. A number of different cell populations including monocytes, neutrophils, NK cells, conventional DCs, and non-hematopoietic cells, such as the respiratory epithelium and endothelium, can produce type I IFNs during virus infection and are, therefore, alternative candidates to mediate systemic signaling.

The systemic regulation of immunity represents an important mechanism for the modulation of the host response to infection that when perturbed during disease, age, or other conditions, could lead to enhanced pathology. Importantly, these systemic interactions are amenable to be exogenously manipulated for the benefit of the host, making them exciting targets for novel therapies.

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• of special interest

•• of outstanding interest

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Highlights

- Virus-infected tissues produce molecules that act as systemic alerts of infection.
- Type I IFNs act as primary alert of infection to distal non-infected tissues.
- Systemic signals optimize both primary and recall anti-viral responses.
- Leukocytes residing in the bone marrow are targets of systemic anti-viral signals.

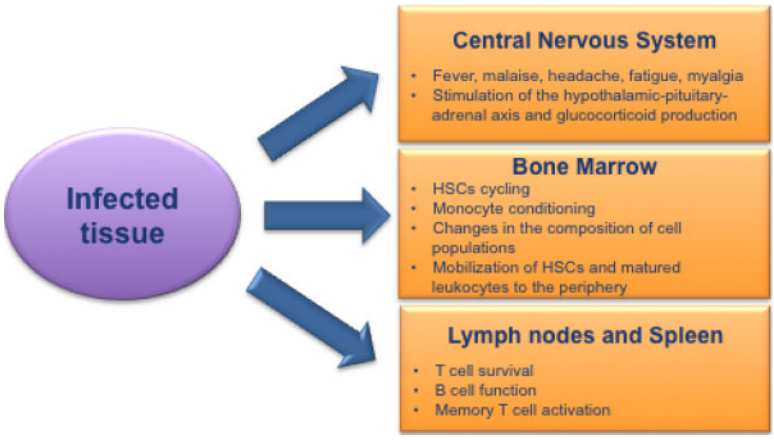

Figure 1. Systemic responses to localized virus infections

Pro-inflammatory signals produced in the infected tissue are disseminated systemically during a localized virus infection. Some of the effects of these systemic signals, such as the induction of fever, have been appreciated for a long time, but a number of others have only recently been recognized. These include the stimulation of the hypothalamic-pituitary-adrenal axis due to physiological stress at the infected site [42], the anti-viral conditioning of leukocytes residing in the bone marrow at the time of infection [9], and the antigen-independent activation of memory T cells during the course of respiratory viral infections [33].

Table 1

Antigen-independent systemic effects of pro-inflammatory molecules produced by virus-infected tissue.

Cytokine	Target Organ	Effect
Type I IFN	Bone marrow	•Anti-viral conditioning of leukocytes [9] •HSC enter the cell cycle [19]
	Lymph node and spleen	•Expression of Granzyme B on memory T cells [33] •Expression of activation markers on T and B cells [25-29]
	CNS	•Fever, sickness [44-46]
IL-6	Bone marrow	•Granulopoiesis [47]
	Spleen and lymph nodes	•CD4+ T cell proliferation and activation [48]
	CNS	•Fever, sickness [46]
TNFa	Bone marrow	•Depletion of B cell precursors [35]
	CNS	•Fever, sickness [15]
IL-1β	CNS	•Fever, sickness [45,46]
LT-α	Bone marrow	•Depletion of B cell precursors [35]
GM-CSF, G-CSF, M-CSF	Bone marrow	•Granulopoiesis [49] •HSC mobilization [50] •Neutrophil activation [51]
CCL-2, CCL-7	Bone marrow	•Monocyte mobilization [37,38]
CXCL1, CCL-3, CXCL10, CCL5, IL-1α, IFNλ, IL12, etc.	Systemic effects during virus infection remain to be defined	