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Perspective

Early host defense against virus infections

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SUMMARY

Early host defense eliminates many viruses before infections are established while clearing others so they remain subclinical or cause only mild disease. The field of immunology has been shaped by broad concepts, including the pattern recognition theory that currently dominates innate immunology. Focusing on early host responses to virus infections, we analyze the literature to build a working hypothesis for the principles that govern the early line of cellular antiviral defense. Aiming to ultimately arrive at a criteria-based theory with strong explanatory power, we propose that both controlling infection and limiting inflammation are key drivers for the early cellular antiviral response. This response, which we suggest is exerted by a set of “microbe- and inflammation-restricting mechanisms,” directly restrict viral replication while also counteracting inflammation. Exploring the mechanisms and physiological importance of the early layer of cellular antiviral defense may open further lines of research in immunology.

INTRODUCTION: EARLY CELLULAR DEFENSE AGAINST VIRUS INFECTIONS

Living organisms are constantly exposed to viruses, as demonstrated by the high abundance of viral genomic material in seawater and sewage¹ and even in the airways of people not exhibiting disease symptoms.^{2,3} This suggests that our immune system eliminates many viruses before they establish infection or does not recognize them as threats, as they are controlled without effects on physiological cellular functions. Indeed, the rapid effectuation of host defenses against invading viruses at the portals of entry or access points into organs is of central importance for the ability of the host to successfully fight microbes and for the eventual outcome of infections.⁴ The importance of early host-pathogen encounters is further emphasized by the wealth of viral mechanisms known to evade and manipulate host cells.^{5–7} Despite this, the early mechanisms of host defenses that guard the mucosal surfaces and target organs to prevent establishment of infections remain poorly explained.

Unifying concepts and theories aid progress in science. They are a prerequisite for the forming of scientific communities, which can be the basis for discussions, meetings, collaborations, and development of ideas. Therefore, constructing the

right conceptual framework for understanding the very early events in innate immune responses to infections may release a scientific potential that could also lead to societal progress. For instance, concept-driven new knowledge on the immediate immune response to microbial challenge may advance the development of vaccines, pan-antiviral therapies, and oncolytic virus therapy, among others, and could also lead to identifying novel primary immunodeficiencies and autoimmune disorders with immediate benefit for patients.

In this perspective, we examine whether the current theories in innate immunology can explain the early events in host defense against virus infections. Finally, building on published data and expanding from previous conceptual discussions by us and others,^{4,8,9} we propose that the guarding of homeostasis through the immediate restriction of viruses and limitation of pathological inflammation plays a large role in the early line of cellular defense against virus infections.

ARE PRRs MEDIATING THE FIRST LINE OF ANTIVIRAL DEFENSE?

Immunology as we understand it today is based on two major paradigms, namely the theories of clonal selection and pattern



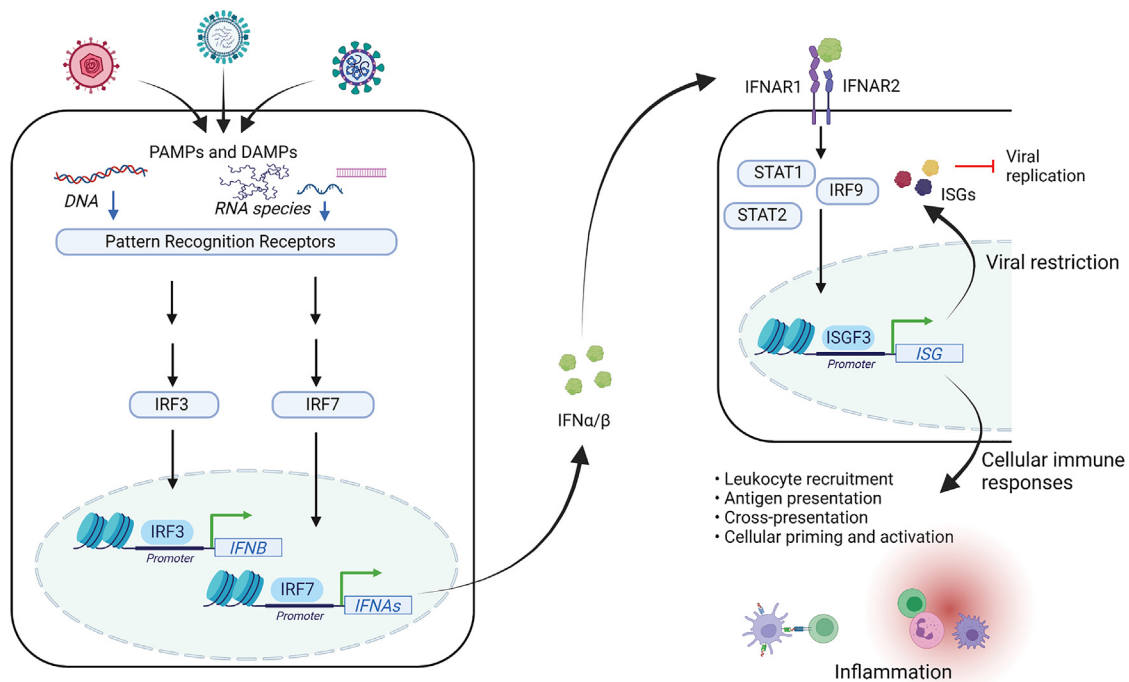


Figure 1. Type I IFN activity in antiviral defense

Type I interferons (IFNs) are expressed by cells after sensing of viruses by PRRs. IFNs are secreted and can activate adjacent cells through the IFNAR1/2 complex to induce IFN-stimulated genes (ISGs). Many ISGs directly restrict viral replication, while others stimulate inflammation and promote lymphocyte activation and specific immunity.

recognition.^{10–12} For the purpose of this perspective, the clonal selection theory, which seeks to explain adaptive immune responses, is not highly relevant and will not be discussed further. The pattern recognition theory states that cells are endowed with a limited number of germline-encoded pattern recognition receptors (PRRs), which bind conserved microbial and misplaced self-molecules termed pathogen-/damage-associated molecular patterns (PAMPs/DAMPs) and activate the cells expressing the PRR. Certain PRRs can also be activated upon disruption of specific cellular processes by virulence factors, so called “effector-triggered immunity.”¹³ The pattern recognition theory was proposed by Charles A. Janeway in 1989¹² and was followed by the identification of cell-associated PRRs in flies, mice, and humans.^{14–16} In this perspective, we define PRRs as germline-encoded receptors that sense PAMPs and DAMPs to instigate signaling cascades ultimately activating auto- and paracrine antimicrobial activity and most often also proinflammatory activities. This does not necessarily include all primordial PRR systems found in prokaryotes. We chose this definition since we are mainly aiming to explain early cellular antiviral defense in multicellular organisms. For the present discussion, the most important aspect of PRRs is their downstream activities.

Sensing of PAMPs and DAMPs by PRRs evokes signaling activity eventually leading to host defense but also potentially inflammatory diseases if activated excessively or over a prolonged period of time.^{17–24} In the case of virus infections, PRR-driven induction of the antiviral cytokines type I interferons (IFN-Is) is

pivotal and plays an important role in early antiviral responses^{25–29} (Figure 1). This has led to the general perception in the field of innate immunity that PRRs constitute the first line of defense against infections. However, as will be discussed below, there are key observations that do not fully fit this hypothesis.

Since the proposal of the pattern recognition theory, the concept has “drifted” so that it is now commonly stated in scientific literature that PRRs constitute the first line of defense against infections.^{30–38} This has likely been driven by the fact that PRRs are indeed germline encoded and can directly sense microbial molecules to induce signaling and expression of antiviral cytokines, most notably IFN-Is and a panel of antimicrobial effector activities. The idea of pattern recognition constituting the first line of host defense was not proposed by Janeway in his original essay or subsequent publications,^{12,39} but it was developed over time by scientists who worked in the realm of the theory.^{30–38} However, a series of data published within the past few years do not support this view of early antiviral defense. First, mouse experiments where the animals are infected at mucosal surfaces have shown that detectable IFN expression and induction of gene expression are not observed within the first day of infection,^{40–42} and IFN deficiency does not translate to elevated virus replication until day 2 of infection.⁴⁰ Such data show a delayed nature of the IFN response relative to the first host-pathogen encounter. Second, strong PRR activation often involves a two-step processes,^{43,44} as well as induced expression of PRRs or signaling proteins, and also

requires PAMP levels to be above a given threshold to induce signaling.^{24,45,46} In the context of the early stages of a virus infection, this means that PRR activation requires the viral load to increase to a certain level to induce substantial signaling and also to be around long enough to activate significant PRR signaling after the pathway has been fully primed. Third, over the past few years, defects in genes encoding constitutive antiviral immune mechanisms acting upstream of PRRs in host defense have been identified to confer susceptibility to specific virus infections.^{47–52} This clearly indicates a non-redundant role for constitutive immune mechanisms in antiviral defense. Fourth, several reports have now shown that defects in specific constitutive immune mechanisms lead to elevated accumulation of viral nucleic acids and associated IFN-I expression,^{53,54} indicating host defense activities acting upstream of PRRs. Fifth, prospective studies have shown that human pathogenic respiratory viruses are frequently detected in the human airways without ongoing or subsequent development of disease.^{2,3} This suggests that subclinical control of virus infections is highly frequent. Sixth, some cell types do not use IFNs as the major system to fight viruses. Most notably, stem cells have been reported to have particularly high basal expression of a specific set of antiviral genes and hence have a pre-set antiviral program in place.^{55,56} Since inflammatory responses compromise the plasticity of stem cells,⁵⁷ this could indicate that in this biological niche, a high constitutive energy cost is beneficial to avoid the potential consequences of local inflammation. Although none of the above examples alone can make a compelling case, they collectively support the conclusion that PRRs and IFNs, and hence the pattern recognition theory, cannot be applied as a unifying and universally valid concept to explain the earliest line of cellular defense against virus infections.

EXISTING KNOWLEDGE ON IMMEDIATE ANTIVIRAL MECHANISMS

Based on the above discussion, it can be argued that current theories in immunology fail to explain the early cellular defense against virus infections (Figure 2A). We propose that the central phenomenon in immunology that remains to be conceptualized is the following *explanandum*: how do cells and tissues exert early antiviral host defense activities without compromising physiological functions? In this work, we use “disturbance of homeostasis” as a term to describe alterations of physiological functions.

To start to approach the question posed above, we will first look into some of the biological processes and systems that have been shown to exert direct cellular antiviral activity (Figure 2B). The first category of processes is direct restriction, whereby host molecules block specific steps in the replication cycle of viruses. This category includes restriction factor proteins, antimicrobial peptides, and also specific host- or microbiota-derived metabolites. For instance, SAMHD1 depletes cells for the pool of deoxynucleoside triphosphates, hence limiting the expression of a panel of viruses with a DNA stage in their replication, such as human immunodeficiency virus (HIV)-1 or herpes simplex virus 1 (HSV-1)^{58–60} (Table 1). In addition, several defen-

sins bind virus surface proteins and cause aggregation, as seen for influenza A virus (IAV),¹²⁹ whereas host metabolites can alter the cellular microenvironment or form post-translational modifications of viral proteins to impair replication.^{106,130} The mode of “virus sensing” is not confined to a pathogen-specific molecular pattern, although this can be the case, as illustrated by TRIM5 α , which senses molecular determinants on the retroviral capsid.¹³¹ Some restriction factors deplete or alter central biomolecules required for virus replication in infected cells, including SAMHD1 and APOBEC3.^{58,59,132} Yet another category of restriction factors binds to host virus-dependency factors, thus competing for interactions with proteins involved in virus replication or targeting them for proteosomal degradation. These categories are exemplified by TMEFF1 and TRIM7, respectively, both elevating the threshold for productive virus replication.^{62,105} Interestingly, several of the virus restriction factors additionally exert antagonistic activity on PRR activation, either through a reduction of the level of PAMPs⁵⁴ or through blockage of PRR signaling by a specific molecular mechanism.⁶³ For instance, TRIM7 targets the adaptor protein STING from the DNA-activated cGAS-STING pathway for degradation,⁶³ while MARCH2 facilitates the degradation of NEMO, which is used in multiple PRR signaling pathways, including the RNA-sensing RIG-like receptor-MAVS pathway.⁷⁴

The second category of direct antiviral mechanisms is autophagy, a process through which cells sequester cytoplasmic content in double-membrane vesicles and target them for degradation by the lysosomal pathway.¹³³ In the case of virus infections, this may be the digestion of incoming viruses or virus replication “factories.” As to how the cellular autophagy machinery senses virus infections, several possibilities exist. First, autophagy is a constitutive process in cells, and hence the basal and unspecific autophagic activity may contribute to antiviral activities in the cytoplasm. Second, cells are endowed with selective autophagy receptors, such as p62/SQSTM1, which detect ubiquitinated virions and recruit the viral cargo to the autophagosome.^{111,134} TRIM family proteins have been suggested to be central for the sensing of a broad range of viruses, including IAV, HSV-1, and encephalomyocarditis virus and linking to the autophagy machinery.^{135,136} Third, cellular systems to sense different forms of cellular stress, such as endoplasmic reticulum (ER) stress and metabolic alterations, have been shown to trigger autophagy,^{137–139} although this can serve both pro- and antiviral roles. As was also observed for a panel of restriction factors, autophagy exerts negative regulation of many PRR signaling pathways.^{112–114} This occurs through a diverse set of mechanisms. In the case of the cGAS-STING pathway, autophagy targets the adaptor protein STING for degradation, thus limiting signaling activities.¹¹² Finally, the close relation between autophagy and viruses is further emphasized by several autophagy proteins directly restricting virus replication independently of autophagy.¹⁴⁰

A third category of antiviral mechanisms involves cell death. The death of cells deprives viruses of their ability to replicate, and cell death mechanisms can, therefore, exert antiviral activity. Data from an evolutionary broad range of species spanning from invertebrates to vertebrates and including a diverse set of viruses, such as vaccinia virus, *Drosophila* C virus, and Sindbis

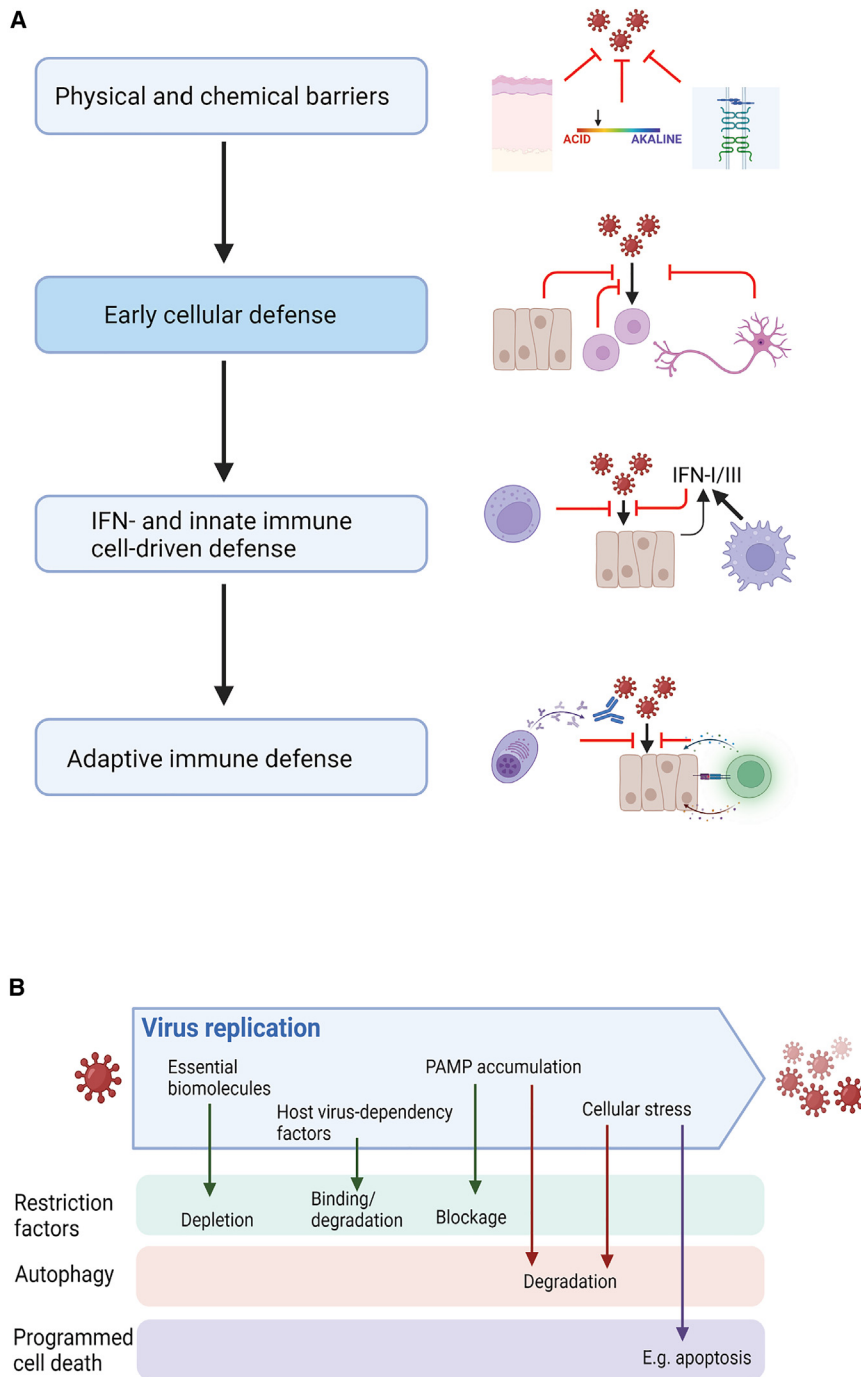


Figure 2. Cellular processes to interfere with viral replication

(A) Illustration of principle levels of host defense against virus infections. We focus on mechanisms and theory in early cellular antiviral defense.

(B) Host cells can interfere with virus infection by depleting essential biomolecules (e.g., nucleotides), modulating the accessibility of host virus-dependency factors, eliminating specific viral molecules, or responding to virus-induced cellular stress. Restriction factors, autophagy, and apoptosis represent three key categories of host cell interference with virus replication.

cells,^{141–143} accumulation of reactive oxygen species,¹⁴⁴ ER stress pathways in the unfolded protein response,^{145,146} and p53-dependent apoptosis.^{123,147} Apoptosis has long been appreciated to be a non-inflammatory form of cell death due to the rapid uptake and digestion of the apoptotic cells by macrophages, with M2 macrophages having the highest phagocytic activity.¹⁴⁸ In addition, more recent data also show that the apoptotic caspases-3 and -7 specifically block signaling from the cGAS-STING pathway following mitochondrial DNA leakage and also through mediation of activation-induced cell death.^{125–127} In addition to the categories of early antiviral defense discussed above, other mechanisms have also been identified, including RNA interference, intracellular nucleases, and soluble lectins.^{149–152} Although these latter mechanisms are not studied in the same detail in relation to virus infections and will not be discussed in detail here, the available data suggest both inhibition of virus replication and PRR signaling, mechanisms that are illustrated by the ability of the lectin surfactant protein D to bind and directly neutralize IAV as well as the elevated inflammation in the lungs of IAV-infected mice lacking the lectin.¹⁵²

For all the antiviral systems discussed above, it is important to mention that several viral immune-evasion mechanisms

have been identified.^{5,6,153} In addition, human genetics studies have demonstrated non-redundant roles for restriction factors and autophagy in the protection against severe infections.^{47–51} Collectively, these two categories of data provide strong evidence in favor of the importance of early cellular host defense mechanisms. The above-described antiviral activities work through very diverse sets of mechanisms. However, they share the common features that they are immediately ready to act, generally do not involve signal amplification, and exert their

effect on the virus, support the conclusion that the cell death of infected cells often exerts an antiviral defense and contributes to the early containment of infections.^{119–124} The understanding of the triggers of antiviral apoptosis remains unresolved and is complicated by the fact that both PRR-dependent and -independent mechanisms induce apoptosis during virus infections. The PRR-independent modes of induction of cell death during virus infections are within the overall category of cellular stress and include the depletion of anti-apoptotic proteins in infected

Table 1. Examples of MIMs and their dual control of viruses and PRR signaling

Category of effector mechanism	Viruses restricted	PRR pathways controlled ^a	Reference
Restriction			
SAMHD1 ^b	HIV-1, HSV-1, EBV, VACV, HBV	cGAS-STING, RLR-MAVS	Maelfait et al., ⁵⁴ Goldstone et al., ⁵⁸ Laguette et al., ⁵⁹ Hollenbaugh et al., ⁶⁰ Maharana et al. ⁶¹
TRIM7 ^c	CVB3, NoV	cGAS-STING, RLR-MAVS	Fan et al., ⁶² Yang et al., ^{63, 65} Luptak et al. ⁶⁴
SLFN5 ^b	HIV-1, HSV-1	IFN signaling (STAT1)	Ding et al., ⁶⁶ Kim et al., ⁶⁷ Arslan et al. ⁶⁸
Tetherin ^a	HIV-1, VSV, HSV-1, SARS-CoV-2	RLR-MAVS	Neil et al., ⁶⁹ Weidner et al., ⁷⁰ Blondeau et al., ⁷¹ Martin-Sancho et al., ⁷² Jin et al. ⁷³
MARCH2 ^c	HIV-1	RLR-MAVS	Chathuranga et al., ⁷⁴ Zhang et al. ⁷⁵
MARCH8 ^b	IAV, VSV, HIV-1	cGAS-STING	Tada et al., ⁷⁶ Villalon-Letelier et al., ⁷⁷ Yang et al. ⁷⁸
APOBEC3s ^a	HIV-1, HCoV-NL63, HBV, AAV	cGAS-STING	Stavrou et al., ⁵³ Sheehy et al., ⁷⁹ Milewska et al., ⁸⁰ Janahi and McGarvey, ⁸¹ Narvaiza et al. ⁸²
SIRT3 ^b	HCMV, AdV, IAV	NLRP3 inflammasome	Koyuncu et al., ⁸³ Liu et al. ⁸⁴
TRIM28/KAP1 ^b	HIV-1, ERVs	RLR-MAVS	Allouch et al., ⁸⁵ Jacobs et al., ⁸⁶ Tie et al. ⁸⁷
MORC3 ^b	ERVs, HSV-1	<i>IFNB1</i> gene transcription	Groh et al., ⁸⁸ Sloan et al., ⁸⁹ Gaidt et al. ⁹⁰
ZAP ^a	SINV, HCMV, JEV, HIV-1	RLR-MAVS	Kozaki et al., ⁹¹ Lin et al., ⁹² Chiu et al., ⁹³ Zhu et al. ⁹⁴
LL-37 ^c	RSV, IAV	AIM2 inflammasome; cGAS-STING	Currie et al., ⁹⁵ Tripathi et al., ⁹⁶ Dombrowski et al., ⁹⁷ Chiliveru et al. ⁹⁸
Surfactant protein D ^c	IAV, HIV-1, SARS-CoV-2	TLR4	Meschi et al., ⁹⁹ Hartshorn et al., ¹⁰⁰ Hsieh et al., ¹⁰¹ Yamazoe et al. ¹⁰²
UPF1, SMG5, SMG7 (NMD) ^c	SFV	<i>TNFA</i> and <i>IL6</i> mRNA stability	Balistreri et al., ¹⁰³ Mino et al. ¹⁰⁴
TMEFF1	HSV-1, HSV-2	–	Chan et al., ⁵² Dai et al. ¹⁰⁵
Succinate	IAV	RLR-MAVS	Guillon et al., ¹⁰⁶ Xiao et al. ¹⁰⁷
Lactate	HSV-1, HSV-2, HIV-1	RLR-MAVS	Isaacs and Xu, ¹⁰⁸ Tyssen et al., ¹⁰⁹ Zhang et al. ¹¹⁰
Autophagy			
	IAV, SARS-CoV-2, SINV, PoV, HSV-2, VZV	cGAS-STING, RLR-MAVS, NLRP3 inflammasome	Hait et al., ⁵⁰ Brinck Andersen et al., ⁵¹ Orvedahl et al., ¹¹¹ Prabakaran et al., ¹¹² Tal et al., ¹¹³ Nakahira et al., ¹¹⁴ Martin-Sancho et al., ¹¹⁵ Wang et al., ¹¹⁶ Gassen et al., ¹¹⁷ Heinz et al. ¹¹⁸
Cell death			
Apoptosis	VACV, DCV, SINV, IAV	cGAS-STING, RLR-MAVS	Chattopadhyay et al., ¹¹⁹ Kerr et al., ¹²⁰ Nainu et al., ^{121,122} Liu et al., ^{123,124} Rongvaux et al., ¹²⁵ White et al., ¹²⁶ Reinert et al., ¹²⁷ Huang et al. ¹²⁸

AAV, adeno-associated virus; AdV, adenovirus; AIM2, absent in melanoma; cGAS, cyclic GMP-AMP synthetase; CVB3, coxsackievirus B3; DCV, *Drosophila* C virus; EBV, Epstein-Barr virus; ERV, endogenous retrovirus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCoV, human coronavirus; HIV-1, human immunodeficiency virus 1; HSV, herpes simplex virus; IAV, influenza A virus; JEV, Japanese encephalitis virus; MAVS, mitochondrial antiviral-signaling protein; NLRP3, NLR family pyrin domain containing 3; NMD, nonsense-mediated decay; NoV, norovirus; PoV, poliovirus; RSV, respiratory syncytial virus; RLR, RIG-like receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFV, Semliki Forest virus; SINV, Sindbis virus; STING, stimulator of interferon genes; TLR, Toll-like receptor; VACV, vaccinia virus; VSV, vesicular stomatitis virus.

^aDirectly by inhibition of specific steps in the signaling pathways or indirectly through reduction of the level of PAMPs.

^bSignificant basal gene expression and further induction by type I/III IFNs (>3-fold, [Interferome.org](https://www.interferome.org)).

^cExpression not regulated by type I/III IFNs (<3-fold, [Interferome.org](https://www.interferome.org)).

antiviral activity without stimulating major inflammatory activities. In fact, several of these processes inhibit PRR activation and inflammation. Thus, the immediate antiviral response is fast, of modest potency, and non-disruptive. This response allows the elimination of modest-to-moderate immediate danger while protecting physiological activities.

IS LIMITING INFLAMMATION AN IMPORTANT PART OF THE EARLY RESPONSE TO INFECTIONS?

It is well described that immune responses must be controlled after microbes have been eliminated in order to avoid unnecessary tissue damage and to facilitate tissue repair. This process

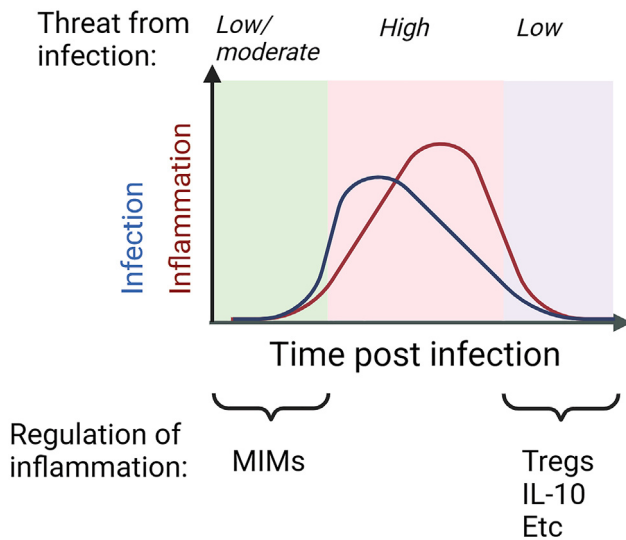


Figure 3. Regulation of inflammation as an important action to avoid immunopathology

Activation of inflammation by PRRs and antigen receptors is important to obtain effective immune responses when the fitness threat from the infection pathogen is high. However, inflammation can also cause pathology and must be tightly controlled. In the efferent phase of an immune response, this is mediated by multiple mechanisms including regulatory T cells (Tregs), interleukin 10, and a wealth of molecular negative feedback loops. It is not known how inflammation is regulated in the afferent phase, but we propose that this includes microbe- and inflammation-restricting mechanisms (MIMs).

encompasses a wealth of mechanisms, including regulatory T cells, interleukin 10, and molecular negative feedback loops¹⁵⁴ (Figure 3). The absence of these mechanisms can lead to immunopathology.¹⁵⁵ In contrast, it is much less well studied whether there are mechanisms in place imposing restriction, in the very early steps of the host interaction with microbes, on the induction of inflammatory activities, including the activation of PRRs. Inflammation is a very broad term and spans from subclinical beneficial activation of antimicrobial responses to lethal acute responses. What is important for the discussion in the present perspective is that the strong activation of acute inflammatory responses as well as prolonged low-/mid-grade activation of inflammatory responses cause pathology.

Based on several of the six points listed earlier, most notably the requirement for super-threshold levels of PAMPs for the activation of some PRRs,^{24,45,46} there are reasons to believe that there is a fitness gain by activating PRRs in a delayed manner. This idea is further supported by the identification of specific mechanisms through which host cells limit the activation of PRRs, as exemplified by the DNA-activated cGAS-STING pathway.^{156,157} For instance, STING is retained in the ER in an inactive state through its interaction with cholesterol, and cholesterol levels in the organelle are transiently reduced upon cGAS activation to allow STING ER-to-Golgi trafficking and activation.¹⁵⁷ Interestingly, deficiency in the gene NPC1 leads to low levels of cholesterol on the ER, and NPC1-deficient mice show constitutive activation of STING and develop neuroinflammation and disease.¹⁵⁸ These observations suggest that it is indeed

important to limit early inflammatory responses and maybe even to delay onset until the levels of microorganisms reach a threshold.

From an evolutionary standpoint, it can be asked whether limiting early innate immune responses provides fitness advantages only in higher and long-lived organisms and hence has emerged late in evolution. In this regard, it is interesting to note that the *Drosophila melanogaster* Myc protein and the catalytic peptidoglycan recognition protein exert negative regulation of the innate Imd pathway, and the absence of either leads to elevated early induction of Imd-driven gene expression and the loss of fitness in flies.^{159,160} Collectively, these data suggest that the loss of fitness due to immunopathology caused by early, excessive activation of PRR signaling is evolutionarily conserved. This, in turn, argues that multicellular organisms harboring PRRs and inflammation-sensitive physiological systems need to balance the PRR-driven responses to the level of threat posed by the invading microorganism.¹⁶¹ In support of this, *Drosophila* populations under strong parasite pressure have evolved to display high constitutively active humoral immune defenses.¹⁶²

GUARDING OF HOMEOSTASIS AS A BEARING PRINCIPLE IN EARLY RESPONSE TO INFECTIONS

From the discussion above, we propose that the governing principle in the very first cellular reactions to virus infections is to interfere with replication through mechanisms that do not disturb homeostasis (Figure 4A). We propose that this is exerted by the classes of mechanisms described above, which we collectively call microbe- and inflammation-restricting mechanisms (MIMs). MIMs exert antiviral activity through specific effector functions and also negatively regulate inflammatory activities. The idea of protection of homeostasis as a central principle in immune responses in general has been suggested in a previous work proposing that inflammation is a response to deviations from homeostasis.^{163–165} A panel of MIMs are listed in Table 1, including their dual control of both virus replication and PRR signaling as discussed in the section above.

The antiviral processes described in the previous section target viral replication in the infected cells without disturbing at the organism level. For instance, when restriction factors selectively target a given step in the virus replication cycle or when the proteasome degrades a viral protein, it does not globally disturb cellular balances and in fact eliminates a factor that could. Other processes do, in addition to the blockage of virus replication, specifically support the reestablishment of the steady-state conditions. For instance, autophagy eliminates dysfunctional mitochondria and protein aggregates.¹³³ Thus, these systems reestablish physiological equilibrium. This contrasts with PRR signaling, which induces inflammation and profoundly affects numerous processes that, in many cases, disturb physiological cellular activities. For instance, inflammation alters neuronal function and brain development.^{166,167} Inflammation also impairs tissue repair and wound healing,^{168,169} alters the electrolyte balance,^{170,171} and reduces body growth,^{172,173} particularly when systemic and chronic.

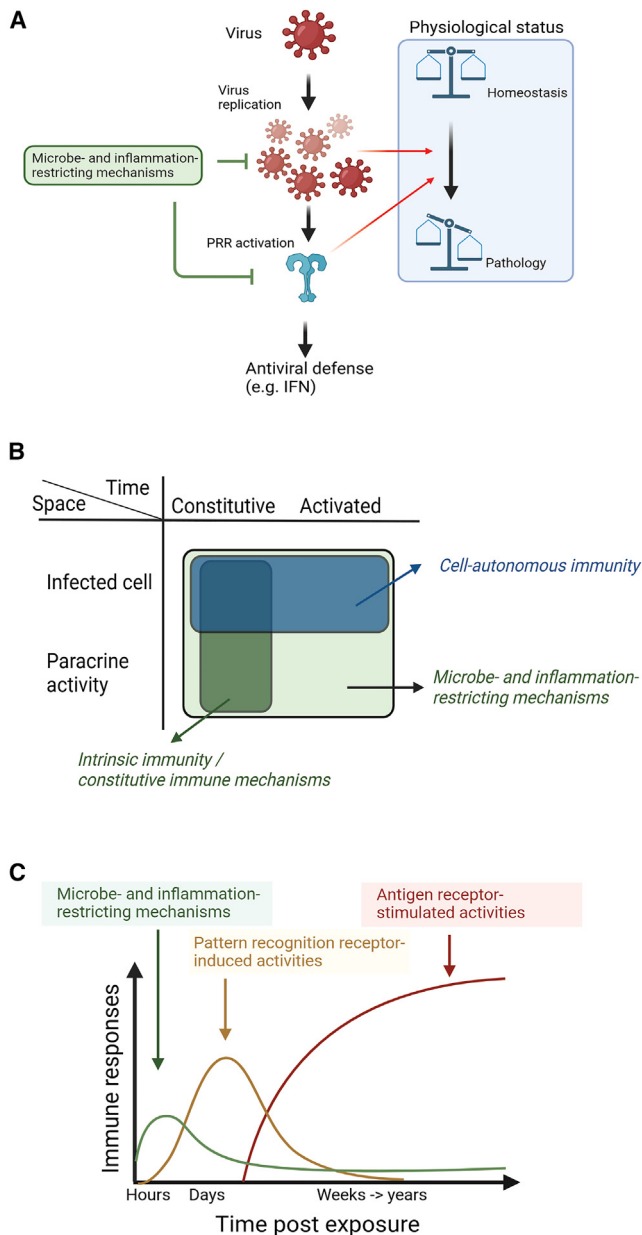


Figure 4. MIMs

(A) Microbe- and inflammation-restricting mechanisms (MIMs) exert homeostasis-protecting activity by blocking virus replication in a non-inflammatory manner and antagonizing PRR activation and activity.

(B) Illustration of the breadth of different proposed concepts in early host defense with respect to time and spatial distribution relative to the infected cell. Cell-autonomous immunity includes host defense mechanisms requiring only the individual infected cell, at the level of sensing and execution. Intrinsic immunity involves host defense mechanisms present at steady state and able to counteract infection without the requirement for infection-induced gene expression. We previously termed these constitutive immune mechanisms. MIMs include both of the above and hence include both constitutive and induced as well as both cell-autonomous and paracrine antimicrobial mechanisms.

(C) MIMs constitute the earliest cellular defense and form a barrier for infection and excessive inflammation. Second, the PRR-driven response gets induced

We propose that a MIM should fulfill all of the following criteria.

- (1) Exert antiviral activity independently of PRRs and antigen-specific receptors.
- (2) Respond to the presence of specific viral or cell-status-related molecules.
- (3) Eliminate virus through specific cellular effector functions that target defined structures or activities.
- (4) Eliminate virus in a non-inflammatory manner and, in some cases, directly limit PRR activation.

This means that MIMs are able to exert their antiviral action independently of the two main categories of immune receptors, as well as independently of IFNs. This can include both constitutive and induced antiviral effector mechanisms. At the same time, the MIMs have molecular specificity at the levels of both sensing and eliminating infection. This makes them clearly distinct from antiviral barriers imposed by physical and chemical mechanisms. Finally, the antiviral action of MIMs is direct and not associated with a cellular program evoking inflammation. Some MIMs will even have the capacity to directly limit PRR signaling and inflammatory activities. Consequently, proper action of MIMs counteracts excessive and prolonged activation of inflammation. As an example of how virus-restricting mechanisms can be evaluated against the MIM criteria, an IFN-induced restriction factor, like IFITM3, would fulfill criteria 2, 3, and 4^{174,175} but not criterion 1 and hence could not be classified as a MIM. Likewise, physical barriers like tight junctions would fulfill criteria 1 and 4 but not 2 and 3 and therefore also could not qualify as a MIM.^{176,177} By contrast, the restriction factors SAMHD1 and TRIM7, as well as the process of autophagy, fulfill all four criteria and thus can be classified as MIMs.^{50,51,54,58–61,111–118} The same is the case for the metabolite succinate, which exerts direct antiviral activity against IAV infection independently of PRRs through a molecularly defined mechanism¹⁰⁶ and directly blocks RIG-I-like receptor (RLR)-MAVS signaling.¹⁰⁷

We would like to add a specific note to criterion 4. Intuitively, many immunologists would assume that by simply limiting infection, PRR signaling would be suppressed. While this is certainly often correct and likely to explain the regulation of PRR activation and inflammation, there are several examples of this not being the case.^{178–180} Moreover, a number of restriction factors and death modalities with antiviral activity amplify immune activities through different mechanisms.^{142,181,182} Therefore, the link between a virus-restricting mechanism and inflammation is more complex than one may anticipate. On this basis, we find it worth including as a criterion for MIMs.

The power of a theoretical framework for a research field will ultimately be determined by its explanatory and predictive power. Based on the criteria above, we claim that if what we are proposing is correct, then the following predictions will also be correct.

and amplified, thus evoking more potent defense activities but also inflammation and co-stimulation of lymphocytes. Third, antigen-receptor-driven immune responses are activated with highly specific immune responses, memory, and inflammation.

- (1) Action of MIMs will enable elimination of infections without causing tissue damage.
- (2) Insufficient action of MIMs will impair early host defense and lead to elevated PRR-driven inflammation.
- (3) MIMs eliminate endogenous DAMPs, thus preventing immunopathology during steady state and limiting inflammation during sterile tissue damage.
- (4) Organs and cell types highly sensitive to immunopathology will have high activity of MIMs and rely much on these mechanisms to eliminate danger.
- (5) Body surfaces frequently exposed to invading pathogens have high activity of MIMs.
- (6) MIMs with dual antimicrobial and anti-inflammatory activity evolved with the emergence of PRRs and cellular immunity.
- (7) The action of MIMs decreases the delivery efficiency of several treatments, including gene therapy, oncolytic viruses, and some types of vaccines.

Future studies should examine the claims listed above. For instance, individuals with defects in MIMs or individuals infected with viruses evading these mechanisms would, according to our proposal, exhibit an elevated early viral load as well as accelerated and augmented inflammatory responses driven by PRRs. This has indeed been observed in a series of studies,^{52–54,62,105,183} although much remains to be done to determine the generality of this phenomenon.

HOMEOSTASIS GUARDING IN RELATION TO PREVIOUSLY PROPOSED THEORIES

Many of the immune mechanisms that we propose to form the early cellular barrier to virus infections are constitutively active, and we have previously reviewed this class of effector molecules in host defense.⁴ Here, we have nevertheless classified the immune activities into homeostasis-guarding versus disruptive, not constitutive versus activated. Although the difference between these two ways of classification may appear marginal, we do believe it allows for the inclusion of a panel of recently discovered inducible early antiviral mechanisms, which we now know control both viral replication and early inflammation (Figure 4B). Included in the homeostasis-guarding category, but not the constitutive category, we find, for instance, virus-induced responses through stress pathways, such as nuclear factor erythroid 2-related factor (Nrf2), bone morphogenetic protein (BMP), and hypoxia-induced factor (HIF) pathways.^{184–188} Similarly, the antiviral activity executed by induction of programmed cell death would not be included in the category of constitutive immune mechanisms,¹⁴² and we still do not know whether the antiviral activity of autophagy is mediated by the basal activity or the elevated autophagic response in infected cells.^{50,111} Prior to this work, several models for the first line of defense have been proposed.¹⁸⁹ This includes the concepts of intrinsic immunity and cell-autonomous host defense.^{8,9} Although they are both strong and with significant explanatory power, they have limitations. For instance, intrinsic immunity is very similar to the constitutive immune mechanisms described above⁴ and thus fails to include the stress-sensing antiviral

mechanisms, although there is now good evidence that they contribute to early control of infections in a non-inflammatory manner.^{121,184,185,188} Regarding cell-autonomous host defense, this theory centers exclusively on the individual cell and does not include paracrine antimicrobial activities such as antimicrobial peptides or the cell-cell transfer of metabolites. Guarding of homeostasis as a unifying principle for the early cellular defense against virus infections, exerted through the action of MIMs, includes all of the above models (Figure 4C) as well as the regulation of inflammation. Thus, we are of the opinion that it will provide a superior basis for further development toward a theory for early cellular antiviral defense.

It could be argued that MIMs are already included in the immune layer often described in immunology textbooks as “chemical and enzymatic barriers” or “complement and antimicrobial peptides/proteins.” However, while this conceptual framework for antimicrobial defense has significant explanatory power mainly for bacterial infections, it only poorly explains virus infections. In particular, it does not include the initial cellular defense reactions against virus infections. It should be emphasized though that we cannot exclude that MIMs and the antimicrobial actions of extracellular proteins over time can be conceptualized under a common framework. This will require more experimental data and an intense effort in scientific theory building.

As is always the case when attempts are made to rigidly categorize biological systems, classifications are not as black and white as proposed. In fact, interactions between theories are seen broadly in immunology, as illustrated, for example, by interactions between the immune responses driven by clonal selection and pattern-recognition-activated responses due to co-stimulation driven by PRRs. As such, theories in immunology are not incommensurable because even though they focus on distinct phenomena (e.g., lymphocytic receptors versus PRRs), the degree of integration of the different immunological compartments is so strong that most of the theoretical work consists of identifying phenomena of interest (here, early cellular antiviral defense), proposing general explanatory mechanisms (here, MIMs), and finally integrating both temporally and mechanistically different local theories into a comprehensive picture of the immune response. Below, we give a couple of examples of this in relation to the framework we are proposing. First, there are clear interactions and overlaps between MIMs and PRR-driven immune responses. Second, there are overlaps in effector functions used to exert antiviral activity. An example of this is restriction factors expressed at significant basal levels but further induced upon PRR activation or cytokine stimulation.^{190–193} Third, tonic signaling by the IFN-I receptor is believed to contribute to the basal level of resistance against infections and to setting the threshold for susceptibility to infections with a panel of viruses, including West Nile virus, IAV, HSV-1, SARS-CoV-2, and others.^{194–198} This immunological tone may in fact be driven by constitutive low-grade PRR signaling driven by microbiota, endogenous retroviruses, or endogenous immunostimulatory RNA species.^{195,197,199} Fourth, the function of a given biological process is context dependent and hence may change during the course of an infection. This is also the case for MIMs. For instance, while autophagy is both antiviral and exerts negative regulation of PRR signaling, it also promotes antigen presentation

by dendritic cells.¹³³ Likewise, while HIF1 α signaling induces early antiviral activity,^{188,200} it can also promote the differentiation of macrophages into proinflammatory M1 macrophages and shape the nature of the CD4⁺ T cell response.^{201,202} Finally, the metabolite succinate exerts direct restriction IAV replication but also promotes the aforementioned M1 macrophage differentiation.¹⁰⁶ These examples of “gray zones” for the idea we are proposing need to be explored in more detail, but it is tempting to speculate that some MIMs exert homeostasis-protecting activity in the early phases of an infection but can secondarily support disruptive immune mechanisms if activated over extended time periods.

REQUIREMENTS FOR CHANGE IN EXPERIMENTAL SYSTEMS WHEN CHANGING RESEARCH FOCUS

When exploring a new scientific question with a different focus than the one it originates from, several things have to be changed in the design of studies. This includes not least the experimental model systems, as results obtained in experimental science are highly dependent on the choice of relevant experimental systems. In the case of early cellular antiviral defense, there will, for instance, be a need to refine the animal infection models used. They will have to be modified to primarily use natural infection routes and, importantly, to be based on more physiologically relevant infection doses. In this regard, transmission models may become an important tool. Most models used today are based on high infection doses and biased toward uncovering phenomena in the realm of the pattern recognition and antigen receptor theories, which is not well adapted for a genuine understanding of early defenses. Second, human stem cell-derived organoid systems and *ex vivo* analysis of primary human cells will also be important to get in-depth knowledge on early virus-host interactions. At the level of discovery, the unbiased screening systems used will have to be designed to identify immediate host defense mechanisms. Interestingly, looking at the literature from the past 5–7 years, human genetics has proven to be the most powerful tool to uncover non-redundant immune mechanisms that seem to fall within the homeostasis-guarding hypothesis,^{47–50,52} followed by screens or systems biology approaches to identify viral immune evasions.^{185,188} We now start to see genome-wide and focused screens with viral replication as a readout also uncovering essential novel mechanisms fulfilling the MIM criteria.^{62,105,115} Finally, the exploration of MIMs should not be limited to highly pathogenic viruses. In fact, low- or non-pathogenic viruses may provide a strong discovery tool to identify cellular barriers that normally prevent these viruses from replication to high levels and cause disease. The recent identification of TMEFF1 as a neuron-specific restriction factor preventing the development of encephalitis by the common virus HSV-1 provides a good example of this.^{52,105} Exploring the explanatory power of MIMs to understand early antiviral defense will require even stronger integration between immunology, virology, and cell biology, and all this will benefit from including an evolutionary perspective.

CONCLUDING REMARKS

The early defense against invading pathogens is of great importance for the eventual outcome of infections, yet it remains

poorly explained. In this article, we argue that the pattern recognition theory cannot explain the early cellular defense against virus infections. Rather, we propose that the earliest line of cellular defense against viruses is mediated by a diverse set of mechanisms, which we call MIMs and which directly interfere with virus replication without causing inflammation and in fact, in many cases, inhibit PRR signaling. We propose that this initial immune repertoire has been selected through the evolution of multicellular organisms for its capacity to eliminate the infectious challenge without causing immunopathology. Many MIMs are constitutively expressed, whereas others are induced in response to cellular stress.

In the concluding remarks of “Approaching the asymptote? Evolution and revolution in immunology,” Charles A. Janeway described how the humoral immunology theory became so dominant that the role for cells in immunology was ignored for a long time.¹² This was changed by the work of Landsteiner and the clonal selection theory by Burnet.^{11,203} Later, the clonal selection theory dominated immunology so much that scientists in the field did not give much attention to immunological mechanisms based on other principles. This again was profoundly changed by the pattern recognition theory proposing pathogen sensing by signaling germline-encoded receptors.¹² It may be time to add that the innate immunity field, which developed from the pattern recognition theory, focused so much on the non-clonal aspect and direct pathogen recognition that we have collectively tended to overlook the fact that PRR activation leads to inflammatory responses that have the potential to compromise fitness and also that PRRs are often expressed at low levels in the resting state and require amplification loops to get fully activated. We believe the early host cellular defense actions to infections are an important part of the inner workings of the immune system, driven by principles that can be conceptualized. This seems to be an important, unexplored frontier in immunology.

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AUTHOR CONTRIBUTIONS

S.R.P. conceived the idea behind the article. S.R.P., A.P., J.G.M., D.O., and T.H.M. examined the literature and each contributed with essential input to the analysis of the field. S.R.P. and T.P. formulated the ideas about theory change, and K.B.W. provided input from a philosophy-of-science point of view. The idea was extensively discussed and revised by all authors. S.R.P. wrote the first draft, and all authors contributed to finalization. The revision was led by S.R.P., with input from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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