Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Antiviral Innate Immunity: Introduction

Friedemann Weber, FB 10 – Institute for Virology, Justus Liebig University Giessen, Giessen, Germany

Glossary

Apoptosis A form of programmed cell death.
Apoptotic bodies Remnants of cells which underwent apoptosis.
Complement system A pathogen-triggered cascade of biochemical reactions involving more than 20 soluble and cell-bound proteins. Complement activation results in opsonization, priming of humoral immune responses, and perforation of membranes.
Cytokines Proteins which mediate cell–cell communication related to pathogen defense. Secreted by immune cells or tissue cells.
Innate immunity Physical and chemical barriers, cells, cytokines, and antiviral proteins which exclude, inhibit, or slow down infection with little specificity and without much adaptation or generation of a long-lasting protective memory.
Interferons (IFNs) Cytokines mediating antiviral activity. Distinguished into type I (IFN-α/β), type II (IFN-γ), and type III (IFN-λ). Type I and type III IFNs directly mediate antiviral activity in responding cells, whereas type II IFN is more immunomodulatory.
Interferon-stimulated response element (ISRE) A promoter element common to all type I IFN-stimulated genes.
Opsonization Tagging of infected cells or pathogens for destruction by phagocytic cells.
Pathogen-associated molecular patterns (PAMPs) Molecular signatures of pathogens used by the innate immune system to distinguish self from non-self. Often highly repetitive patterns.
Pattern recognition receptors (PRRs) Intracellular and extracellular receptors recognizing specific PAMPs.
Phagocytosis Uptake of particles by cells.

Introduction

Viruses attempting to conquer a mammalian body are faced with an impressive array of hurdles. "Innate immunity" in a wider sense comprises all sorts of factors which exclude, inhibit, or slow down infections in a rapid manner but with little specificity and without adaptation or generation of a long-lasting protective memory. Many of these efficient and not at all primitive defenses are evolutionarily old and can be found in all metazoans. For the sake of brevity, however, the discussion in this article is mostly restricted to mammals. RNA interference, the innate immune system of plants and non-vertebrates, is not covered.

Mammalian innate immune defenses against virus infections can be divided into several distinct parts such as mechanical and chemical barriers (not further mentioned here), defensins, complement system, phagocytic/cytolytic cells of the immune system which act in a nonspecific manner, and cytokines.

Defensins

Defensins are small, cysteine-rich cationic, amphipathic peptides with broad activity against bacteria, fungi, and viruses. They are produced by immune cells and skin and mucosal epithelial cells, and are present on epithelia and in body fluids. On top of their constitutive expression levels, defensin genes can be induced by viral infection. Their most common antimicrobial function is the formation of destructive pores in membranes of pathogens including enveloped viruses. Defensins can however also block infection by enveloped and non-enveloped viruses alike by aggregating the particles, blocking receptor binding, inhibiting virus entry, particle uncoating or intracellular trafficking, interfere with essential cell signaling or viral gene expression, or act by other, ill-understood mechanisms. Moreover, besides these direct antiviral activities, defensins were shown to attract immune cells and modulate adaptive immune responses. Since defensins activities are mostly studied in cell culture, it is thought that their immunomodulatory action is currently underestimated.

Complement System

The complement system (which "complements" the adaptive immune system in the defense against pathogens) primes the adaptive immune response and is also directly effective against pathogens. Complement activation is achieved by specific receptors recognizing pathogens or immunocomplexes. Three different pathways are being distinguished which are termed the classical pathway (triggered by antigen–antibody complexes), the mannan-binding lectin pathway (triggered by lectin binding of pathogen surfaces), and the alternative pathway (triggered by complement factor C3b-coated pathogen surfaces). They all activate a cascade of reactions involving more than 20 soluble and cell-bound proteins, thus resulting in a rapid and massive response. The

complement system is able to (1) tag infected cells and pathogens for destruction by phagocytic cells (opsonization), (2) prime humoral immune responses, and (3) perforate membranes of infected cells by the membrane-attack complex. In response, viruses have evolved effective countermeasures such as incorporation of cellular complement-regulatory proteins into particles or expressing specific inhibitors in infected cells.

Cellular Innate Immunity

Macrophages/monocytes, granulocytes, neutrophils, natural killer cells, and dendritic cells belong to the cellular branch of the innate immune system. Monocytes circulate in the bloodstream for several hours before they differentiate into macrophages. These potent phagocytic cells either continue patrolling or they permanently settle in particular tissues (i.e., the Kupffer cells of the liver), being able to rapidly remove viral particles and apoptotic bodies. Activated macrophages also synthesize inflammatory cytokines such as IFN-γ and tumor necrosis factor (TNF)-α, thus triggering an adaptive immune response. Granulocytes are also able to remove viral particles and apoptotic bodies by phagocytosis. They are rapidly attracted to inflammatory sites and enter the tissue by transendothelial migration. Both macrophages and granulocytes cleave the ingested viral proteins into fragments and present them to T lymphocytes. Neutrophils (polymorphnuclear cells) are also phagocytosing pathogens, among other directly acting activities. Their most fascinating ability is however the release of neutrophil extracellular traps (NETs), which are networks of proteins and chromatin that immobilize and inactivate extracellular pathogens. Natural killer (NK) cells are able to recognize infected cells in an antigen-independent manner and destroy them by their cytotoxic activity. Also, they rapidly produce large amounts of IFN-γ to activate the adaptive immune system. NK cells are regulated by a fine balance between stimulatory and inhibitory receptors. One of their prominent features is their ability to destroy cells which lack MHC I molecules on their surface. As many viruses downregulate MHC expression in order to avoid an adaptive immune response, NK surveillance represents an important early warning and attack system against virus infections.

A key connection between the innate and the adaptive immune system is provided by dendritic cells (DCs). These specialized immune cells sample antigen at the site of infection, activate themselves and the surrounding tissue cells by cytokine synthesis, and then migrate to secondary lymphatic organs in order to mobilize T cells against the presented antigen. The differentiation of DCs into efficient antigen-presenting cells (APCs) is achieved by cytokine production which, in turn, is triggered by stimulation of receptors recognizing pathogen-specific molecular patterns (PAMPs). Two main types of DCs are being distinguished: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). mDCs are an early split-off of the myeloid bone marrow precursors, that is, the stem cells which are also at the root of macrophage/monocyte and granulocyte differentiation, among others. Depending on the location, several subsets of mDCs such as Langerhans cells (residing in epidermis and epithelia) or interstitial cells are being distinguished. pDCs, which are not segregated into subpopulations, are derived from lymphatic precursor cells, that also generate the B and T cells, for example. Both mDCs and pDCs can sense viral infection by several intra- and extracellular PAMP receptors (see below). Depending on the DC type, high levels of interleukins or IFNs are being produced which coin the subsequent immune reaction. pDCs are potent producers of the antiviral type I IFNs.

Antiviral Cytokines: The Type I Interferons

Isaacs and Lindenmann discovered in 1957 that cells which had been in contact with inactivated virus particles secrete a soluble factor which confers cellular resistance to influenza viruses, a phenomenon called “interference”. In the subsequent years, it became more and more clear that the so-called type I IFN (encompassing IFN-β and a set of IFN-α subtypes) system is our primary defense mechanism against viral infections. In fact, humans with genetic defects in the IFN signaling pathway have a bad prognosis as they die at an early age of viral diseases which would otherwise pose little problems. Similarly, knockout mice with a defective type I IFN system quickly succumb to viral pathogens of all sorts although they have an intact adaptive immune system.

In response to virus infection, pDCs are particularly well equipped to synthesize and secrete IFN-α/β, but in principle all nucleated cells are able to do so. In an autocrine and paracrine manner, IFNs trigger a signaling chain leading to the expression of genes for potent antiviral proteins which limit further viral spread. In addition, IFNs initiate, modulate, and enhance the adaptive immune response. The signaling events which culminate in the direct IFN-dependent restriction of virus growth can be divided into three steps, namely (1) transcriptional induction of IFN synthesis, (2) IFN signaling, and (3) antiviral mechanisms.

New Kids in the Gut: The Type III Interferons

Type III IFNs (IFN-λs), a relatively recent discovery, are distinct antiviral cytokines with many features in common with type I IFNs. IFN-λ1, -λ2, and -λ3 are induced by virus PAMPs and normally signal through the JAK/STAT cascade, but use a separate receptor. They are able to activate expression of interferon-stimulated genes (ISGs) and have been shown to inhibit replication of viruses. However, whereas all nucleated cells express the receptor for type I IFNs, the type III IFN receptor is limited to epithelial cells on mucosal barriers. IFN-λs are therefore important for limiting the infection and transmission by respiratory and gastrointestinal viruses. Moreover, while type I IFN signaling activates ISG expression in a fast, strong and transient manner, type III IFN signaling is characterized by a weaker,

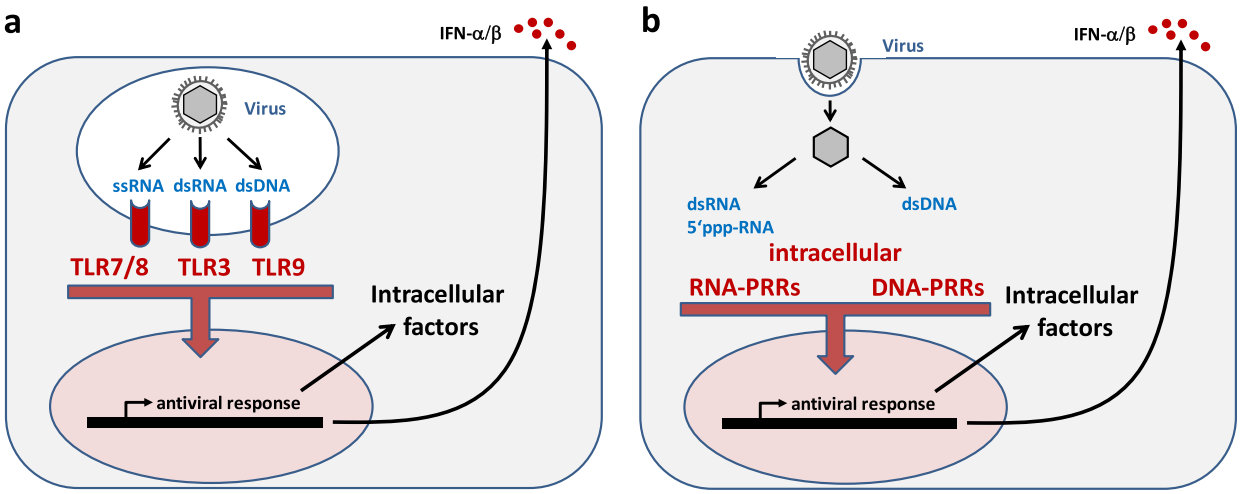

Fig. 1 Depending on the virus, ssRNA, dsRNA, 5′ppp-RNA, dsDNA, or combinations thereof represent characteristic by-products of infection (i.e., PAMPs) which are recognized by PRRs to induce production of antiviral IFN-α/β and intracellular factors with antiviral or regulatory function. The viral PAMP signature molecules are recognized in the endosome by TLRs (a), and after entry into the cytoplasm by intracellular PRRs (b).

delayed, but longer-lasting ISG response. Besides the direct antiviral effect mediated by ISGs, IFN-λs are stimulating adaptive immune responses. Interestingly, type III IFNs are also responsible for the elevated immunogenicity of live attenuated vaccines as compared to inactivated vaccines, since only the former are triggering IFN-λ production. Thus, IFN- λs are complementing the IFN response by conferring a lasting, local protection at anatomical sites which are most exposed to viral intruders.

Interferon Induction

Nucleic acids are the main PAMPs of viruses, being recognized by a number of pattern recognition receptors (PRRs) to initiate induction of IFN genes (see Fig. 1). Classes of virus-triggered PRRs can be divided into the endosomal toll-like receptors (TLRs) and various intracellular (mostly cytoplasmic) receptors. It is thought that the TLRs can be activated by viral nucleic acids that had been released from virus particles (or endocytosed remnants of infected cells) that were dissolved by the endosomal low pH and/or degradative enzymes. Major PAMPs are double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), 5′-triphosphorylated (ppp) RNAs, and double-stranded DNA (dsDNA). dsRNA and 5′ppp-RNA are underrepresented in uninfected cells, thus predestining them as a immunorelevant markers of non-self. In the case of ssRNA and dsDNA, it is thought that unusual locations (e.g., endosome or cytoplasm for DNA), a lack of cell-typical modifications (e.g., methylation), or specific secondary structures are responsible for triggering antiviral responses. Moreover it should be noted that a full-blown infection converts the heterogeneous population of cellular nucleic acids into a pool of largely homogeneous, highly abundant viral RNAs and/or DNAs. Thus, immunogenicity could also be caused by over-representation of uniform RNA or DNA species.

dsRNA is an almost ubiquitous by-product of virus infection that is sensed by a multitude of PRRs. In the endosome it is recognized by the TLR3, and in the cytoplasm by the RNA helicases RIG-I and MDA-5 (collectively termed RIG-I-like receptors, RLRs) and the protein kinase PKR. Substantial amounts of dsRNA are produced by viruses with a positive-strand ssRNA or with a dsRNA genome (e.g., coronaviruses or reoviruses, respectively) during genome transcription and replication. For DNA viruses (e.g., Herpes viruses or poxviruses), it is thought that dsRNAs are formed either by hybridization of read-through transcripts from promoters on opposite DNA strands, or from secondary structures present on particular viral RNAs. Viruses with a negative-strand ssRNA genome (e.g., influenza virus) are unique in that they do not produce substantial amounts of long dsRNA, since their genome and antigenome RNAs are always encapsidated by viral nucleoprotein. In the cytoplasm, their genomes are recognized by RIG-I in a 5′-triphosphate-dependent manner. In addition a short dsRNA region, formed by the annealing of complementary 5′ and 3′ ends of the RNA genome (the so-called "panhandle"), is essential for RIG-I to be activated.

Viral ssRNAs can be recognized in the endosome by TLR7 and -8.

The third important PAMP, viral dsDNA, is again recognized both by an endosomal receptor, TLR9, and a series of intracellular receptors such as e.g., IFI16, DDX41, RNA polymerase III, and cGAS. dsDNA recognition by RNA polymerase III actually represents a crosstalk between the RNA-PRRs and the DNA-PRRs, since the polymerase transcribes viral DNA into 5′ppp-dsRNA which then activates RIG-I. A similar second messenger principle is realized by cGAS (cGAMP synthase) which produces cyclic di-GMP-AMP (cGAMP) molecules in response to cytoplasmic dsDNA. cGAMP, in turn, activates the adapter protein STING (stimulator of interferon genes) and hence downstream antiviral signaling.

Besides nucleic acids, some viral proteins can provoke a TLR response such as the envelope proteins of respiratory syncytial virus and measles virus by activating TLR4 and TLR2, respectively.

All PRRs are triggering signaling chains (with partial crosstalk and usage of common adapters and kinases) which canonically culminate in activation the IFN regulatory factor (IRF) -3, the general immune-regulatory transcription factor NF-κB, and the stress-activated transcription factor AP-1. In cooperation, they upregulate IFN gene expression. This leads to a "first wave" of IFN production (IFN-β and IFN-α4 in mice) which triggers the expression of the transcription factor IRF-7. IRF-7 is a master regulator of IFN gene expression cooperating with IRF-3 for full activity. IRF-7 can be activated in the same way as IRF-3 and is responsible for a positive-feedback loop that initiates the synthesis of several IFN-α subtypes as the 'second-wave' IFNs.

While all cells with a nucleus are thought to be equipped with the set of intracellular PRRs, expression of TLRs is more restricted to epithelial and immune cells. mDCs, for example, can sense dsRNA by the classic intracellular RLR pathway and, in addition, by TLR3. pDCs sense the presence of viral ssRNA or dsDNA by TLR7, TLR8, and TLR9 to transcriptionally activate multiple IFN-α genes. This broad and strong IFN induction is due the presence of constitutively expressed IRF-7 in pDCs, which enables them to bypass the dependency on IRF-3 and to directly launch a "second-wave"-like IFN response. IRF-7 is further upregulated in response to IFN and generates a positive-feedback loop for high IFN-α and IFN-β production. Furthermore, TLR7 and TLR9 are retained in the endosomes of pDCs to allow prolonged IFN induction signaling.

Type I IFN Signaling

IFN-β and the multiple IFN-α subspecies activate a common type I IFN receptor (IFNAR) which signals to the nucleus through the so-called JAK–STAT pathway (Fig. 2). The signal transducer and activator of transcription (STAT) proteins are latent cytoplasmic transcription factors which become phosphorylated by the Janus kinases JAK1 and TYK2. Phosphorylated STAT1 and STAT2 recruit a third factor, IRF9, to form a complex known as IFN-stimulated gene factor 3 (ISGF3) which translocates to the nucleus and binds to the IFN-stimulated response element (ISRE) in the promoter region of ISGs.

The collective term "ISGs" implies a common, uniform mode of regulation. In fact, however, there are three different classes of ISGs, first of all those classical ones responding to IFN signaling (STAT dependent), those responding either to IFN signaling or to PRR activation by PAMPs (universal ISGs), and those that exclusively respond to PRR activation (IRF dependent). The latter ones are not ISGs in a proper sense (but often called so), since they are stimulated by infection rather than by IFN. Moreover, for some ISGs regulation can differ between animal species or between cell types, and by far not all ISGs are entirely characterized with respect to the ISG class they belong to.

Direct Antiviral Effects of Type I IFNs

Type I IFNs activate the expression of several hundred STAT dependent ISGs of which only a fraction has been studied in great detail. Well characterized examples with broad antiviral activity are the 2′–5′ OAS/RNaseL system, protein kinase R (PKR), RNA-specific adenosine deaminase 1 (ADAR1), ISG20, IFN-induced tetratricopeptide repeat (IFIT) protein 1, the Mx proteins, viperin, and tetherin. 2′–5′ OAS and PKR are constitutively expressed in normal cells in a latent, inactive form. Basal mRNA levels are upregulated by IFN-α/β and these enzymes need to be activated by viral dsRNA. The 2′–5′ OAS catalyzes the synthesis of short 2′–5′ oligoadenylates that activate

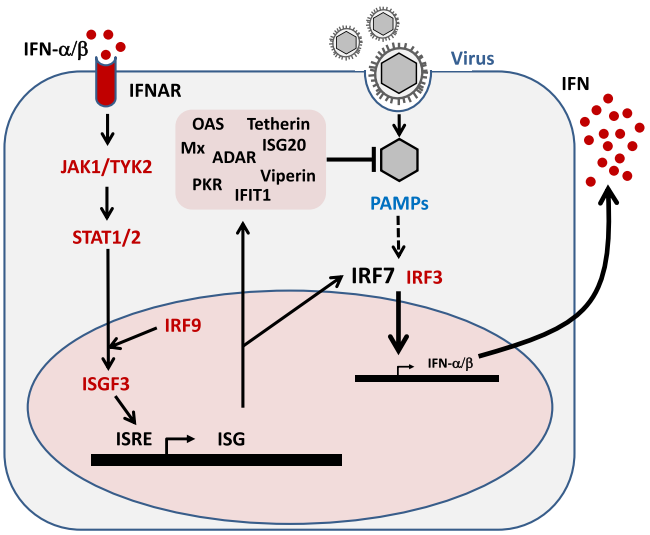

Fig. 2 IFN-α and IFN-β bind to the type I IFN receptor (IFNAR) and activate the expression of numerous ISGs via the JAK/STAT pathway. OAS, ISG20, Mx, ADAR, PKR, Tetherin, Viperin and IFIT1 are examples of proteins with antiviral activity. IRF-7 amplifies the IFN response by upregulating PAMP-dependent expression of several IFN subtypes.

the endoribonuclease RNaseL. RNaseL, an ISG in most species (humans are an exception expressing it constitutively), degrades viral and cellular RNAs. PKR is a serine-threonine kinase that phosphorylates – among other substrates – the α-subunit of the eukaryotic translation initiation factor eIF2 to block translation of cellular and viral mRNAs. PKR also plays a role in virus-induced NF-κB activation, as described above. ADAR1 catalyzes on viral dsRNAs the deamination of adenosine to inosine. As a result the secondary structure is destabilized due to a change from an AU base pair to the less stable IU base pair, and the accumulating mutations are hampering viral replication. Recent research showed that ADAR1 is important to suppress the formation of dsRNA structures by endogenous Alu retroelements. In ADAR1-deficient animals, endogeneous RNAs are not edited, and the arising dsRNAs activate the PRRs MDA5 and PKR, leading to chronic IFN induction, inhibition of mRNA translation, and eventually autoimmunity. ISG20 is on one hand an exonuclease that degrades viral ssRNA, but in the other hand it was recently found to downmodulate translation of non-self mRNAs in an RNAse-independent manner. IFIT1 is expressed at extremely high levels after IFN stimulation or PRR signaling and sequesters viral RNA with a 5′ppp end or an unmethylated cap. Mx proteins are enwrapping viral nucleocapsids, thus preventing the viral polymerase from elongation of transcription. Viperin (Radical S-adenosyl methionine domain containing 2, RSAD2) is an enzyme that converts the nucleotide CTP to a chain terminator for viral RNA-dependent RNA polymerases. Tetherin (bone marrow stromal cell antigen 2; BST2) is a transmembrane protein able to restrict the release of enveloped virus particles from the plasma membrane.

The antiviral profiles of the IFN effectors listed above are distinct but often overlapping. Mx proteins, for example, mainly inhibit segmented negative-strand RNA viruses and also Semliki Forest virus, whereas the 2′–5′ OAS/RNaseL system appears more important against positive-strand RNA viruses. Moreover, only rarely the presence of one particular IFN effector explains host resistance. Rather, it is the sum of antiviral factors affecting, for example, genome stability, genetic integrity, transcription, and translation that confers the full antiviral power of IFN.

Indirect Antiviral Effects of Type I IFNs

Besides the effector proteins listed above, several ISGs contribute in a more indirect manner to the enhancement of both innate and adaptive immune responses. Virus-sensing (and in part antiviral) PRRs such as TLR3, PKR, RIG-I, and MDA5 are by themselves upregulated in an IFN-dependent manner. Similarly, IRF-7 and and STAT1, the key factors of type I IFN and ISG transcription, respectively, are ISGs. The strong positive-feedback loop mediated by the upregulation of these PRRs and transcription factors is counterbalanced by several negative regulators (e.g., LGP2, SOCS, PIAS), which are either ISGs or depend on IFN signaling for their suppressive action.

Type I IFNs can directly enhance clonal expansion and memory formation of CD8 + T cells. Also, IFNs promote NK cell-mediated cytotoxicity and trigger the synthesis of other cytokines such as IFN-γ or IL-15 which modulate the adaptive immune response, enhance NK cell proliferation, and support CD8 + T-cell memory. Moreover, by upregulating TLRs, MHCs, and costimulatory molecules, IFNs enable APCs (most prominently DCs) to become competent in presenting viral antigens and stimulating the adaptive immune response.

Innate Immunity Memory

Since long, the lack of any type of memory is used as a feature distinguishing innate from adaptive immunity. It became meanwhile clear, however, that IFNs can reprogram cell responses by leaving epigenomic signatures on promoters, mostly by post-translational modifications of histones. This memory-like mechanism can last for weeks, and explains the long-known phenomenon of "priming", i.e., that a first small shot of IFNs is potentiating the effect of a second IFN treatment. A phenomenon related to priming is "innate immunity training". Here, prior inflammation or infection enhances a second innate response and inflammation, again via changing epigenenomic signatures.

Tonic IFN Levels

Although the classical model outlined above depicts that PRR-triggered upregulation of IFN-β starts from level zero, at least at barrier tissues basal levels of IFN expression are maintained constantly. This "tonic" IFN expression is thought to be a reaction to commensal bacteria, and primes the organism for rapidly reacting to pathogenic invaders.

Viral Counterstrategies

Given the massive direct and indirect antiviral effects of type I IFNs, it comes as no surprise that viruses had evolved efficient countermeasures. In fact, most viruses investigated so far were found to actively inhibit either IFN induction, IFN signaling, antiviral ISG action, or combinations thereof. A common strategy to avoid IFN induction seems to be the targeting of treacherous dsRNA or 5′ppp structures by binding, modifying, or degradation through viral factors, the so-called IFN antagonists. Moreover, many viral features such as encapsidating genomic RNA by nucleoprotein (negative-strand RNA viruses), hiding replication

complexes in intracellular membrane compartments (positive-strand RNA viruses) or multiple protein sheets (dsRNA viruses), as well as replicating in the nucleus (orthomyxoviruses) can be regarded as passive strategies to minimize generation and exposure of PAMPs to PRRs. Active strategies include sequestration or degradation of key factors of antiviral signaling like PRRs, kinases, IRFs, STATs or even RNA polymerase II itself. The bundle of these measures, i.e., the individual anti-IFN profile of a particular virus, can represent a major marker for host range, cell tropism, and virulence. Weak anti-IFN capabilities can render a virus unfit in a given host, whereas strong IFN suppression enables productive replication. Fine-tuning the IFN antagonistic activities may allow the adaption to optimal host-to-host transmission. Depending on the particular transmission mode and host population density, either massive, damaging viremia (like e.g., for arthropod- or aerosol-transmitted pathogens) or lower-level, locally restricted or chronic infection (e.g., herpes, papilloma or hepatitis C viruses) are positively selected for. In the case of the persistent infections, long-term production of IFN can even be beneficial for the virus as it results in an immunosuppression aimed at limiting immunopathology. Thus, the balance and timing of activation versus suppression of the IFN response can determine the outcome of infection, ranging from a straight fending off (host wins by early antiviral IFN action) to acute disease (virus wins by suppressing early IFN action) to chronic viral disease (constant IFN levels maintain infection by suppressing immune responses). In any case, the simple equation: strong IFN antagonism = virulent virus, weak IFN antagonism = harmless virus, should be applied with some caution.

Good Cop–Bad Cop

Given their massive impact on the cellular gene expression profile, it is quite expected that type I IFNs have not only antiviral, but also antiproliferative and immunomodulatory effects. Treatment with IFNs is an established therapy against several viral and malignant diseases such as hepatitis B, hepatitis C, Kaposi's sarcoma, papillomas, multiple sclerosis, and several leukemias and myelomas. However, the strong and systemic effects of IFNs do not come without a price. Administration of IFN can locally produce inflammation, and systemically cause fever, fatigue, malaise, myalgia, and anemia. It is no coincidence that these latter are "flu-like" symptoms, since in many acute infections IFNs play a dominant role. The effects of IFN which are desired and beneficial if restricted to the site of first infection can turn into a life-threatening "cytokine storm" if it becomes systemic. Severe acute respiratory syndrome (SARS) and human infections with H5N1 influenza viruses are examples of such out-of-control innate immune responses. Moreover, long-term and high IFN levels are facilitating persistent infections, as discussed above, and IFN therapy can aggravate autoimmune disorders. Another "dark side" aspect is the so-called interferonopathies. Patients with mutated PRRs or IRFs exhibit type IFN gene expression signatures and are prone to autoimmune diseases. Chronic production of IFNs causes maturation of mDCs, which in turn activate autoreactive T and B cells.

Concluding Remarks

The concept of innate immunity certainly comprises more than the IFN system (see above), but type I and type III IFNs represent a central part. These cytokines not only have direct antiviral effects but also orchestrate the first defense reactions and the subsequent adaptive immune response, thus determining the course of infection. The fact that basically every virus appears to have evolved one or several countermeasures for controlling the IFN response is testament to its importance. In addition, IFNs are not only antiviral, but also effective tumor suppressors. Tumor cells often eliminate the IFN system during the transformation process. The payoff is an increased susceptibility to infection, an Achilles heel which is exploited by the therapeutic concept of oncolytic viruses. Tumor selectivity of such viruses can be even more increased by using IFN-sensitive mutants. The inability of those mutants to fight the IFN response is complemented by the mutations of the tumor cells, thus allowing virus growth. At the same time, these viruses are unable to infect the IFN-competent healthy cells.

Cells had to cope with viruses since the early days in the primordial pond. No wonder innate immune responses are so astonishingly multi-faceted, consisting of a wide array of cells, signaling chains and effector molecules solely dedicated to the elimination of infectious intruders. Viruses are the most abundant biological entities on earth, but most accidental contacts are not even noticed by us. Only those viruses which had evolved tailor-made counterstrategies can break through and establish infection for long enough to be multiplied and transmitted further. The innate immune system may be old, but as long as there are viruses (and tumors), it will never come out of fashion.

Further Reading

Ablasser., A., Hur, S., 2019. Regulation of cGAS- and RLR-mediated immunity to nucleic acids. Nature Immunology 21, 17–29.
Barrat, F.J., Crow, M.K., Ivashkiv, L.B., 2019. Interferon target-gene expression and epigenomic signatures in health and disease. Nature Immunology 20, 1574–1583.
Holers, V.M., 2014. Complement and its receptors: New insights into human disease. Annual Review of Immunology 32, 433–459.
Reizis, B., 2019. Plasmacytoid dendritic cells: Development, regulation, and function. Immunity 50, 37–50.
Schmid, S., Mordstein, M., Kochs, G., García-Sastre, A., Tenoever, B.R., 2010. Transcription factor redundancy ensures induction of the antiviral state. Journal of Biological Chemistry 285, 42013–42022.
Schoggins, J.W., 2019. Interferon-stimulated genes: What do they all do? Annual Review of Virology 6, 567–584.

Versteeg, G.A., García-Sastre, A., 2010. Viral tricks to grid-lock the type I interferon system. Current Opinion in Microbiology 13, 508–516.
Wilson, S.S., Wiens, M.E., Holly, M.K., Smith, J.G., 2016. Defensins at the mucosal surface: Latest insights into defensin-virus interactions. Journal of Virology 90, 5216–5521.
Ye, L., Schnepf, D., Staeheli, P., 2019. Interferon-λ orchestrates innate and adaptive mucosal immune responses. Nature Reviews Immunology 19, 614–625.