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Decoding the complexity of type I interferon to treat persistent viral infections

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Abstract

Type I interferons (IFN-I) are a broad family of cytokines that are central to the innate immune response. These proteins have long been appreciated for the critical roles they play in restraining viral infections and shaping antiviral immune responses. However, in recent years there has been increased awareness of the immunosuppressive actions of these proteins as well. While there are many current therapeutic applications to manipulate IFN-I pathways we have limited understanding of the mechanisms by which these therapies are actually functioning. In this review we highlight the diversity and temporal impact of IFN-I signaling, discuss the current therapeutic uses of IFN-I, and explore the strategy of blocking IFN-I to alleviate immune dysfunction in persistent virus infections.

Keywords

type I interferon; persistent; virus; LCMV; immunosuppression; therapy; immune activation; HIV

Type I Interferon: a broad family of antiviral cytokines

Type I interferons (IFN-I) are one of the body's primary defense systems against all varieties of viral infection. In order to accomplish this incredible feat, IFN-I signaling has evolved astonishing diversity and redundancy. Intracellular pattern recognition molecules efficiently detect the presence of viral genomes and replication products and in turn elicit the production of IFN-I. Multiple types of nucleic acid sensors can be involved and different cellular populations can recognize virus in unique ways[1]. This is the first level in which diversity of IFN-I responses is generated. For example, nearly all somatic cells are equipped with caspase recruitment domain (CARD) containing sensors such as retinoic acid inducible gene-I (RIG-I) and melanocyte differentiation antigen 5 (MDA5) molecules in the cytosol [2, 3]. These recognition molecules translate the presence of viral nucleic acids to the expression of one specific type of IFN-I, IFNβ, via adaptor molecules and the transcription factor interferon regulatory factor 3 (IRF3) in response to direct infection[4]. On the other

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hand specific subsets of immune cells are able to detect virus, even when they themselves are not infected, via the expression of pattern recognition molecules [such as toll like receptors (TLR)] that in turn stimulate robust IFN-I responses [1].

Once the virus is sensed there is another level of diversity in the species of IFN-I that is produced. The IFN family consists of seven classes in total, best understood are the 13 subtypes of IFNα and the single IFNβ protein, but interferon K, ω, ε, δ and τ are also present [5]. Although the entire cytokine family signals through a single dimeric receptor, IFNAR, there is evidence that individual subtypes of IFN-I can differentially interact with the IFNAR1 or IFNAR2 subunits, potentially resulting in unique downstream effects[6]. For example, IFNα species with high affinity for IFNAR2 trigger enhanced antiviral activities[7] Further, IFNβ has recently been described to associate and signal through IFNAR1 independent of IFNAR2, suggesting a potentially elevated potency of IFNβ [8]. IFNAR itself lacks intrinsic signaling ability and canonically relies on association with janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins to enact the expression of interferon stimulated genes (ISGs)[6]. Signaling is again diversified at this level via the potential activation and dimerization of multiple different STAT molecules. IFNAR receptor ligation typically autophophorylates TYK2 and Jak1 resulting in the activation of STAT1, 2, 3, or 5 [9]. However, in certain cell types STAT4 and STAT6 can also be phosphorylated in response to IFNα signaling [10, 11]. Activated STATs then associate with one of nine different IRF proteins to activate common and non-overlapping gene expression profiles [12]. IFN-I can also activate 'alternative' signaling pathways such as MAP kinase, PI3-kinase and others further diversifying responses to this family of cytokines [13]. The end outcome of IFN-I signaling is the activation of more than 300 ISGs with active antiviral and immunomodulatory functions [14, 15]. These multiple levels of diversity in the IFN-I system allow for the integration of various signals within the immune and cellular environment to modulate and tailor the IFN response to control the pathogen at hand. Understanding the specific integration of signals at play in any given disease state will be critical to deciphering how the activation of a single cytokine system can lead to the control of diverse pathogens, and importantly, will be critical for developing targeted therapeutic manipulation of IFN-I to treat diverse types of disease.

Multiple downstream effects of IFN-I: pushing and pulling the immune response

IFN-I were initially characterized in 1957 for their ability to interfere with viral infection of chicken chorioallantioc membranes [16]. However, in the 50+ years since, our knowledge of the direct antiviral roles of these proteins as well as their ability to modulate both innate and adaptive immunity has blossomed. Some of the most prominent antiviral ISGs downstream of the IFNAR code for the proteins *Mx1* and the double stranded RNA-activated enzymes: protein kinase (PKR) and 2′–5′Oas [15]. Mx proteins bind directly to critical viral components to inhibit their functions [17] whereas PKR and OAS interfere with viral replication via blockade of cellular transcription and protein synthesis machinery [18, 19]. These genes are so powerfully induced by IFN-I that their expression (along with other IFN-I inducible genes) is often used as a gauge of IFN-I signaling in multiple disease and infectious states and is cumulatively referred to as the 'interferon signature'[20–22]. While genetic deficiencies in any single one of these proteins confers increased susceptibility to infections, some residual antiviral activity remains in animals ablated for all three pathways indicating that additional antiviral mechanisms are stimulated by IFN-I[23]. Supplementary to direct antiviral effects, IFN-I also modulate the innate and adaptive immune response to pathogens[24, 25]. IFN-I can dictate the immune environment both through signaling directly to immune cells or indirectly via alteration of the cytokine and chemokine milieu. IFN-I plays a critical role *in*

vivo in the expansion of CD4 T cell responses[26] and the maturation and maintenance of CD8 T cell responses both directly, and indirectly via enhancement of antigen presenting cells (APC)[27–29].

Yet, IFN-I effects are not unconditionally positive and there are also many immunoregulatory and even immunosuppressive actions of this cytokine [30]. For example, IFN-I signals the expression of the immunoregulatory cytokine IL-10 in flu infection to dampen T cell responses and restrict immunopathology[31]. Similarly, therapeutic IFNβ treatment of patients with multiple sclerosis leads to increased levels of IL-10 as well enhanced expression of PDL1 on monocytes allowing for the silencing of autoreactive T cell responses[32, 33]. The immunoregulatory effects of IFN-I signaling have likely evolved to preserve homeostasis within the immune system and the organism overall, but how this incredible diversity of downstream effects of IFN-I signaling is coordinated and the specific triggers guiding distinct effects is not fully understood. Ultimately, a molecular and cellular understanding of how to elicit a specific outcome of IFN-I signaling would be invaluable to truly harness IFN therapeutically in a targeted and perhaps disease specific manner.

Intervening with IFN-I in the clinic

Given the incredibly pleiotropic nature of IFN-I, it is perhaps not surprising that amplifying and interfering with this pathway has been attempted therapeutically in a number of diverse disease indications (Figure 1). A majority of the IFN-I intervening drugs on the market involve boosting levels of the cytokine, however blocking antibodies to IFN have been humanized and are currently in clinical trials[34, 35]. Interestingly, IFN-I administrated after an acute viral infection is not particularly effective[36, 37]. While it has been tested in several clinical trials of respiratory infections, the overall consensus is that the side effects (such as nosebleeds) preclude use of IFN-I therapy clinically for acutely resolved respiratory infections[36, 37]. Interestingly, these studies demonstrate that IFNα2a given prophylactically can prevent respiratory infection, although it is ineffective if given therapeutically. This suggests that in situations where the body will naturally overcome the infection, late treatment with IFN-I may not further enhance endogenous IFN-I effects.

In the case of persistent infections, therapeutic administration of IFN-I can be highly effective in some situations. Recombinant IFNα treatment has been used clinically in hepatitis C virus (HCV) infection for more than 20 years[38]. HCV is a persistent viral infection that can lead to severe fibrosis and cirrhosis of the liver [38]. The current standard of care for HCV involves administration of pegylated IFNα2b in combination with the antiviral drug Ribavirin [38]. However, in as many as 60% of patients, this regime is ineffective at eradicating HCV infection[38]. In fact, how IFN-I treatment leads to clearance of HCV is not entirely apparent. In the many patients that respond to IFNα therapy, the direct antiviral properties are presumably responsible for the quenching of viral titers. However, some patients fail to have a sustained virologic response following IFNα and Ribavirin treatment. While there are probably many reasons for this treatment failure, one common characteristic of patients that fail therapy is an initially heightened IFN-I signature prior to the onset of treatment that fails to substantially increase with therapy [20, 39]. These data indicate that once a certain level of IFN-I signaling is reached it is not further heightened by adding more IFNα and suggest that in these situations cells, or subsets of cells, encountering chronic IFN-I may react differently (or not at all) to more IFN-I. Further, it remains to be determined how IFN-I affects the system in cases where viral clearance is not attained and particularly whether IFN-I boosting is detrimental and enhances immunosuppression and immune dysfunction. These diverse outcomes for a common signal shed light not only on the tight balance between the antiviral and the immune inhibitory effects of IFN-I during virus

infections, but also on the value of assessing the basal IFN signature of patients prior to initiation of any therapeutic treatment that manipulates IFN-I levels [22].

IFNα has also shown some efficacy in reducing viral titers in certain situations of HIV infection[40]. Combination antiretroviral therapy (cART) is highly effective in reducing HIV titers and partially resurrecting the immune system of infected individuals[41]. However in many cases IFN-I signatures remain elevated even in patients who respond to cART[41]. In the absence of cART, IFNα treatment alone cannot limit viral replication,[42] although this treatment can continue to restrain viral replication in a cohort of patients with suspended cART therapy[40]. Similar to the situation in HCV infection, the chronic IFN-I signaling in HIV may limit or alter the effect of IFN therapies. cART suppression of viral replication may allow the immune system to overcome refractiveness to IFN-I signals and refresh responsiveness of the system to the beneficial effects of IFN-I. Mechanistically understanding why IFNα treatment alone fails to control HIV, differential pathways activated by IFN-I in the cART treated and untreated patients, and what physiologic parameters are improved by cART that facilitate IFNα efficacy will be critical to design successful IFN intervening therapies for HIV.

It is not only persistent virus infections that can be therapeutically impacted by IFN-I treatment. Multiple doses and formulations of IFNα have been used to treat and control many types of cancers including leukemia and melanoma [43, 44]. Potentially many of the pleiotropic effects of IFN-I could play a role in the treatment of these diseases, including direct inhibition of angiogenesis and tumor proliferation, as well as enhancement of anti-tumor immune responses[44]. A recent appreciation for the role of host IFN-I production in the efficacy of radiation treatment has revealed a role for IFN-I in enhancing dendritic cell priming of anti-tumor CD8 T cell responses[45]. IFN-I therapy in melanoma to suppress remnant metastasis is most successful in patients with recently removed tumors, while the efficacy of these drugs in advanced disease states is quite poor [43]. While this is hypothesized to be the result of immune skewing towards a Th2 profile[43], it is also possible that the advanced disease state results in chronic levels of IFN signaling that trigger immunosuppression similar to what is observed in persistent virus infections. Further, the dosage of IFN-I used in cancer applications is significantly higher but temporally shorter than in cases of viral disease, which may favor the anti-proliferative cytostatic effects of IFN-I [46].

So far all the clinical applications of IFN-I that have been discussed have attempted to exploit the immune stimulatory effects of IFN-I. However, in the case of multiple sclerosis (MS), a progressive inflammatory disease of the central nervous system that is commonly treated with recombinant IFNβ therapy, the immunoregulatory effects of IFN-I are likely critical[47–49]. IFNβ therapy for MS has been in use since 1993 and has proven effective in preserving blood brain barrier integrity, delaying instances of disease relapse, and improving cognitive function [50]. As is the case in most clinical manipulations of IFN-I, the mechanisms by which IFNβ is acting to relieve MS are unclear. Although no consensus has been reached, studies have implicated immunomodulatory effects of IFNβ as critical to disease relief[30]. One study identified an ability of IFNβ to reduce proteolytic enzymes that destroy blood brain barrier integrity[47]. Other studies highlight the ability of IFNβ to dampen the expression of immunostimulatory cytokines[48, 49] and to trigger immunosuppressive factors (most notably IL-10 and PDL1)[51, 52]. Thus, the suppressive aspects of IFN-I that hinder control of one disease are in other situations highly beneficial. A comparative analysis of IFN-I in these systems, could lead to understanding of how the suppressive and stimulatory mechanisms are engendered and can be specifically targeted and harnessed therapeutically.

Blocking IFN-I to control persistent LCMV infection and the potential implications for effective anti-HIV therapy

Recently, two independent laboratories have demonstrated that anti-IFNR1 antibody blockade quenches immune activation and immunosuppression and facilitates clearance of persistent lymphocytic choriomeningitis virus (LCMV). Anti-IFNR1 administration resulted in (i) reduced chronic inflammation; (ii) restoration of immune cellularity [i.e., increased dendritic cells (DC), macrophages, NK cells, B cells, CD4 and CD8 T cells]; (iii) enhanced survival and/or maintenance of CD4 T cells; (iv) increased IFNγ expression/ potency; (v) maintenance of lymphoid tissue architecture (vi) and reduced expression of multiple factors and cell types that inhibit antiviral immunity (e.g., PDL1, IL-10, suppressive DC[53, 54]), indicating that IFN-I signaling drives many of the immune dysfunctions and suppressive mechanisms associated with persistent virus infections. In addition to the negative effects, the antiviral aspects of IFN-I are sustained, indicating that the positive and negative mechanisms of IFN-I signaling are simultaneously present (Figure 2).

Unlike IFNAR−/− mice that never control LCMV infection[51, 52, 55], transient antibody blockade of the IFNAR initiated at the onset or during established persistent LCMV infection reversed these immune dysfunctions and diminished the immunosuppressive program, ultimately leading to enhanced control of the persistent infection. Mechanistically, this enhanced control upon inhibiting IFN-I signaling is likely multifactoral: improved cellular interactions (both spatially in the organized tissue and compositionally with the type of APC present, combined with decreased suppressive signals, diminished levels of chronic inflammation, and elevated levels and potency of pro-inflammatory factors, likely work in conjunction to facilitate the accelerated control of persistent LCMV infection. Yet, how persistent LCMV infection is specifically controlled upon IFN-I blockade is not clear since enhancement of the two main effector mechanisms that directly eliminate virus infection (i.e., virus-specific CD8 T cells and antibody) were not observed. Further, the precise mechanisms that stimulate IFN-I signaling throughout the course of persistent infection (i.e., after the initial burst of IFN-I in the first few days of infection); how IFN-I differentially induce antiviral, immunostimulatory and immunosuppressive functions; and ultimately, the downstream mechanisms IFN-I target to potentiate viral persistence are still unknown. These are active areas of research that should lead to important insights into the host-based mechanisms underlying viral persistence and a better understanding of how anti-IFNR1 therapy might be harnessed clinically.

Acute and persistent LCMV infections initially trigger robust IFN-I responses that are quantifiable in the circulation and decrease 3–4 days post infection[56]. This acute decrease in IFN-I has been suggested to facilitate persistence by prematurely ceasing the antiviral control of more aggressive viruses and consistent with this notion, exogenous addition of IFN-I or genetic enhancement of IFN-I at the onset of infection augments control of an otherwise persistent LCMV infection[56, 57]. However, administration of IFN-I once persistence has been established does not decrease virus titers[56], again corroborating the highly complex temporal nature of IFN-I signaling toward modulating the immune response and controlling virus replication of non cytopathic viruses. On the other hand, the immune system has a stringent requirement for IFN-I signals to contain cytopathic viruses that are themselves capable of inducing severe pathology, throughout the course of infection. [58]. As a result, a major concern of any type of therapeutic strategy aimed to inhibit IFN-I activity is enhanced susceptibility to, or reactivation of, cytopathic viruses that in the absence of IFN-I containment become life-threatening. This is a critical caveat that must be heavily weighed and closely monitored in interferon blocking therapies.

HIV is in many ways a disease of immune activation (reviewed in[59, 60]). Unchecked immune activation in HIV is associated with multiple immunologic dysfunctions, including aberrant T cell activation, dysfunctional B cell responses and polyclonal B cell activation, alterations in innate immune capacity, disruption of lymphoid architecture and increased morbidity and mortality from HIV and co-infecting pathogens (reviewed in [59–61]). While the root cause of this elevated activation state is still unknown, IFN-I is emerging as a key component [62]. In fact, there is quite a bit of correlative evidence that reduced IFN-I signals would benefit disease outcome in persistent infections such as HIV. For example, although African green monkeys and rhesus macaques both develop persistent SIV infections, SIV infection rarely causes AIDS in African green monkeys, whereas rhesus macaques progress to AIDS similarly to HIV infected humans[21, 63, 64]. A major difference between these infections is the lack of a sustained IFN-I gene expression signature in the African green monkeys that is seen in rhesus macaques during SIV infection[21, 63, 64]. A similar dichotomy in IFN-I signaling is observed between HIV progressors and long-term non-progressors[65] (although this may be an effect of decreased HIV titers as opposed to a cause of the non-progressor phenotype). Further, strategies that indirectly[66–69] or directly[70, 71] target IFN-I show indications of decreased immune activation and immunosuppressive factors. Given that HIV infection results in life-long viral persistence and chronic IFN-I signaling [59, 60] it is enticing to extrapolate the results of the LCMV studies toward the mechanisms of HIV persistence and the roles of IFN-I as an underlying mechanism of disease progression.

These studies expose the duality of IFN-I signaling: possessing the capacity to simultaneously drive antiviral and immune stimulatory functions while also inducing many of the suppressive factors associated with persistent virus infections (Figure 2)[51, 52]. The positive and negative effects of IFN-I signaling are simultaneous, but may have temporal importance with the antiviral and immune enhancing impact being dominant early but giving way at later time points to dominance of the detrimental effects of chronic IFN-I stimulation (although it is important to note that the antiviral effects of IFN-I are still ongoing throughout the infection[52]). Understanding how the temporal reaction to IFN-I is mediated is perplexing, but could be due to a variety of changes in the immune response as persistent infection progresses, including alterations in the cell types present, how cells react to IFN-I in the context of other factors present in the later stages of infection and/or switches in IFN-I subtypes produced-- to name a few. This constant enhancement and repression of the immune response during persistence undoubtedly manifests both directly and indirectly and likely with weighted differences in different cell types. However, if the mechanisms that distinctly drive the positive and negative effects of IFN-I signaling can be uncoupled, then it may be possible to maintain the antiviral and immune stimulatory effects IFN-I while inhibiting the suppressive effects. Further, as multiple immunosuppressive factors are driven by IFN-I in persistent infection, blocking IFN-I signaling could simultaneously abrogate these signals at their root while also diminishing the chronic activation that continually wears down the already over-stimulated immune response..

Given that IFN-I signaling is critical to control virus infection, its blockade may foster secondary virus infections or enhance pathology of cytopathic viruses. Recent Phase I trials using an IFNAR blocking antibody in patients with systemic sclerosis [35] or an antibody directed at IFNα in systemic lupus erthematosus[72] did not report any increased incidence of infection[73], at least over the relatively short period of study (3 months). Yet, the possibility of enhanced of susceptibility to secondary viral infections upon IFN-I blockade particularly in HIV infection (i.e., an already debilitated immune environment) should be closely monitored.

Concluding remarks

The incredibly pleiotropic effects of IFN-I necessitate fine-tuning of potential therapeutic agents. Although we have extensive knowledge of the diversity of signaling pathways activated by IFN-I, the links between specific pathways and discrete outcomes are not well understood (Box 1). For example, at this time we cannot dissect the specific signal transduction events that lead to expression of immunosuppressive molecules versus the expression of antiviral molecules, or immune enhancing pathways. Further, we do not fully understand the individual contributions of different IFN-I family members and if they can be targeted to prevent specific aspects of IFN-I signaling (e.g., inhibit the IFN-I types that drive the suppressive functions of IFN-I while preserving those that mediate the antiviral and immune enhancing effects). Such an achievement would be an important advancement over blocking the entire IFN-I system (i.e., the IFNAR) and as such, should be thoroughly explored in persistent virus infection.

Box 1

Outstanding questions

- What is the IFN signature in any given disease state?
- How are specific effects of IFN signaling driven? What are the individual contributions of different IFN-I subtypes toward IFN-I signaling diversity and how do the various IRF and STAT molecules that are recruited coordinate distinct signaling outcomes?
- What are the most important mechanisms restored by blocking IFN-I that allow for control of persistent infection and what are the critical mechanisms of IFN-I signaling that should be retained?

While many correlates of immune dysfunction have been demonstrated between LCMV and HIV, the role of IFN-I in HIV immune dysfuntion is not yet clearly defined. Therefore, whether blocking IFN-I will similarly enhance immune function and allow for control HIV infection remains to be seen. Further, low-level chronic immune activation (potentially in part mediated by IFN-I signaling) is ongoing in many patients with cART suppressed HIV replication[41]. In this situation, IFN-I blockade may be useful to halt ongoing immune deterioration. Ideally, an understanding of when to enhance and when to block the IFN-I pathway will facilitate the translation of this exciting therapeutic concept into clinical reality.

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HIGHLIGHTS

- Type I interferons (IFN-I) underlie many of the immune dysfunctions associated with persistent virus infection.
- IFN-I simultaneously have critical antiviral and immunomodulatory functions during viral persistence.
- Blocking IFN-I in a mouse model enhanced the immune response to control persistent virus infection.
- Therapeutically interfering with IFN-I signaling could help treat multiple disease states.

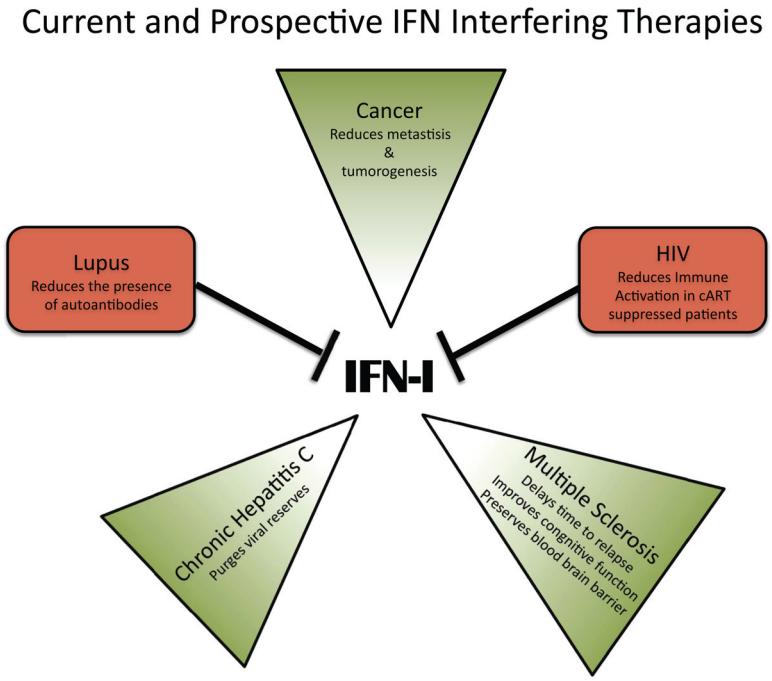

Figure 1. Select current and prospective IFN-I interfering therapies

Multiple IFN-I interfering drugs are currently available in the clinic with many more in the pipeline. A majority of IFN-I therapies are aimed at amplifying IFN-I signals (depicted in green); however, prospective therapies blocking IFN-I (red) are emerging. While the precise molecular mechanisms of action are unknown in most cases, the effects of IFN-I therapies in several disease indications are indicated.

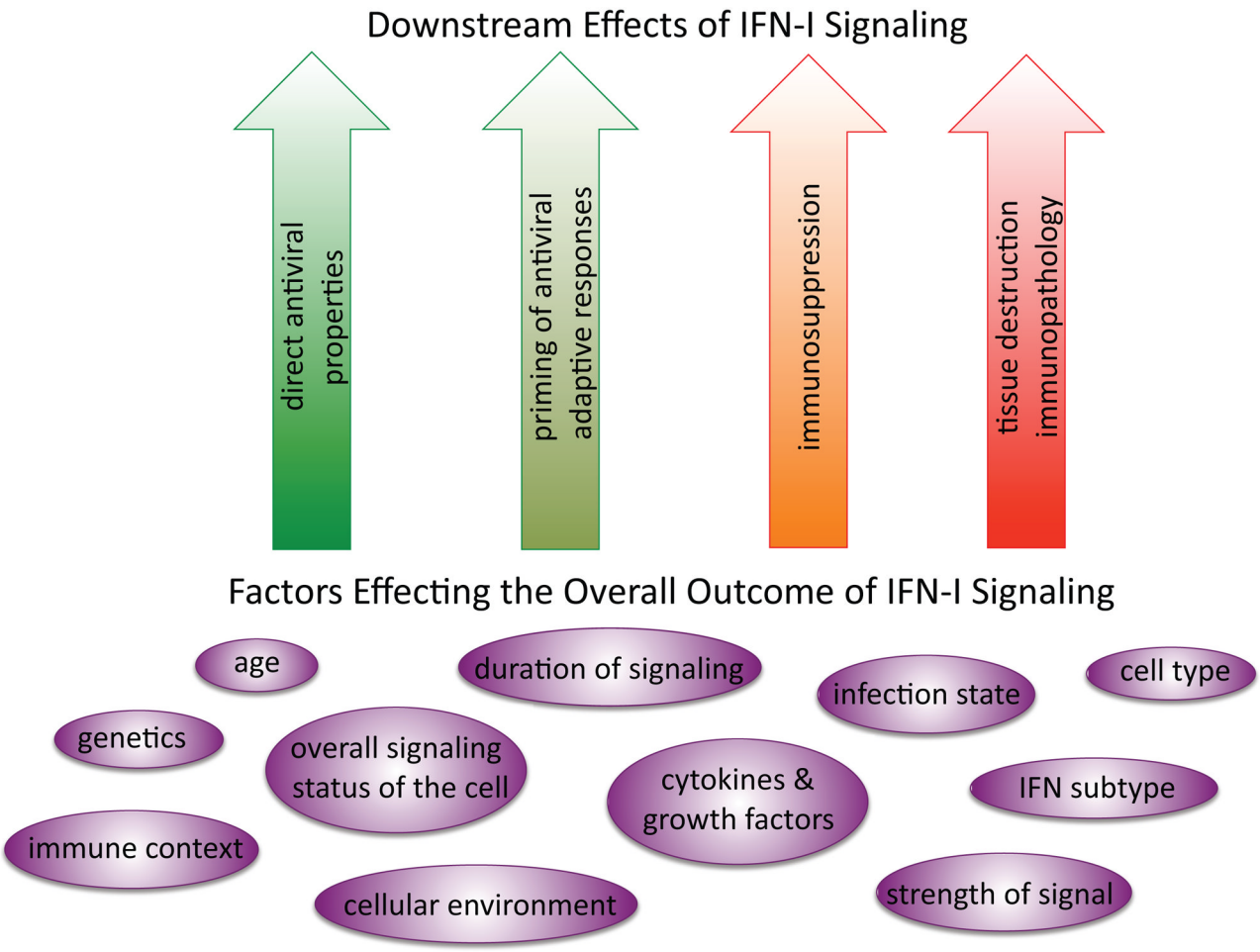

Figure 2. Factors affecting the outcome of type I interferon signaling

Throughout the course of viral infection IFN-I is simultaneously driving antiviral and pro-immune pathways (shown in the green arrows) in addition to the expression of immunosuppressive factors and immunopathology (shown in the red arrows). The end outcome of IFN-I signaling is likely determined by a multitude of factors working in concert, a portion of which are indicated in purple. In the course of a normal infection this is necessary to both control initial viral replication while adaptive immunity is ramping up, and to dampen antiviral immune responses when the virus has been cleared. However, when virus replication is able to persist in the face of IFN-I responses, the antiviral and immune enhancing impact of IFN-I are retained, but for reasons that are currently unclear, the suppressive mechanisms become dominant leading to many cellular and tissue dysfunctions associated with persistent virus infections.