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REVIEW

Interferons and beyond: Induction of antiretroviral restriction factors

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Abstract

Antiviral restriction factors are structurally and functionally diverse cellular proteins that play a key role in the first line of defense against viral pathogens. Although many cell types constitutively express restriction factors at low levels, their induction in response to viral exposure and replication is often required for potent control and repulse of the invading pathogens. It is well established that type I IFNs efficiently induce antiviral restriction factors. Accumulating evidence suggests that other types of IFN, as well as specific cytokines, such as IL-27, and other activators of the cell are also capable of enhancing the expression of restriction factors and hence to establish an antiviral cellular state. Agents that efficiently induce restriction factors, increase their activity, and/or render them resistant against viral antagonists without causing general inflammation and significant side effects hold some promise for novel therapeutic or preventive strategies. In the present review, we summarize some of the current knowledge on the induction of antiretroviral restriction factors and perspectives for therapeutic application.

KEYWORDS
innate immunity, viral pathogens, cytokines, antiviral state

1 | INTRODUCTION

In order to replicate and spread efficiently in their respective hosts, viruses exploit a large number of cellular factors.[1,2] Consequently, elimination of so-called dependency factors that are essential for viruses is emerging as a new therapeutic strategy.[3–5] Accumulating evidence also demonstrates, however, that cells actually represent a hostile environment for viral replication. The reason for this is that innumerable past encounters with pathogens have driven the evolution of specific cellular antiviral proteins, which are referred to as restriction factors.[6] Restriction factors are structurally and functionally diverse, cell-intrinsic proteins that often target common viral components, such as the membrane or the viral genome, or render the cellular environment non-permissive for viral replication. Thus, they are frequently active against viruses belonging to different families.[7] Because of this enormous functional and structural diversity and because many cellular proteins exert antiviral effects under specific experimental conditions, it is a challenging task to clearly define the criteria for a "real" restriction factor.[8,9] For the sake of simplicity, we broadly apply this term to intrinsic cellular factors reported to display antiviral activity in the present review.

Antiviral restriction factors can be constitutively expressed and active in some cell types. Thus, they have the potential to protect their host against invading pathogens without previous encounters or induction. Examples are the multipass transmembrane proteins serine incorporator (SERINC)3 and SERINC5, which have recently been identified as inhibitors of retroviral infectivity.[10,11] They are active at basal expression levels and, in contrast to most other restriction factors, lack any apparent inducibility by IFNs or other stimuli.[10,11] These

Abbreviations: APOBEC, apolipoprotein B mRNA editing catalytic polypeptide-like; ART, antiretroviral therapy; CCR, CC chemokine receptor; CD, cluster determinant; CDK1, cyclin-dependent kinase 1; cGAS, cyclic GMP-AMP synthase; CRISPR, clustered regularly interspaced short palindromic repeat; EBI3, Epstein-Barr virus-induced gene 3; Env, envelope; FIV, feline immunodeficiency virus; GAS, IFNγ activation site; GAF, IFNγ activation factor; GBP5, guanylate-binding protein 5; HCV, hepatitis C virus; HMM, high molecular mass; HPV, human papillomavirus; HHV, human herpesvirus; iDC, immature monocyte-derived dendritic cell; IFITM, IFN-induced transmembrane protein; IFNAR, IFNα/β receptor; IRF, interferon regulatory factor; ISGF, IFN-stimulated gene factor; ISG, IFN-stimulated gene; ISRE, interferon stimulated response element; LMM, low molecular mass; LTR, long terminal repeat; L-Trp, L-tryptophan; MDM, monocyte-derived macrophage; Mx, myxovirus-resistance protein; NFAT, nuclear factor of activated T cells; OAS, 2′-5′-oligoadenylat synthetase; PAMP, pathogen-associated molecular pattern; PBMC, peripheral blood mononuclear cell; PRR, pattern recognition receptor; RIG-I, retinoic acid inducible gene I; RT, reverse transcription; SAM, synergistic activation mediator; SAMHD1, SAM domain and HD domain-containing protein 1; SDF-1, stromal cell-derived factor 1; SERINC, serine incorporator; sgRNA, single guide RNA; SIV, simian immunodeficiency virus; SPTBN1, spectrin beta non-erythrocytic 1; TF, transmitted/founder; TNFα, tumor necrosis factor α; TRIM5α, tripartite motif-containing protein 5; Vif, virus infectivity factor; VLP, virus-like particle; ZAP, zinc-finger antiviral protein; ZFN, zinc finger nuclease

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factors may affect viral spread as the ability of the accessory viral protein Nef to counteract SERINC5 correlates with the reported prevalence of simian immunodeficiency viruses (SIV) in their respective host.[12] In fact, although restriction factors are often poorly effective against well-adapted viruses due to effective mechanisms of evasion and/or counteraction, they seem to play an important role in protection against viral cross-species transmission.[13] The reason for this is that these cellular factors are typically under high positive selection pressure for change, either to become resistant against viral antagonists or to gain activity against newly emerging pathogens.[6] To exert their full antiviral potential, however, many restriction factors must be upregulated and/or activated as part of the immune response to invading pathogens.[13–15]

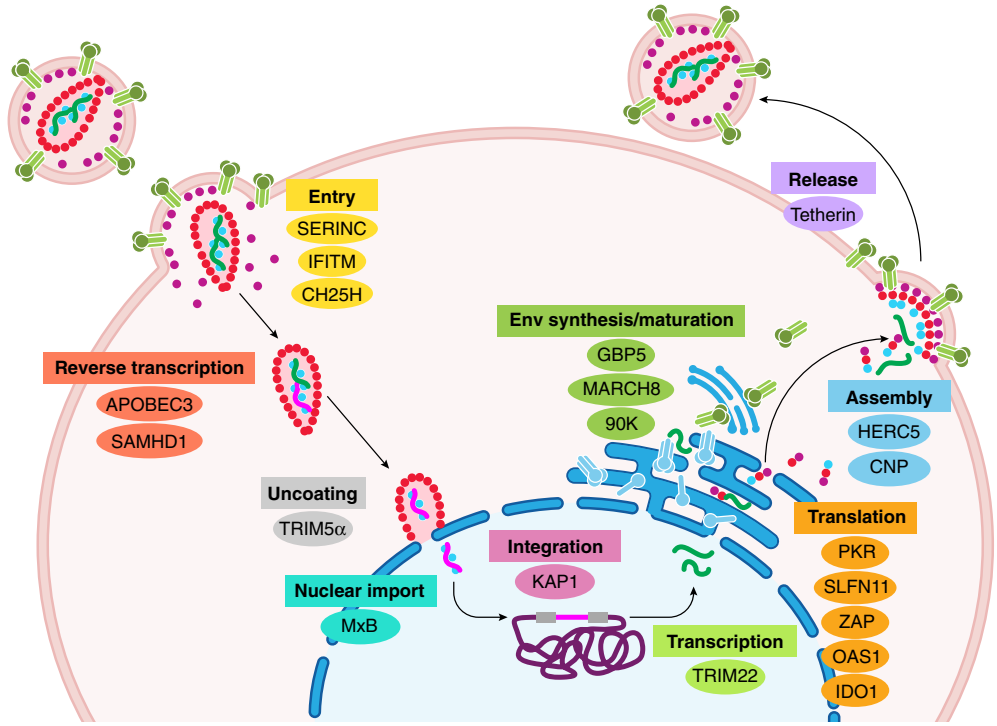
Innate immune responses are activated through the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) that induce antiviral defense mechanisms and also alert and shape adaptive immune responses. In addition to the classical PRRs, such as toll-like receptors (TLRs) and retinoic acid inducible gene I (RIG-I)-like receptors or the cytosolic DNA-sensor cyclic GMP-AMP synthase (cGAS), also restriction factors, such as tetherin and tripartite motif-containing protein 5 (TRIM5α), might sense viral PAMPs and activate antiviral signaling cascades.[16–18] PRR-induced signaling cascades converge at a few key transcription factors, that is, NF-κB and interferon regulatory factor (IRF)3/7 that induce the expression and secretion of IFNs and other inducible pro-inflammatory cytokines. Upon binding to their cognate receptors on virally infected as well as uninfected bystander cells, type I IFNs induce the expression of hundreds of IFN-stimulated genes (ISGs), including a variety of antiviral restriction factors.[19] As outlined below, accumulating evidence shows that also other classes of IFNs, various cytokines and cellular activation levels modulate the expression and activity of antiviral effector proteins. Viral infections continue to represent a major threat to human health and cause millions of deaths each year.[20] Thus, a better understanding of the induction and means to strengthen the human antiviral defense mechanisms is of great importance. Here, we summarize some of our knowledge about the induction of antiretroviral restriction factors and potential prospects for therapeutic and preventive applications. Although the main focus is on antiretroviral cellular proteins, most restrictions factors target various viral pathogens and have thus relevance beyond HIV and AIDS.

2 | INTERFERONS

IFNs are induced in response to pathogenic stimuli and represent the best-characterized mediators of innate antiviral immune responses.[21,22] IFNs act in an autocrine or paracrine manner to induce a variety of restriction factors that may target almost every step of the retroviral replication cycle (summarized in Fig. 1). As outlined below, IFNs are divided into three families, represented by type I, type II, and type III IFNs, with distinct but overlapping functions.

The human type I IFN family comprises 13 IFNα subtypes, IFNβ, as well as the less well-defined IFNε, IFNκ, and IFNω.[22] All of them bind to the same heterodimeric receptor complex consisting of the subunits IFN-alpha/beta receptor chain (IFNAR)1 and IFNAR2 and induce signaling through the JAK-STAT pathway (Fig. 2, left) to transcriptionally activate expression of their target ISGs. However, different IFNα subtypes might use distinct contacts and exhibit different binding affinities for the IFNAR1 and IFNAR2 subunits, leading to differential signaling outcomes.[23,24] Especially the subtypes IFNα6, IFNα8, IFNα13, and IFNα14 evolved under strong purifying selection, suggesting important and non-redundant functions in antiviral immunity.[25] The role of type I IFN during retroviral infection is complex.[8,26] SIV infection studies in rhesus macaques showed that blockage of the type I IFN receptor is associated with increased viral loads, concomitant with reduced antiviral gene expression and accelerated depletion of CD4+ T cells, resulting in the development of simian AIDS.[27] Conversely, administration of IFNα2 initially upregulated expression of antiviral factors and prevented systemic infection. However, prolonged treatment induced IFN desensitization and ultimately favored viral replication.[27] Unexpectedly, plasma type I IFN levels and restriction factor expression in untreated HIV-1-infected individuals show a positive correlation with the viral loads.[28] Thus, due to adaptation to their human host, pandemic HIV-1 strains have apparently become so effective in evading or counteracting restriction factors, that they are degraded to indicators rather than inhibitors of viral replication. However, while endogenous levels of IFN are often not sufficient to control HIV-1 replication, IFNα/Ribavirin treatment of antiretroviral therapy (ART)-naïve HIV-1/hepatitis C virus (HCV) co-infected individuals was associated with a pronounced, but transient reduction in plasma HIV-1 loads and significantly enhanced expression of the antiviral proteins apolipoprotein B mRNA editing catalytic polypeptide-like (APOBEC)3G, APOBEC3F, tetherin, and ISG15 in CD4+ T cells.[29] Interestingly, induction of tetherin expression showed the strongest correlation with reduction of HIV-1 viral loads, suggesting that this antiviral factor, which physically tethers progeny viral particles to the cell surface,[30] may play a significant role in the transient IFNα-mediated suppression of HIV-1 viremia. Furthermore, the extent of APOBEC-associated viral hyper-mutations correlated with APOBEC3G and APOBEC3F mRNA copy numbers during IFNα/Ribavirin treatment.[29] These results show that high levels of IFN transiently suppress viral replication during the chronic phase of HIV-1 infection and clearly indicate that the induction of restriction factors contributes to this effect.

Notably, the acute phase of *de novo* HIV-1 infection is characterized by peak viral loads accompanied by elevated levels of IFNα and other cytokines.[31] Interestingly, transmitted/founder (TF) viruses, which are responsible for primary viral infection and initial spread, are less sensitive to inhibition by IFNα than viral isolates from the same patient isolated during the asymptomatic, chronic phase of HIV infection.[32] This suggests that resisting IFNα-induced antiviral effects provides a selection advantage during HIV-1 transmission and the acute phase of infection. It was also shown that TF HIV-1 strains are particularly resistant to inhibition by IFN-induced transmembrane proteins (IFITMs), which impair viral entry into target cells.[33] Furthermore, pandemic group M (major) HIV-1 strains counteract the IFN-inducible restriction factor tetherin more efficiently than rare group N and P HIV-1 isolates, which resulted from independent zoonotic transmissions.[34] Potent



Restriction factor	Proposed mechanism of restriction	Reported inducers	References
SERINC3/5	Incorporates into progeny virions and inhibits fusion with target cells	None[1]	[10, 11]
IFITM1/2/3	Inhibits membrane fusion and/or Env incorporation	IFNα, IFNε, PHA/IL-2	[33, 43, 57, 125-128]
CH25H	Inhibits membrane fusion by generating 25-hydroxycholesterol	IFNα, IFNγ, TLR2, TLR3, TLR4, TLR9	[129]
APOBEC3	Interferes with processivity of reverse transcription and induces lethal hypermutations during cDNA synthesis through cytidine deamination	A3D: PHA A3F: IFNα A3G: IFNα, IFNβ, IFNγ, PHA, IL-27, IL-2 IL-15, IL-7 A3H: IFNα, LPS, PHA	[70, 85, 91, 130-135]
SAMHD1	Hydrolyzes cellular deoxynucleotide triphosphates (dNTPs)	IFNα, IFNβ, IFNγ, IL-12, IL-18, TLR9	[136-140]
TRIM5α	Binds to and accelerates fragmentation of the capsid, thereby interfering with cDNA synthesis	IFNα, IFNβ, IFNε, PHA	[43, 85, 141-143]
MxB	Reduces nuclear abundance of viral cDNA by inhibiting uncoating, nuclear import and/or integrity of the PIC	IFNα, IFNε	[43, 144-146]
KAP1 (TRIM28)	Induces deacetylation of integrase		[147]
TRIM22	Interferes with Sp1-driven transcriptional activation of the LTR	IFNα, IFNβ, IFNγ	[148, 149]
PKR	Blocks translation by phosphorylating eIF2α	IFNα, IFNβ, IL-27	[70, 150]
SLFN11	Inhibits viral protein synthesis in a condon-usage-specific manner	IFNα, IFNβ	[98, 151]
ZAP	Degrades multiply spliced viral mRNAs	IFNα[2]	[152, 153]
OAS1 + RNaseL	OAS1 generates 2', 5'-oligoadenylates that activate RNaseL to degrade viral (m)RNA	IFNα, IFNβ, IFNε, IFNω, IFNλ	[40, 44, 66, 154]
IDO1	Inhibits viral protein production through depletion of L-Tryptophan	IFNα, IFNγ	[49, 50]
HERC5 + ISG15	Inhibits assembly by ISGylation of Gag	HERC5: IFNβ, IFNε, TNFα, LPS, IL-1β ISG15: IFNα, IFNβ, IFNω, IFNλ	[43, 44, 66, 155-159]
CNP	Binds Gag and inhibits particle assembly		[160]
GBP5	Reduces infectivity of progeny virions through inhibition of Env maturation and incorporation	IFNα, IFNγ, IL-2, IL-27	[54, 72, 74]
MARCH8	Reduces Env incorporation into viral particles by downregulating it from the cell surface	IFNα	[59]
90K	Reduces incorporation of mature gp120 and gp41 into progeny virions	IFNα, IFNγ	[58]
Tetherin	Tethers budding virions to the plasma membrane	IFNα, IFNβ, IFNε, IFNγ,PHA, IL-27	[30, 39, 43, 71, 85, 95]

FIGURE 1 **Inducibility and mode of action of antiretroviral restriction factors.** Binding of gp120 to CD4 and CXCR4 or CCR5 triggers fusion of the viral and the cellular membrane, releasing the capsid into the cytoplasm. Following reverse transcription of the genomic RNA, the disassembling capsid allows transport of the viral cDNA into the nucleus, where it is integrated into the host genome. Spliced RNAs are exported from the nucleus and translated into viral proteins, which assemble at the plasma membrane together with unspliced RNAs. Monomeric gp160 Env precursor proteins trimerize in the endoplasmic reticulum, undergo proteolytic processing into the functional subunits gp120 and gp41 in the Golgi complex, and are finally transported to the plasma membrane for incorporation into budding virions. After virion release, the viral protease processes Gag and Gag-Pol polyproteins to form infectious viral particles. Restriction factors targeting various steps of the retroviral replication cycle are shown. Their antiviral modes of action, as well as different inducers are listed in the table. Note that the magnitudes of induction of restriction factor expression can vary significantly, depending on the cell type and the experimental system. The absence of listed stimuli does not exclude inducibility, unless this is specifically stated. [1]SERINC3/5 is not induced by IFNα, IFNβ, PHA, and LPS. [2]Induction of the short isoform (ZAPS) has been shown

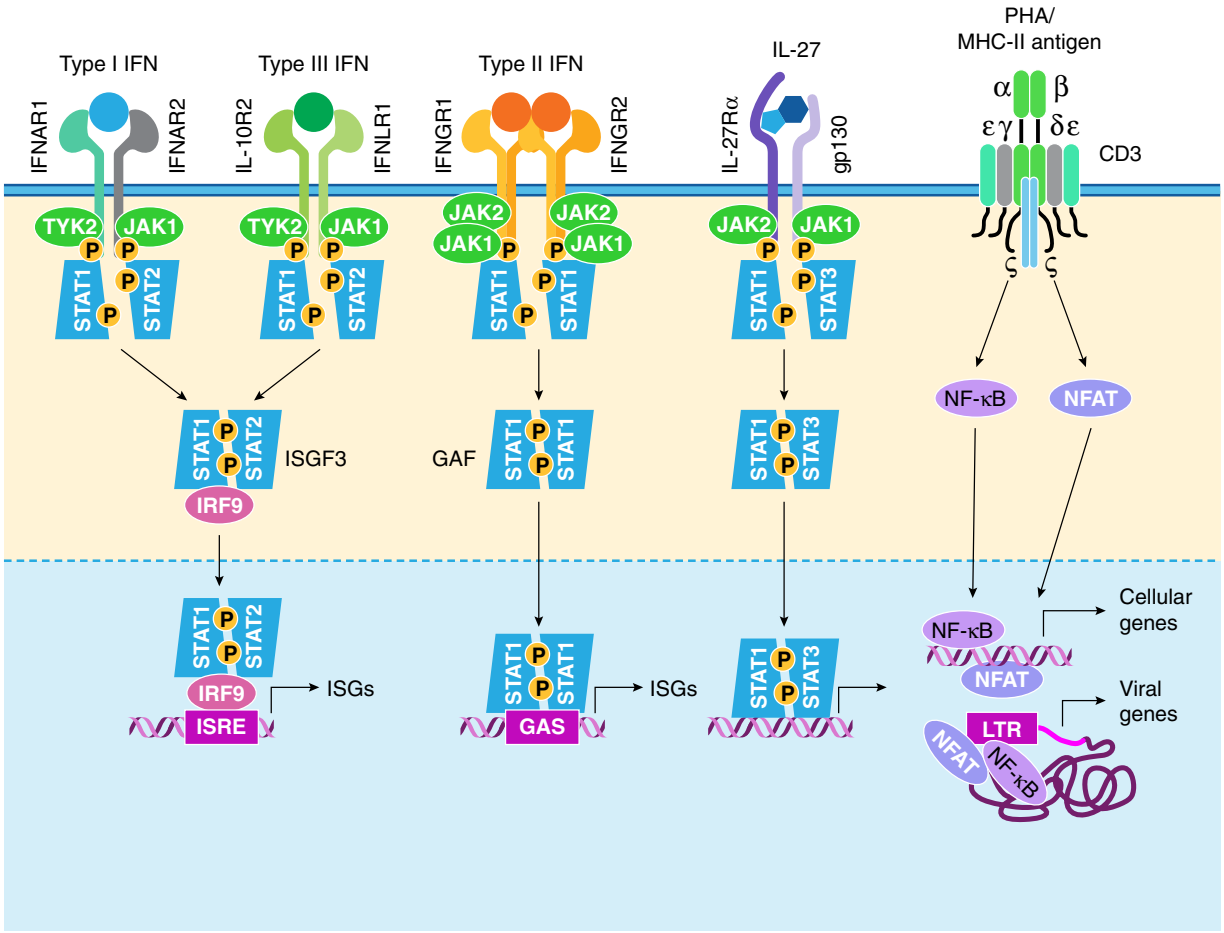


FIGURE 2 **Signaling pathways induced by IFNs, IL-27, and T cell receptor stimulation.** The three types of IFN interact with distinct receptor complexes. Type I IFNs (IFNα, IFNβ, IFNε, IFNκ, IFNω) bind to a heterodimer of IFNalpha/beta receptor 1 and 2 (IFNAR1 and IFNAR2), whereas the IL-10 receptor 2 (IL-10R2) associates with IFNλ receptor 1 (IFNLR1) to bind the four IFNλ subtypes. A tetramer consisting of two IFNGR1 (IFNγ receptor 1) and two IFNGR2 (IFNγ receptor 2) chains binds IFNγ dimers. Following binding by IFNs, signal transduction is initiated by autophosphorylation of pre-assembled tyrosine kinases and recruitment and phosphorylation of the signal transducers and activators of transcription (STATs). STAT1/STAT2 heterodimers associate with IFN regulatory factor 9 (IRF9) to form the IFN-stimulated gene factor 3 (ISGF3), whereas STAT1 homodimerizes to form the IFNγ activation factor (GAF). These complexes translocate to the nucleus and bind to IFN-stimulated response elements (ISRE) or a IFNγ activation site (GAS), respectively to induce gene expression. The IL-27 receptor is composed of the IL-27Rα subunit and the IL-6 receptor component gp130. Binding of IL-27, which is a heterodimeric protein consisting of the IL-27 p28 subunit and the Epstein-Barr virus induced gene 3 (EBI3) subunit, to its receptor induces target gene expression via STAT1/STAT3 heterodimers. The T cell receptor complex is an octomeric complex formed by two variable α and β chains associated with the three dimeric signaling molecules CD3δ/ε, CD3γ/ε, and CD3ζ/ζ. Stimulation of the T cell receptor activates central transcription factors, such as NF-κB and NFAT. Those transcription factors play a dual role during HIV-1 infection because they induce expression of cellular antiviral genes, but also bind the LTR promoter for efficient initiation of viral transcription

antagonism of human tetherin contributes to the low IFN sensitivity of TF HIV-1 strains[35] and may have been a prerequisite for the effective spread of HIV/AIDS.[36] Notably, the relative IFN-resistance of TF HIV-1 strains maps to different regions in the viral genome and can most often not be assigned to specific known restriction factors, suggesting that additional ISGs that play a relevant role in HIV-1 transmission remain to be discovered.

Although type I IFN signaling enhances viral control during the acute phase of infection, chronically elevated IFN levels are associated with immune exhaustion due to loss of CD4+ T cells and progression to AIDS. Thus, whether type I IFNs have beneficial or detrimental effects on the clinical course of HIV-1 infection is under debate.[37] Most clinical trials investigating viral control during IFN therapy utilized the IFNα2 subtype, which is one of the subtypes that is predominantly produced by plasmacytoid dendritic cells upon HIV-1 infection.[38] Recent data show, however, that IFNα subtype expression upon HIV-1 infection and antiviral potency correlate inversely: IFNα subtypes present in larger quantities during HV-1 infection (IFNα1, -2, and -5) exert only modest antiviral activity, whereas IFNα8, -6, and -14 are produced to a lower extent but restrict HIV-1 more potently in gut lamina propria mononuclear cell cultures and PBMCs.[38,39] The antiviral potency of the various IFNα subtypes correlated with their binding affinity to the IFNAR2 subunit and induction of the restriction factors myxovirus-resistance protein (Mx)B and tetherin.[38] Early administration of IFNα14 potently suppressed HIV-1 replication in an *in vivo* model using humanized mice, whereas the same clinical dose of IFNα2 showed only moderate protective effects.[39] The antiviral effects of IFNα14 correlated with induction of tetherin and MxB transcripts, as

well as increased APOBEC3G signature mutations in HIV-1 proviral DNA.[39] Thus, it will be interesting to further investigate, whether IFNα subtypes that induce restriction factors more potently than IFNα2, might provide an improved therapeutic approach for the control of HIV-1 *in vivo*.

In contrast to other IFNs, the proximal promoter of IFNε lacks response elements for IRFs, NF-κB, or STATs. Thus, IFNε expression is not inducible by conventional PRR signaling pathways.[40] Nonetheless, IFNε plays an important role in the defense against sexually transmitted pathogens, such as HSV type 2 and *Chlamydia*.[40] Although IFNε is constitutively expressed in cells of the female reproductive tract, its expression levels are hormonally regulated, that is, induced by estrogen and downmodulated by progesterone.[40] Interestingly, the susceptibility of macaques to vaginal SHIV infection is elevated in the second half of the menstrual cycle, when progesterone levels are high.[41] In addition, components of the innate, humoral, and cell-mediated immunity are suppressed by sex hormones.[42] Thus, IFNε levels might contribute to protection from sexual HIV transmission. In fact, it has been reported that IFNε enhances TRIM5α, HECT and RLD domain containing E3 ubiquitin protein ligase 5 (HERC5), MxB, IFITM3, and tetherin mRNA levels in PBLs and might act at multiple steps of the HIV-1 replication cycle.[43] Finally, an early study suggested that also IFNω induces the expression of antiviral factors.[44] Specifically, the authors showed that elevated levels of ISG15 contribute to the antiviral effect of IFNω, which also inhibited HIV-1 strains that are largely resistant to IFNα2 treatment. This is in agreement with more recent evidence suggesting that the different type I IFN subtypes and family members induce distinct combinations of ISGs, although all of them bind to the same receptor complex. Thus, further analyses of the correlation of distinct ISG patterns with antiviral activity might allow the identification of as-yet-unknown restriction factors.

In contrast to type I IFNs, humans encode only one form of type II IFN (IFNγ) that is mainly produced by activated T cells and NK cells and known to exert antiviral as well as antineoplastic activity.[45] Binding of the homodimeric IFNγ to its receptor complex, formed by two pairs of the receptor chains IFNGR1 and IFNGR2, induces activation of STAT1 through JAK1/JAK2-mediated phosphorylation and finally transcriptional activation of target genes containing the IFNγ activation site (GAS) in their promoter[46] (Fig. 2, left). Although IFNγ levels are elevated as part of the cytokine storm during acute HIV-1 infection,[31] it has been thought that the direct antiviral effects are modest and that IFNγ predominantly potentiates the effects of the type I IFNs.[47,48] Accumulating evidence suggests, however, that IFNγ also more directly contributes to antiretroviral immunity by inducing the expression of several restriction factors (Fig. 1). For example, Kane and colleagues[49] recently identified IDO1 as an inhibitor of retroviral gene expression. Expression of IDO1 is more strongly induced by IFNγ than by type I IFN[50] and, as observed for other antiretroviral restriction factors,[51] IDO1 expression levels are elevated during HIV-1 infection.[52] IDO1 catalyzes the initial rate limiting step in the conversion of L-tryptophan (L-Trp) to kynureine[53] and appears to inhibit HIV-1 by an indirect mechanism, that is, through depletion of L-Trp, since inhibition of the enzymatic activity of IDO1, as well as L-Trp supplementation relieved the block in retroviral gene expression.[49] Another antiviral factor that is induced at least as efficiently by IFNγ as by type I IFNs is guanylate-binding protein 5 (GBP5), which reduces infectivity of HIV-1 progeny virions by interfering with processing and incorporation of envelope (Env) glycoproteins.[54] GBPs belong to the superfamily of IFN-inducible GTPases and are well-known inhibitors of diverse intracellular pathogens.[55] Accordingly, *gbp5* knockout strongly diminished the anti-HIV-1 effect of IFNy in THP-1 cells.[54] Recent data show that IFNγ also induces an antiviral state in CD4+ T cells as well as in several T cell lines, where late replication steps following viral gene expression were blocked.[56] Interestingly, however, HIV-1 TF and two tested HIV-2 strains were largely resistant to IFNγ-induced inhibition. Although the exact mechanisms remained elusive, the viral Env glycoprotein of TF HIV-1 strains seems to overcome the IFNγ-induced late block.[56] An unusual trade-off, leading to increased Env expression at the cost of reduced levels of the accessory protein Vpu, has been shown to reduce HIV-1 sensitivity against GBP5.[54] Similar mechanisms might be used to partially overcome restriction by other IFN-inducible inhibitors targeting Env glycoproteins, such as IFITMs,[57] 90K,[58] or membrane associated ring-CH-type finger 8 (MARCH8).[59] It has also been reported that treatment of THP-1 cells with IFNγ, but not type I IFNs inhibits single round HIV-1 infection.[56] Thus, IFNα and IFNγ seem to induce overlapping but distinct sets of antiviral genes and may cooperate to achieve an effective antiviral state.

Type III IFNs, also called IFNλ, are the most recently discovered class of the three types of IFN,[60,61] represented by four family members in humans: IFNλ1 (IL-29), IFNλ2 (IL-28A), IFNλ3 (IL-28B), and IFNλ4.[62] The heterodimeric receptor for IFNλ is composed of the specific IFNλ receptor chain 1 (IFNLR1/IL-28RA) and the shared IL-10 receptor chain 2 (IL-10R2). Engagement of the IFNλ receptor induces signaling cascades that resemble those of type I IFNs and induce the formation of IFN-stimulated gene factor 3 (ISGF3), consisting of phosphorylated STAT heterodimers and IRF9, which translocates to the nucleus and induces expression of target genes carrying IFN stimulated response elements (ISRE) in their promoter region (Fig. 2, left).[62] Despite the related signaling cascades and an overlapping repertoire of producer cells,[63,64] accumulating evidence suggests that all IFN families have distinct roles in compartmentalized antiviral actions, although the three types of IFN certainly show multiple levels of cross-regulation and cooperation to achieve effective protection against pathogens with minimal damage to the host. Although a lot of information has been gained about the effect of type I IFNs on HIV-1 replication, a possible role for IFNλ is only emerging. It has been shown that macrophages carry the IFNλ receptor subunits and *in vitro* stimulation with IFNλ inhibits HIV-1 infection.[65] The antiviral activity seems to be partly dependent on the induction of the chemokines CCL3 and CCL4, which might interfere with infection through interaction with CCR5, the coreceptor for HIV-1 entry into macrophages. Moreover, IFNλ also enhanced APOBEC3G and APOBEC3F expression, although it remained unclear whether this upmodulation contributed to the observed antiretroviral effect and whether it was a direct effect of IFNλ, or a side effect of type I IFN upregulation.[65] A study comparing the inhibitory effect of different members of the IFNλ family in monocyte-derived macrophages (MDM) revealed, that IFNλ1, IFNλ3, and to a lesser extent IFNλ2 induced expression of several ISGs.[66]

The induced ISGs included potential HIV-1 inhibitors such as 2'-5'-oligoadenylat synthetase (OAS)1 or ISG15, which degrade viral RNAs or inhibit viral particle assembly, respectively. In line with enhanced ISG expression, IFNλ1 and IFNλ3 inhibited HIV-1 more potently than IFNλ2.[66] The antiviral effect of type III IFNs seems not to be limited to macrophages, since also pre-treatment of primary CD4+ T cells with IFNλ1 and IFNλ2 suppressed HIV-1 integration and post-transcriptional events.[67]

Altogether, increasing knowledge about the induction, function, and relevance of the different types of IFN has been achieved in the past years. Nonetheless, many questions about their specific functions and interactions with one another and other components of the immune system remain to be addressed. It is also noteworthy that only a small portion of the many hundreds of ISGs has been functionally characterized and that antiviral restriction factors seem to represent only a minor part of them.[49,68]

3 | INTERLEUKIN 27

As the upregulation of restriction factors apparently provides a barrier for HIV-1 replication and may also be effective against many other viral pathogens, it is an interesting question whether some cytokines might induce antiviral restriction factors more specifically and/or efficiently than IFNs and thus cause less severe side effects. Accumulating evidence suggests that IL-27 holds some promise as therapeutic antiviral agent.[69] IL-27 is a heterodimeric protein consisting of the IL-27 p28 subunit and the Epstein-Barr virus-induced gene 3 (EBI3) subunit. It belongs to the IL-12 family of cytokines, which also includes IL-12, IL-23, and IL-35. IL-27 signals via JAK-STAT activation and its receptor is a heterodimer of gp130 and IL-27Rα (Fig. 2, middle). Gp130 is ubiquitously expressed on a large variety of cell types, whereas IL-27Rα is only found on T cells, B cells, monocytes, neutrophils, NK cells, mast cells, and at low levels on macrophages and hepatocytes.[69] It has been shown that IL-27 inhibits HIV-1 replication in CD4+ T cells as well as in macrophages and may induce sets of antiviral genes similar to those stimulated by type I IFN.[70,71]

Although it is evident that IL-27 exerts antiviral effects, it is under debate whether this is mainly due to direct induction of antiviral effector proteins or intermittent induction of type I IFNs. Greenwell-Wild and colleagues[72] showed that IL-27 treatment of CD4+ T cells and MDM immediately activates JAK-STAT signaling but delayed induction of APOBEC expression because the latter requires generation of type I IFNs as intermediate signal transducers. Conversely, IFNα treatment induced both the p28 and the EBI3 components of the IL-27 heterodimer and enhanced expression of the IL-27Rα receptor subunit in a JAK-STAT-dependent manner. Notably, other IL-12 cytokine family members, such as IL-12 and IL-23, were also upregulated by IFNα but, in contrast to IL-27, failed to inhibit HIV-1 replication in MDM.[72] These results suggest a circuitous connection between IFNs and IL-27 in HIV-1 host defense and indicate that IL-27 might exert its antiretroviral effect through induction of type I IFN and subsequent upregulation of APOBEC cytidine deaminases.

Another study reported, however, that IL-27 inhibits HIV-1 replication in MDM and (less efficiently) in CD4+ T cells without inducing expression of IFNα, IFNβ, or IFNγ.[70] Microarray analysis showed that IL-27 significantly induced expression of various ISGs (i.e., MxA, OAS2, double stranded RNA-dependent protein kinase [PKR]/EIF2AK, and APOBEC3G) in MDM but not in CD4+ T cells. In further support of an IFN-independent antiviral activity of IL-27, cocktails of IFN-neutralizing antibodies did not abrogate HIV-1 inhibition by IL-27, but decreased the antiviral effect of IFNs.[70] More recently, it has been reported that IL-27 also increases expression of the restriction factor tetherin in human T cells and monocytes independently of type I IFN induction.[71] In support of a direct role in antiviral immunity, IL-27 has been reported as potent type I IFN-independent inhibitor of CCR5-tropic HIV-1 replication in immature monocyte-derived dendritic cells (iDCs).[73] Again, the antiretroviral effect was specific for IL-27 and not shared by other IL-12 cytokine family members. The exact mechanism needs further investigation, but the preliminary results suggested a post-entry, pre-integration block since vesicular stomatitis virus G glycoprotein pseudotyped viruses were also inhibited and HIV-1 late reverse transcription (RT) cDNA products were reduced in IL-27-treated iDCs. A gene expression microarray revealed that 129 genes were upregulated in IL-27-treated iDCs including some ISGs, such as MxA and OAS2. However, no classical anti-HIV restriction factors were induced and the microarray analyses as well as qRT-PCR and screening of the supernatants did not reveal any evidence for type I IFN induction by IL-27.[73]

In addition to inducing antiretroviral restriction factors directly or via type I IFN induction, IL-27 may also suppress HIV-1 replication by other mechanisms. For example, it has been reported that IL-27 promotes monocyte differentiation into macrophages that are non-permissive for HIV-1 infection.[74] Unlike reported in other publications,[70,71] no IL-27-mediated enhancement of tetherin and APOBEC3G expression was observed.[74] However, heterokaryons between MDM cultured in the presence and absence of IL-27 were found to be fully susceptible to HIV-1 infection, suggesting the lack of a virus-dependency factor in IL-27-treated macrophages. Comparison of genes that were downmodulated in the presence of IL-27 with previously described dependency factors acting early after entry[1] revealed the host protein spectrin beta non-erythrocytic 1 (SPTBN1) as the only factor present in both groups. How exactly SPTBN1 promotes HIV-1 replication in macrophages remains to be determined, but it was suggested that it associates with the viral capsid and matrix proteins and might play a role in the uncoating process.[74] It has further been suggested that the induction of microRNAs contributes to the broad antiviral effect of IL-27 in macrophages but no direct evidence for this hypothesis was presented.[75]

In further support of a complex role of IL-27 in innate antiviral immunity, it has been reported that noninfectious papilloma virus-like particles (VLPs) may inhibit HIV-1 replication via induction of IL-27 expression.[76] Gene expression profiling of cells cultured in the presence of HPV VLPs revealed that IL-27 was one of the factors with strongest induction in PBMCs and MDM, whereas type I IFNs were only strongly upregulated in PBMCs. The inhibitory effect was independent of the HIV-1 coreceptor tropism, but associated with

the induction of several antiviral genes including IRF1, IRF8, MxA, and OAS1.

Although the exact mechanisms through which IL-27 exerts its antiretroviral effect remain largely elusive and may be cell type dependent, accumulating *in vitro* data clearly suggest a relevant role of IL-27 in innate antiviral immunity. Several studies examined the role of IL-27 in HIV-1-infected individuals. Frequently, however, the cohort size was small and the observed differences moderate, which helps to explain some of the discrepancies in the literature. Guzzo and colleagues[77] found a trend for a negative correlation between IL-27 and HIV-1 plasma levels. In a subsequent study, they observed that treatment of PBMCs from uninfected individuals with IL-27 markedly increases expression of gp130 and various cytokines (IL-6, IL-10, and TNFα), whereas these effects of IL-27 were strongly diminished in PBMCs from viremic HIV-1-infected donors, suggesting that HIV-1 infection deregulates IL-27 functions.[78] Other studies also reported that the plasma IL-27 concentrations are decreased in treatment-naïve HIV/AIDS patients compared with the healthy controls but increased after initiation of ART.[79] In support of a protective role, the concentrations of plasma IL-27 positively correlated with the CD4+ T cell counts and were negatively associated with HIV viral load.[79,80] It is controversial, however, whether the levels of IL-27 are reduced,[78] enhanced,[80,81] or unaltered[82] in HIV-1-infected individuals compared with the uninfected healthy controls. Notably, the most recent study, performing broad-based analyses of plasma protein profiles in 96 HIV-infected, treatment-naïve individuals with differential viral loads reported highly significant positive correlations between plasma IL-27 levels and viral RNA loads, as well as proviral HIV-DNA copy numbers.[83] In contrast to previous results, soluble IL-27 plasma levels negatively correlated with CD4+ T cell counts and the breadth and magnitude of the total virus-specific T cell responses. These findings do, however, not contradict an inhibitory role of IL-27 in HIV-1 infection. As mentioned above, the expression levels of type I IFN and restriction factors also correlate inversely with CD4+ T cell counts and positively with the levels of HIV-1 plasma viremia[28] because both are induced as part of the antiviral immune response but often unable to control HIV-1 replication due to viral evasion or counteraction. *In vitro* studies have shown that IL-27 exhibits broad antiviral activity and inhibits the replication of HIV-1, HIV-2, HCV, SIV, HSV-2, and Kaposi's sarcoma-associated herpesvirus (HHV-8), although the underlying mechanisms remain to be determined.[74,84] Thus, further studies on the therapeutic potential of IL-27 as a potential antiviral therapeutic cytokine are warranted.

4 | CELLULAR ACTIVATION AND FURTHER CYTOKINES

A large proportion of HIV-1 replication *in vivo* occurs in activated CD4+ T cells. Thus, it might be surprising that *in vitro* activation of PBMCs with the mitogenic lectin PHA strongly induces the expression of antiviral restriction factors including APOBEC3 family members, tetherin, TRIM5α, and ISG15.[85] Notably, however, PHA-mediated crosslinking of cell surface glycoproteins, including the CD3 T cell receptor, activates transcription factors such as nuclear factor of activated T cells (NFAT) and NF-κB,[86,87] which do not only regulate expression of cellular genes, but also activate the HIV long terminal repeat (LTR) promoter and shift the PHA net effect towards a phenotype that supports viral replication[88] (Fig. 2, right). The influence of the cellular activation state on the susceptibility of HIV-1 infection is clearly more complex than anticipated. For example, the expression of antiviral factors may explain why specific T cell subsets support HIV-1 entry but not viral gene expression[89] and further studies seem highly warranted.

Notably, the activity of antiretroviral restriction factors does not always directly correlate with their expression levels. For example, APOBEC3G exists in a low molecular mass (LMM) form, which restricts HIV, and in enzymatically inactive, high molecular mass (HMM) complexes that do not exert antiviral activity.[90] While stimulation of PBLs with PHA, IL-2, IL-15, or IL-7 induces APOBEC3G expression, it also promotes formation of antivirally inactive HMM complexes and HIV-1 seems to preferentially infect cells containing these inactive HMM complexes.[91] Furthermore, it has been shown that IL-2 treatment inhibits HIV-1 replication in MT-2 cells via induction and virion incorporation of LMM APOBEC3G,[92] although the relevance of this finding for HIV-1 infection of primary T cells remains to be determined. Another HIV-1 restriction factor, which is modulated not only on the transcriptional, but also on the post-transcriptional level, is SAM domain and HD domain-containing protein 1 (SAMHD1). The activity of SAMHD1, which hydrolyzes dNTPs and restricts HIV-1 replication in myeloid and quiescent CD4+ T cells, is regulated by phosphorylation.[93] In cycling cells, SAMHD1 is phosphorylated at T592 by cyclin A2/CDK1 and loses its restricting phenotype. Notably, it has been reported that type I IFN reduces,[93] whereas IL-2 and IL-7 induce T592 phosphorylation of SAMHD1,[94] suggesting a complex regulation of its antiviral activity. Furthermore, the polarizing cytokines IL-4 and IL-10 have been shown to inhibit replication of CCR5 tropic HIV-1 in MDM, although not as efficiently as type I IFN. In case of the latter, the inhibitory effect was associated with increased expression levels of TRIM5α, cyclophilin A, APOBEC3G, SAMHD1, TRIM22, tetherin, and three prime repair exonuclease 1 (TREX-1), whereas it remained unclear which factors contributed to the antiviral effects of cytokine treatment.[95]

It has been shown that the expression levels of restriction factors do not correlate with control of HIV-1 replication or a clinical benefit *in vivo*.[96] This was further corroborated in a comparative analysis of the expression levels of 34 host restriction factors and cellular activation levels in CD4+ T cells between elite controllers, HIV-1-infected (untreated) non-controllers, ART-suppressed, and uninfected individuals, showing that the cumulative expression of anti-HIV-1 genes was higher in untreated non-controllers as compared with the elite controllers, ART-suppressed, or uninfected controls.[97] Cumulative restriction factor expression correlated directly with viral load, CD4+ T cell activation, and ISG15 levels, a marker for IFN exposure. The only exception was schlafen family member 11 (SLFN11), a codon usage-based inhibitor of HIV-1 protein synthesis,[98] which was expressed at significantly higher levels in elite controllers compared with untreated non-controllers and ART-suppressed individuals.[97]

A recent study examined the plasma levels of 87 cytokines in four groups of women: 73 elite controllers, 42 under anti-retroviral therapy, 42 with efficient viral replication, and 48 HIV-uninfected individuals.[99] It was found that HIV infection is generally associated with increased levels of stromal cell-derived factor 1 (SDF-1)/ C-X-C motif chemokine ligand (CXCL)12, the ligand of the HIV-1 coreceptor CXCR4, whereas four cytokines (CCL14, CCL21, CCL27, and XCL1) were elevated in elite controllers but not in non-controllers or individuals on ART. Individually, SDF-1β, CCL14, and CCL27 inhibited replication of an R5 tropic HIV-1 strain, whereas SDF-1β, CCL21, and CCL14 inhibited replication of an X4 tropic strain. In combination, SDF-1α/β, CCL21, XCL1, CCL14, and CCL27 strongly inhibited HIV-1 replication in PBMC cultures irrespective of the viral coreceptor tropism. An mRNA profiling array measuring the expression of 31 different innate restriction factors revealed significant upregulation of IFITM1/2 in CD4+ T cells treated with this cytokine pool. Modest increases could be confirmed by qRT-PCR and Western blot, but no functional assays were performed to show that IFITMs are responsible for the observed antiviral effects. Although these findings suggest a protective role of some cytokines against HIV-1 replication *in vivo*, further studies are required to obtain more definitive proof because the differences in plasma levels between the groups and the antiviral effects of the individual cytokines were modest.[99]

5 | SYNTHETIC TRANSCRIPTIONAL ACTIVATORS

Some restriction factors target conserved viral components or create a cellular environment that is unfavorable for replication, making it difficult for the viral pathogens to develop resistance. Furthermore, while well-adapted pathogens, such as pandemic HIV-1 strains, are typically largely resistant to restriction factors at expression levels naturally achieved in infected individuals, antiviral effectors might "overpower" viral antagonists or evasion mechanisms at higher expression levels. Thus, controlled induction of endogenous restriction factors without causing generalized immune activation is of significant interest. Specific induction of APOBEC3G and 3B expression in cells that normally do not express these restriction factors (HEK293T and CEM-SS cells) was achieved[100] using an engineered Cas9-based transcriptional activation system developed by Konermann and colleagues.[101] In this system, a DNA-cleavage-incompetent version of the nuclease Cas9, fused to the potent VP64 transactivation domain is recruited to specific promoter regions by a single guide RNA (sgRNA). The sgRNA contains two terminal loops, specifically interacting with the MS2 bacteriophage coat protein, which is expressed as a fusion protein containing transcription activation domains derived from the NF-κB subunit p65 and from heat shock factor 1. Binding of this complex, termed synergistic activation mediator (SAM), to its target site upstream of the transcriptional start site potently activated expression of specific target genes. Importantly, induction of APOBEC3G and APOBEC3B led to proviral APOBEC signature mutations in target cells,[100] providing proof-of-concept evidence that increased expression of restriction factors has suppressive effects on HIV-1 *in vitro*.

6 | GENETIC APPROACHES TO HARNESS RESTRICTION FACTORS FOR THERAPY AND PREVENTION

Sustained control of HIV replication by ART currently requires lifelong compliance with strict treatment regimens that are complicated by insufficient accessibility, viral resistance, and drug-related side effects. Thus, short-term or even single-shot treatment options that allow durable control of HIV replication, often referred to as "functional cure," are of enormous clinical interest.[102,103] Current approaches to achieve this include the addition of anti-HIV genes, disruption of cellular HIV dependency factors,[4] or direct targeting of integrated proviral genomes[104,105] in autologous CD4+ T cells or hematopoietic stem cells by engineered genome editing nucleases. Motivated by the unique case of the "Berlin patient," who has remained HIV-1 free without ART since receiving a CCR5Δ32/Δ32 stem cell transplantation,[106,107] the first of several human trials targeting *ccr5* by zinc finger nucleases (ZFN) was already launched in 2009.[108] Thus far, the studies demonstrated the safety of the transplanted ZFN-modified autologous CD4+ T cells, but also limited protective effects of *ccr5* disruption.[4] The latter can be explained by low editing rates and the fact that the transplanted cells do not fully replace the susceptible wild-type CD4+ T cells in the host. Further clinical trials are currently investigating the potential of genome-engineered hematopoietic stem/progenitor cells, which could provide a permanent source of protected cells and efficiently block replication of CCR5-tropic HIV.[4] However, it should be noted that the protective effect of *ccr5* disruption might be overcome by the emergence of CXCR4-tropic HIV-1 strains, a phenomenon that frequently occurs during advanced HIV-1 infection, but has also been observed after short time treatment with the CCR5 antagonist Maraviroc.[109,110]

Elimination of viral dependency factors is an interesting approach but bears the risk of adverse effects as these cellular proteins might also exert relevant physiological functions. Modification of restriction factors to render them active against HIV-1 or resistant to viral antagonists provides another promising avenue for the application of genome editing approaches in clinical development. For example, although capsid mutations render HIV-1 resistant to untimely uncoating by human TRIM5α, they do not protect against TRIM5α orthologs from other species.[111] Thus, expression of heterologous TRIM5α, or specific modification of endogenous human TRIM5α may be useful strategies to inhibit HIV-1 replication. Proof of concept evidence comes from cats, which are a natural host of feline immunodeficiency virus (FIV), a lentivirus that is susceptible to species-specific restriction factors, just like HIV-1. Introduction of rhesus macaque TRIMCyp, into the cat germline rendered their lymphocytes fully resistant against FIV infection.[112] Another strategy would be to prevent inactivation of restriction factors by viral antagonists. In fact, it has been shown that a single amino acid substitution (D128K) in human APOBEC3G prevents degradation by the HIV-1 accessory protein Vif.[113] Thus, just a few or even single amino acid changes in human restriction factors that are unlikely to have adverse effects might fully restore their activity against human pathogens such as HIV-1.

It is beyond the scope of the present review to provide an in depth discussion of the many genome modifications that could render humans or other species resistant to HIV or other viruses and this has been the topic of recent reviews.[104,114] Notably, a substantial number of clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9-based gene editing trials in humans have been initiated for the treatment of genetic disorders and cancers.[115,116] The results of these studies will provide important insights into the safety of these approaches and the enormous advances in targeted genome editing certainly make it an interesting strategy to achieve resistance against dangerous pathogens without the need of continuous drug intake.[117] However, therapeutic application of these technologies still faces major obstacles, such as low editing rates and genotoxicity resulting from off target effects. The safety of these approaches might be increased by the utilization of engineered nucleases showing reduced off-target editing, such as transcription activator-like effector nucleases (TALENs)[118] and significant progress is made in increasing the efficiency of *in vivo* delivery of CRISPR/Cas9.[119] However, in addition to overcoming technical challenges, ethical issues have to be considered with the ultimate goal to achieve rational ethical and regulatory frameworks for safe and effective therapeutic use of genome editing technologies to combat infectious diseases.[120]

7 | CONCLUDING REMARKS

The ever-ongoing molecular arms race between viruses and their hosts represents a fascinating but also highly complex area of research. It is quite remarkable that some restriction factors have been around for many millions of years, and are still capable of inhibiting present day viral pathogens.[121–124] In fact, restriction factors usually have some advantages over other antiviral agents as they are often broadly active and viral pathogens frequently cannot just become resistant by the acquisition of point mutations. Some well-adapted viral pathogens, however, have evolved specific antagonists and are thus hardly affected by the restriction factors they encounter in their natural hosts. Frequently, however, even well-adapted viruses are efficiently inhibited if restriction factors are expressed at unusually high levels or insensitive to viral antagonists. Thus, efficient induction or genetic modification of restriction factors represents promising strategies to achieve better control of viral replication. Recent evidence suggests that millions of years of virus-host coevolution may have driven the emergence of cytokines that could be used to induce specific subsets of restriction factors to levels that are sufficient to block viral replication without causing harmful inflammation. However, our understanding of the functions and interplay between the numerous inducers and effectors of this first-line antiviral defense is far from being complete. Despite enormous research efforts and significant progress, infectious viral diseases are still on the advance and represent a major health problem. Thus, a better understanding of the framework of effectors and modulators of the antiviral immune response is needed and may lead to the development of alternative preventive or therapeutic approaches.

AUTHORSHIP

D.H. and F.K. wrote the review.

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DISCLOSURES

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