

Antiviral restriction factors in immunity and disease: Regulation and dysregulation of their effector functions

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Antiviral factors from the cell autonomous innate immunity are essential cellular proteins that inhibit viral replication and play a central role in the host's defense against infections. Novel technologies now enable the high-throughput screening of these antiviral factors and facilitate detailed characterization of their molecular mechanisms. In this review, we explore the diverse effector functions of these proteins, focusing on their restriction of molecular processes and their interactions with viral components. We also highlight how the dysregulation or genetic mutations of antiviral factors can contribute to the onset and development of diseases. Finally, we emphasize their dual role in immunity and pathology and discuss how interdisciplinary approaches will continue to advance the field.

Introduction

Early and effective response against infection is crucial in antiviral immunity. Antiviral factors, also referred to as restriction factors, are cellular proteins that confer intrinsic or cell-autonomous innate immunity to viral pathogens by inhibiting viral entry or replication. Restriction factors are a group of proteins that are able to restrict the viral replication cycle through a wide variety of mechanisms, ranging from transcriptional silencing to degradation of cellular biomolecules. Here we focused on restriction factors whose activity has been described in mammals. Although the precise definition of restriction factors has been debated, they share a set of common features: they have direct antiviral activities and generally not part of a complex signaling cascade, they can be constitutively expressed in most cell types and are often upregulated by interferon (IFN) (i.e a secreted cytokine with antiviral functions), and they often present signatures of positive selection (i.e the rapid fixation of beneficial non-synonymous mutations) as a result of the arms race between host and virus [1, 2].

The term “restriction factor” was first introduced in the early 1970s when the Friend virus susceptibility protein 1 (Fv1) was identified as restricting the retroviral Murine Leukemia Virus (MLV) infection in mice [3]. Since then, cell-intrinsic restriction factors have been identified to interfere with virtually all steps of the viral cycle and all virus types as part of the first line of defense against these pathogens.

Several of these factors, such as SAMHD1 [4] and Tetherin/BST-2 [5], have been extensively studied, with their molecular mechanisms and corresponding viral resistance strategies described in detail. However, new restriction factors are still actively being discovered and technologies such as genome-wide CRISPR screenings have facilitated the identification of these proteins [6], which will surely lead to the discovery of unexpected restriction mechanisms.

Although restriction factors have often been classified according to the step of the viral cycle they inhibit [2, 7], many of these proteins exert their inhibitory action through common effector functions, such as nucleic acid degradation or protein-protein interactions. For instance, RNA-degrading restriction factors may act either by directly degrading viral RNA or by targeting viral mRNA, thereby preventing the synthesis of viral proteins. Moreover, these restriction factors are often broadly effective, inhibiting not only a wide array of viruses but also diverse viral families [2]. However, these powerful effector functions can also be directed against endogenous cellular components or processes under physiological conditions, and may therefore be harmful to the host. Highlighting the molecular mechanisms by which restriction factors antagonize the viral cycle can enhance our understanding of how these proteins successfully inhibit different viruses and how the dysregulation of innate restriction factors can have deleterious effects on the host.

As studies of antiviral responses in different host-pathogen models progress, new restriction factors and associated mechanisms are characterized. Moreover, new insights arise on how restriction factors can be implicated in diseases, notably in inflammatory diseases, cancer and autoimmune disorders [8–10]. In this review, we explore different effector mechanisms through which restriction factors inhibit viral replication cycles and describe dysregulations in their effector functions and the resulting detrimental effects in the host. We aim to provide specific examples of restriction factors acting as drivers of disease and illustrate how these disease-driving mechanisms could be related or not with their antiviral activity. Finally, we offer our perspective on how restriction factors can both inhibit the viral cycle and act as drivers of disease, and how the field continuously evolves towards a more integral view of restriction factors.

Box 1. Key definitions.

Restriction factor Cellular protein that confers intrinsic, cell-autonomous innate immunity by directly inhibiting viral entry or replication.

Effector mechanism The specific molecular process (nucleic acid degradation, transcription/translation inhibition, direct protein–virus interaction. . .) through which a restriction factor exerts its antiviral activity.

Interferon (IFN) Secreted cytokine with antiviral functions; many restriction factors are constitutively expressed and further upregulated by IFN signaling.

Positive selection The rapid fixation of beneficial non-synonymous mutations – a genomic signature of the evolutionary arms race between host restriction factors and viruses.

Nucleotide or nucleic acid degradation

An important mechanism that inhibits the viral cycle is the degradation of viral RNA/DNA or the prevention of viruses from synthesizing new genetic material (Fig. 1). A well studied example of this mechanism is the Sterile Alpha Motif and HD domain-containing protein 1 (SAMHD1),

a deoxynucleoside triphosphate triphosphohydrolase that hydrolyzes dNTPs into deoxyribonucleosides and inorganic triphosphates. This protein is widely expressed at a basal level and highly expressed in myeloid lineage cells. It is also known to restrict HIV-1 by inhibiting reverse transcription and viral complementary DNA (cDNA) synthesis through the depletion of cellular dNTPs [11]. After this catabolic activity had been described, SAMHD1 was also shown to act as a restriction factor via RNase activity by degrading genomic RNA of HIV-1 and other retroviruses [12]. However, the role of RNA degradation in SAMHD1-mediated restriction has been debated, and a recent study has shown that RNA-bound SAMHD1 does not have a dNTPase or RNase activity [13]. The precise role of the catalytic activities of SAMHD1 in viral restriction remains to be elucidated.

Cellular-intrinsic proteins that show antiviral activity through the targeting of nucleic acid material can also be drivers of disease. For instance, genetic mutations in SAMHD1 cause an inflammatory encephalopathy called Aicardi–Goutières syndrome (AGS). The specific consequences of defects in SAMHD1 function in this disease are still being studied. Recently, SAMHD1 has been shown to regulate innate immunity by lowering cellular RNA levels and therefore inhibiting the release of immunogenic double-stranded RNA from RNA-protein condensates. The mutations in SAMHD1 could therefore lead to an activation of immune response against cellular RNA and be linked to the inflammation and neurodegeneration seen in AGS [14]. Moreover, restriction factors are sometimes associated with cancer progression, often because of their ability to disrupt physiological processes. Multiple studies have aimed to determine the role of SAMHD1 in cancer, with different roles being observed depending on the cancer type. In ovarian cancer, SAMHD1 depletion seems to induce upregulation of proinflammatory cytokines and an activation of innate immune cell signaling, and is consequently linked with improved prognosis [15]. In solid cancers, a positive prognosis has also been associated with low or no expression of SAMHD1, explained by its ability to modulate DNA damage response and a consequent increase in γ -H2AX and apoptosis in SAMHD1-depleted cells (Fig. 2A) [16].

Other examples of restriction factors that inhibit the viral cycle through modification or degradation of nucleic acids include RNaseL, Zinc-finger Antiviral Protein (ZAP) and the Apolipoprotein B mRNA Editing Catalytic Polypeptide-like (APOBEC) family. RNaseL is able to cleave viral RNA when activated by the 2'-5'-linked oligoadenylates produced by the 2'-5'-oligoadenylate synthetase 1 (OAS1) protein [2]. Recently, OAS1 gain-of-function variants have been shown to cause an autoinflammatory immunodeficiency through RNase L-mediated dysfunctions, that include cleavage of cellular RNA. This immunodeficiency can be cured by inhibiting RNaseL [17]. ZAP, also known as poly(ADP-ribose) polymerase-13 (PARP13) selectively binds and degrades viral RNA, and is active against a wide variety of viruses, including HIV-1 and hepatitis B virus [18]. Finally, members of the APOBEC family induce the deamination of cytosines to uracils and consequently introduce point mutations in viral genomes. The full scope of their antiviral activity still remains to be discovered, with new antagonizing effects against viruses still being reported [19]. In this family, APOBEC3A drives tumor development by a DNA deamination-dependent mechanism [20].

Transcription inhibition

In the presence of viral DNA, another restriction mechanism is the inhibition of viral gene transcription (Fig. 1). The KRAB-associated protein 1 (KAP1), also known as tripartite motif containing 28 (TRIM28) is a core component of the constitutive heterochromatin machinery and recruits repressive histone modifiers that silence genes through H3K9 trimethylation. In addition, KAP1-mediated DNA methylation can also silence the transcription of viral genes in both RNA and DNA viruses. It was recently demonstrated that in Epstein-Barr Virus (EBV), KAP1 interacts with the γ -interferon-inducible protein 16 (IFI16) to silence the EBV lytic switch protein ZEBRA, facilitating its heterochromatinization and leading to viral latency [21]. For Moloney murine leukemia virus (MoLV) silencing, KAP1 is recruited to the provirus 5' long-terminal, which results in a potent transcriptional silencing. The latter is dependent on the K779 residue of the protein [22]. The extent of KAP1 antiviral activity remains to be elucidated in other viruses, notably

in HIV where its role remains elusive.

KAP1 also illustrates how dysregulation of transcription-inhibiting restriction factors can lead to detrimental phenotypes. A recent pan-cancer analysis showed that KAP1 is more expressed in various tumor tissues than in normal tissues, and that its abnormal expression is associated with poorer prognosis. Specifically, higher expression of KAP1 was positively correlated with tumor mutational burden and microsatellite instability [23]. KAP1 parental and maternal pathogenic variants have also been reported to cause renal embryonal tumors, probably through a deregulated transcriptional landscape during nephrogenesis that ultimately leads to tumorigenesis [24]. Additionally, constitutive KAP1 phosphorylation through the B-cell receptor signaling pathway was higher in chronic lymphocytic leukemia (CLL) patients compared to control patients, with KAP1 depletion decelerating cell cycle progression of CLL cells (Fig. 2B) [25]. Importantly, the mechanism by which restriction factors inhibit the viral cycle can be different to the mechanism by which they are involved in diseases. For example, KAP1 was recently reported to stabilize the mRNA of the MYCN proto-oncogene, with KAP1 knockdown decreasing MYCN-mediated neuroblastoma progression [26].

MxA and MxB proteins are large GTPases of the dynamin superfamily that also act as restriction factors by inhibiting viral transcription. MxA acts as a restriction factor against a wide range of viruses including orthomyxoviruses and paramyxoviruses. Although known to accumulate in the cytoplasm, MxA was also shown to mediate transcription inhibition of the influenza virus genome by forming a complex with the viral nucleoprotein (NP) [27]. Recent studies on the link between MxA and disease have mostly focused on its influence on sensitivity to chemotherapeutic agents or its relationship with prognosis [28, 29]. MxB, another large GTPase, restricts various viruses through multiple antiviral mechanisms, including significantly reducing hepatitis B virus and herpesvirus RNA transcription, as well as inhibiting proviral DNA integration [30–32]. Besides MxA binding of a viral protein and MxB restriction that seems to be dependent on GTPase activity, other mechanisms of transcription inhibition have also been described. In addition to

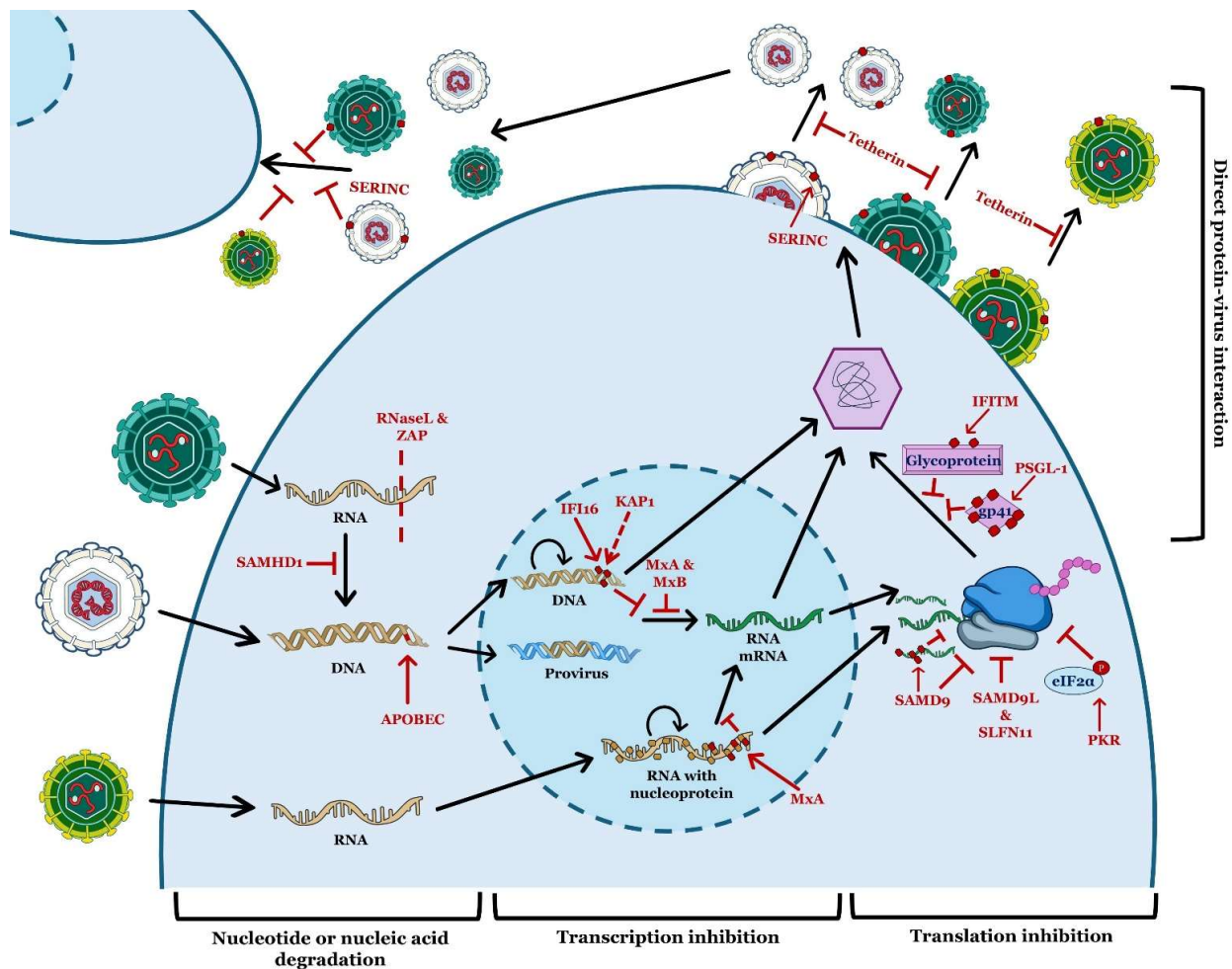


Figure 1. Restriction factors inhibit the viral cycle through different effector mechanisms. Two RNA viruses (green: retrovirus / yellow: ssRNA virus) and one DNA virus (white) are used to illustrate restriction factor activity through the different stages of the viral cycle. Blue cells represent host cells. Only nucleic acids from viral origin are represented. Restriction factors are depicted in red. Arrows indicate binding, dashed arrows indicate indirect effects.

its role in EBV latency, IFI16 is a nuclear DNA sensor that binds the herpes simplex virus 1 (HSV-1) genome in a sequence-independent manner [33]. IFI16 accumulates on the genome by interacting with the backbone of dsDNA, reduces the association of transcription factors and leads to gene repression [34]. A wide set of studies on the role of IFI16 in driving cancers, mostly through immune signaling, have been performed, and showed recently that it promotes clear renal cell carcinoma due to increased levels of IL6 [8].

Translation inhibition

Restriction factors can also inhibit the viral cycle by affecting viral protein translation (Fig. 1). The sterile alpha motif domain-containing 9 and 9-like proteins (SAMD9/9L) are encoded by paralogous genes and are ubiquitously expressed in

many human tissues, where they are known to be poxvirus restriction factors that inhibit translation [35]. SAMD9 induces stress antiviral granules that inhibit translation by a mechanism including inhibition of ribosome entry and sequestration of viral RNA [36]. Recently, SAMD9L but not SAMD9 has also been shown to restrict HIV-1 and primate lentiviruses through the inhibition of viral and cellular translation. SAMD9L inhibits the late stages of viral replication in interferon-stimulated cells through restriction of viral protein synthesis. Interestingly, this inhibition was mediated by a Schlafen-like active site, identified by homology with the SLFN11, SLFN12, and SLFN13 Schlafen proteins that also act as cell autonomous restriction factors by inhibiting translation [37].

Pathogenic variants of SAMD9 are the cause of a complex multisystem disorder named MIRAGE

syndrome (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy), which was first described in 2016 and is due to gain-of-function mutations in the SAMD9 growth repressor gene that generate tissue hypoplasia. This syndrome is still being studied for the large range of phenotypic manifestations, as well as the different missense variants that drive the phenotypes [38]. SAMD9L mutations can cause severe autoinflammatory disease and ataxia-pancytopenia. Although SAMD9L already inhibits translation in physiological conditions, this activity is greatly increased both by missense and by truncating mutations. Moreover, phenotypic alterations triggered by truncating mutations might indicate an allosteric regulation of SAMD9L by its C terminus that, when lost, can lead to the exaggerated translational repression (Fig. 2C) [9]. The dramatic phenotypes caused by SAMD9/9L mutations highlight the importance of some restriction factors not only in innate immunity proteins but also as regulators of physiological processes that upon deregulation can lead to deleterious phenotypes.

Numerous other proteins are both able to inhibit translation of viral proteins and implicated in disease. Protein kinase R (PKR) is an interferon-induced kinase activated by binding to viral dsRNA and known to impair viral translation through the phosphorylation of the translation initiation factor eIF2 α . Interestingly, this translational shutdown has been shown to be driven by APOBEC3B [39]. The activation of PKR has been linked to neurodegenerative disorders and has been hypothesized to be an initiator of deregulated translation in Alzheimer's disease lymphocytes via p53 [10]. As mentioned above, members of the Schlafen family of proteins can also downregulate viral protein synthesis. For example, SLFN11 has been proven to restrict flavivirus and HIV-1 infection, in a mechanism that seems to involve tRNA nucleolytic activity, as shown for SLFN13 [40]. SLFN11 is also a putative DNA/RNA helicase considered as a guardian of the genome that has been shown to destabilize stalled replication forks and therefore drive Fanconi anemia [41]. The mechanisms by which the wide range of translation inhibitory proteins can trigger diseases still remain largely unknown.

Direct protein-virus interaction

The best characterized example of a protein inhibiting the viral cycle only through physical interaction with viral components is perhaps tetherin (Fig. 1). Also known as bone marrow stromal antigen 2 (BST2) or CD317, tetherin was named after its ability to physically tether virions to the plasma membrane of infected cells and therefore prevent viral particle release. Tetherin is a cell membrane embedded dimer composed of a cytoplasmic region, a transmembrane helix, an extracellular coiled coil domain, and a C-terminal membrane anchor. The C-terminal anchor of tetherin is responsible for the attachment to the budding virus and it is the ectodomain that bends and allows the transition between the membrane bound tetherin and the bridge structure between the membrane and the virion [42]. The antiviral activity of tetherin has been documented for an extensive range of viruses that include HIV-1, influenza A virus, and vesicular stomatitis virus. This list of targeted viruses will continue to extend, as exemplified by recent work proving rabies virus inhibition via this mechanism [43].

In the past years, a growing body of evidence showed that tetherin can have an oncogenic role. Importantly, as a transmembrane glycoprotein, tetherin is also expressed in differentiated human B cells and enhances cell-cell interaction in the pre-B cell stages of differentiation [44]. In colorectal cancer, in vivo and in vitro experiments showed that upregulation of tetherin increased the infiltration of tumor-associated macrophages, polarizing them to an M2 phenotype which in turn leads to an immunosuppressive tumor microenvironment [45]. In oral squamous cell carcinoma (OSCC), tetherin was shown to activate the epidermal growth factor receptor (EGFR) signaling pathway, important for proliferation and apoptosis in mammalian cells. Specifically, tetherin overexpression enhanced OSCC cell proliferation, inhibited OSCC cell apoptosis and induced resistance to the gefitinib antitumor agent (Fig. 2D) [44].

Additional restriction factors are also able to bind viral components to restrict the viral cycle. Two members of the interferon-induced transmembrane (IFITM) family of proteins, IFITM2 and IFITM3, have been shown to antagonize the HIV-1 envelope glycoprotein (Env) by interacting with it in cells

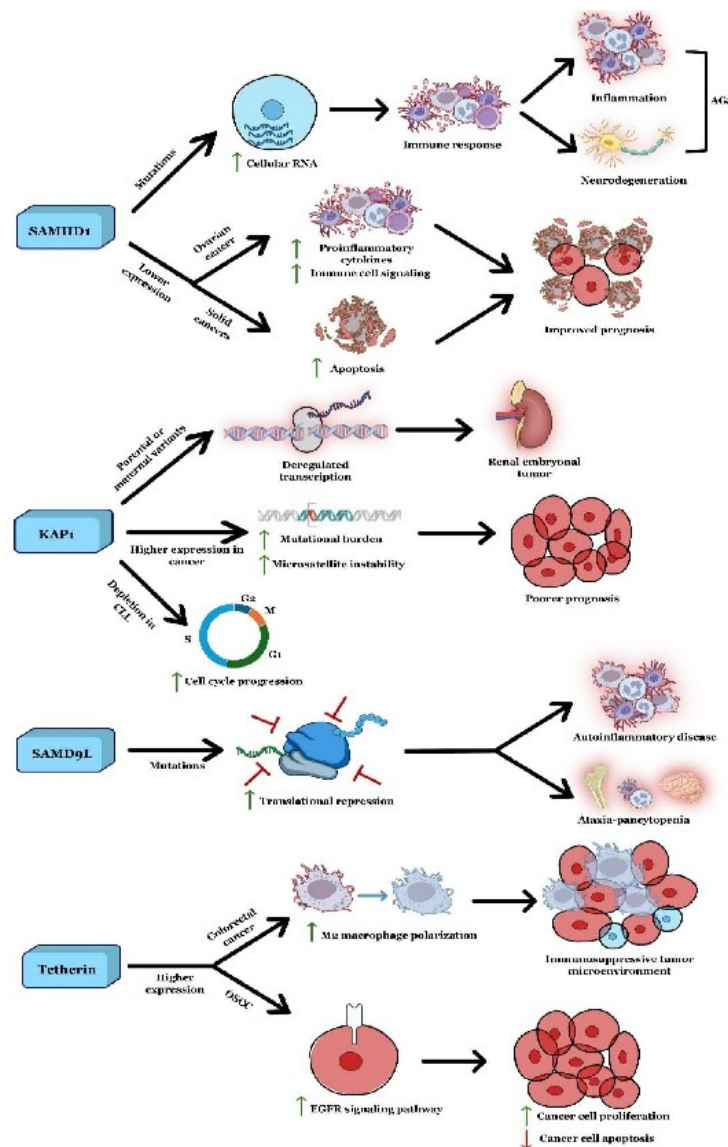


Figure 2. Restriction factors as drivers of disease. The potential disease-driving roles of one protein from each type of effector mechanism are summarized. **A.** SAMHD1. **B.** KAP1. **C.** SAMD9L. **D.** Tetherin. Blue cells represent host cells. Red cells represent cancer cells. Red shading symbolizes dysfunction or dysregulation. In immune cells, the red outline indicates activation. OSCC: Oral squamous cell carcinoma. CLL: chronic lymphocytic leukemia. AGS: Aicardi–Goutières syndrome.

and thereby impairing correct virion assembly [46]. IFITM3 has been identified as a γ -secretase modulatory protein in Alzheimer's disease, with experiments showing that knockout of IFITM3 reduces γ -secretase activity and thereby the formation of amyloid plaques. These results point to IFITM3 as a link between neuroinflammation and Alzheimer's disease [47]. The serine incorporator SERINC3 and SERINC5 proteins have recently been reported to restrict viral infection after the presence in the envelopes of HIV-1 virions was shown to reduce infectivity and to disrupt virus membrane asymmetry [48]. Interestingly, SERINC proteins have not yet

been reported as drivers of disease. The P-selectin glycoprotein ligand 1 (PSGL-1) protein also restricts HIV-1 infection by binding and sequestering the gp41 protein at the plasma membrane, inhibiting envelope incorporation in the virions [49]. The PSGL-1 protein has been proposed as an immune checkpoint and in an endotoxemia mice model, the blockage of PSGL-1 by an antibody significantly increased survival and decreased lung injury and levels of inflammatory factors [50].

Table 1. Antiviral restriction factors and their roles as disease drivers.

Type of effector mechanism	Restriction factor	Restriction mechanism	Role as a disease driver
Nucleotide or nucleic acid degradation	SAMHD1 [4, 11–16]	Inhibition of cDNA synthesis, hydrolysis dNTPs	Aicardi–Goutières syndrome, depletion improves prognosis in some cancers
	RNaseL [2, 17]	Degradation viral RNA	OAS1-mediated autoinflammatory immunodeficiency
	ZAP/PARP13 [18]	Degradation viral RNA	Not reported
	APOBEC family [19, 20]	Induction of hypermutation by deamination	Tumor development
Transcription inhibition	KAP1/TRIM28 [21–26]	Gene silencing by recruitment of histone modifiers, DNA methylation	Higher tumor mutational burden and microsatellite instability, renal embryonal tumor, cell cycle progression in chronic lymphocytic leukemia, stabilization of MYCN mRNA
	MxA [27–29]	GTPase activity, formation of a complex with viral nucleoprotein	Promotion of resistance to chemotherapy
	MxB [30–32]	GTPase activity	Not reported
	IFI16 [8, 21, 33, 34]	Accumulation on the ds-DNA viral genome	Promotion of clear renal cell carcinoma
Translation inhibition	SAMD9 [35, 36, 38]	Inhibition of ribosome entry and sequestration of viral RNA	MIRAGE syndrome
	SAMD9L [9, 35, 37]	Restriction of viral protein synthesis through a Schlafen-like active site	Severe autoinflammatory disease and ataxia-pancytopenia
	PKR [10, 39]	Phosphorylation of the eIF2 α initiation factor	Deregulation of translation in Alzheimer's disease lymphocytes
	SLFN11 [40, 41]	tRNA nucleolytic activity	Fanconi anemia
Direct protein-virus interaction	Tetherin/BST2/CD317 [42–45]	Tethering of budding virus to the infected cell	Immunosuppressive tumor microenvironment, enhances cell proliferation and inhibits cell apoptosis in oral squamous cell carcinoma
	IFITM family [46, 47]	Impairment of virion assembly through glycoprotein binding	Amyloid plaques formation
	SERINC family [48]	Disruption of virus membrane asymmetry	Not reported
	PSGL-1 [49, 50]	Inhibition of viral assembly through sequestration of gp41 protein	Blockage increases survival in an endotoxemia mice model

Concluding remarks

Restriction mechanisms used by antiviral factors are able to target virtually all the steps of the viral cycle and depend on physical interactions as well as enzymatic or signaling activities (Table 1). Because viral replication and host cellular systems depend on the same molecular mechanisms, namely, replication, transcription and translation, strategies used by cells to restrict viral infection can have dele-

terious effects on physiological processes. However, restriction factors can also drive pathological phenotypes through processes that are independent of their antiviral activity. In this review, we have illustrated the main mechanisms by which most proteins of the autonomous innate immune system can block the viral cycle. Additional mechanisms such as ISGylation of viral proteins or modification of membrane fluidity have also been described as important levels of innate cellular responses against

certain viruses.

The restriction factors discussed in this review highlight the variety of biological activities that can converge on the inhibition of a single molecular process. As our knowledge of viral infectious mechanisms progresses, more cellular proteins that use novel mechanisms to inhibit the viral cycle will be discovered. These studies will also evolve as we leverage new technologies such as CRISPR-based screens that are already being used in the high-throughput discovery of antiviral factors. Moreover, the disease-driving mechanisms discussed here stress the importance of studying restriction factor function beyond immune response. An important part of these proteins are involved in cellular processes outside of antiviral response and can as such disturb key biological processes such as cell apoptosis and proliferation. Overall, our understanding of restriction factors will be crucial to elucidate the complexity of antiviral response and the role antiviral proteins and mechanisms can have in organisms as a whole.

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