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Review

From APOBEC to ZAP: Diverse mechanisms used by cellular restriction factors to inhibit virus infections

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ABSTRACT

Antiviral restriction factors are cellular proteins that inhibit the entry, replication, or spread of viruses. These proteins are critical components of the innate immune system and function to limit the severity and host range of virus infections. Here we review the current knowledge on the mechanisms of action of several restriction factors that affect multiple viruses at distinct stages of their life cycles. For example, APOBEC3G deaminates cytosines to hypermutate reverse transcribed viral DNA; IFITM3 alters membranes to inhibit virus membrane fusion; MXA/B oligomerize on viral protein complexes to inhibit virus replication; SAMHD1 decreases dNTP intracellular concentrations to prevent reverse transcription of retrovirus genomes; tetherin prevents release of budding virions from cells; Viperin catalyzes formation of a nucleoside analogue that inhibits viral RNA polymerases; and ZAP binds virus RNAs to target them for degradation. We also discuss countermeasures employed by specific viruses against these restriction factors, and mention secondary functions of several of these factors in modulating immune responses. These important examples highlight the diverse strategies cells have evolved to combat virus infections.

1. Introduction

Antiviral restriction factors are cellular proteins that target specific stages of virus life cycles to limit virus replication. These factors generally target virus features or replication mechanisms that are broadly conserved within virus orders or families [1]. Restriction factors are a critical component of the innate immune response to virus infections, and are often essential for slowing virus replication in vivo until an adaptive immune response can further reduce or eliminate infections. Restriction factors are most often encoded by interferon (IFN) stimulated genes (ISGs), allowing the simultaneous induction of multiple factors via IFN to inhibit virus replication through distinct mechanisms [2].

The multifactorial and sometimes redundant effect of multiple ISG-encoded restriction factors on a specific virus is thought to be a critical adaptation to the evolutionary pressure provided by rapidly mutating viruses that can evolve to evade or counteract individual restriction factors [3]. Indeed, many examples have been described in which virus proteins induce the inactivation or degradation of particularly detrimental restriction factors. Likewise, viruses also utilize strategies to mask their recognition by restriction factors or mutate protein domains or genomic features that would otherwise interact with restriction factors. Virus mutations allowing evasion of restriction factors can also promote the counter-evolution of the host. Although host evolution occurs over much longer timescales than virus evolution, the relatively rapid evolution of restriction factors compared to other host genes in response to virus adaptations has been suggested to be an identifying signature of restriction factor genes [4]. The constant cycles of virus and host counter-evolution have been referred to as Red Queen interactions, a literary reference to the Red Queen's race in Lewis Carroll's *Through the Looking-Glass* in which running is required to stay in the same place. In addition to viral adaptations to individual restriction factors, pathogenic mammalian viruses usually encode broad antagonists of the IFN induction or signaling pathways to restrain the overall induction of restriction factors [5]. Given the inherent mutability of viruses and their mechanisms of immune evasion, a multipronged host immune response is thus required for defense, including numerous restriction factors. A list of known restriction factors active against human viruses and the specific virus life cycle stages at which they act are shown in Table 1.

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Table 1
Known antiviral restriction factors and the stage(s) of virus life cycles that they inhibit. Asterisks indicate that these factors are discussed in detail in this review article.

Restriction factor	Stage of virus life cycle	References
ADAP2	Entry	[199]
APOBEC3A,B,C,D,F,G*,H	Reverse transcription, transcription, replication	[6,200–204]
B4GALNT2	Entry	[205]
CH25H	Entry	[206,207]
CypA,E	Transcription, replication	[208–210]
DDX21	Assembly	[211]
HERC5	Assembly, nuclear export	[212]
ISG15	Assembly, replication	[213]
ISG20	Replication	[214]
IFI16	Transcription	[215]
IFIT1,2,3,5	Translation	[216,217]
IFITM1,2,3*	Entry	[40]
KAP1 (TRIM28)	Integration, transcription	[218]
LGALS3BP	Assembly	[219,220]
MOV10	Nuclear import	[221,222]
MXA*,B*	Nuclear import, transcription	[71,78–80]
MYPOP	Transcription	[223]
PAI-I	Egress	[224]
PKP2	Replication	[225]
PKR	Translation	[226,227]
RNase L/OAS	Assembly	[228]
RIN2	Entry	[205]
SAMD9	Assembly	[229]
SAMHD1*	Reverse transcription, transcription	[101,102]
SERINC 3,5	Entry	[230,231]
SLFN11	Translation	[232]
SPOC1	Transcription	[233]
Stannin	Entry	[234]
Tetherin*	Egress	[125,127]
TM9SF2	Entry	[205]
TRIM5a	Uncoating	[235–238]
TRIM22	Transcription	[239]
TRIM25	Replication	[240]
TRIM32	Transcription	[241]
TRIM56	Replication	[242]
VIPERIN*	Transcription	[157]
ZAP*	Translation	[176,180]
ZMPSTE4	Entry	[55]

The discovery of restriction factors has also provided us with a deeper understanding of why some cell types and some hosts are particularly susceptible to specific viruses. For example, restriction factors can contribute to the cell type specificity of some viruses by preventing infection of cell types in which certain restriction factors are highly expressed or activated under basal conditions. Likewise, restriction factors can influence the host range of specific viruses. This can occur when viruses evolve to evade a restriction factor in one host while remaining susceptible to homologous, but non-identical, factors in other hosts. Further, we are beginning to appreciate that human susceptibility to virus infections can be influenced by mutations in relevant restriction factor genes. To illustrate the numerous concepts cited above, we review here the current state of knowledge regarding several important restriction factors chosen from Table 1. These specific factors described below were selected because they provide compelling examples of virus inhibition involving unique enzymatic and non-enzymatic mechanisms of action against a broad array of distinct viruses at multiple stages of their life cycles. Indeed, they also provide illustration of the concepts of virus-host co-evolution, cell type-specific virus restriction, virus host range restriction, and effects of restriction factor mutations on severity of infection. In addition to better understanding of virus-host interactions, the discovery and mechanistic characterization of restriction factors may ultimately help to identify susceptible points in the replication cycles of specific viruses for targeted antiviral development.

2. APOBEC3G

Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G (APOBEC3G or A3G), was identified in 2002 as an antiviral protein active against HIV-1 [6], and it has also been shown to inhibit other retroviruses, as well as Hepatitis B virus (HBV) [6,7]. A3G belongs to the APOBEC family of cytidine deaminases, almost all of which share some degree of antiviral functionality [6–8], with each member also sharing a conserved zinc coordination motif which functions in nucleic acid substrate binding [9]. A3G possesses two homologous domains termed catalytic domains 1 and 2, though only the second catalytic domain has intact enzymatic activity (Fig. 1). A3G is a particularly potent restriction factor among the APOBEC family, and is basally expressed at varying levels in different cell types and is inducible by IFNs [10,11].

The exact mechanism of viral inhibition utilized by A3G and whether deaminase activity is required was initially an area of contention in this field [12–17]. Ultimately, A3G has been shown to inhibit retrovirus and HBV replication in deaminase-dependent and -independent manners [18–20]. Using a deaminase-independent mechanism, A3G prevents viral reverse transcription [8,21,22], while the deaminase-dependent functionality of A3G induces hypermutation of viral genomes via cytidine deamination [23–25] (Fig. 2). Independent of its deaminase activity, A3G can bind to the retroviral RNA template or ssDNA wherein A3G can act as a physical block to viral reverse transcriptase (RT) [21,26]. The ability of A3G to act as a block on the viral template strand has been linked to its ability to form an oligomer [22]. More specifically, A3G dimerization and oligomerization reduces its dissociation from viral ssDNA, suggesting that A3G oligomer formation promotes physical attachment to viral nucleic acids [8,22]. Additionally, A3G has been shown to directly interact with RT, which could potentially decrease RT function or contribute to blockade of RT processivity, though the precise effect of this interaction is not fully understood [26].

In order to function effectively as a cytidine deaminase active against HIV-1, A3G first needs to be incorporated into progeny HIV-1 virions, and this ability to incorporate into virions distinguishes A3G from most other APOBEC family members. Specifically, A3G localizes with the viral genetic material and is subsequently encapsidated into nascent virions as they assemble [27,28]. Encapsidation of A3G is facilitated through, and dependent on, the direct interaction of A3G with the nucleocapsid region of the HIV-1 Gag protein [29–31]. Once encapsidated, A3G interacts with the viral genome following subsequent infection by and uncoating of the virus in a new cell. A3G deaminates residues on the negative sense single stranded HIV-1 reverse transcribed DNA. This deamination causes deoxycytidine to deoxyuridine mutations leading to guanine-to-adenosine transformations once the virus completes reverse transcription [23–25,32]. The high substitution rate of nucleic acids within the viral DNA leads to production of non-viable virus via introduction of unstable or nonfunctional amino acid substitutions and introduction of stop codons. A3G can also cause mutations in other retroviruses and HBV [7]. Interestingly, A3G-induced hypermutation is thought to contribute minimally to HIV-1 evolution rates due to an “all or nothing” phenomenon in which A3G-mutated viruses are usually non-viable [33,34].

One of the first discovered examples of a viral countermeasure for a specific restriction factor is the degradation of A3G by the HIV-1 accessory protein known as Vif [6,32]. Indeed, Vif has been shown to almost completely prevent the virion incorporation of A3G in the presence of Cul5, elongins B and C, and Rbx1 [35,36]. These proteins together form an E3 ubiquitin ligase complex that ubiquitinates and targets A3G for proteasomal degradation [35,36]. Similarly, the HBV X protein (HBx) has been suggested to decrease A3G levels in infected cells through an exocytosis mechanism [37]. The existence of Vif and HBx as viral countermeasures to A3G, a potent antiviral restriction factor, highlights the ongoing evolutionary race between viruses and

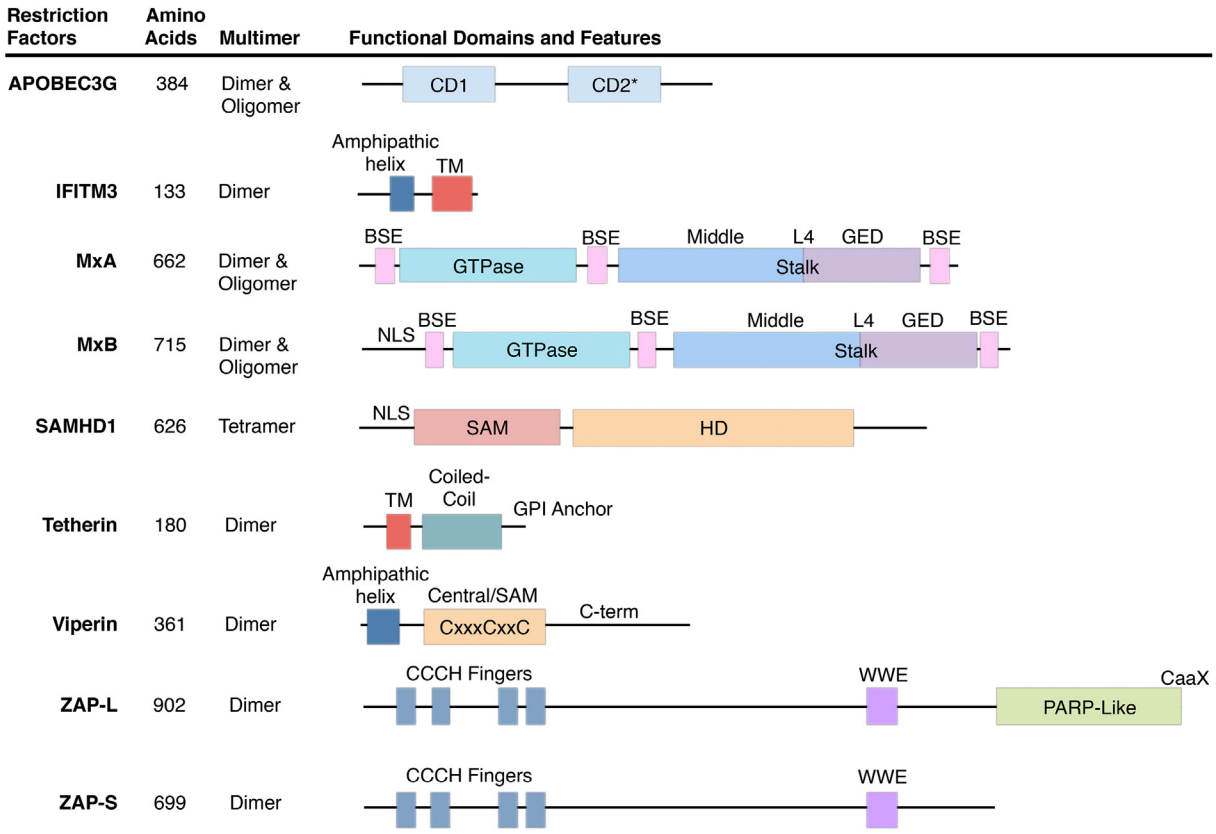

Fig. 1. Antiviral restriction factors utilize diverse functional domains and structural features. Domain architecture for individual restriction factors are shown with amino acid lengths and the multimeric state in which the protein possesses restriction activity. Abbreviations: CD, catalytic domain; *indicates enzymatic activity; TM, transmembrane domain; NLS, nuclear localization sequence; BSE, bundle signaling element; GED, GTPase effector domain; SAM, sterile alpha motif (in SAMHD1) or S-Adenosyl methionine (in Viperin); GPI, glycosylphosphatidylinositol; CxxxCxxC, Fe-S binding motif containing three cysteine residues separated by any amino acids (x); C-term, C-terminal domain; PARP, poly(ADP-ribose) polymerase; CaaX, prenylation consensus site comprised of a cysteine residue followed by two aliphatic amino acids, and any amino acid. HD, CCCH, and WWE domains are named for specific amino acid sequence elements.

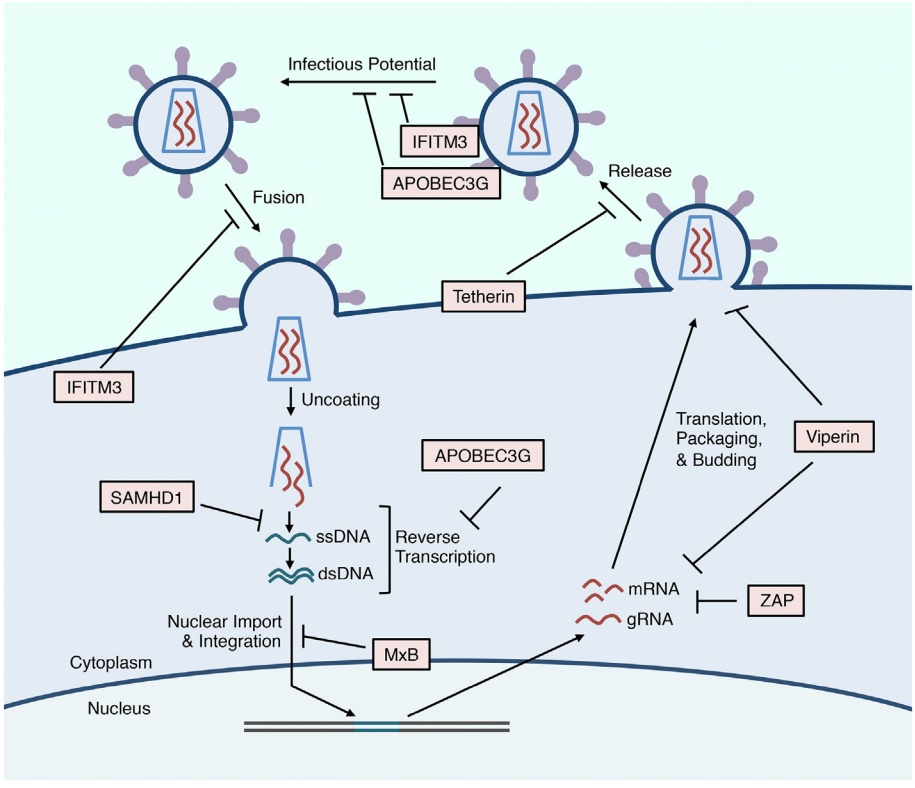

Fig. 2. Restriction factors inhibit virus replication at multiple stages of the viral life cycle. The replication cycle of a retrovirus is depicted and inhibition of specific life cycle stages by individual restriction factors is indicated. IFITM3 inhibits virus fusion and is also incorporated into nascent virion membranes to limit the fusogenicity/infectious potential of the virus. IFITM3 is primarily associated with inhibition of fusion at virus endosomes, but is shown here inhibiting fusion at the cell surface for graphical simplicity. SAMHD1 depletes dNTPs thereby inhibiting viral reverse transcription. APOBEC3G blocks reverse transcriptase processivity and also deaminates/hypermutates viral ssDNA. APOBEC3G associates with viral genomic material and is packaged into nascent virions, thus allowing its activity to impair replication in newly infected cells. MxB interacts with viral proteins and prevents nuclear import and integration of reverse transcribed viral DNA. ZAP interacts with viral RNAs possessing CG dinucleotide sequences and targets them for degradation. Viperin affects membrane composition to affect virus budding and also enzymatically produces a small molecule that inhibits viral RNA polymerases. Tetherin provides a physical tether preventing nascent virions from being released from the cell. Viral countermeasures active against these proteins are not depicted.

their hosts.

3. IFITM3

IFN-induced transmembrane protein 3 (IFITM3) is a 133 amino acid protein that associates with membranes via a transmembrane domain and a palmitoylated amphipathic helix (Fig. 1) [38,39]. Although it does not possess any known enzymatic activity, IFITM3 utilizes several mechanisms to limit virus infection of cells. The first described and most extensively studied antiviral mechanism for IFITM3 is its ability to block virus entry (Fig. 1). For influenza virus, this inhibition was mapped to the virus fusion step, which occurs in cellular endosomes where IFITM3 is abundantly localized [40–42]. Indeed, while virus endocytosis occurs similarly in control cells versus cells expressing IFITM3, virus fusion and genome deposition into the cytoplasm does not occur when IFITM3 is present, and virus is likely degraded in lysosomes [41,42]. Live-cell microscopy of infection with fluorescent molecule-loaded virus demonstrated that virus-to-endosome membrane hemifusion occurs normally in cells expressing IFITM3, suggesting that IFITM3 blocks the transition from membrane hemifusion to the opening of a fusion pore [41]. IFITM3 broadly inhibits the fusion of viruses, such as influenza virus, that enter cells via endocytosis, as well as HIV [38,43–45], indicating that it inhibits a highly conserved feature of the membrane fusion process even among viruses with divergent fusion proteins (Fig. 2).

Two studies have suggested that IFITM3 or related proteins can decrease membrane fluidity [46,47]. Additionally, IFITM3 antiviral activity is neutralized by the membrane-destabilizing drug amphotericin B [46] or by specific membrane curvature-inducing lipids [47]. Together, these reports suggest that IFITM3 alters membranes to prevent virus fusion. Disruption of membrane cholesterol homeostasis was suggested as a possible mechanism underlying this effect [48], but a role for cholesterol in inhibition of infections by IFITM3 has not been supported by subsequent studies [41,49]. More recently, the aforementioned amphipathic helix within IFITM3 and its amphipathicity were shown to be required for antiviral activity, and specifically for inhibition of membrane fusion mediated by viral proteins [38]. Likewise, the palmitoylation sites adjacent to the amphipathic helix are critical for antiviral activity and are likely involved in targeting or anchoring the helix to membranes [39,50–53]. Given the ability of amphipathic helices to induce membrane curvature, it is possible that the IFITM3 amphipathic helix induces or stabilizes local membrane curvature in a manner that disfavors fusion. IFITM3 dimerization, which is also required for antiviral activity [54], may serve to amplify the local effects of IFITM3 on membrane curvature. The antiviral function of IFITM3 has also been suggested to require interaction with a zinc metallopeptidase, ZMPSTE24, though ZMPSTE24 also functions as an antiviral restriction factor independently of IFITMs [55]. Additional studies with model lipid membranes will likely be required to elucidate the precise molecular mechanism by which the IFITM3 amphipathic helix and relevant cofactors act to prevent membrane fusion.

In addition to the role of IFITM3 in preventing virus entry via inhibition of fusion, it also provides additional protective mechanisms. In cells that become infected prior to induction of IFITM3, replicating virus incorporates newly upregulated IFITM3 and other related IFITM proteins into the membrane envelope of nascent budding virions [44,56]. The presence of these IFITMs reduces virion infectivity, likely through a mechanism that alters membrane fusion dynamics [44,56] (Fig. 2). This ability of IFITMs to incorporate into virions to decrease infectivity was first shown in HIV-1 infections, and was subsequently demonstrated for more than a dozen distinct viruses, including viruses that fuse at the plasma membrane and are otherwise resistant to IFITM3 inhibition in endosomes [57]. An additional effect of IFITM3 in inhibiting the processing of the HIV-1 env protein has also been described [58]. Further, a unique function of IFITM3 in inhibiting the type I IFN and IL-6 induction pathways has been identified, which may serve to limit virus-induced inflammatory pathologies in some instances [59,60]. Overall, in addition to broadly impacting virus infections by incorporating into both host and virus membranes, IFITM3 may also directly impair the replication of certain viruses, and may provide feedback inhibition of certain inflammatory pathways.

IFITM3 KO mice experience more severe influenza virus, West Nile virus, cytomegalovirus, and Chikungunya virus infections than WT mice, and likewise, SNPs in human *IFITM3* have been correlated with increased severity of influenza virus and Hantaan virus infections, as well as to more rapid progression of HIV-associated disease (the numerous studies demonstrating the critical importance of IFITM3 for antiviral defense in vivo were recently reviewed in [61]). It was also recently uncovered that the long-known resistance of human stem cells to virus infections is largely due to their IFN-independent expression of high levels of IFITMs that diminish as the cells differentiate [62]. Given the strong inhibition of infections by IFITM3, it is perhaps not surprising that strains of influenza virus and HIV-1 with reduced susceptibility to IFITM3 inhibition have been reported [63–65]. In the case of influenza virus, this reduced susceptibility correlates with adaptation of the hemagglutinin protein allowing the viruses to fuse at a higher pH and thus earlier in the endocytic pathway where IFITM3 is less abundant [64]. Resistance of HIV-1 to IFITM3 inhibition has also been mapped to mutations in its fusion glycoprotein [63,66]. To date, no viral proteins have been discovered that directly antagonize IFITM3 activity. However, specific coronaviruses paradoxically co-opt IFITM3 to enhance their entry, though the underlying mechanisms are not clear [67,68]. On the host side, some non-human primate species have duplicated their IFITM3 gene one or more times over the course of evolution [45]. Mutation of motifs that govern localization and stability are common in the duplicated genes, and this has been suggested to provide greater antiviral coverage of distinct host cell membrane compartments in these species [45].

4. MxA and MxB

Myxovirus resistance (Mx) proteins are dynamin-like GTPases [69] that are not constitutively expressed in most cells types, and are under the control of IFN signaling [70]. Humans have two Mx proteins, MxA and MxB, which differ in their cellular localization [71,72]. Human MxA is largely cytoplasmic [71] though oligomeric forms of MxA can accumulate around the nuclear periphery [73]. MxA restricts a broad range of viruses including RNA viruses, such as influenza A virus [74], and DNA viruses, such as hepatitis B virus [75]. Demonstrating the importance of Mx proteins in vivo, many laboratory mouse strains, such as balb/c and C57BL/6, lack a functional MxA homolog, and this contributes to the high susceptibility of these strains to influenza virus infections as compared to outbred or Mx-reconstituted mice [76,77]. MxB is primarily known to act against HIV-1 [78–80]. MxB localization to the nuclear envelope is governed by an N-terminal nuclear localization signal (NLS) [81]. Appending the NLS of MxB to MxA was sufficient to target MxA to the nuclear envelope and convert MxA into an HIV-1 restriction factor [82], suggesting that MxB and MxA may employ overlapping antiviral mechanisms even though their cellular sites of action are different.

Mx GTPases have an N-terminal GTPase domain, followed by a middle domain, and a C-terminal GTPase effector domain, commonly referred to as a GED [83] (Fig. 1). The antiviral activity of Mx proteins depends on intricate 3-dimensional configurations. The C-terminal GED interacts with the N-terminal GTPase domain to form the active site for GTPase activity, which is required for antiviral activity against several viruses [84]. Mx proteins dimerize via intermolecular interactions occurring between structured regions called the stalk, and mutations in the stalk prevent oligomerization and antiviral activity [85]. Within the stalk region lies a key unstructured loop called loop 4 (L4) that forms critical interactions with viral components and is positively selected in primates [86]. Higher order Mx configurations resemble ring-like

structures and are formed as a result of intermolecular interactions between dimers, wherein the stalk of one molecule interacts with a region of another molecule called the bundle signaling element (BSE) that is comprised of three distinct regions of the protein that interact upon proper folding [87].

Intermolecular Mx interactions play a significant role in the antiviral mechanism. For example, it is proposed that, prior to primary transcription, viral ribonucleoprotein complexes are surrounded by ring-like MxA multimers that interfere with subsequent steps of the influenza virus life cycle [87]. However, conflicting evidence indicates that MxA acts at a step after primary transcription in which dimerization, but not higher-order oligomerization is required for antiviral activity of MxA against IAV [73]. Recent work also suggests that MxA requires cofactors, such as IFITM2, for its activity against influenza virus, although understanding the mechanistic link between these two ISGs will require additional studies [88]. Similar to recognition of ribonucleoprotein complexes by MxA, MxB dimers act against HIV-1 by recognizing the HIV capsid protein at the nuclear envelope to prevent nuclear import and genome integration [89,90] (Fig. 2). Interestingly, human isolates of influenza A virus are largely insensitive to restriction by human MxA, while avian viruses are highly sensitive [91]. Recent reports have identified sites on the nucleoprotein that dictate sensitivity of human and avian influenza viruses to MxA [92,93], overall suggesting that MxA is an important barrier for restricting transmission of avian influenza viruses to humans. Likewise, HIV-1 capsid protein mutations can reduce sensitivity to MxB restriction [78–80], further exemplifying the complex virus-host evolutionary landscape.

5. SAMHD1

Human sterile alpha motif and HD-domain containing protein 1 (SAMHD1) is the only enzyme with deoxynucleoside triphosphate triphosphohydrolase (dNTPase) activity in mammalian cells [94]. SAMHD1 degrades dNTPs into deoxynucleoside and inorganic triphosphate and, together with the enzyme responsible for dNTP biosynthesis, plays a key role in maintaining a balanced dNTP intracellular concentration. SAMHD1 is ubiquitously expressed in all cell types, where it localizes in both the cytoplasm and nucleus, and exists as a monomer, dimer or tetramer, with oligomerization being induced by binding of GTP and dGTP [95]. Tetramerization is essential for SAMHD1 dNTPase activity [96], which resides in its central HD domain. This domain is also responsible for the nucleic acid binding ability of SAMHD1 [97] (Fig. 1).

Due to its ability to regulate dNTP homeostasis and nucleic acid metabolism, SAMHD1 is considered a pleiotropic molecule involved in several cellular processes. A correlation between SAMHD1 and the cell cycle has been suggested by numerous studies proposing a control of SAMHD1 activity during cell cycle progression. Indeed, these reports show that SAMHD1 is active during the G_0–G_1 phases of the cell cycle, but is inactive in the S-phase, in which high dNTP levels are required to ensure efficient DNA replication [98]. Moreover, SAMHD1 inhibits cell growth and proliferation, delays cell cycle progression and induces spontaneous apoptosis in acute myeloid leukemia- and cutaneous T-cell lymphoma-derived cell lines [99,100], providing a further link between SAMHD1 and the cell cycle.

SAMHD1 was identified in 2011 as a restriction factor of human immunodeficiency virus type 1 (HIV-1) infection in dendritic cells (DCs) and macrophages, and in resting $CD4^+$ T cells, each of which are non-dividing cells in which SAMHD1 dNTPase function is active [101,102]. Further, via mass spectrometry analysis, it was discovered that SAMHD1 is the target of the lentiviral protein X (Vpx) encoded by HIV-2 and some strains of simian immunodeficiency virus (SIV) [101,102]. Vpx counteracts SAMHD1-mediated restriction of HIV-1 infection by binding to the C-terminal domain of SAMHD1 and inducing its degradation by the proteasome. The mechanism by which SAMHD1 inhibits HIV-1 infection relies on its dNTPase activity. SAMHD1 depletes the dNTP pools, thus preventing HIV-1 reverse transcription, leading to abortive infection [103,104] (Fig. 2). Additional reports have shown that, through the same mechanism, SAMHD1 is able to restrict other retroviruses and certain DNA viruses, including herpes simplex virus type 1, vaccinia virus and hepatitis B virus [105,106].

Mechanistic studies unveiled, at least in part, how SAMHD1 restriction ability is regulated. Resolution of the SAMHD1 crystal structure revealed that mutation of dGTP binding sites in the allosteric domain impairs SAMHD1 tetramerization, dNTPase activity, and restriction of HIV-1 infection, suggesting that dGTP-dependent tetramerization is critical for the catalytic activity of the enzyme [107]. In addition to the structural features necessary to maintain its activity, post-translational modification of SAMHD1 also controls its function. Phosphorylation of SAMHD1 at threonine 592 (T592) by cell cycle regulatory complexes including cyclin A, CDK1, CDK2 and CDK6 impairs its ability to block HIV-1 infection [108–111] and destabilizes tetramer formation [112]. SAMHD1 contains a cyclin binding motif that mediates the interaction with these cyclin-CDK complexes and that influences SAMHD1 protein expression, stability and phosphorylation, as well as tetramerization, dNTPase activity and HIV-1 restriction [113]. Increased phosphorylation of SAMHD1 during the S-phase of the cell cycle due to the high expression levels of cyclin A-CDK1-CDK2 complexes correlates with increased sensitivity of dividing cells to HIV-1 infection, suggesting a tight link between SAMHD1 restriction ability and cell cycle progression.

Depletion of dNTPs is thought to be the primary mechanism by which SAMHD1 restricts virus infections. However, addition of exogenous deoxynucleotides does not fully rescue HIV-1 infection in target cells, suggesting that SAMHD1 restriction may also occur through a dNTPase-independent mechanism. Additionally, while T592 phosphorylation blocks HIV-1 restriction, it does not completely abolish SAMHD1 dNTPase activity [109], further supporting the hypothesis that an additional restriction mechanism may exist. It has been proposed that the ability of SAMHD1 to degrade incoming HIV-1 genomic RNA through an RNase activity may contribute to HIV-1 restriction [114]. However, these findings were refuted by other studies [115], and whether SAMHD1 possesses RNase activity and whether this is involved in restricting HIV-1 infection is still under debate.

SAMHD1 is reported to be mutated in some human patients affected by Aicardi Goutières Syndrome (AGS), an auto-inflammatory disorder mimicking congenital viral infections and sharing similarities with systemic lupus erythematosus, such as aberrant accumulation of type I IFN in the cerebrospinal fluid and serum [116,117]. Moreover, a transcriptome analysis in macrophages from SAMHD1 KO mice showed that the expression levels of 123 ISGs were spontaneously increased in comparison to macrophages from SAMHD1 wild-type mice, and this effect was dependent on IFN-I signaling, as the phenotype was reversed in mice with double KO of SAMHD1 and type I IFN receptor [118]. Collectively, these reports linked SAMHD1 to innate immunity and suggested that SAMHD1 functions as negative regulator of innate immune responses. Notably, the *SAMHD1* promoter does not contain the conventional IFN-responsive elements found in other ISGs, but it can be bound and activated by interferon regulatory factor 3 (IRF3), a transcription factor that is activated by virus infection and that is involved in induction of type I IFN [119], indicating that SAMHD1 expression is upregulated concurrently with IFN production.

Recent work has provided insights into the mechanisms by which SAMHD1 regulates innate immune responses against viruses. IRF7 and inhibitor of NF-κB kinase subunit epsilon (IKKε) were identified as SAMHD1 binding partners, and it was discovered that SAMHD1 reduces IKKε-mediated IRF7 phosphorylation, thus limiting type I IFN induction during virus infection [120]. SAMHD1 also blocks activation of NF-κB signaling by binding to NF-κB 1/2 and reducing phosphorylation of the NF-κB inhibitory protein IκBα [120]. Another group implicated IRF3 as the major mediator of SAMHD1-induced control of innate immune activation, and described involvement of the PI3K/Akt/IRF3 pathway is

ISG induction in SAMHD1 KO monocytic THP-1 cells [121]. These data also suggest that SAMHD1 suppresses IFN responses through its purported RNase activity, though the source of RNA and the RNA sensor that is involved remain to be identified in these experimental conditions. Additionally, a recent study has established a role for SAMHD1 in stimulating degradation of DNA fragments at stalled DNA replication forks, which prevents these fragments from stimulating an IFN response [122]. Unlike HIV-2 and SIV strains, HIV-1 does not use Vpx to degrade SAMHD1, but can establish productive infection in target cells. It has been speculated that less pathogenic HIV-1 may rely on SAMHD1-mediated immune suppression to dampen the triggering of antiviral innate immune responses. A study performed in rhesus macaques infected with two SIV strains showed that Vpx is required in vivo for the establishment of productive infection in memory $CD4^+$ T lymphocytes, confirming the role of SAMHD1 in retroviral replication and virus-induced immunodeficiency in vivo [123]. However, additional studies in animal models will help to further investigate how SAMHD1 controls innate immune responses during HIV-1 infection.

6. Tetherin

Bone marrow stromal antigen 2 (BST2, more often referred to as tetherin) was first implicated as an antiviral protein when it was identified as a target of the HIV-1 protein Vpu, although its function in restricting HIV-1 remained unclear [124,125]. It was not until its mechanism of action was elucidated that BST2 was aptly renamed tetherin for its ability to tether budding HIV-1 virions to the cell membrane [125]. Numerous groups have since confirmed this ability of tetherin to inhibit the release of HIV-1 via the tethering mechanism for which it was named [126,127]. Indeed, tetherin utilizes an N-terminal transmembrane (TM) domain and a C-terminal glycosylphosphatidylinositol (GPI) anchor (Fig. 1) to attach to the plasma membrane and simultaneously incorporate into HIV-1 particle membranes to physically anchor virions to the plasma membrane [126,128–130] (Fig. 2).

There are several points of contention in this field involving the dimerization of tetherin molecules in relation to is activity. It is widely believed that dimerization of tetherin is indispensable for its activity against HIV-1, but dimerization may not be required for the restriction of all viruses inhibited by tetherin [131,132]. Moreover, the conformation of tetherin dimers has been a subject of debate in the field. It was originally unclear whether the dimers oriented in a parallel or antiparallel fashion, but multiple studies utilizing domain mutagenesis and crystallography showed that the dimers orient in a parallel manner [126,133]. After this finding, there was still disagreement as to how the dimers inserted into the membranes of the cell and budding virus. In one of the earlier works describing the activity of tetherin, it was concluded that the homodimers insert indiscriminately into the membranes [126]. However, a more recent study screened an extensive library of engineered tetherin dimer constructs and found that although it was possible for either membrane-associated domain to interact with the budding virion, the C-terminal GPI anchor preferentially interacted with the viruses, as these interactions occurred at approximately five times the rate of TM domain-virion interactions [130].

In terms of the properties of tetherin that allow it to anchor virions to the plasma membrane, it has been shown that a conserved coiled-coil domain within the protein allows for flexibility when tethering virions, while disulfide bonds between the dimerized coils maintain stability of the tethers [128,129,133,134]. Although murine tetherin lacks exact structural homology to the human homolog, it similarly restricts release of both HIV-1 and Moloney murine leukemia virus [135–137]. While tetherin is sometimes referred to as an intrinsic antiviral protein due to its basal expression in many cell types, both human and murine tetherin are ISGs, and it is appreciated that increased levels of tetherin induced by IFN provides increased antiviral activity beyond baseline tetherin levels [135,138].

Canonical assembly and egress of HIV-1 particles occurs at the plasma membrane in epithelial cells and T cells, while in macrophages, HIV-1 replicates in intracellular virus-containing vesicles (VCCs) [139]. In addition to its plasma membrane localization, tetherin has been shown to localize to VCCs and effectively inhibit HIV-1 release in macrophages [140]. The broad activity of tetherin against HIV-1 has led many to hypothesize that the protein does not interact with specific viral proteins but rather acts in a more generalized manner. Supporting this line of thought, tetherin has been shown to inhibit a diverse range of human viruses in addition to HIV-1, including influenza A virus [141–143], vesicular stomatitis virus [144], Lassa virus [145,146], and Hepatitis B virus [147]. In each of these cases, viral egress is significantly limited in the presence of tetherin, highlighting the broad antiviral activity of this protein.

Tetherin also plays a role in the immune response to infections. Following infection with HIV-1, tetherin promotes viral sensing and a subsequent NF-κB-driven inflammatory response to the virus [148]. Additionally, tetherin-deficient mice exhibit weaker natural killer cell, dendritic cell, and CD8+ T-cell responses to Friend retrovirus, coupled with higher viral loads, suggesting that tetherin is essential for an adequate immune response to this virus [149,150]. In each case, the immunostimulatory activity of tetherin was linked to a cytoplasm-facing endocytosis motif that is not involved in its tethering activity [148–150].

In rare instances, tetherin has been shown to increase viral replication and dissemination. The egress of human cytomegalovirus (CMV), for example, is not restricted by tetherin and the virus conversely replicates to higher titers in the presence of tetherin [151]. It has been hypothesized that interaction between tetherin and CMV at the cell surface facilitates viral entry [151]. Further, several viruses encode proteins that antagonize or counteract the activity of tetherin. Tetherin exhibits little to no inhibitory activity against HIV-1 in the presence of Vpu, as it has been shown that Vpu co-localizes with tetherin and facilitates its removal from the plasma membrane and degradation via endosomal trafficking [127,152]. HIV-2 and simian immunodeficiency viruses, most of which lack Vpu, utilize other proteins to downregulate tetherin at the cell surface [153]. The Ebola virus glycoprotein (GP) has also been shown to counteract the activity of tetherin, and it was recently discovered that GP blocks the interaction between tetherin and the Ebola virus protein VP40 [154,155]. Overall, the multiple mechanisms by which tetherin directly and indirectly influences viral infections, as well as the variety of viral countermeasures, highlight its significance as a key antiviral restriction factor.

7. Viperin

The Viperin (virus inhibitory protein, endoplasmic reticulum associated, interferon inducible) gene was first identified as two cDNA fragments named cig5 and cig33 that were induced in human cytomegalovirus (HCMV) infected fibroblasts [156]. It was later discovered that cig5 and cig33 were fragments of the single Viperin gene that was induced by IFN stimulation, and displayed potent activity against HCMV [157]. Induction of Viperin can also occur via an IFN independent mechanism during virus infections via activation of the IRF1/3 transcription factors [158]. As a member of the radical S-adenosyl L-methionine (SAM) superfamily of enzymes, Viperin (also called radical SAM-domain containing 2 or RSAD2) reduces SAM to a 5′deoxyadenosyl radical intermediate via an iron-sulfur (Fe-S) cluster binding motif that is conserved among SAM enzymes [159,160]. This Fe-S binding motif containing a conserved CxxxCxxC sequence is located within the central domain of the protein (Fig. 1) and is required for antiviral function against HIV, HCMV, Bunyamwera virus and Hepatitis C Virus (HCV) [161–164]. In addition to the central domain, Viperin has an N-terminal domain containing an amphipathic helix that is responsible for its cellular localization to the cytosolic face of the ER [165,166], and a highly conserved C-terminal domain, which is required for its dimerization and antiviral functions against HCV and

dengue virus (DENV) [166–169] (Fig. 1).

Viperin has been reported to restrict viruses via multiple mechanisms. At the stage of HIV-1 and influenza virus release from cells, Viperin can disrupt formation of lipid raft membrane domains that promote viral egress [162,170], though whether Viperin plays a major role in restricting HIV infection of cells remains an area of contention [162,171]. Alternatively, Viperin acts against flaviviruses such as DENV and HCV by interaction with viral components. The binding of the N-terminal amphipathic helix to the HCV NS5A protein is required for HCV restriction [166] possibly by competing with a proviral host protein for binding with NS5A [166,172]. Similarly, Viperin interaction with the DENV NS3 protein via its C-terminus is required to limit DENV replication [167]. For HCV and DENV-2 restriction, the SAM domain was shown to be dispensable [166,167]. However, a recent landmark study demonstrated that Viperin utilizes a SAM-dependent mechanism to terminate RNA replication catalyzed by RNA-dependent RNA polymerases of multiple flaviviruses, including DENV and HCV [173]. Viperin catalyzes the conversion of cytidine triphosphate (CTP) to a previously unknown biological molecule, 3′-deoxy-3′,4′-didehydro-CTP (ddhCTP), that functions as a chain terminator for viral RNA extension by RNA-dependent RNA polymerases (RdRP) encoded by flaviviruses, such as HCV and Zika virus, but not picornavirus RdRP derived from poliovirus [173]. Treating Zika virus infected Vero cells with ddhCTP prevented virus replication and release with up to a 200-fold reduction in viral titer [173]. Viperin is the only restriction factor known to produce a small molecule that directly inhibits the viral replication machinery.

While exciting progress has been made in elucidating Viperin's mechanisms of action, several important questions remain. It is unclear why Viperin can catalyze a SAM-mediated mechanism against flaviviruses [173] even though the SAM domain is dispensable for flavivirus restriction [166,167]. This indicates that Viperin may possess multiple independent mechanisms to prevent viral replication. Indeed, Viperin also plays a role in enhancing IFN production by plasmacytoid dendritic cells in response to TLR ligands in addition to its direct antiviral effects [174]. The relevance of this role in vivo is yet to be investigated. Additionally, the exact role of the conserved C-terminal domain remains unknown, although it is required for antiviral activity against several viruses [166–168]. Possible roles for the C-terminal domain could include dimerization and/or facilitating the catalytic function of the SAM domain. Consistent with this facilitating role, mutating Trp361 in the C-terminus, which is required for interacting with the cytosolic Fe-S protein assembly (CIA) machinery that installs the Fe-S cluster into Viperin [175], abrogated the antiviral activity of Viperin [163]. It remains to be tested whether Trp361 and the CIA pathway are required for the SAM-dependent conversion of CTP to ddhCTP. Finally, it will be of interest to determine why ddhCTP blocks RdRPs from some viruses but not others [173], thereby enabling rational design of drugs that target the RNA replication machinery.

8. ZAP

Zinc finger antiviral protein (ZAP) is a broad spectrum antiviral protein first characterized by its ability to inhibit murine leukemia virus replication in rat cells [176]. ZAP is most abundantly found in the cytoplasm and restricts a wide array of viruses through several distinct mechanisms. In humans, two alternatively spliced ZAP isoforms exist. These short and long isoforms are referred to as ZAP-S and ZAP-L. ZAP-L contains a defective PARP (poly ADP-ribose polymerase)-like domain that is not present in the ZAP-S isoform (Fig. 1). This PARP domain is not enzymatically active but is important for the restriction of alphaviruses by ZAP-L, as mutation of this motif reduces its antiviral activity [177,178]. Both variants of ZAP contain four CCCH (cysteine-cysteine-cysteine-histidine) type zinc finger motifs at the N terminus, which are involved in binding viral RNA and mediating its degradation by recruiting the RNA processing exosome [176,179,180] (Fig. 1). The N-terminus is also involved in hetero- or homodimerization of ZAP isoforms [181]. Though these isoforms are similar, they restrict distinct viruses and respond to IFNs variably. For example, ZAP-L restricts MLV and alphaviruses more effectively than ZAP-S [177,178], possibly due to both its PARP domain, as well as farnesylation (Fig. 1), which uniquely targets ZAP-L to endolysosome membranes and promotes its antiviral activity [182]. Another discrepancy between S and L isoforms is that although both isoforms are induced by IFNs, ZAP-S is more highly increased by IFN treatment and virus infection [183,184]. Although ZAP-S appears to have less direct virus restriction activity than ZAP-L, ZAP-S also associates with the virus sensor RIG-I and aids in the production of type I IFNs by boosting RIG-I signaling [185].

Despite their differences, ZAP-S and -L both restrict a wide range of viruses including alphaviruses, filoviruses, Hepatitis B virus, influenza A virus, and retroviruses [176,183,186–192]. In addition, ZAP also restricts retrotransposition of Long Interspaced Element-1 (LINE-1), which is the only active retrotransposon in the human genome, by reducing the accumulation of LINE-1 RNA and its encoded proteins [190]. Thus, ZAP is not only a viral restriction factor but is also a critical regulator of integrated viral components and their activity within the human genome.

Much work has been focused on the ZAP mechanism of action, which is multifaceted and involves distinct cellular pathways. ZAP can directly interact with viral RNAs by binding to a virus specific sequence, called a ZAP responsive element (ZRE) [183], and recruit the RNA processing exosome to degrade the targeted viral RNA [179–181,193] (Fig. 2). In fact, ZAP's ability to bind viral RNA has been appreciated for some time but how ZAP broadly recognizes foreign RNAs was unclear. Recent seminal work demonstrated that the nucleotide composition of viral genomes, particularly the presence of CG dinucleotides, was the key contributor to ZAP mediated restriction of viruses [194]. Vertebrate genomes have a lower than expected numbers of CG dinucleotides, likely due to C to T mutations over the course of evolution. This dearth of CG dinucleotides is mimicked in many RNA virus genomes, including HIV-1, but the driving evolutionary force behind this was previously a mystery [194,195]. Examining HIV-1 with codons altered to contain an increased CG content while preserving the amino acid code showed that this altered virus replicated poorly in cells. Using an siRNA screen, it was determined that ZAP was responsible for restriction of the CG-containing virus, i.e., virus replication could be restored by depletion of ZAP [194]. Additionally, crosslinking-immunoprecipitation-sequencing experiments confirmed that ZAP selectively binds to CG enriched segments, providing a general mechanism whereby ZAP differentiates foreign genetic elements via the presence of CG dinucleotides [194] and thus suggesting that ZAP may be the evolutionary driver of viral mimicry of CG suppressed genomes.

Translation of incoming *Alphavirus* RNA may also be blocked when ZAP is present in cells [186], possibly by interfering with the translation initiation factors elF4G and elF4A [196]. Indeed, it has been shown that TRIM25, an E3 ubiquitin ligase, interacts with ZAP, is required for its activation, and enhances its ability to inhibit the translational activity of Sindbis virus [191]. As mentioned above, ZAP also indirectly inhibits viral infections by functioning as a downstream amplifier of the innate antiviral response. Using siRNA knockdown, ZAP was identified as a signaling cofactor that amplifies RIG-I activity, thereby promoting the production of IFNs and heightening the production of additional restriction factors [185]. Indeed, induction of IFNs by 5′ triphosphate-modified RNA, a RIG-I ligand, is increased by ZAP in a manner that is not dependent on the ZAP PARP domain [185].

Although ZAP restricts a broad range of viruses, VSV, poliovirus, and HSV-1 are among the viruses that are not restricted in ZAP overexpressing cells [186]. This observation is yet to be explained, but may involve CG dinucleotide content in these viruses or other evasion mechanisms. In fact, some viruses have evolved specific ZAP countermeasures. Enterovirus 71, which is a causative agent of hand-foot-mouth disease, utilizes its 3C protease to cleave and inactivate ZAP

[197]. Additionally, siRNA knockdown experiments identified the influenza A virus NS1 protein as an antagonist of ZAP-S [192], suggesting a dynamic relationship between viral proteins and ZAP.

9. Perspectives

The factors reviewed here are among the dozens of cellular proteins that are reported to limit virus infections [1,2] (Table 1), and additional antiviral restriction factors likely remain to be discovered. As seen in these selected examples, antiviral restriction factors target viruses at multiple stages in their life cycles, including entry, replication, and egress. Importantly, the enzymatic and non-enzymatic mechanisms utilized by these factors are diverse and their biochemical regulation within cells is complex. Understanding these mechanisms, honed by evolution, may ultimately inspire therapeutic strategies in which these mechanisms are mimicked or manipulated. For example, the enzymatic product of Viperin, ddhCTP, may serve as an antiviral molecule or starting point for development of new therapeutics given its specific inhibition of viral RdRPs without toxic effects on host cells. Similarly, better understanding of the countermeasures employed by viruses against restriction factors may also provide therapeutic targets for enabling these natural immune defense mechanisms in infections where they are otherwise inactivated.

It is also interesting to note that several of the restriction factors surveyed here serve dual functions as immunomodulators. IFITM3 serves as a feedback inhibitor of type I IFN induction by targeting the IRF3 transcription factor for autophagosomal degradation [60]. Likewise, IFITM3 has been implicated in decreasing IL-6 production by dendritic cells [59]. SAMHD1 has been similarly shown to negatively modulate IFN production by inhibiting NF-kB and IRF7 activation [120]. Conversely, Viperin enhances signaling downstream of TLRs to increase IFN production in plasmacytoid dendritic cells [174]. ZAP similarly enhances RIG-I-mediated signaling to increase type I IFN induction in infected cells [185]. Thus, many restriction factors increase or decrease immune responses to virus infections, and it will be interesting to delineate how these activities impact viral pathogenesis in vivo in comparison to their direct virus restriction abilities.

Finally, an exciting frontier in the restriction factor field is the emerging investigation of the genetic diversity among humans in the genes encoding these factors. Identification of deleterious polymorphisms may explain susceptibilities of individuals to severe infections, and this knowledge may ultimately inform personalized medicine approaches, such as vaccine prioritization or other measures to prevent or monitor specific infections [61,198]. Indeed, IFITM3 polymorphisms are among the only reproducibly identified genetic loci that correlate with enhanced severity of influenza virus infections [61,198]. Conversely, identifying mutations in humans or other species that expand restriction capabilities of individual factors via evasion of viral countermeasures could provide additional insights into infection susceptibilities and the evolving interaction interfaces between viruses and host factors. Overall, the investigation of cellular antiviral restriction factors will continue to critically inform our understanding of virus-host interaction dynamics, and we expect that appreciation of the medical importance of these factors will continue to grow.

Transparency document

The Transparency document associated with this article can be found, in online version.

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References

[1] J.W. Schoggins, D.A. MacDuff, N. Imanaka, M.D. Gainey, B. Shrestha, J.L. Eitson, K.B. Mar, R.B. Richardson, A.V. Ratushny, V. Litvak, R. Dabelic, B. Manicassamy, J.D. Aitchison, A. Aderem, R.M. Elliott, A. Garcia-Sastre, V. Racaniello, E.J. Snijder, W.M. Yokoyama, M.S. Diamond, H.W. Virgin, C.M. Rice, Pan-viral specificity of IFN-induced genes reveals new roles for cGAS in innate immunity, Nature 505 (2014) 691–695.

[2] J.W. Schoggins, S.J. Wilson, M. Panis, M.Y. Murphy, C.T. Jones, P. Bieniasz, C.M. Rice, A diverse range of gene products are effectors of the type I interferon antiviral response, Nature 472 (2011) 481–485.

[3] N.K. Duggal, M. Emerman, Evolutionary conflicts between viruses and restriction factors shape immunity, Nat. Rev. Immunol. 12 (2012) 687–695.

[4] M.D. Daugherty, H.S. Malik, Rules of engagement: molecular insights from host-virus arms races, Annu. Rev. Genet. 46 (46) (2012) 677–700.

[5] A. Garcia-Sastre, Ten strategies of interferon evasion by viruses, Cell Host Microbe 22 (2017) 176–184.

[6] A.M. Sheehy, N.C. Gaddis, J.D. Choi, M.H. Malim, Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein, Nature 418 (2002) 646–650.

[7] M. Bonvin, F. Achermann, I. Greeve, D. Stroka, A. Keogh, D. Inderbitzin, D. Candinas, P. Sommer, S. Wain-Hobson, J.P. Vartanian, J. Greeve, Interferon-inducible expression of APOBEC3 editing enzymes in human hepatocytes and inhibition of hepatitis B virus replication, Hepatology 43 (2006) 1364–1374.

[8] M. Morse, R. Huo, Y. Feng, I. Rouzina, L. Chelico, M.C. Williams, Dimerization regulates both deaminase-dependent and deaminase-independent HIV-1 restriction by APOBEC3G, Nat. Commun. 8 (2017) 597.

[9] A. Jarmuz, A. Chester, J. Bayliss, J. Gisbourne, I. Dunham, J. Scott, N. Navaratnam, An anthropoid-specific locus of orphan C to U RNA-editing enzymes on chromosome 22, Genomics 79 (2002) 285–296.

[10] F.X. Wang, J. Huang, H. Zhang, X. Ma, APOBEC3G upregulation by alpha interferon restricts human immunodeficiency virus type 1 infection in human peripheral plasmacytoid dendritic cells, J. Gen. Virol. 89 (2008) 722–730.

[11] F.A. Koning, E.N. Newman, E.Y. Kim, K.J. Kunstman, S.M. Wolinsky, M.H. Malim, Defining APOBEC3 expression patterns in human tissues and hematopoietic cell subsets, J. Virol. 83 (2009) 9474–9485.

[12] E. Miyagi, S. Opi, H. Takeuchi, M. Khan, R. Goila-Gaur, S. Kao, K. Strebel, Enzymatically active APOBEC3G is required for efficient inhibition of human immunodeficiency virus type 1, J. Virol. 81 (2007) 13346–13353.

[13] A.J. Schumacher, G. Hache, D.A. Macduff, W.L. Brown, R.S. Harris, The DNA deaminase activity of human APOBEC3G is required for Ty1, MusD, and human immunodeficiency virus type 1 restriction, J. Virol. 82 (2008) 2652–2660.

[14] E.P. Browne, C. Allers, N.R. Landau, Restriction of HIV-1 by APOBEC3G is cytidine deaminase-dependent, Virology 387 (2009) 313–321.

[15] E.N. Newman, R.K. Holmes, H.M. Craig, K.C. Klein, J.R. Lingappa, M.H. Malim, A.M. Sheehy, Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity, Curr. Biol. 15 (2005) 166–170.

[16] K. Shindo, A. Takaori-Kondo, M. Kobayashi, A. Abudu, K. Fukunaga, T. Uchiyama, The enzymatic activity of CEM15/Apobec-3G is essential for the regulation of the infectivity of HIV-1 virion but not a sole determinant of its antiviral activity, J. Biol. Chem. 278 (2003) 44412–44416.

[17] K.N. Bishop, R.K. Holmes, M.H. Malim, Antiviral potency of APOBEC proteins does not correlate with cytidine deamination, J. Virol. 80 (2006) 8450–8458.

[18] P. Turelli, B. Mangeat, S. Jost, S. Vianin, D. Trono, Inhibition of hepatitis B virus replication by APOBEC3G, Science 303 (2004) 1829.

[19] D.H. Nguyen, S. Gummuluru, J. Hu, Deamination-independent inhibition of hepatitis B virus reverse transcription by APOBEC3G, J. Virol. 81 (2007) 4465–4472.

[20] J. Kock, H.E. Blum, Hypermutation of hepatitis B virus genomes by APOBEC3G, APOBEC3C and APOBEC3H, J. Gen. Virol. 89 (2008) 1184–1191.

[21] Y. Iwatani, D.S. Chan, F. Wang, K.S. Maynard, W. Sugiura, A.M. Gronenborn, I. Rouzina, M.C. Williams, K. Musier-Forsyth, J.G. Levin, Deaminase-independent inhibition of HIV-1 reverse transcription by APOBEC3G, Nucleic Acids Res. 35 (2007) 7096–7108.

[22] K.R. Chaurasiya, M.J. McCauley, W. Wang, D.F. Qualley, T. Wu, S. Kitamura, H. Geertsema, D.S. Chan, A. Hertz, Y. Iwatani, J.G. Levin, K. Musier-Forsyth, I. Rouzina, M.C. Williams, Oligomerization transforms human APOBEC3G from an efficient enzyme to a slowly dissociating nucleic acid-binding protein, Nat. Chem. 6 (2014) 28–33.

[23] H. Zhang, B. Yang, R.J. Pomerantz, C. Zhang, S.C. Arunachalam, L. Gao, The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA, Nature 424 (2003) 94–98.

[24] D. Lecossier, F. Bouchonnet, F. Clavel, A.J. Hance, Hypermutation of HIV-1 DNA in the absence of the Vif protein, Science 300 (2003) 1112.

[25] B. Mangeat, P. Turelli, G. Caron, M. Friedli, L. Perrin, D. Trono, Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts, Nature 424 (2003) 99–103.

[26] X. Wang, Z. Ao, L. Chen, G. Kobinger, J. Peng, X. Yao, The cellular antiviral protein APOBEC3G interacts with HIV-1 reverse transcriptase and inhibits its function during viral replication, J. Virol. 86 (2012) 3777–3786.

[27] V. Zennou, D. Perez-Caballero, H. Gottlinger, P.D. Bieniasz, APOBEC3G incorporation into human immunodeficiency virus type 1 particles, J. Virol. 78 (2004) 12058–12061.
[28] V.B. Soros, W. Yonemoto, W.C. Greene, Newly synthesized APOBEC3G is incorporated into HIV virions, inhibited by HIV RNA, and subsequently activated by RNase H, PLoS Pathog. 3 (2007) e15.
[29] S. Cen, F. Guo, M. Niu, J. Saadatmand, J. Deflassieux, L. Kleiman, The interaction between HIV-1 Gag and APOBEC3G, J. Biol. Chem. 279 (2004) 33177–33184.
[30] A. Schafer, H.P. Bogerd, B.R. Cullen, Specific packaging of APOBEC3G into HIV-1 virions is mediated by the nucleocapsid domain of the gag polyprotein precursor, Virology 328 (2004) 163–168.
[31] T.M. Alce, W. Popik, APOBEC3G is incorporated into virus-like particles by a direct interaction with HIV-1 Gag nucleocapsid protein, J. Biol. Chem. 279 (2004) 34083–34086.
[32] K. Stopak, C. de Noronha, W. Yonemoto, W.C. Greene, HIV-1 Vif blocks the antiviral activity of APOBEC3G by impairing both its translation and intracellular stability, Mol. Cell 12 (2003) 591–601.
[33] K.A. Delviks-Frankenberry, O.A. Nikolaitchik, R.C. Burdick, R.J. Gorelick, B.F. Keele, W.S. Hu, V.K. Pathak, Minimal contribution of APOBEC3-induced G-to-A hypermutation to HIV-1 recombination and genetic variation, PLoS Pathog. 12 (2016) e1005646.
[34] A.E. Armitage, K. Deforche, C.H. Chang, E. Wee, B. Kramer, J.J. Welch, J. Gerstoft, L. Fugger, A. McMichael, A. Rambaut, A.K. Iversen, APOBEC3G-induced hypermutation of human immunodeficiency virus type-1 is typically a discrete "all or nothing" phenomenon, PLoS Genet. 8 (2012) e1002550.
[35] X. Yu, Y. Yu, B. Liu, K. Luo, W. Kong, P. Mao, X.F. Yu, Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex, Science 302 (2003) 1056–1060.
[36] M. Kobayashi, A. Takaori-Kondo, Y. Miyauchi, K. Iwai, T. Uchiyama, Ubiquitination of APOBEC3G by an HIV-1 Vif-Cullin5-Elongin B-Elongin C complex is essential for Vif function, J. Biol. Chem. 280 (2005) 18573–18578.
[37] R. Chen, X. Zhao, Y. Wang, Y. Xie, J. Liu, Hepatitis B virus X protein is capable of down-regulating protein level of host antiviral protein APOBEC3G, Sci. Rep. 7 (2017) 40783.
[38] N.M. Chesarino, A.A. Compton, T.M. McMichael, A.D. Kenney, L. Zhang, V. Soewarna, M. Davis, O. Schwartz, J.S. Yount, IFITM3 requires an amphipathic helix for antiviral activity, EMBO Rep. 18 (2017) 1740–1751.
[39] J.S. Yount, B. Moltedo, Y.Y. Yang, G. Charron, T.M. Moran, C.B. Lopez, H.C. Hang, Palmitoylome profiling reveals S-palmitoylation-dependent antiviral activity of IFITM3, Nat. Chem. Biol. 6 (2010) 610–614.
[40] A.L. Brass, I.C. Huang, Y. Benita, S.P. John, M.N. Krishnan, E.M. Feeley, B.J. Ryan, J.L. Weyer, L. van der Weyden, E. Fikrig, D.J. Adams, R.J. Xavier, M. Farzan, S.J. Elledge, The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus, Cell 139 (2009) 1243–1254.
[41] T.M. Desai, M. Marin, C.R. Chin, G. Savidis, A.L. Brass, G.B. Melikyan, IFITM3 restricts influenza A virus entry by blocking the formation of fusion pores following virus-endosome hemifusion, PLoS Pathog. 10 (2014) e1004048.
[42] E.M. Feeley, J.S. Sims, S.P. John, C.R. Chin, T. Pertel, L.M. Chen, G.D. Gaiha, B.J. Ryan, R.O. Donis, S.J. Elledge, A.L. Brass, IFITM3 inhibits influenza A virus infection by preventing cytosolic entry, PLoS Pathog. 7 (2011) e1002337.
[43] J. Lu, Q. Pan, L. Rong, W. He, S.L. Liu, C. Liang, The IFITM proteins inhibit HIV-1 infection, J. Virol. 85 (2011) 2126–2137.
[44] A.A. Compton, T. Bruel, F. Porrot, A. Mallet, M. Sachse, M. Euvrard, C. Liang, N. Casartelli, O. Schwartz, IFITM proteins incorporated into HIV-1 virions impair viral fusion and spread, Cell Host Microbe 16 (2014) 736–747.
[45] A.A. Compton, N. Roy, F. Porrot, A. Billet, N. Casartelli, J.S. Yount, C. Liang, O. Schwartz, Natural mutations in IFITM3 modulate post-translational regulation and toggle antiviral specificity, EMBO Rep. 17 (2016) 1657–1671.
[46] T.Y. Lin, C.R. Chin, A.R. Everitt, S. Clare, J.M. Perreira, G. Savidis, A.M. Aker, S.P. John, D. Sarlah, E.M. Carreira, S.J. Elledge, P. Kellam, A.L. Brass, Amphotericin B increases influenza A virus infection by preventing IFITM3-mediated restriction, Cell Rep. 5 (2013) 895–908.
[47] K. Li, R.M. Markosyan, Y.M. Zheng, O. Golfetto, B. Bungart, M. Li, S. Ding, Y. He, C. Liang, J.C. Lee, E. Gratton, F.S. Cohen, S.L. Liu, IFITM proteins restrict viral membrane hemifusion, PLoS Pathog. 9 (2013) e1003124.
[48] S. Amini-Bavil-Olyaee, Y.J. Choi, J.H. Lee, M. Shi, I.C. Huang, M. Farzan, J.U. Jung, The antiviral effector IFITM3 disrupts intracellular cholesterol homeostasis to block viral entry, Cell Host Microbe 13 (2013) 452–464.
[49] F. Wrensch, M. Winkler, S. Pohlmann, IFITM proteins inhibit entry driven by the MERS-coronavirus spike protein: evidence for cholesterol-independent mechanisms, Viruses 6 (2014) 3683–3698.
[50] J.C. Hach, T. McMichael, N.M. Chesarino, J.S. Yount, Palmitoylation on conserved and nonconserved cysteines of murine IFITM1 regulates its stability and anti-influenza A virus activity, J. Virol. 87 (2013) 9923–9927.
[51] T.M. McMichael, L. Zhang, M. Chemudupati, J.C. Hach, A.D. Kenney, H.C. Hang, J.S. Yount, The palmitoyltransferase ZDHHC20 enhances interferon-induced transmembrane protein 3 (IFITM3) palmitoylation and antiviral activity, J. Biol. Chem. 292 (2017) 21517–21526.
[52] A. Percher, S. Ramakrishnan, E. Thinon, X. Yuan, J.S. Yount, H.C. Hang, Mass-tag labeling reveals site-specific and endogenous levels of protein S-fatty acylation, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 4302–4307.
[53] J.S. Yount, R.A. Karssemeijer, H.C. Hang, S-palmitoylation and ubiquitination differentially regulate interferon-induced transmembrane protein 3 (IFITM3)-mediated resistance to influenza virus, J. Biol. Chem. 287 (2012) 19631–19641.
[54] S.P. John, C.R. Chin, J.M. Perreira, E.M. Feeley, A.M. Aker, G. Savidis, S.E. Smith, A.E. Elia, A.R. Everitt, M. Vora, T. Pertel, S.J. Elledge, P. Kellam, A.L. Brass, The CD225 domain of IFITM3 is required for both IFITM protein association and inhibition of influenza A virus and dengue virus replication, J. Virol. 87 (2013) 7837–7852.
[55] B. Fu, L. Wang, S. Li, M.E. Dorf, ZMPSTE24 defends against influenza and other pathogenic viruses, J. Exp. Med. 214 (2017) 919–929.
[56] K. Tartour, R. Appourchaux, J. Gaillard, X.N. Nguyen, S. Durand, J. Turpin, E. Beaumont, E. Roch, G. Berger, R. Mahieux, D. Brand, P. Roingeard, A. Cimarelli, IFITM proteins are incorporated onto HIV-1 virion particles and negatively imprint their infectivity, Retrovirology 11 (2014) 103.
[57] K. Tartour, X.N. Nguyen, R. Appourchaux, S. Assil, V. Barateau, L.M. Bloyet, J. Burlaud Gaillard, M.P. Confort, B. Escudero-Perez, H. Gruffat, S.S. Hong, M. Moroso, O. Reynard, S. Reynard, E. Decembre, N. Ftaich, A. Rossi, N. Wu, F. Arnaud, S. Baize, M. Dreux, D. Gerlier, G. Paranhos-Baccala, V. Volchkov, P. Roingeard, A. Cimarelli, Interference with the production of infectious viral particles and bimodal inhibition of replication are broadly conserved antiviral properties of IFITMs, PLoS Pathog. 13 (2017) e1006610.
[58] J. Yu, M. Li, J. Wilkins, S. Ding, T.H. Swartz, A.M. Esposito, Y.M. Zheng, E.O. Freed, C. Liang, B.K. Chen, S.L. Liu, IFITM proteins restrict HIV-1 infection by antagonizing the envelope glycoprotein, Cell Rep. 13 (2015) 145–156.
[59] M.A. Stacey, S. Clare, M. Clement, M. Marsden, J. Abdul-Karim, L. Kane, K. Harcourt, C. Brandt, C.A. Fielding, S.E. Smith, R.S. Wash, S.G. Brias, G. Stack, G. Notley, E.L. Cambridge, C. Isherwood, A.O. Speak, Z. Johnson, W. Ferlin, S.A. Jones, P. Kellam, I.R. Humphreys, The antiviral restriction factor IFN-induced transmembrane protein 3 prevents cytokine-driven CMV pathogenesis, J. Clin. Invest. 127 (2017) 1463–1474.
[60] L.Q. Jiang, T. Xia, Y.H. Hu, M.S. Sun, S. Yan, C.Q. Lei, H.B. Shu, J.H. Guo, Y. Liu, IFITM3 inhibits virus-triggered induction of type I interferon by mediating autophagosome-dependent degradation of IRF3, Cell. Mol. Immunol. (2017) (Available online).
[61] A. Zani, J.S. Yount, Antiviral protection by IFITM3 in vivo, Curr. Clin. Microbiol. Rep. (2018) (Available at: https://link.springer.com/article/10.1007/s40588-018-0103-0).
[62] X.F. Wu, V.L.D. Thi, Y.M. Huang, E. Billerbeck, D. Saha, H.H. Hoffmann, Y.M. Wang, L.A.V. Silva, S. Sarbanes, T. Sun, L. Andrus, Y. Yu, C. Quirk, M. Li, M.R. MacDonald, W.M. Schneider, X.L. An, B.R. Rosenberg, C.M. Rice, Intrinsic immunity shapes viral resistance of stem cells, Cell 172 (2018) (423-+).
[63] Y. Wang, Q. Pan, S. Ding, Z. Wang, J. Yu, A. Finzi, S.L. Liu, C. Liang, The V3 loop of HIV-1 Env determines viral susceptibility to IFITM3 impairment of viral infectivity, J. Virol. 91 (2017).
[64] T. Gerlach, L. Hensen, T. Matrosovich, J. Bergmann, M. Winkler, C. Peteranderl, H.D. Klenk, F. Weber, S. Herold, S. Pohlmann, M. Matrosovich, pH optimum of hemagglutinin-mediated membrane fusion determines sensitivity of influenza A viruses to the interferon-induced antiviral state and IFITMs, J. Virol. 91 (2017).
[65] T.L. Foster, H. Wilson, S.S. Iyer, K. Coss, K. Doores, S. Smith, P. Kellam, A. Finzi, P. Borrow, B.H. Hahn, S.J.D. Neil, Resistance of transmitted founder HIV-1 to IFITM-mediated restriction, Cell Host Microbe 20 (2016) 429–442.
[66] S. Ding, Q. Pan, S.L. Liu, C. Liang, HIV-1 mutates to evade IFITM1 restriction, Virology 454–455 (2014) 11–24.
[67] X. Zhao, F. Guo, F. Liu, A. Cuconati, J. Chang, T.M. Block, J.T. Guo, Interferon induction of IFITM proteins promotes infection by human coronavirus OC43, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 6756–6761.
[68] X. Zhao, M. Sehgal, Z. Hou, J. Cheng, S. Shu, S. Wu, F. Guo, S.J. Le Marchand, H. Lin, J. Chang, J.T. Guo, Identification of residues controlling restriction versus enhancing activities of IFITM proteins on entry of human coronaviruses, J. Virol. (2018) 92.
[69] M. Nakayama, K. Nagata, A. Kato, A. Ishihama, Interferon-inducible mouse Mx1 protein that confers resistance to influenza virus is GTPase, J. Biol. Chem. 266 (1991) 21404–21408.
[70] O. Haller, P. Staeheli, G. Kochs, Interferon-induced Mx proteins in antiviral host defense, Biochimie 89 (2007) 812–818.
[71] M. Aebi, J. Fah, N. Hurt, C.E. Samuel, D. Thomis, L. Bazzigher, J. Pavlovic, O. Haller, P. Staeheli, cDNA structures and regulation of two interferon-induced human Mx proteins, Mol. Cell. Biol. 9 (1989) 5062–5072.
[72] P. Staeheli, O. Haller, Interferon-induced human protein with homology to protein Mx of influenza virus-resistant mice, Mol. Cell. Biol. 5 (1985) 2150–2153.
[73] P.E. Nigg, J. Pavlovic, Oligomerization and GTP-binding requirements of MxA for viral target recognition and antiviral activity against influenza A virus, J. Biol. Chem. 290 (2015) 29893–29906.
[74] J. Pavlovic, T. Zurcher, O. Haller, P. Staeheli, Resistance to influenza virus and vesicular stomatitis virus conferred by expression of human MxA protein, J. Virol. 64 (1990) 3370–3375.
[75] E. Gordien, O. Rosmorduc, C. Peltekian, F. Garreau, C. Brechot, D. Kremsdorf, Inhibition of hepatitis B virus replication by the interferon-inducible MxA protein, J. Virol. 75 (2001) 2684–2691.
[76] T.M. Tumpey, K.J. Szretter, N. Van Hoeven, J.M. Katz, G. Kochs, O. Haller, A. Garcia-Sastre, P. Staeheli, The Mx1 gene protects mice against the pandemic 1918 and highly lethal human H5N1 influenza viruses, J. Virol. 81 (2007) 10818–10821.
[77] P.S. Pillai, R.D. Molony, K. Martinod, H. Dong, I.K. Pang, M.C. Tal, A.G. Solis, P. Bielecki, S. Mohanty, M. Trentalange, R.J. Homer, R.A. Flavell, D.D. Wagner, R.R. Montgomery, A.C. Shaw, P. Staeheli, A. Iwasaki, Mx1 reveals innate pathways to antiviral resistance and lethal influenza disease, Science 352 (2016) 463–466.
[78] C. Goujon, O. Moncorge, H. Bauby, T. Doyle, C.C. Ward, T. Schaller, S. Hue, W.S. Barclay, R. Schulz, M.H. Malim, Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection, Nature 502 (2013) (559-+).
[79] Z. Liu, Q. Pan, S. Ding, J. Qian, F. Xu, J. Zhou, S. Cen, F. Guo, C. Liang, The

interferon-inducible MxB protein inhibits HIV-1 infection, Cell Host Microbe 14 (2013) 398–410.
[80] M. Kane, S.S. Yadav, J. Bitzegeio, S.B. Kutluay, T. Zang, S.J. Wilson, J.W. Schoggins, C.M. Rice, M. Yamashita, T. Hatziioannou, P.D. Bieniasz, MX2 is an interferon-induced inhibitor of HIV-1 infection, Nature 502 (2013) (563-+).
[81] K. Melen, P. Keskinen, T. Ronni, T. Sareneva, K. Lounatmaa, I. Julkunen, Human MxB protein, an interferon-alpha-inducible GTPase, contains a nuclear targeting signal and is localized in the heterochromatin region beneath the nuclear envelope, J. Biol. Chem. 271 (1996) 23478–23486.
[82] C. Goujon, O. Moncorge, H. Bauby, T. Doyle, W.S. Barclay, M.H. Malim, Transfer of the amino-terminal nuclear envelope targeting domain of human MX2 converts MX1 into an HIV-1 resistance factor, J. Virol. 88 (2014) 9017–9026.
[83] O. Haller, G. Kochs, Interferon-induced mx proteins: dynamin-like GTPases with antiviral activity, Traffic 3 (2002) 710–717.
[84] M. Schwemmle, M.F. Richter, C. Herrmann, N. Nassar, P. Staeheli, Unexpected structural requirements for GTPase activity of the interferon-induced MxA protein, J. Biol. Chem. 270 (1995) 13518–13523.
[85] S. Gao, A. von der Malsburg, S. Paeschke, J. Behlke, O. Haller, G. Kochs, O. Daumke, Structural basis of oligomerization in the stalk region of dynamin-like MxA, Nature 465 (2010) 502–506.
[86] P.S. Mitchell, C. Patzina, M. Emerman, O. Haller, H.S. Malik, G. Kochs, Evolution-guided identification of antiviral specificity determinants in the broadly acting interferon-induced innate immunity factor MxA, Cell Host Microbe 12 (2012) 598–604.
[87] S. Gao, A. von der Malsburg, A. Dick, K. Faelber, G.F. Schroder, O. Haller, G. Kochs, O. Daumke, Structure of myxovirus resistance protein a reveals intra- and intermolecular domain interactions required for the antiviral function, Immunity 35 (2011) 514–525.
[88] D. Dornfeld, A.H. Dudek, T. Vausselin, S.C. Gunther, J.F. Hultquist, S. Giese, D. Khokhlova-Cubberley, Y.C. Chew, N.J. Krogan, A. Garcia-Sastre, M. Schwemmle, M.L. Shaw, SMARCA2-regulated host cell factors are required for MxA restriction of influenza A viruses, Sci. Rep. 8 (2018).
[89] J.L. Fribourgh, H.C. Nguyen, K.A. Matreyek, F.J.D. Alvarez, B.J. Summers, T.G. Dewdney, C. Aiken, P. Zhang, A. Engelman, Y. Xiong, Structural insight into HIV-1 restriction by MxB, Cell Host Microbe 16 (2014) 627–638.
[90] F.J.D. Alvarez, S.D. He, J.R. Perilla, S. Jang, K. Schulten, A.N. Engelman, S.H.W. Scheres, P.J. Zhang, CryoEM structure of MxB reveals a novel oligomerization interface critical for HIV restriction, Sci. Adv. 3 (2017).
[91] J. Dittmann, S. Stertz, D. Grimm, J. Steel, A. Garcia-Sastre, O. Haller, G. Kochs, Influenza A virus strains differ in sensitivity to the antiviral action of Mx-GTPase, J. Virol. 82 (2008) 3624–3631.
[92] C.M. Deeg, E. Hassan, P. Mutz, L. Rheinemann, V. Gotz, L. Magar, M. Schilling, C. Kallfass, C. Nurnberger, S. Soubies, G. Kochs, O. Haller, M. Schwemmle, P. Staeheli, In vivo evasion of MxA by avian influenza viruses requires human signature in the viral nucleoprotein, J. Exp. Med. 214 (2017) 1239–1248.
[93] B. Manz, D. Dornfeld, V. Gotz, R. Zell, P. Zimmermann, O. Haller, G. Kochs, M. Schwemmle, Pandemic influenza A viruses escape from restriction by human MxA through adaptive mutations in the nucleoprotein, PLoS Pathog. 9 (2013) e1003279.
[94] D.C. Goldstone, V. Ennis-Adeniran, J.J. Hedden, H.C. Groom, G.I. Rice, E. Christodoulou, P.A. Walker, G. Kelly, L.F. Haire, M.W. Yap, L.P. de Carvalho, J.P. Stoye, Y.J. Crow, I.A. Taylor, M. Webb, HIV-1 restriction factor SAMHD1 is a deoxynucleoside triphosphate triphosphohydrolase, Nature 480 (2011) 379–382.
[95] X. Ji, Y. Wu, J. Yan, J. Mehrens, H. Yang, M. DeLucia, C. Hao, A.M. Gronenborn, J. Skowronski, J. Ahn, Y. Xiong, Mechanism of allosteric activation of SAMHD1 by dGTP, Nat. Struct. Mol. Biol. 20 (2013) 1304–1309.
[96] J. Yan, S. Kaur, M. DeLucia, C. Hao, J. Mehrens, C. Wang, M. Golczak, K. Palczewski, A.M. Gronenborn, J. Ahn, J. Skowronski, Tetramerization of SAMHD1 is required for biological activity and inhibition of HIV infection, J. Biol. Chem. 288 (2013) 10406–10417.
[97] A. Goncalves, E. Karayel, G.I. Rice, K.L. Bennett, Y.J. Crow, G. Superti-Furga, T. Burckstummer, SAMHD1 is a nucleic-acid binding protein that is mislocalized due to Aicardi-Goutieres syndrome-associated mutations, Hum. Mutat. 33 (2012) 1116–1122.
[98] E. Franzolin, G. Pontarin, C. Rampazzo, C. Miazzi, P. Ferraro, E. Palumbo, P. Reichard, V. Bianchi, The deoxynucleotide triphosphohydrolase SAMHD1 is a major regulator of DNA precursor pools in mammalian cells, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 14272–14277.
[99] S. Bonifati, M.B. Daly, C. St Gelais, S.H. Kim, J.A. Hollenbaugh, C. Shepard, E.M. Kennedy, D.H. Kim, R.F. Schinazi, B. Kim, L. Wu, SAMHD1 controls cell cycle status, apoptosis and HIV-1 infection in monocytic THP-1 cells, Virology 495 (2016) 92–100.
[100] K.M. Kodigepalli, M. Li, S.L. Liu, L. Wu, Exogenous expression of SAMHD1 inhibits proliferation and induces apoptosis in cutaneous T-cell lymphoma-derived HuT78 cells, Cell Cycle 16 (2017) 179–188.
[101] K. Hrecka, C. Hao, M. Gierszewska, S.K. Swanson, M. Kesik-Brodacka, S. Srivastava, L. Florens, M.P. Washburn, J. Skowronski, Vpx relieves inhibition of HIV-1 infection of macrophages mediated by the SAMHD1 protein, Nature 474 (2011) 658–661.
[102] N. Laguette, B. Sobhian, N. Casartelli, M. Ringeard, C. Chable-Bessia, E. Segeral, A. Yatim, S. Emiliani, O. Schwartz, M. Benkirane, SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx, Nature 474 (2011) 654–657.
[103] H. Lahouassa, W. Daddacha, H. Hofmann, D. Ayinde, E.C. Logue, L. Dragin, N. Bloch, C. Maudet, M. Bertrand, T. Gramberg, G. Pancino, S. Priet, B. Canard, N. Laguette, M. Benkirane, C. Transy, N.R. Landau, B. Kim, F. Margottin-Goguet, SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates, Nat. Immunol. 13 (2012) 223–228.
[104] H.M. Baldauf, X. Pan, E. Erikson, S. Schmidt, W. Daddacha, M. Burggraf, K. Schenkova, I. Ambiel, G. Wabnitz, T. Gramberg, S. Panitz, E. Flory, N.R. Landau, S. Sertel, F. Rutsch, F. Lasitschka, B. Kim, R. Konig, O.T. Fackler, O.T. Keppler, SAMHD1 restricts HIV-1 infection in resting CD4(+) T cells, Nat. Med. 18 (2012) 1682–1687.
[105] J.A. Hollenbaugh, P. Gee, J. Baker, M.B. Daly, S.M. Amie, J. Tate, N. Kasai, Y. Kanemura, D.H. Kim, B.M. Ward, Y. Koyanagi, B. Kim, Host factor SAMHD1 restricts DNA viruses in non-dividing myeloid cells, PLoS Pathog. 9 (2013) e1003481.
[106] T. Gramberg, T. Kahle, N. Bloch, S. Wittmann, E. Mullers, W. Daddacha, H. Hofmann, B. Kim, D. Lindemann, N.R. Landau, Restriction of diverse retroviruses by SAMHD1, Retrovirology 10 (2013) 26.
[107] C. Zhu, W. Gao, K. Zhao, X. Qin, Y. Zhang, X. Peng, L. Zhang, Y. Dong, W. Zhang, P. Li, W. Wei, Y. Gong, X.F. Yu, Structural insight into dGTP-dependent activation of tetrameric SAMHD1 deoxynucleoside triphosphate triphosphohydrolase, Nat. Commun. 4 (2013) 2722.
[108] A. Cribier, B. Descours, A.L. Valadao, N. Laguette, M. Benkirane, Phosphorylation of SAMHD1 by cyclin A2/CDK1 regulates its restriction activity toward HIV-1, Cell Rep. 3 (2013) 1036–1043.
[109] T.E. White, A. Brandariz-Nunez, J.C. Valle-Casuso, S. Amie, L.A. Nguyen, B. Kim, M. Tuzova, F. Diaz-Griffero, The retroviral restriction ability of SAMHD1, but not its deoxynucleotide triphosphohydrolase activity, is regulated by phosphorylation, Cell Host Microbe 13 (2013) 441–451.
[110] C. St Gelais, S. de Silva, J.C. Hach, T.E. White, F. Diaz-Griffero, J.S. Yount, L. Wu, Identification of cellular proteins interacting with the retroviral restriction factor SAMHD1, J. Virol. 88 (2014) 5834–5844.
[111] E. Pauls, A. Ruiz, R. Badia, M. Permanyer, A. Gubern, E. Riveira-Munoz, J. Torres-Torronteras, M. Alvarez, B. Mothe, C. Brander, M. Crespo, L. Menendez-Arias, B. Clotet, O.T. Keppler, R. Marti, F. Posas, E. Ballana, J.A. Este, Cell cycle control and HIV-1 susceptibility are linked by CDK6-dependent CDK2 phosphorylation of SAMHD1 in myeloid and lymphoid cells, J. Immunol. 193 (2014) 1988–1997.
[112] L.H. Arnold, H.C. Groom, S. Kunzelmann, D. Schwefel, S.J. Caswell, P. Ordonez, M.C. Mann, S. Rueschenbaum, D.C. Goldstone, S. Pennell, S.A. Howell, J.P. Stoye, M. Webb, I.A. Taylor, K.N. Bishop, Phospho-dependent regulation of SAMHD1 oligomerisation couples catalysis and restriction, PLoS Pathog. 11 (2015) e1005194.
[113] C. St Gelais, S.H. Kim, V.V. Maksimova, O. Buzovetsky, K.M. Knecht, C. Shepard, B. Kim, Y. Xiong, L. Wu, A cyclin-binding motif in human SAMHD1 is required for its HIV-1 restriction, dNTPase activity, tetramer formation, and efficient phosphorylation, J. Virol. 92 (2018).
[114] J. Ryoo, J. Choi, C. Oh, S. Kim, M. Seo, S.Y. Kim, D. Seo, J. Kim, T.E. White, A. Brandariz-Nunez, F. Diaz-Griffero, C.H. Yun, J.A. Hollenbaugh, B. Kim, D. Baek, K. Ahn, The ribonuclease activity of SAMHD1 is required for HIV-1 restriction, Nat. Med. 20 (2014) 936–941.
[115] J.M. Antonucci, C. St Gelais, S. de Silva, J.S. Yount, C. Tang, X. Ji, C. Shepard, Y. Xiong, B. Kim, L. Wu, SAMHD1-mediated HIV-1 restriction in cells does not involve ribonuclease activity, Nat. Med. 22 (2016) 1072–1074.
[116] G.I. Rice, J. Bond, A. Asipu, R.L. Brunette, I.W. Manfield, I.M. Carr, J.C. Fuller, R.M. Jackson, T. Lamb, T.A. Briggs, M. Ali, H. Gornall, L.R. Couthard, A. Aeby, S.P. Attard-Montalto, E. Bertini, C. Bodemer, K. Brockmann, L.A. Brueton, P.C. Corry, I. Desguerre, E. Fazzi, A.G. Cazorla, B. Gener, B.C. Hamel, A. Heiberg, M. Hunter, M.S. van der Knaap, R. Kumar, L. Lagae, P.G. Landrieu, C.M. Lourenco, D. Marom, M.F. McDermott, W. van der Merwe, S. Orcesi, J.S. Prendiville, M. Rasmussen, S.A. Shalev, D.M. Soler, M. Shinawi, R. Spiegel, T.Y. Tan, A. Vanderver, E.L. Wakeling, E. Wassmer, E. Whittaker, P. Lebon, D.B. Stetson, D.T. Bonthron, Y.J. Crow, Mutations involved in Aicardi-Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response, Nat. Genet. 41 (2009) 829–832.
[117] G.I. Rice, G.M. Forte, M. Szynkiewicz, D.S. Chase, A. Aeby, M.S. Abdel-Hamid, S. Ackroyd, R. Allcock, K.M. Bailey, U. Balottin, C. Barnerias, G. Bernard, C. Bodemer, M.P. Botella, C. Cereda, K.E. Chandler, L. Dabydeen, R.C. Dale, C. De Laet, C.G. De Goede, M. Del Toro, L. Effat, N.N. Enamorado, E. Fazzi, B. Gener, M. Haldre, J.P. Lin, J.H. Livingston, C.M. Lourenco, W. Marques Jr., P. Oades, P. Peterson, M. Rasmussen, A. Roubertie, J.L. Schmidt, S.A. Shalev, R. Simon, R. Spiegel, K.J. Swoboda, S.A. Temtamy, G. Vassallo, C.N. Vilain, J. Vogt, V. Wermenbol, W.P. Whitehouse, D. Soler, I. Olivieri, S. Orcesi, M.S. Aglan, M.S. Zaki, G.M. Abdel-Salam, A. Vanderver, K. Kisand, F. Rozenberg, P. Lebon, Y.J. Crow, Assessment of interferon-related biomarkers in Aicardi-Goutieres syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study, Lancet Neurol. 12 (2013) 1159–1169.
[118] R. Behrendt, T. Schumann, A. Gerbaulet, L.A. Nguyen, N. Schubert, D. Alexopoulou, U. Berka, S. Lienenklaus, K. Peschke, K. Gibbert, S. Wittmann, D. Lindemann, S. Weiss, A. Dahl, R. Naumann, U. Dittmer, B. Kim, W. Mueller, T. Gramberg, A. Roers, Mouse SAMHD1 has antiretroviral activity and suppresses a spontaneous cell-intrinsic antiviral response, Cell Rep. 4 (2013) 689–696.
[119] S. Yang, Y. Zhan, Y. Zhou, Y. Jiang, X. Zheng, L. Yu, W. Tong, F. Gao, L. Li, Q. Huang, Z. Ma, G. Tong, Interferon regulatory factor 3 is a key regulation factor for inducing the expression of SAMHD1 in antiviral innate immunity, Sci. Rep. 6 (2016) 29665.
[120] S. Chen, S. Bonifati, Z. Qin, C. St Gelais, K.M. Kodigepalli, B.S. Barrett, S.H. Kim, J.M. Antonucci, K.J. Ladner, O. Buzovetsky, K.M. Knecht, Y. Xiong, J.S. Yount, D.C. Guttridge, M.L. Santiago, L. Wu, SAMHD1 suppresses innate immune responses to viral infections and inflammatory stimuli by inhibiting the NF-kappaB

and interferon pathways, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E3798–E3807.
[121] C. Oh, J. Ryoo, K. Park, B. Kim, M.B. Daly, D. Cho, K. Ahn, A central role for PI3K-AKT signaling pathway in linking SAMHD1-deficiency to the type I interferon signature, Sci. Rep. 8 (2018) 84.
[122] F. Coquel, M.J. Silva, H. Techer, K. Zadorozhny, S. Sharma, J. Nieminuszczy, C. Mettling, E. Dardillac, A. Barthe, A.L. Schmitz, A. Promonet, A. Cribier, A. Sarrazin, W. Niedzwiedz, B. Lopez, V. Costanzo, L. Krejci, A. Chabes, M. Benkirane, Y.L. Lin, P. Pasero, SAMHD1 acts at stalled replication forks to prevent interferon induction, Nature 557 (2018) 57–61.
[123] M. Shingai, S. Welbourn, J.M. Brenchley, P. Acharya, E. Miyagi, R.J. Plishka, A. Buckler-White, P.D. Kwong, Y. Nishimura, K. Strebel, M.A. Martin, The expression of functional Vpx during pathogenic SIVmac infections of rhesus macaques suppresses SAMHD1 in CD4+ memory T cells, PLoS Pathog. 11 (2015) e1004928.
[124] S.J. Neil, S.W. Eastman, N. Jouvenet, P.D. Bieniasz, HIV-1 Vpu promotes release and prevents endocytosis of nascent retrovirus particles from the plasma membrane, PLoS Pathog. 2 (2006) e39.
[125] S.J. Neil, T. Zang, P.D. Bieniasz, Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu, Nature 451 (2008) 425–430.
[126] D. Perez-Caballero, T. Zang, A. Ebrahimi, M.W. McNatt, D.A. Gregory, M.C. Johnson, P.D. Bieniasz, Tetherin inhibits HIV-1 release by directly tethering virions to cells, Cell 139 (2009) 499–511.
[127] N. Van Damme, D. Goff, C. Katsura, R.L. Jorgenson, R. Mitchell, M.C. Johnson, E.B. Stephens, J. Guatelli, The interferon-induced protein BST-2 restricts HIV-1 release and is downregulated from the cell surface by the viral Vpu protein, Cell Host Microbe 3 (2008) 245–252.
[128] A. Hinz, N. Miguet, G. Natrajan, Y. Usami, H. Yamanaka, P. Renesto, B. Hartlieb, A.A. McCarthy, J.P. Simorre, H. Gottlinger, W. Weissenhorn, Structural basis of HIV-1 tethering to membranes by the BST-2/tetherin ectodomain, Cell Host Microbe 7 (2010) 314–323.
[129] K.A. Ozcan, C.E. Berndsen, Bending of the BST-2 coiled-coil during viral budding, Proteins 85 (2017) 2081–2087.
[130] S. Venkatesh, P.D. Bieniasz, Mechanism of HIV-1 virion entrapment by tetherin, PLoS Pathog. 9 (2013) e1003483.
[131] T. Sakuma, A. Sakurai, J. Yasuda, Dimerization of tetherin is not essential for its antiviral activity against Lassa and Marburg viruses, PLoS One 4 (2009) e6934.
[132] A.J. Andrew, E. Miyagi, S. Kao, K. Strebel, The formation of cysteine-linked dimers of BST-2/tetherin is important for inhibition of HIV-1 virus release but not for sensitivity to Vpu, Retrovirology 6 (2009) 80.
[133] H.L. Schubert, Q. Zhai, V. Sandrin, D.M. Eckert, M. Garcia-Maya, L. Saul, W.I. Sundquist, R.A. Steiner, C.P. Hill, Structural and functional studies on the extracellular domain of BST2/tetherin in reduced and oxidized conformations, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 17951–17956.
[134] M. Swiecki, S.M. Scheaffer, M. Allaire, D.H. Fremont, M. Colonna, T.J. Brett, Structural and biophysical analysis of BST-2/tetherin ectodomains reveals an evolutionary conserved design to inhibit virus release, J. Biol. Chem. 286 (2011) 2987–2997.
[135] R.A. Liberatore, P.D. Bieniasz, Tetherin is a key effector of the antiretroviral activity of type I interferon in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 18097–18101.
[136] C. Goffinet, S. Schmidt, C. Kern, L. Oberbremer, O.T. Keppler, Endogenous CD317/tetherin limits replication of HIV-1 and murine leukemia virus in rodent cells and is resistant to antagonists from primate viruses, J. Virol. 84 (2010) 11374–11384.
[137] M. Swiecki, Y. Wang, S. Gilfillan, D.J. Lenschow, M. Colonna, Cutting edge: paradoxical roles of BST2/tetherin in promoting type I IFN response and viral infection, J. Immunol. 188 (2012) 2488–2492.
[138] E. Bartee, A. McCormack, K. Fruh, Quantitative membrane proteomics reveals new cellular targets of viral immune modulators, PLoS Pathog. 2 (2006) e107.
[139] G. Raposo, M. Moore, D. Innes, R. Leijendekker, A. Leigh-Brown, P. Benaroch, H. Geuze, Human macrophages accumulate HIV-1 particles in MHC II compartments, Traffic 3 (2002) 718–729.
[140] H. Chu, J.J. Wang, M. Qi, J.J. Yoon, X. Chen, X. Wen, J. Hammonds, L. Ding, P. Spearman, Tetherin/BST-2 is essential for the formation of the intracellular virus-containing compartment in HIV-infected macrophages, Cell Host Microbe 12 (2012) 360–372.
[141] B. Mangeat, L. Cavagliotti, M. Lehmann, G. Gers-Huber, I. Kaur, Y. Thomas, L. Kaiser, V. Piguet, Influenza virus partially counteracts restriction imposed by tetherin/BST-2, J. Biol. Chem. 287 (2012) 22015–22029.
[142] K. Gnirss, P. Zmora, P. Blazejewska, M. Winkler, A. Lins, I. Nehlmeier, S. Gartner, A.S. Moldenhauer, H. Hofmann-Winkler, T. Wolff, M. Schindler, S. Pohlmann, Tetherin sensitivity of influenza A viruses is strain specific: role of hemagglutinin and neuraminidase, J. Virol. 89 (2015) 9178–9188.
[143] M.A. Yondola, F. Fernandes, A. Belicha-Villanueva, M. Uccelini, Q. Gao, C. Carter, P. Palese, Budding capability of the influenza virus neuraminidase can be modulated by tetherin, J. Virol. 85 (2011) 2480–2491.
[144] J.M. Weidner, D. Jiang, X.B. Pan, J. Chang, T.M. Block, J.T. Guo, Interferon-induced cell membrane proteins, IFITM3 and tetherin, inhibit vesicular stomatitis virus infection via distinct mechanisms, J. Virol. 84 (2010) 12646–12657.
[145] T. Sakuma, T. Noda, S. Urata, Y. Kawaoka, J. Yasuda, Inhibition of Lassa and Marburg virus production by tetherin, J. Virol. 83 (2009) 2382–2385.
[146] S.R. Radoshitzky, L. Dong, X. Chi, J.C. Clester, C. Retterer, K. Spurgers, J.H. Kuhn, S. Sandwick, G. Ruthel, K. Kota, D. Boltz, T. Warren, P.J. Kranzusch, S.P. Whelan, S. Bavari, Infectious Lassa virus, but not filoviruses, is restricted by BST-2/tetherin, J. Virol. 84 (2010) 10569–10580.
[147] R. Yan, X. Zhao, D. Cai, Y. Liu, T.M. Block, J.T. Guo, H. Guo, The interferon-inducible protein tetherin inhibits hepatitis B virus virion secretion, J. Virol. 89 (2015) 9200–9212.
[148] R.P. Galao, A. Le Tortorec, S. Pickering, T. Kueck, S.J. Neil, Innate sensing of HIV-1 assembly by tetherin induces NFkappaB-dependent proinflammatory responses, Cell Host Microbe 12 (2012) 633–644.
[149] S.X. Li, B.S. Barrett, K.J. Heilman, R.J. Messer, R.A. Liberatore, P.D. Bieniasz, G. Kassiotis, K.J. Hasenkrug, M.L. Santiago, Tetherin promotes the innate and adaptive cell-mediated immune response against retrovirus infection in vivo, J. Immunol. 193 (2014) 306–316.
[150] S.X. Li, B.S. Barrett, K. Guo, G. Kassiotis, K.J. Hasenkrug, U. Dittmer, K. Gibbert, M.L. Santiago, Tetherin/BST-2 promotes dendritic cell activation and function during acute retrovirus infection, Sci. Rep. 6 (2016) 20425.
[151] K. Viswanathan, M.S. Smith, D. Malouli, M. Mansouri, J.A. Nelson, K. Fruh, BST2/tetherin enhances entry of human cytomegalovirus, PLoS Pathog. 7 (2011) e1002332.
[152] R.S. Mitchell, C. Katsura, M.A. Skasko, K. Fitzpatrick, D. Lau, A. Ruiz, E.B. Stephens, F. Margottin-Goguet, R. Benarous, J.C. Guatelli, Vpu antagonizes BST-2-mediated restriction of HIV-1 release via beta-TrCP and endo-lysosomal trafficking, PLoS Pathog. 5 (2009) e1000450.
[153] B. Jia, R. Serra-Moreno, W. Neidermyer, A. Rahmberg, J. Mackey, I.B. Fofana, W.E. Johnson, S. Westmoreland, D.T. Evans, Species-specific activity of SIV Nef and HIV-1 Vpu in overcoming restriction by tetherin/BST2, PLoS Pathog. 5 (2009) e1000429.
[154] R.L. Kaletsky, J.R. Francica, C. Agrawal-Gamse, P. Bates, Tetherin-mediated restriction of filovirus budding is antagonized by the Ebola glycoprotein, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 2886–2891.
[155] J.K. Gustin, Y. Bai, A.V. Moses, J.L. Douglas, Ebola virus glycoprotein promotes enhanced viral egress by preventing Ebola VP40 from associating with the host restriction factor BST2/tetherin, J. Infect. Dis. 212 (Suppl. 2) (2015) S181–S190.
[156] H. Zhu, J.P. Cong, T. Shenk, Use of differential display analysis to assess the effect of human cytomegalovirus infection on the accumulation of cellular RNAs: induction of interferon-responsive RNAs, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 13985–13990.
[157] K.C. Chin, P. Cresswell, Viperin (cig5), an IFN-inducible antiviral protein directly induced by human cytomegalovirus, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 15125–15130.
[158] E. Dixit, S. Boulant, Y. Zhang, A.S. Lee, C. Odendall, B. Shum, N. Hacohen, Z.J. Chen, S.P. Whelan, M. Fransen, M.L. Nibert, G. Superti-Furga, J.C. Kagan, Peroxisomes are signaling platforms for antiviral innate immunity, Cell 141 (2010) 668–681.
[159] K.S. Duschene, J.B. Broderick, The antiviral protein viperin is a radical SAM enzyme, FEBS Lett. 584 (2010) 1263–1267.
[160] G. Shaveta, J. Shi, V.T. Chow, J. Song, Structural characterization reveals that viperin is a radical S-adenosyl-L-methionine (SAM) enzyme, Biochem. Biophys. Res. Commun. 391 (2010) 1390–1395.
[161] C. Carlton-Smith, R.M. Elliott, Viperin, MTAP44, and protein kinase R contribute to the interferon-induced inhibition of Bunyamwera *Orthobunyavirus* replication, J. Virol. 86 (2012) 11548–11557.
[162] N. Nasr, S. Maddocks, S.G. Turville, A.N. Harman, N. Woolger, K.J. Helbig, J. Wilkinson, C.R. Bye, T.K. Wright, D. Rambukwelle, H. Donaghy, M.R. Beard, A.L. Cunningham, HIV-1 infection of human macrophages directly induces viperin which inhibits viral production, Blood 120 (2012) 778–788.
[163] D. Jiang, H. Guo, C. Xu, J. Chang, B. Gu, L. Wang, T.M. Block, J.T. Guo, Identification of three interferon-inducible cellular enzymes that inhibit the replication of hepatitis C virus, J. Virol. 82 (2008) 1665–1678.
[164] J.Y. Seo, R. Yaneva, E.R. Hinson, P. Cresswell, Human cytomegalovirus directly induces the antiviral protein viperin to enhance infectivity, Science 332 (2011) 1093–1097.
[165] E.R. Hinson, P. Cresswell, The N-terminal amphipathic alpha-helix of viperin mediates localization to the cytosolic face of the endoplasmic reticulum and inhibits protein secretion, J. Biol. Chem. 284 (2009) 4705–4712.
[166] K.J. Helbig, N.S. Eyre, E. Yip, S. Narayana, K. Li, G. Fiches, E.M. McCartney, R.K. Jangra, S.M. Lemon, M.R. Beard, The antiviral protein viperin inhibits hepatitis C virus replication via interaction with nonstructural protein 5A, Hepatology 54 (2011) 1506–1517.
[167] K.J. Helbig, J.M. Carr, J.K. Calvert, S. Wati, J.N. Clarke, N.S. Eyre, S.K. Narayana, G.N. Fiches, E.M. McCartney, M.R. Beard, Viperin is induced following dengue virus type-2 (DENV-2) infection and has anti-viral actions requiring the C-terminal end of viperin, PLoS Negl. Trop. Dis. 7 (2013) e2178.
[168] K.H. Van der Hoek, N.S. Eyre, B. Shue, O. Khantisitthiporn, K. Glab-Ampi, J.M. Carr, M.J. Gartner, L.A. Jolly, P.Q. Thomas, F. Adikusuma, T. Jankovic-Karasoulos, C.T. Roberts, K.J. Helbig, M.R. Beard, Viperin is an important host restriction factor in control of Zika virus infection, Sci. Rep. 7 (2017) 4475.
[169] J.Y. Seo, R. Yaneva, P. Cresswell, Viperin: a multifunctional, interferon-inducible protein that regulates virus replication, Cell Host Microbe 10 (2011) 534–539.
[170] X. Wang, E.R. Hinson, P. Cresswell, The interferon-inducible protein viperin inhibits influenza virus release by perturbing lipid rafts, Cell Host Microbe 2 (2007) 96–105.
[171] E.S. Lim, L.I. Wu, H.S. Malik, M. Emerman, The function and evolution of the restriction factor viperin in primates was not driven by lentiviruses, Retrovirology 9 (2012) 55.
[172] S. Wang, X. Wu, T. Pan, W. Song, Y. Wang, F. Zhang, Z. Yuan, Viperin inhibits hepatitis C virus replication by interfering with binding of NS5A to host protein hVAP-33, J. Gen. Virol. 93 (2012) 83–92.
[173] A.S. Gizzi, T.L. Grove, J.J. Arnold, J. Jose, R.K. Jangra, S.J. Garforth, Q. Du, S.M. Cahill, N.G. Dulyaninova, J.D. Love, K. Chandran, A.R. Bresnick, C.E. Cameron, S.C. Almo, A naturally occurring antiviral ribonucleotide encoded

by the human genome, Nature 558 (2018) 610–614.
[174] T. Saitoh, T. Satoh, N. Yamamoto, S. Uematsu, O. Takeuchi, T. Kawai, S. Akira, Antiviral protein viperin promotes toll-like receptor 7- and toll-like receptor 9-mediated type I interferon production in plasmacytoid dendritic cells, Immunity 34 (2011) 352–363.
[175] A.S. Upadhyay, K. Vonderstein, A. Pichlmair, O. Stehling, K.L. Bennett, G. Dobler, J.T. Guo, G. Superti-Furga, R. Lill, A.K. Overby, F. Weber, Viperin is an iron-sulfur protein that inhibits genome synthesis of tick-borne encephalitis virus via radical SAM domain activity, Cell. Microbiol. 16 (2014) 834–848.
[176] G. Gao, X. Guo, S.P. Goff, Inhibition of retroviral RNA production by ZAP, a CCCH-type zinc finger protein, Science 297 (2002) 1703–1706.
[177] S. Glasker, M. Toller, B.M. Kummerer, The alternate triad motif of the poly(ADP-ribose) polymerase-like domain of the human zinc finger antiviral protein is essential for its antiviral activity, J. Gen. Virol. 95 (2014) 816–822.
[178] J.A. Kerns, M. Emerman, H.S. Malik, Positive selection and increased antiviral activity associated with the PARP-containing isoform of human zinc-finger antiviral protein, PLoS Genet. 4 (2008) e21.
[179] X. Guo, J.W. Carroll, M.R. Macdonald, S.P. Goff, G. Gao, The zinc finger antiviral protein directly binds to specific viral mRNAs through the CCCH zinc finger motifs, J. Virol. 78 (2004) 12781–12787.
[180] X. Guo, J. Ma, J. Sun, G. Gao, The zinc-finger antiviral protein recruits the RNA processing exosome to degrade the target mRNA, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 151–156.
[181] S. Chen, Y. Xu, K. Zhang, X. Wang, J. Sun, G. Gao, Y. Liu, Structure of N-terminal domain of ZAP indicates how a zinc-finger protein recognizes complex RNA, Nat. Struct. Mol. Biol. 19 (2012) 430–435.
[182] G. Charron, M.M. Li, M.R. MacDonald, H.C. Hang, Prenylome profiling reveals S-farnesylation is crucial for membrane targeting and antiviral activity of ZAP long-isoform, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 11085–11090.
[183] R. Mao, H. Nie, D. Cai, J. Zhang, H. Liu, R. Yan, A. Cuconati, T.M. Block, J.T. Guo, H. Guo, Inhibition of hepatitis B virus replication by the host zinc finger antiviral protein, PLoS Pathog. 9 (2013) e1003494.
[184] J.L. Goodier, G.C. Pereira, L.E. Cheung, R.J. Rose, H.H. Kazazian Jr., The broad-spectrum antiviral protein ZAP restricts human retrotransposition, PLoS Genet. 11 (2015) e1005252.
[185] S. Hayakawa, S. Shiratori, H. Yamato, T. Kameyama, C. Kitatsuji, F. Kashigi, S. Goto, S. Kameoka, D. Fujikura, T. Yamada, T. Mizutani, M. Kazumata, M. Sato, J. Tanaka, M. Asaka, Y. Ohba, T. Miyazaki, M. Imamura, A. Takaoka, ZAPS is a potent stimulator of signaling mediated by the RNA helicase RIG-I during antiviral responses, Nat. Immunol. 12 (2011) 37–44.
[186] M.J. Bick, J.W. Carroll, G. Gao, S.P. Goff, C.M. Rice, M.R. MacDonald, Expression of the zinc-finger antiviral protein inhibits alphavirus replication, J. Virol. 77 (2003) 11555–11562.
[187] S. Muller, P. Moller, M.J. Bick, S. Wurr, S. Becker, S. Gunther, B.M. Kummerer, Inhibition of filovirus replication by the zinc finger antiviral protein, J. Virol. 81 (2007) 2391–2400.
[188] Y. Zhu, G. Chen, F. Lv, X. Wang, X. Ji, Y. Xu, J. Sun, L. Wu, Y.T. Zheng, G. Gao, Zinc-finger antiviral protein inhibits HIV-1 infection by selectively targeting multiply spliced viral mRNAs for degradation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 15834–15839.
[189] C.H. Liu, L. Zhou, G. Chen, R.M. Krug, Battle between influenza A virus and a newly identified antiviral activity of the PARP-containing ZAPL protein, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 14048–14053.
[190] J.B. Moldovan, J.V. Moran, The zinc-finger antiviral protein ZAP inhibits LINE and Alu retrotransposition, PLoS Genet. 11 (2015) e1005121.
[191] M.M. Li, Z. Lau, P. Cheung, E.G. Aguilar, W.M. Schneider, L. Bozzacco, H. Molina, E. Buehler, A. Takaoka, C.M. Rice, D.P. Felsenfeld, M.R. MacDonald, TRIM25 enhances the antiviral action of zinc-finger antiviral protein (ZAP), PLoS Pathog. 13 (2017) e1006145.
[192] Q. Tang, X. Wang, G. Gao, The short form of the zinc finger antiviral protein inhibits influenza A virus protein expression and is antagonized by the virus-encoded NS1, J. Virol. 91 (2017).
[193] G. Chen, X. Guo, F. Lv, Y. Xu, G. Gao, p72 DEAD box RNA helicase is required for optimal function of the zinc-finger antiviral protein, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 4352–4357.
[194] M.A. Takata, D. Goncalves-Carneiro, T.M. Zang, S.J. Soll, A. York, D. Blanco-Melo, P.D. Bieniasz, CG dinucleotide suppression enables antiviral defence targeting non-self RNA, Nature 550 (2017) 124–127.
[195] S. Karlin, J. Mrazek, Compositional differences within and between eukaryotic genomes, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 10227–10232.
[196] Y. Zhu, X. Wang, S.P. Goff, G. Gao, Translational repression precedes and is required for ZAP-mediated mRNA decay, EMBO J. 31 (2012) 4236–4246.
[197] L. Xie, B. Lu, Z. Zheng, Y. Miao, Y. Liu, Y. Zhang, C. Zheng, X. Ke, Q. Hu, H. Wang, The 3C protease of enterovirus A71 counteracts the activity of host zinc-finger antiviral protein (ZAP), J. Gen. Virol. 99 (2018) 73–85.
[198] A.D. Kenney, J.A. Dowdle, L. Bozzacco, T.M. McMichael, C. St Gelais, A.R. Panfil, Y. Sun, L.S. Schlesinger, M.Z. Anderson, P.L. Green, C.B. Lopez, B.R. Rosenberg, L. Wu, J.S. Yount, Human genetic determinants of viral diseases, Annu. Rev. Genet. 51 (2017) 241–263.
[199] Q. Shu, N.J. Lennemann, S.N. Sarkar, Y. Sadovsky, C.B. Coyne, ADAP2 is an interferon stimulated gene that restricts RNA virus entry, PLoS Pathog. 11 (2015) e1005150.
[200] Q. Yu, D. Chen, R. Konig, R. Mariani, D. Unutmaz, N.R. Landau, APOBEC3B and APOBEC3C are potent inhibitors of simian immunodeficiency virus replication, J. Biol. Chem. 279 (2004) 53379–53386.
[201] H.L. Wiegand, B.P. Doehle, H.P. Bogerd, B.R. Cullen, A second human antiretroviral factor, APOBEC3F, is suppressed by the HIV-1 and HIV-2 Vif proteins, EMBO J. 23 (2004) 2451–2458.
[202] Y.H. Zheng, D. Irwin, T. Kurosu, K. Tokunaga, T. Sata, B.M. Peterlin, Human APOBEC3F is another host factor that blocks human immunodeficiency virus type 1 replication, J. Virol. 78 (2004) 6073–6076.
[203] H. Chen, C.E. Lilley, Q. Yu, D.V. Lee, J. Chou, I. Narvaiza, N.R. Landau, M.D. Weitzman, APOBEC3A is a potent inhibitor of adeno-associated virus and retrotransposons, Curr. Biol. 16 (2006) 480–485.
[204] J.F. Hultquist, J.A. Lengyel, E.W. Refsland, R.S. LaRue, L. Lackey, W.L. Brown, R.S. Harris, Human and rhesus APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H demonstrate a conserved capacity to restrict Vif-deficient HIV-1, J. Virol. 85 (2011) 11220–11234.
[205] B.E. Heaton, E.M. Kennedy, R.E. Dumm, A.T. Harding, M.T. Sacco, D. Sachs, N.S. Heaton, A CRISPR activation screen identifies a pan-avian influenza virus inhibitory host factor, Cell Rep. 20 (2017) 1503–1512.
[206] S.Y. Liu, R. Aliyari, K. Chikere, G. Li, M.D. Marsden, J.K. Smith, O. Pernet, H. Guo, R. Nusbaum, J.A. Zack, A.N. Freiberg, L. Su, B. Lee, G. Cheng, Interferon-inducible cholesterol-25-hydroxylase broadly inhibits viral entry by production of 25-hydroxycholesterol, Immunity 38 (2013) 92–105.
[207] M. Blanc, W.Y. Hsieh, K.A. Robertson, K.A. Kropp, T. Forster, G. Shui, P. Lacaze, S. Watterson, S.J. Griffiths, N.J. Spann, A. Meljon, S. Talbot, K. Krishnan, D.F. Covey, M.R. Wenk, M. Craigon, Z. Ruzsics, J. Haas, A. Angulo, W.J. Griffiths, C.K. Glass, Y. Wang, P. Ghazal, The transcription factor STAT-1 couples macrophage synthesis of 25-hydroxycholesterol to the interferon antiviral response, Immunity 38 (2013) 106–118.
[208] E. Sokolskaja, L. Berthoux, J. Luban, Cyclophilin A and TRIM5alpha independently regulate human immunodeficiency virus type 1 infectivity in human cells, J. Virol. 80 (2006) 2855–2862.
[209] Z. Keckesova, L.M. Ylinen, G.J. Towers, Cyclophilin A renders human immunodeficiency virus type 1 sensitive to Old World monkey but not human TRIM5 alpha antiviral activity, J. Virol. 80 (2006) 4683–4690.
[210] Z. Wang, X. Liu, Z. Zhao, C. Xu, K. Zhang, C. Chen, L. Sun, G.F. Gao, X. Ye, W. Liu, Cyclophilin E functions as a negative regulator to influenza virus replication by impairing the formation of the viral ribonucleoprotein complex, PLoS One 6 (2011) e22625.
[211] G. Chen, C.H. Liu, L. Zhou, R.M. Krug, Cellular DDX21 RNA helicase inhibits influenza A virus replication but is counteracted by the viral NS1 protein, Cell Host Microbe 15 (2014) 484–493.
[212] Y. Tang, G. Zhong, L. Zhu, X. Liu, Y. Shan, H. Feng, Z. Bu, H. Chen, C. Wang, Herc5 attenuates influenza A virus by catalyzing ISGylation of viral NS1 protein, J. Immunol. 184 (2010) 5777–5790.
[213] C. Zhao, T.Y. Hsiang, R.L. Kuo, R.M. Krug, ISG15 conjugation system targets the viral NS1 protein in influenza A virus-infected cells, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 2253–2258.
[214] L. Espert, G. Degols, C. Gongora, D. Blondel, B.R. Williams, R.H. Silverman, N. Mechti, ISG20, a new interferon-induced RNase specific for single-stranded RNA, defines an alternative antiviral pathway against RNA genomic viruses, J. Biol. Chem. 278 (2003) 16151–16158.
[215] G.R. Gariano, V. Dell'Oste, M. Bronzini, D. Gatti, A. Luganini, M. De Andrea, G. Gribaudo, M. Gariglio, S. Landolfo, The intracellular DNA sensor IFI16 gene acts as restriction factor for human cytomegalovirus replication, PLoS Pathog. 8 (2012) e1002498.
[216] D.J. Hui, C.R. Bhasker, W.C. Merrick, G.C. Sen, Viral stress-inducible protein p56 inhibits translation by blocking the interaction of eIF3 with the ternary complex eIF2.GTP.Met-tRNAi, J. Biol. Chem. 278 (2003) 39477–39482.
[217] M.J. de Veer, H. Sim, J.C. Whisstock, R.J. Devenish, S.J. Ralph, IFI60/ISG60/IFIT4, a new member of the human IFI54/IFIT2 family of interferon-stimulated genes, Genomics 54 (1998) 267–277.
[218] D. Wolf, S.P. Goff, TRIM28 mediates primer binding site-targeted silencing of murine leukemia virus in embryonic cells, Cell 131 (2007) 46–57.
[219] Q. Wang, X. Zhang, Y. Han, X. Wang, G. Gao, M2BP inhibits HIV-1 virion production in a vimentin filaments-dependent manner, Sci. Rep. 6 (2016) 32736.
[220] V. Lodermeyer, G. Ssebyatika, V. Passos, A. Ponnurangam, A. Malassa, E. Ewald, C.M. Sturzel, F. Kirchhoff, M. Rotger, C.S. Falk, A. Telenti, T. Krey, C. Goffinet, The antiviral activity of the cellular glycoprotein LGALS3BP/90K is species specific, J. Virol. 92 (2018).
[221] R. Burdick, J.L. Smith, C. Chaipan, Y. Friew, J. Chen, N.J. Venkatachari, K.A. Delviks-Frankenberry, W.S. Hu, V.K. Pathak, P body-associated protein Mov10 inhibits HIV-1 replication at multiple stages, J. Virol. 84 (2010) 10241–10253.
[222] X. Wang, Y. Han, Y. Dang, W. Fu, T. Zhou, R.G. Ptak, Y.H. Zheng, Moloney leukemia virus 10 (MOV10) protein inhibits retrovirus replication, J. Biol. Chem. 285 (2010) 14346–14355.
[223] E. Wustenhagen, F. Boukhallouk, I. Negwer, K. Rajalingam, F. Stubenrauch, L. Florin, The Myb-related protein MYPOP is a novel intrinsic host restriction factor of oncogenic human papillomaviruses, Oncogene (2018), https://www.nature.com/articles/s41388-018-0398-6.
[224] M. Dittmann, H.H. Hoffmann, M.A. Scull, R.H. Gilmore, K.L. Bell, M. Ciancanelli, S.J. Wilson, S. Crotta, Y. Yu, B. Flatley, J.W. Xiao, J.L. Casanova, A. Wack, P.D. Bieniasz, C.M. Rice, A serpin shapes the extracellular environment to prevent influenza A virus maturation, Cell 160 (2015) 631–643.
[225] L. Wang, B. Fu, W. Li, G. Patil, L. Liu, M.E. Dorf, S. Li, Comparative influenza protein interactomes identify the role of plakophilin 2 in virus restriction, Nat. Commun. 8 (2017) 13876.
[226] E. Meurs, K. Chong, J. Galabru, N.S. Thomas, I.M. Kerr, B.R. Williams, A.G. Hovanessian, Molecular cloning and characterization of the human double-

stranded RNA-activated protein kinase induced by interferon, Cell 62 (1990) 379–390.
[227] E.F. Meurs, Y. Watanabe, S. Kadereit, G.N. Barber, M.G. Katze, K. Chong, B.R. Williams, A.G. Hovanessian, Constitutive expression of human double-stranded RNA-activated p68 kinase in murine cells mediates phosphorylation of eukaryotic initiation factor 2 and partial resistance to encephalomyocarditis virus growth, J. Virol. 66 (1992) 5805–5814.
[228] J. Chebath, P. Benech, M. Revel, M. Vigneron, Constitutive expression of (2′-5′) oligo A synthetase confers resistance to picornavirus infection, Nature 330 (1987) 587–588.
[229] J. Liu, G. McFadden, SAMD9 is an innate antiviral host factor with stress response properties that can be antagonized by poxviruses, J. Virol. 89 (2015) 1925–1931.
[230] Y. Usami, Y. Wu, H.G. Gottlinger, SERINC3 and SERINC5 restrict HIV-1 infectivity and are counteracted by Nef, Nature 526 (2015) 218–223.
[231] A. Rosa, A. Chande, S. Ziglio, V. De Sanctis, R. Bertorelli, S.L. Goh, S.M. McCauley, A. Nowosielska, S.E. Antonarakis, J. Luban, F.A. Santoni, M. Pizzato, HIV-1 Nef promotes infection by excluding SERINC5 from virion incorporation, Nature 526 (2015) 212–217.
[232] M. Li, E. Kao, X. Gao, H. Sandig, K. Limmer, M. Pavon-Eternod, T.E. Jones, S. Landry, T. Pan, M.D. Weitzman, M. David, Codon-usage-based inhibition of HIV protein synthesis by human schlafen 11, Nature 491 (2012) 125–128.
[233] S. Schreiner, S. Kinkley, C. Burck, A. Mund, P. Wimmer, T. Schubert, P. Groitl, H. Will, T. Dobner, SPOC1-mediated antiviral host cell response is antagonized early in human adenovirus type 5 infection, PLoS Pathog. 9 (2013) e1003775.
[234] A. Lipovsky, A. Erden, E. Kanaya, W. Zhang, M. Crite, C. Bradfield, J. MacMicking, D. DiMaio, J.W. Schoggins, A. Iwasaki, The cellular endosomal protein stannin inhibits intracellular trafficking of human papillomavirus during virus entry, J. Gen. Virol. 98 (2017) 2821–2836.
[235] Z. Keckesova, L.M. Ylinen, G.J. Towers, The human and African green monkey TRIM5alpha genes encode Ref1 and Lv1 retroviral restriction factor activities, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 10780–10785.
[236] T. Hatziioannou, D. Perez-Caballero, A. Yang, S. Cowan, P.D. Bieniasz, Retrovirus resistance factors Ref1 and Lv1 are species-specific variants of TRIM5alpha, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 10774–10779.
[237] M.J. Perron, M. Stremlau, B. Song, W. Ulm, R.C. Mulligan, J. Sodroski, TRIM5alpha mediates the postentry block to N-tropic murine leukemia viruses in human cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 11827–11832.
[238] M.W. Yap, S. Nisole, C. Lynch, J.P. Stoye, Trim5alpha protein restricts both HIV-1 and murine leukemia virus, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 10786–10791.
[239] S.D. Barr, J.R. Smiley, F.D. Bushman, The interferon response inhibits HIV particle production by induction of TRIM22, PLoS Pathog. 4 (2008) e1000007.
[240] N.R. Meyerson, L. Zhou, Y.R. Guo, C. Zhao, Y.J. Tao, R.M. Krug, S.L. Sawyer, Nuclear TRIM25 specifically targets influenza virus ribonucleoproteins to block the onset of RNA chain elongation, Cell Host Microbe 22 (2017) 627–638 (e627).
[241] B. Fu, L. Wang, H. Ding, J.C. Schwamborn, S. Li, M.E. Dorf, TRIM32 senses and restricts influenza a virus by ubiquitination of PB1 polymerase, PLoS Pathog. 11 (2015) e1004960.
[242] J. Wang, B. Liu, N. Wang, Y.M. Lee, C. Liu, K. Li, TRIM56 is a virus- and interferon-inducible E3 ubiquitin ligase that restricts pestivirus infection, J. Virol. 85 (2011) 3733–3745.