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Antiviral drug discovery: broad-spectrum drugs from nature

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Antiviral drug discovery: broad-spectrum drugs from nature

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The development of drugs with broad-spectrum antiviral activities is a long pursued goal in drug discovery. It has been shown that blocking co-opted host-factors abrogates the replication of many viruses, yet the development of such host-targeting drugs has been met with skepticism mainly due to toxicity issues and poor translation to *in vivo* models. With the advent of new and more powerful screening assays and prediction tools, the idea of a drug that can efficiently treat a wide range of viral infections by blocking specific host functions has re-bloomed. Here we critically review the state-of-the-art in broad-spectrum antiviral drug discovery. We discuss putative targets and treatment strategies, taking particular focus on natural products as promising starting points for antiviral lead development.

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1. Introduction & background

This review centres on the concept of host-acting antiviral drugs (HAAs) with broad-spectrum activities as opposed to directly acting antivirals (DAAs) with high virus selectivity. Promising natural products that show diverse antiviral activity ranges are summarized.

The focus is on such compounds that are active against different virus families or genera rather than virus serotypes or strains of a given genus.

1.1 Viral infections: a global threat

Viruses continue to threaten global health. The firsts to name are the hepatitis B (HBV) and C (HCV) viruses, and the human immunodeficiency virus (HIV) that still are causing a worldwide death toll of approximately 0.6 million, 0.5 million and 2 million individuals per year, respectively [1-3] (Table 1). Influenza springs to mind as amongst the biggest viral killers of all times. It comes along as pandemics caused by newly assorted viral strains. Its rapid expansion worldwide is caused by a fast expansion within infected humans with nasal peak virus titers already 2 days post infection and efficient air-born transmissibility [4]. Measles virus, despite the existence of an efficient vaccine and global vaccine coverage of 84% of world's children, has nonetheless caused around 120 thousand deaths in 2012 [5]. Then there is the large group of emerging viruses for which no efficient vaccine or specific therapy is available today. They originate in most cases from infected animals and have an RNA genome that guarantees genetic variability with rapid adaptability [6, 7]. In terms of global spread, the dengue virus with its estimated 100 million apparent and 300 million unapparent infections in the year 2010 is alarming [8]. While most infections remain asymptomatic, the number of cases with dengue fever and dengue haemorrhagic fever has significantly increased over the last decades [9]. Other viral outbreaks like those of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 [10], the Middle East respiratory coronavirus (MERS-CoV) in 2012 [11], and the very recent Ebola virus (EBOV) outbreak in West Africa in 2014 [12] were comparatively tiny in numbers. Nonetheless they received large media coverage due to their epidemic potential and high mortality rates of 10%, 30% and up to 90% respectively.

Besides in the natural surroundings, there are deadly viruses in research laboratories. The smallpox-causing Variola viruses have killed an estimated 300-500 million individuals solely during the 20th century [21]. Due to tremendous global efforts and the existence of an efficient virus vaccine, smallpox was eradicated in 1979 [22], however Variola viruses still exist in diverse laboratories while vaccination campaigns have ended. Recent gain-of-function experiments with influenza viruses have artificially generated highly virulent and transmissible new virus strains that as such have never existed before [23, 24]. Any release of either of these viruses, be it deliberate or by mistake, could have devastating consequences as they would enter a non-vaccinated, fully susceptible human population [25, 26]. Thus, considering the continuous spread of major viral pathogens as well as unpredictable viral outbreaks of old or novel virus strains, it seems advisable to have an arsenal of countermeasures ready for the prevention of global health.

1.2 Current challenges in antiviral treatment

The arsenal of antivirals is complex and consists of (i) directly acting antivirals (DAAs), i.e. drugs that directly affect virus-derived components including viral proteins and viral genomes and (ii) host-acting antivirals (HAAs), i.e. modifiers of host factors or host pathways that affect virus life cycles as well as immune response components or immune response modifiers including antibodies, interferons and vaccines. As of March 2014, there were 50 specific DAAs approved by the American Food and Drug Association (FDA). 26 of these are directed against HIV. The other main targets are hepatitis B and C viruses, different herpes viruses and influenza viruses (Data provided by Antiviral InteliStrat, www.antiviralintelistrat.com). In most cases, DAAs act on viral polymerases and proteases, however also virus entry and exit steps or chromosomal integration of retroviruses are common points of interference. The group of host-acting antivirals (HAAs) is very heterogeneous. Vaccines, the classical, preventive weapons against virus infections, as well as antibodies or interferons will not be covered in this review. Instead, we will highlight compounds that transmit their antiviral activity via acting on cellular components or pathways that viruses use for their expansion. Such HAAs are not yet approved by the FDA as antivirals, but are the subject of multiple, promising current research and development projects.

The target spectrum of the approved DAAs is a reflection of (1) the needs to control particularly persistent infections for which no vaccine is available and (2) the tremendous efforts that was put into

Table 1. Estimates on global prevalence, incidence and treatment of selected viral infections (HIV, HCV, HBV, DENV, influenza virus), and co-infections (HIV/HCV, HIV/HBV, HIV/TB) worldwide

Virus	Infected[a]	Newly infected[a]	Antiviral treatment[b]	Ref.
Mono-infections				
HIV	35	2.3	ART [d]	13
HCV	150	3-4	Peg-IFNα/Ribavirin + Boceprevir/Telaprevir	2
HBV	240	0.6 [+]	Tenofovir/Emtricitabine	1, 14
DENV	50-100 [c]	0.5 [+]	None	15
Influenza	10% adults; 30% children *	3-5 [+]	Oseltamivir; Zanamivir	16, 17
Co-infections				
HIV/HCV	4 [#]	N.a.	Boceprevir/Telaprevir + Peg IFNα/Ribavirin + ART [d]	18
HIV/HBV	3.5 [#]	N.a.	ART [d] + Tenofovir/Emtricitabine	19
HIV/TB	11	1.1	ART [d] + TBCT [e]	20

[a]: In millions; [b]: Standard of care; [c]: Cases per year; [d]: ART, antiretroviral therapy, different formulations; e: TBCT, tuberculosis combination therapy (rifampin, isoniazid, ethambutol, and pyrazinamide); *: Seasonal epidemics; +: Cases with severe illness or death; #: Prevalence is exacerbated in risk groups, i.e. 80% of drug-injection HIV-infected users are co-infected with HCV, 20% infected with HBV in endemic areas. N.a.: Not assessed. HIV (human immunodeficiency virus), HCV (hepatitis C virus), HBV (hepatitis B virus), DENV (dengue virus), TB (tuberculosis)

HIV research. Indeed it was the HIV epidemic that became apparent in the 1980s plus the noise generated by AIDS activists that massively boosted antiviral research. With the launch of the first HIV protease inhibitors in 1995, the potency of antiviral therapy to convert a nursing case into a healthy virus carrier became evident. This was the starting point to shift the slowly progressing, fatal HIV-induced immunodeficiency into a controllable chronic infection. At the same time, the rapid dynamics of infecting viruses was recognized together with the error-prone nature of retrovirus and RNA virus replication as the underlying mechanisms for the rapid selection of drug-resistance during antiviral monotherapy. This hurdle can be overcome by antiviral combination therapy, providing that antivirals with non-overlapping resistance profiles are available. The impressive progress in HIV and HCV therapeutics clearly demonstrates that this can be the case. To now go beyond, there are important challenges ahead. How to get access to the latent reservoir of infections with HIV and HBV? Can one completely cure HIV or HBV infections? How to best manage viral co-infections like those of HIV and HCV that require complex drug regimen with drug-drug interactions and overlapping drug toxicities? How to protect individuals during outbreaks of highly pathogenic virus infections? Possible answers to these and related questions may derive from joining the knowledge of antiviral drug development with the rapidly growing field of systems virology.

2 Strategies of antiviral drug development

Viruses are intracellular parasites with a limited set of encoded genes. Their life cycles are completely dependent on cellular factors and pathways. These features are the underlying principles of two fundamentally different antiviral drug development strategies, the "many for one" and the "one for many" strategy.

2.1 Many for one: many drugs, one target

Aim of this antiviral drug development strategy is to find compounds that inhibit a particular viral target of a particular virus. As any virus has a specific set of viral genes, this strategy leads to drugs that are mainly virus-selective with none or little activity against different viruses or even different genotypes of the same virus [27, 28]. Direct-acting antivirals (DAAs) derived from such a strategy have been proven successful in either curing an infection or maintaining it asymptomatic. Most notable are the currently developed anti-HCV protease and polymerase inhibitors that in combination have a potential for curing close to all chronic HCV infections [29]. However, DAAs are still challenged with unsolved issues such as elevated costs, both for development and implementation [30], emergence of pathogen resistance [31], poor treatment responses in selected patient groups [32-35] or drug-drug interactions leading to toxicity [36-40]. These problems become even more relevant in co-infections as of HIV and HCV, for which combination treatment can be a clinical challenge [38, 41, 42]. For example, inhibitors of viral proteases are subject to degradation by cytochrome 3A4 (CYP3A4) and co-administration of so-called booster drugs like ritonavir or cobicistat that inhibit CYP3A4 is often required. As other CYP isoforms are also (partially) inhibited by the boosters, the treatment of co-morbidities with additional drugs may require individual modifications, and the overall assessment of all potential drug-drug-interactions is highly complex [39, 43-45]. Furthermore, these issues come in hand with another relevant problem: when there are many drugs against a single viral target, virus variation may generate cross-resistant mutants that would reduce therapy efficiency [46, 47]. Thus there is a need to develop antiviral drugs that could alone be effective against different viral pathogens. Such broad-spectrum antivirals (BSAs) could in principle alleviate some of the burdens of current DAAs and expand the application spectrum.

2.2. One for many: the broad-spectrum alternative

This antiviral drug development strategy aims at designing drugs with broad-spectrum antiviral activities. The first caveat in the development of BSAs is that viruses are highly diverse, both in structure and in replication strategies. Hence, the development of a DAA with broad-spectrum activity is a difficult task. However, as viruses are bound to utilize the host cellular machinery to propagate, they are critically dependent on cellular factors that are up- or down-regulated as needed. Examples are the down-regulation of membrane receptors [48-53], the up-regulation of the lipid metabolism [54], the use of the mRNA processing machinery [55] or the hijacking of components of the endosomal-sorting complex (ESCRT) required for virus export from infected cells [56-63] (see 2.4 for details). Moreover, as the life cycle of different viruses share common cellular factors and pathways, it is feasible that these could be used as targets for the design of broad-spectrum antivirals. Indeed, there are a number of chemical compounds that target common host factors and are at various levels of antiviral drug development (see under 3.2). In addition, with the advent of better screening technologies, we now know that the number of host factors associated with viral replication is strikingly large [64-67]. This provides a vast space to explore further antiviral targets [68]. Nonetheless, the development of such host-acting and broad-spectrum antivirals has its own challenges to meet.

2.3 Pros and cons of broad-spectrum antivirals (BSAs)

The putative advantages and disadvantages of BSAs are listed in **Figure 1**. The main advantage is that host-acting BSAs can cover multiple viruses and genotypes while reducing at the same time the likelihood of resistance development [69, 70]. In the clinical setting, applications of BSAs might range from rapid management of new or DAA-resistant viral strains [71] and of viral outbreaks [12] to reducing therapy complexity of viral co-infections [72-75]. In addition, BSAs would be ideal as a first-line treatment or the prophylaxis of acute virus infections such as respiratory tract or sexually transmitted infections [76, 77]. So far, a main disadvantage associated with host-acting BSAs is the apparent poor translation of *in vitro* results to *in vivo* therapy. Thus, excellent antiviral profiles from cell-line-based assays might not be reflected *in vivo* because systemic mechanisms may compensate the blocked target effect. On the other hand, the identification of host factor targets that are essential for viral replication but redundant for the cell is critical for reducing putative toxicities associated with blocking cellular pathways [69]. At the end however, the level of toxicity that can be tolerated will critically depend on the viral threat and the required time of treatment.

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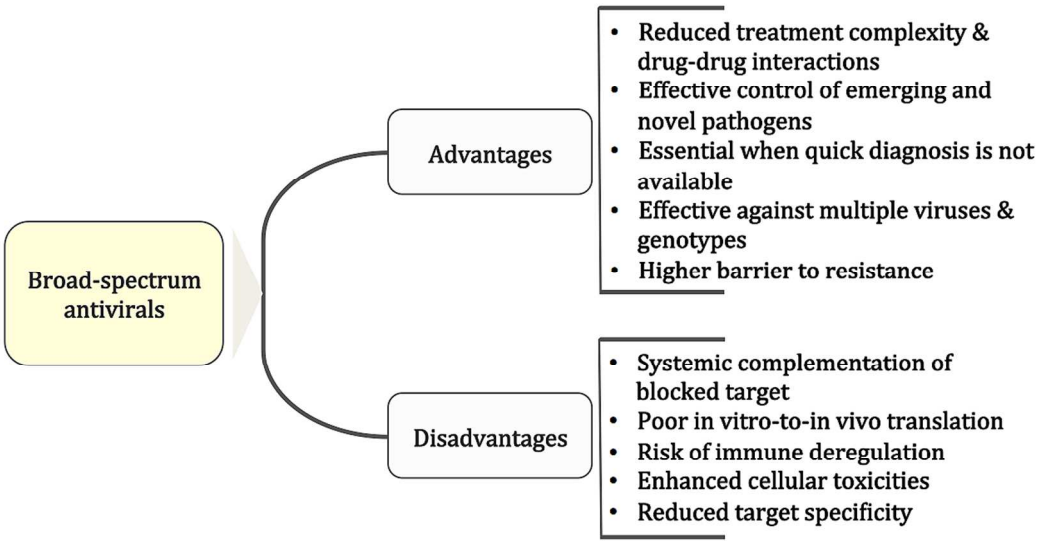

Figure 1. Putative advantages and disadvantages of broad-spectrum antiviral drugs. A drug that targets a common host factor might be effective against different viruses and decrease the likelihood of drug resistance development. However, it may result in a narrower therapeutic window as expected from *in vitro* studies. See text for details.

2.4 Approaches for BSA design

Current strategies for broad-spectrum antiviral drug development are focused on i) targeting host factors used for viral replication and, ii) targeting host factors that are naturally involved in viral restriction.

2.4.1 Targeting common host-factors used for viral replication

There are a large number of host factors and pathways associated with viral replication that are being explored for BSA development. An important target for BSA is the cellular lipid metabolism [78-80]. Examples are anionic phospholipids such as phosphatidylinositols that are found predominantly in early endosomes and intracellular membranes [81, 82]. Blockade of anionic phospholipids has been show to inhibit the replication of HCV [83], HIV [84], HBV, dengue virus (DENV) and yellow fever virus (YFV) [85]. Targeting lysobisphosphatidic acid (LBPA), which plays a role in cargo trafficking within endosomes, cholesterol mobilization and the formation of multivesicular bodies [86] has also been shown to inhibit influenza virus, vesicular stomatitis virus (VSV), Lassa Fever virus (LFV) and lymphocytic choriomeningitis virus (LCMV) [61, 87-89]. Depletion of components of the coat protein complex I (COPI) affects the entry of influenza virus and VSV and the endocytosis and vesicular transport of HCV and HIV [90-92].

The targeting of host factors associated with viral replication complexes (VRCs) such as ADP-ribosylation factor 1 (ARF1), guanine nucleotide exchange factor 1 (GBF1) and phosphatidylinositol kinase 4III (PI4IIIKα/β) has also been shown to inhibit the replication of HCV, several enteroviruses such as picornavirus (PV), Aichi virus (AiV) and Coxsackie virus B3 (CVB3), as well as rhinovirus, mouse hepatitis coronavirus (MHV) and HIV-1 [81, 93-101].Some viruses such as DENV and HCV are known to induce up-regulation of lipid synthesis for their replication [54]. Lipid rafts are described to be involved in entry, assembly and/or budding of influenza virus, HCV, VSV, HIV-1, Epstein Barr virus (EBV), Ebola virus (EBOV), Marburg virus (MARV), DENV, West Nile virus (WNV) and Herpes Simplex virus (HSV) (Table 2). Down-regulation of the lipid metabolism by siRNA or by licensed drugs such as statins has been shown to inhibit the replication of many viruses (see below).

Viruses also hijack host factors involved in protein folding such as cyclophilin A and endoplasmic reticulum (ER)-associated α-glucosidases [102]. Cyclophilin A (CypA) belongs to the family of peptidyl-prolyl-cis-trans isomerases (PPIase) and is involved in protein folding, trafficking, formation of multiprotein complexes (MPC) and other cellular functions [103, 104]. CypA interacts with viral proteins supporting viral replication [69]. CypA inhibitors such as cyclosporine A (CsA) have been shown to inhibit the replication of HIV, HCV, influenza virus, CoV, HBV, HSV, human cytomegalovirus (HCMV), VSV, vaccinia virus (VV) and human papillomavirus (HPV) [105-114]. Alisporivir (Debio-025) and SCY-635, both CsA analogues, have shown antiviral activity against HCV *in vivo* and are currently in combination with other anti-HCV compounds in various clinical trials [115, 116]. ER α-glucosidases I and II play a critical role in glycosylation of viral proteins [102]. Inhibition

of ER α-glucosidases has shown to affect viral particle assembly and/or secretion of HBV, HIV, HSV-1, influenza virus, parainfluenza virus, measles virus (MV), MARV, EBOV, HCV and other members of the Flaviviridae, such as bovine viral diarrhea virus (BVDB), DENV, WNV, and japanese encephalitis virus (JEV) [117]. Celgosivir has been proven effective against HCV and DENV infections *in vitro* and *in vivo* [118, 119]. A description of the antiviral effect of these compounds is provided in section 3 of this review.

Another putative target for BSA is the endosomal-sorting complex required for transport (ESCRT) that is involved in trafficking of viral proteins to the cell surface or into multivesicular bodies [57, 60, 63]. siRNA downregulation of components of the ESCRT and associated factors such as ALIX has been shown to block cell entry of VSV, LFV, and LCMV, and cell exit of HIV and hepatitis A virus (HAV) [56, 58, 61, 62, 87]. However, a non-toxic chemical compound has not yet been released for clinical use.

2.4.2 Targeting common host-factors involved in viral restriction

Eukaryotic cells have a myriad of effector molecules and mechanisms to protect their entity against microbial invaders including viruses. Such defenses are part of the innate immune response that is triggered when a cell becomes infected. Sensing of viral components via toll-like receptors (TLRs), the nucleotide binding and oligomerization domain-like receptors (NOD) [120, 121] or cytosolic sensors like RIG-I or MDA5 [122] subsequently leads to the activation of type I interferons (IFNs) which themselves induce hundreds of IFN-stimulated genes (ISGs) with divergent antiviral effector functions [123, 124]. Well-studied examples are the MxA and MxB proteins [125, 126], IFN-induced proteins with tetratricopeptide repeats (IFIT) and IFN-induced transmembrane proteins (IFITM) to name just a few [127]. They all dampen down virus growth albeit with different selectivity, mechanisms and points of interference. It was therefore suggested that one BSA strategy could be to chemically enhance the expression or activity of some ISGs [122, 128]. One such approach is the use of immunostimulatory compounds to target specific TLRs or NODs [129]. Two TRL7 agonist drugs, imiquimod and gardiquimod, have been proven successful in activating ISGs and improving host´s immunity to HPV and rhinovirus infections [130, 131]. While imiquimod is currently approved by the FDA for the treatment of HPV [132], many other TLR agonists and antagonists are under pre- or clinical evaluation. Likewise, two NOD2 agonists, MF-59 and MTP-PE, are currently under investigation for immunotherapies against HIV and influenza [133, 134]. Although more studies are needed to assess the BSA range of immunomodulating drugs, the overall strategy is highly promising. Further aspects not covered here are reviewed in [129, 135].

3 Natural products as a source for broad-spectrum antiviral drugs

3.1 Why natural products?

Natural products have been – and continue to be - a rich source of drugs [136, 137]. To base the search for treatments of a given medical condition on natural products has a variety of advantages: Natural products exhibit a large structural diversity and complexity that remains unmatched by other drug formats [138, 139]. Diversity of chemical matter is an important prerequisite to address the diversity of biological target space, in particular in the context of phenotypic screenings that capture full biological pathways rather than single protein domains [140-142]. The structural complexity of natural products, often regarded as a drawback with respect to synthetic accessibility, has been successfully mastered due to vastly improved methods of organic synthesis and/or genetic engineering [143]. A key advantage of natural products lies in the evolutionary pre-selection and optimization of chemical matter towards biological significance. As natural product biosynthesis is associated with considerable metabolic costs, compounds without significant advantages for their producers would have probably been eliminated in the course of evolution. In fact, numerous studies of natural products have disclosed biological functions that were advantageous for the microbial or eukaryotic producers in their (non-human) environment, but at the same time possessed high relevance for the treatment of human diseases [142]. While natural products have been the source of drugs for almost every indication, their importance is most pronounced in the field of infectious diseases where they have provided the chemical template for the majority of antibacterial and antifungal drugs [144]. Their role in antiviral drug development is less obvious, though, as nearly all marketed antiviral drugs today are produced by chemical synthesis. However, natural products have made significant contributions to antiviral drug discovery. Nucleoside analogs (containing other sugars than ribose or desoxyribose) represent the by far most important class of antiviral drugs. It should be noted that two early prototypes of nucleotide analogs, named spongouridine **(1)** and spongothymidine **(2)**, have been discovered in the 1950's from marine sources[145-147]. Also the DNA polymerase inhibitor arabinosyladenine **(3)**, marketed as Vidarabin, has been discovered from natural sources – but it happened years after its chemical synthesis [148]. Finally, the close similarity between ribavirin **(4)**, a cornerstone in multiple antiviral treatment regimens, and natural products like pyrazomycin **(5)** or showdomycin is remarkable [149, 150]. Thus, while nucleotide analoging as a central principle of defeating viruses was addressed by nature, it was independently explored and developed for medical use by means of chemical synthesis.

Here structures (1), (2), (3), (4) and (5)

3.2 Natural products with broad-spectrum antiviral activities: source and mode-of-action

Many substances from diverse natural sources such as bacteria, fungi, plants and animals have been described to have antiviral properties. A selection of those exerting BSA activities are shown in Figure 2, Table 2 and described below.

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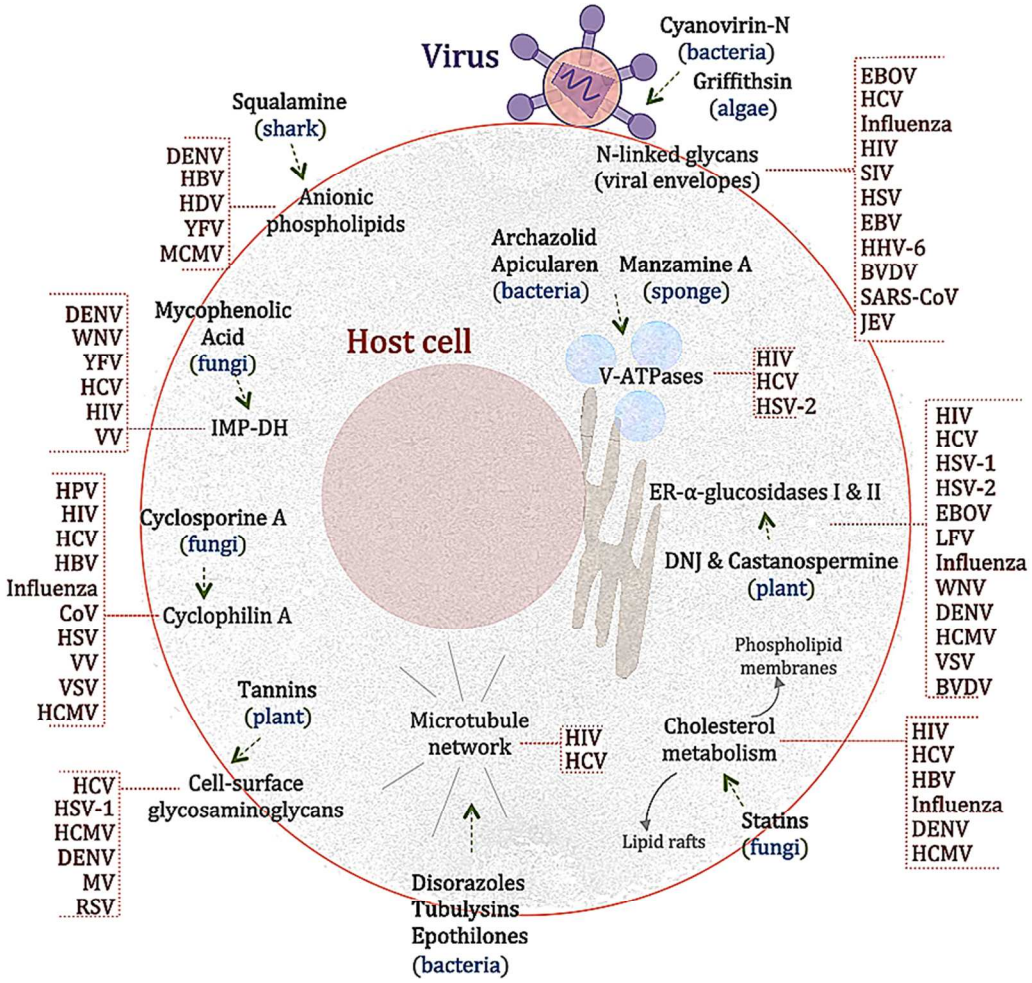

Figure 2. Schematic representation linking selected natural products with their principal targets and their antiviral activity spectrum. The sources of the compounds are given in brackets. Compounds are a selection made from an extensive literature search up to April 2014. Abbreviations (in alphabetical order): AdV (adenovirus), BVDV (bovine viral diarrhea virus), CoV-A59 (coronavirus A59), DENV (dengue virus), DNJ (1-deoxynojirimycin), EBOV (Ebola virus), EBV (Epstein Barr virus), HBV (hepatitis B virus), HCMV (human cytomegalovirus), HCV (hepatitis C virus), HDV (hepatitis D virus), HHV-6 (human herpesvirus 6), HIV (human Immunodeficiency virus), HPV (human papillomavirus), HSV (herpes simplex virus, various), IMP-DH (inosine monophosphate dehydrogenase), Influenza (Influenza virus), JEV (japanese encephalitis virus), LFV (Lassa fever virus), MCMV (mouse cytomegalovirus), MV (Measles virus), Parainfluenza (parainfluenza virus), RSV (Rous Sarcoma virus), SARS-CoV (severe acute respiratory syndrome coronavirus), SIV (simian immunodeficiency virus), VSV (vesicular stomatitis virus), VV (vaccinia virus), WNV (West Nile virus), YFV (Yellow Fever virus).

3.2.1 BSAs derived from fungi: cyclosporine, statins and mycophenolic acid

Cyclosporine A (CsA) (6) is a cyclic peptide isolated from the fungus *Hypocladium inflatum gams*, which was first shown to exert immunosuppressive activities (reviewed in [151]). The antiviral activity and mechanism of action of CsA was first described for HIV [152] and for VV [153]. CsA inhibits cellular cyclophilins that interact with HIV Gag polyproteins [152] and late proteins of VV [154], thereby facilitating their correct folding and assembly of replication complexes. Thus, the antiviral mode of action of CsA is to block these associations and as a consequence abrogate viral replication. Subsequent studies with CsA have shown that also HPV, HBV, HCV, influenza virus, coronaviruses, VSV and HCMV could be inhibited by similar mechanisms [69, 105-108, 111, 112, 115, 155]. CsA has an additional immunosuppressive effect through the inhibition of calcineurin that would counteract the antiviral efficacy *in vivo*. Therefore, derivatives of CsA have been prepared by semisynthesis that are devoid of calcineurin activity, but maintain the cyclophilin inhibition. The most advanced congeners are alisporivir (or DEB025) **(7)** and SCY-

635 **(8)** [116]. Although virus mutations that confer resistance to alisporivir have been reported [109, 110], a synergistic effect when used in combination with anti-HCV DAAs has been noted [156] and the drug is in clinical trials for the treatment of HCV infection [69]. Additional *in vivo* studies with other relevant viruses will determine whether cyclophilin inhibitors will be of broad applicability.

Here structures (6), (7) and (8)

Statins are HMG-CoA reductase inhibitors first isolated from the fungus *Penicillium citrinum* in the early 1970s [157]. The main effect of statin treatment is the decrease in total and low-density lipoprotein (LDL) cholesterol both *in vitro* and *in vivo* [158]. Statins have also been described to have immune-modulatory properties [159]. The antiviral effect of statins was first recognized for HCV [160]. In that study, Ye and colleagues demonstrated that treatment with lovastatin **(9)** efficiently impaired the replication of HCV sub-genomic replicons in cell culture by disrupting membrane components of viral replication complexes. The addition of geranylgeraniol, which is involved in protein trafficking to membrane compartments, restored viral replication thus suggesting a non-direct antiviral activity of statins. Antiviral effects of statins have also been described for HBV, HIV, influenza virus, DENV, HCMV and norovirus [161-169]. However the antiviral efficacy of statins *in vivo* was only marginal and drug-drug interactions with DAAs have been reported [170, 171]. While this terminated further use of statins as antiviral drugs, the data taken together underline the important role of the host´s lipid metabolism in viral replication [78].

Here structure (9)

Mycophenolic acid (MPA) (10), an inhibitor of eukaryotic inosine monophosphate dehydrogenase (IMP-DH), was first isolated from the fungus *Penicillium stoloniferum* [172]. Similar to ribavirin, MPA blocks nucleic acid synthesis by interfering with *de novo* purine biosynthesis [173]. However, as opposed to ribavirin, MPA has not been shown to have mutagenic properties. Mycophenolate mofetil, a MPA prodrug, has been described to have immunosuppressive properties [174]. MPA was first observed to limit the cytopathic effects of VV, HSV and MV in cell culture [175]. Since then, the drug has been reported to inhibit the replication of Hantaan River virus, DENV, WNV, HBV, HEV, HCV, HIV and poxviruses by affecting viral nucleic acid synthesis [176-182]. *In vivo* MPA alone is not effective against HSV, but it has been shown to enhance the anti-HSV activities of acyclovir, gancyclovir and pencyclovir in experimental animals [183]. Interestingly, MPA has also been shown to synergize with antiretroviral drugs [184, 185] as well as with cyclosporin A and IFN-a in HCV inhibition [181]. However, due to its mode of action, the long-term use of MPA might lead to development of drug resistance as it was previously shown for Sindbis virus [186].

Here structure (10)

3.2.2 BSAs derived from plants: castanospermine, 1-deoxynojirimycin, chebulagic acid and punicalagin

Castanospermine (CST) **(11)** and **1-deoxynojirimycin** (DNJ) **(12)** are alkaloids isolated from the chestnut tree *Castanospermum australae* and from mulberry leaves, respectively. CST, its derivative celgosivir (6 O-butanoyl castanospermine) and DNJ have been described to inhibit the replication of multiple viruses both *in vitro* and *in vivo* [117-119, 187-197] (Table 2). In mammalian cells both compounds block the function of ER α-glucosidases I and II. These enzymes are in charge of trimming glucose residues added to N-linked glycans during protein synthesis in the ER [198].

This addition is an intermediate step that enhances the efficiency of protein folding in the glycoprotein maturation process [198]. The BSA mechanism of CST and DNJ is thus suggested to be the disruption of the folding of some viral glycoproteins leading to poor expression of mature envelopes and reduced infectivity [189, 199, 200]. Given the broad range antiviral effects of blocking the host glycoprotein processing machinery, new screening campaigns with different glucosidase inhibitors might identify compounds with enhanced BSA effects. Indeed, many other glucosidase inhibitors isolated from natural sources exist (see [201] for an extensive overview) that may be considered for testing as BSA.

Here structures (11) and (12)

Tannins are antimicrobial secondary metabolites commonly found in plants [202]. Hydrolysable tannins have been described to exert inhibitory effects against viruses, bacteria and eukaryotic microorganisms [203]. **Chebulagic acid** (CHLA) **(13)** and **punicalagin** (PUG**) (14)** are two hydrolysable tannins isolated from the tree *Terminalia chebula* that were initially found to inhibit HIV [204]. CHLA and PUG have also antiviral activities against HCMV, HCV, DENV, MV and RSV [205]. PUG treatment also protected mice challenged with an otherwise lethal dose of enterovirus [206]. While the exact mechanism of action of CHLA and PUG is not entirely elucidated, it is suggested that these compounds inhibit the interaction between viral glycoproteins and cellular glycosaminoglycans (GAGs) [207]. GAGs are carbohydrates present on the surface and in the extracellular matrix of cells that have been shown to be required for the infection of several viruses [208-213]. Of note, two other hydrolysable tannins isolated from mango (*Mangifera indica)* were shown to inhibit influenza virus and Coxsackie virus *in vitro* [214]. Although more studies are needed to clarify the antiviral mechanism of action exerted by hydrolysable tannins, these plant-derived substances might be a good starting point for BSA development.

Here structures (13) and (14)

3.2.3 BSAs derived from bacteria: cyanovirin-N, labyrinthopeptin-A1, and myxobacteria-derived metabolites

Cyanovirin-N (CV-N) (15) is a peptide isolated from the cyanobacterium *Nostoc ellipsosporum* first found to inhibit HIV-1, HIV-2 and SIV [215]. It was later reported to also exhibit *in vitro* virucidal activity against HCV, influenza virus, HSV-1, and EBOV [215-219]. CV-N binds with great affinity to high-mannose oligosaccharides found on viral envelope glycoproteins [220] and inhibits entry into target cells. For influenza and HIV, however, adaptive mutations might arise that cause loss of high-mannose sites and render the viruses resistant to CV-N [221, 222].

Here structures (15)

Nevertheless, antiviral studies with CV-N *in vivo* against neuroaminidase-inhibitor resistant influenza, Zaire strain of EBOV in mice, and studies performed with transmission models of HIV and SIV suggest that CV-N has potential for use as prophylaxis and early post-exposure treatment [216, 219, 223-225]. Still, whether CV-N has a binding partner in the host has not been determined yet and further

studies are needed to assess the safety of CV-N as a therapeutic drug.

Table 2. Broad-spectrum antiviral properties of selected natural products. Abbreviations as in Figure 2.

Compound name	Antiviral against	Available inhibitory data	Ref
Cyclosporine	HPV	90% inhibition with 10 μM in HaCaT cells	105
	HIV	0.07 to 4.7 μM Effective concentration 50 (EC_{50}) in TZM-bl assay	109
	HBV	70% inhibition with up to 20 μg/mL in Huh7 cells	107
	Influenza	90% inhibition with 10 μg/mL in MDCK cells	112
	SARS-CoV	90% inhibition with 16 μM in Vero and Huh7 cells	108, 113
	HSV-1	90% inhibition with 25 μM in monkey kidney cells	155
	VV	97% inhibition with 16 to 40 μM in culture cells	153
	VSV	90% inhibition with 26 μM in BHK cells	106
	HCMV	Virus production delayed 6 days under 0.5 μM in mice	111
	HCV	1 μg/mL: 80% less viral RNA from MH-14 cells; 45 nM EC_{50} for alisporivir	69, 226
Statins (several)	HCV	lovastatin EC_{50} = 0.9 - 2.16 μM in OR6 cells	171
	HBV	Selectivity Index (SI) = 3.44 in infected HepG2.2.15 cells with fluvastatin	162
	Influenza	SI = 21 in influenza infection in vitro assays with fluvastatin	164, 168
	HIV	50% less p24 production from isolates in PBMCs under 50 μM lovastatin	165, 227
	DENV	lovastatin SI = 1.4 in Vero cells and 4.5 in HMEC-1 cells	167
	HCMV	50% less IE1 protein expression in U373-MG cells with 10 μM simvastatin	169
Mycophenolic Acid	DENV	EC_{50} =1.9 μM in human hepatoma cells	179
	WNV	EC_{50} = 10 μg/mL in primary glial cells	179
	YFV	EC_{50} = 0.4 μg/mL in Hep3B cells	179
	HCV	75% inhibition with 1.0–6.0 μg/mL MPA using Luc-viruses	181
	HIV	4 μM = complete suppression of virus replication in CD4 T-cell cultures	177
	VV	50% inhibition in plaque reduction assays with 0.2–3 μM in Vero cells	228
Castanospermine (CST) & Deoxynojirimycin (DNJ)	HCMV	0.8 mM (CST) and 1 mM (DNJ) plaque reduction assay in HEF cells	189
	HSV-2	EC_{50} < 4μM in plaque assay	190, 191
	HIV	100 μg/mL 100% syncitia inhibition in H9 and CD4-Jurkat cells	188, 199, 229, 230
	BVDV	Celgosivir: 16 μM EC_{50} in plaque assay; CST: 110 μM	193
	HCV	CST: low effect; DNJ EC_{50} > 100; DNJ derivatives: $EC_{50} \geq 4$ μM in Huh7 cells	118, 194, 231
	DENV	EC_{50} = 6 μM in BHK cells	119, 192, 195, 232
	WNV	DNJ derivative > 90% inhibition under 15 μM in MDBK cells	102, 117
	EBOV	DNJ derivative > 90% inhibition under 15 μM in MDBK cells	102, 117
	LFV	DNJ derivative > 90% inhibition under 15 μM in MDBK cells	102, 117
	VSV	DNJ derivative > 90% inhibition under 15 μM in MDBK cells	102, 117
	Influenza	10 pg/mL: 90% of the viral glycopeptides endoglucosaminidase H	187, 233
Chebulagic Acid & Punicalagin	HCMV	SI = 12/17 (Chebulagic / Punicalagin) in HEL cells	205
	HCV	SI = 19/13 in Huh7.5 cells	205
	DENV	SI = 12/19 in Vero cells	205
	MV	SI = 10/11 in CHO cells	205
	RSV	SI = 642/490 in Hep-2 cells	205
	HSV	SI = 18.62/14.5 in A549 cells	207
	AdV	SI = 1.60/1.62 in A549 cells	205
Cyanovirin-N	EBOV	EC_{50} = 100 nM; virus CPE in Vero cells 7 days post infection (d.p.i.)	216
	HCV	EC_{50} = 1.6 nM in Huh7 cells infected with HCVpp	217
	Parainfluenza	SI > 1.9 in HEp1 cells	218

Table 2. Broad-spectrum antiviral properties of selected natural products. ***Continued***

Compound name	Antiviral against	Available inhibitory data	Ref
Cyanovirin-N	Influenza A	SI > 228 in MDCK cells	218
	Influenza B	SI > 20 in MDCK cells	218
	HIV	EC_{50} = 0.1 - 17 nM in PBMC (by Reverse Transcriptase activity assay of supernatants)	215
	SIV	EC_{50} = 11 nM	215
	HSV-1	SI = 158 in Vero cells	219
	EBV	SI = 4.3 in P3Hr1 cells	218
	HHV-6	SI = 4.4 in HSB-2 cells	218
	BVDV	SI = 13 in MDBK cells	218
Labyrinthopeptin	HIV	EC_{50} = 0.70 – 3.3 µM	234, 235
	HSV (various)	EC_{50} = 0.29 – 2.8 µM	234, 235
Apicularen	HPV	SI = 3 - 6 in Hela cells	236
	HIV	Z-score = -1.9 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	75% inhibition (replication), 99.5% inhibition (whole life cycle) in Huh7cells	238
Crocapeptin	HIV	Z-score = -1.8 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	Z-score = -8.6 in primary screen in Huh7 cells under 2.3 µM	238
Noricumazole	HIV	Z-score = -1.01 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	Z-score = -6.3 in primary screen in Huh7 cells under 2.3 µM	238
Disorazole	HIV	Z-score = -1.31 to -1.78 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	Z-score = -6.9 in primary screen in Huh7 cells under 2.3 µM	238
Epothilone	HIV	Z-score = -2.38 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	95% (replication), around 99% (whole life cycle) inhibition in Huh7cells under 2.3 µM	238
Tubulysin	HIV	Z-score = -1.34 to -2.47 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	95% (replication), around 99% (whole life cycle) inhibition in Huh7cells under 2.3 µM	238
Archazolid	HIV	Z-score = -1.4 in primary screen in TZM-bl cells under 2.5 µM	237
	HCV	77% (replication), 99% (whole life cycle) inhibition in Huh7cells under 2.3 µM	238
Mycalamide	Polio Virus	MIC 5 ng/disc (assay not described, n.d.)	239
	HSV-1	MIC 5 ng/disc (assay n.d.)	240
	Influenza	32 µM of a Mycalamide analog; 60 to 90% plaque reduction in MDCK cells	241
	CoV-A59	Mice survival 14 days after A59 CoV infection under 0.1 mg/kg of 2% mycalamide A	240
Dragmacidin & Manzanine	HSV-2	EC_{50} = 96 µM HSV in colorimetric plaque-reduction assay; 0.9 µM HIV in MT4 cells	242-244
	HIV	HIV EC_{50} = 4.2 µM (assay n.d.); anti-HSV MIC= 0.05 µg/mL (assay n.d.)	242-244
Griffithsin	HIV	SI = 2000 against HIV_{lai} in MT4 cells; SI >20000 against HIV_{bal} in human PBMCs	245
	HCV	EC_{50} = 14 nM against JFH1 HCVcc in Huh-7 cells	246
	SARS-CoV	EC_{50} = 14 nM in Vero 76 cells	247
	JEV	EC_{50} = 20 nM BHK- 21 cells	248
	SIV	SI = 500 against SIV_{mac} in CEMx174 cells	245
Squalamine	DENV	100 µg/mL 100% inhibition human endothelial cells	85
	HBV	20 µg/mL 80% inhibition in human hepatocytes	85
	HDV	20 µg/mL 80% inhibition in human hepatocytes	85
	YFV	Hamster 15 mg/kg daily dose, 100% survival after 8 days compared to control animals	85
	MCMV	BALB/c mice, 10 mg/kg daily dose intraperitoneal, no virus detected 14 d.p.i.	85

Lantibiotics are peptides with unusual amino acids produced by several gram-positive bacteria [249, 250]. **Labyrinthopeptin A1 (LabyA1) (16)** belongs to a novel class of carbacyclic lantibiotics [251, 252] that was isolated from the actinomycete *Actinomadura namibiensis*. LabyA1 was recently shown to inhibit both HIV and HSV at sub-micromolar concentrations *in vitro* [234, 235]. The compound is suggested to block viral entry by interacting with viral envelopes and to prevent cell-to-cell transmission. What makes LabyA1 appealing is its effectiveness against resistant HIV and HSV viruses, its synergistic effects with standard antiretroviral drugs, and the absence of an inflammatory response of PBMC's. Laby A1 was nontoxic to vaginal lactobacilli [234], thus making it an excellent candidate microbicide for the prevention of sexually transmitted virus infections. Although HIV and HSV are non-related viruses, the question remains whether LabyA1 might be effective against a broader range of viral pathogens.

Here structure (16)

Myxobacteria are soil bacteria known to be producers of highly bioactive secondary metabolites [253]. These have been shown to exhibit a wide range of activities such as antifungal and antibacterial properties (see [254, 255] for further details). Two recent antiviral screens using a library of compounds derived from the secondary metabolism of myxobacteria have identified several compounds with overlapping activities against HIV and HCV [237, 238] (Table 2). Among these are **crocapeptin B (17)**, a cyclic depsipeptide isolated from the myxobacterium *Chondromyces crocatus* described to have inhibitory activity against serine proteases [256] and **noricumazole A (18)**, an oxazole- and isochromanone-containing metabolite isolated from *Sorangium cellulosum* shown to block ion channels [257, 258].

Other anti-HIV and anti-HCV hits were compounds known to inhibit tubulin polymerization, namely **disorazoles (19)**, polyketides isolated from the myxobacterium *Sorangium cellulosum*, and **tubulysins (20)**, unusual peptides derived from the myxobacterium *Archangium gephyra* ([237] and references therein). **Epothilones (21)**, a group of macrolides that enhance tubulin polymerization and that are approved for cancer treatment, were also inhibiting HIV and HCV. Modulation of the host´s microtubule network is known to influence the replication of many and diverse viruses [259, 260]. However, chemical blockade of microtubules is associated with toxicities that, so far, hamper the development of these compounds as antiviral drugs.

Here structures (17), (18), (19), (20) and (21)

Both antiviral screens also identified two highly specific V-ATPase inhibitors, **apicularen (22)** and **archazolid (23)**, as anti-HIV and anti-HCV hits [237, 238]. Recently, Müller *et al.* also described apicularen as an inhibitor of HPV replication [236]. Evidence from genome-wide siRNA screens and other studies highlighted the dependency on host´s V-ATPases for the replication of diverse viruses like HCV, DENV, WNV, influenza virus, and HIV (Table 2 and references therein).

Here structures (22) and (23)

V-ATPases translocate protons from the cytoplasm into intracellular compartments and through the plasma membrane. This activity is important for the function and trafficking of internal organelles such as vacuoles, endosomes, or lysosomes, which are in turn used by viruses for entry, translation, assembly or budding [261, 262]. However, blocking these proton pumps also leads to other physiological changes in the host cell ([263] and references therein), and thus the benefit-risk ratio of such compounds as BSAs *in vivo* remains to be determined.

3.2.4 BSAs derived from marine life: Natural products from sponges, griffithsin from red algae and squalamine from dogfish shark

The number and diversity of natural products isolated from marine sources continues to grow [264]. Two recent reviews describe the biological activities, including antiviral properties, of several compounds isolated from marine organisms [265, 266]. Here we refer briefly to compounds with BSAs derived from marine sponges (reviewed in [239]), and to squalamine, a compound isolated from the dogfish shark [85].

Similar to myxobacteria, marine sponges produce an ample number of secondary metabolites with diverse biological activities [267]. Of note, the first antiviral drug approved by the FDA, the nucleoside Ara-A (Vidarabine), was isolated from a marine sponge [239]. **Mycalamide A** and **B (24),** two natural products isolated from *Mycale* sponges, have shown antiviral activities against coronaviruses [240], HSV and Polio virus [268]. It was suggested that the compounds inhibit viral protein synthesis by direct binding to ribosomes, a well-described host cell target for the compound class [269]. However, some analogues of mycalamides are described to inhibit influenza virus *in vitro* by binding to the viral nucleoprotein (NP), thereby impeding its association with viral RNA [241]. Thus, whether mycalamides exert their antiviral action by targeting host factors, viral components or both is still not clear.

Here structure (24)

Two alkaloids isolated from *Halicortex* sponges, **dragmacidin F (25)** and **manzamine A (26)**, have also been described to inhibit HSV and HIV [270]. Although the exact mechanism of viral inhibition is not clear, dragmacidin F is a serine-threonine protein phosphatase inhibitor [271] and manzamine A targets V-ATPases [272], thus providing clues of their BSA action. The viral dependency on host´s V-ATPases was described above, and serine-threonine phosphatases are known to play several roles in viral replication [273, 274]. Whether dragmacidin targets host and virus-encoded serine-threonine phosphatases [275] is not known.

Here structures (25) and (26)

Griffithsin (GRFT) (27), a 13-kDa lectin isolated from the red alga *Griffithsia sp*. [276], was first shown to bind to oligosaccharides on the surface of the HIV envelope glycoprotein gp120 and block viral entry [276]. Similar to CV-N, it interacts with terminal mannose residues found in N-linked glycans of the viral envelope [277]. By a similar mechanism, GRFT inhibits SIV, HCV, SARS-CoV, HSV and JEV [245-248, 278, 279], thus exhibiting broad-spectrum antiviral activities. When applied in combination with antiretroviral therapy, GRFT shows a synergistic inhibitory effect [280]. Interestingly, unlike other lectins, GRFT does not induce production of pro-inflammatory cytokines in treated human peripheral blood mononuclear cells [278]. It

has been shown to safely protect mice from genital HSV [279] and monkeys from vaginal SIV infection [245], thus having promising properties for preventing virus infections. Selection of GRFT-resistant HIV variants has been observed. However, as this requires an extensive loss of glycans and multiple amino acid sequence changes [281], GRFT represents an interesting candidate natural product to be developed into a broad-spectrum antiviral drug.

Here structure (27)

Squalamine (28), an amphipathic sterol isolated from tissue of the dogfish shark *Squalus acanthias* [282], has been recently described to inhibit infections by DENV, HBV, HDV, YFV and mouse cytomegalovirus (MCMV) [85]. Squalamine has a high affinity for anionic phospholipids and is able to neutralize the negative charge of its membrane-associated targets without affecting cell membrane composition [283]. Thus, it was suggested that squalamine might disturb the electrostatic associations of host and viral proteins in membrane compartments, rendering the cells unable to support viral replication [85]. More studies are needed to determine whether protein displacement by squalamine affects the replication of other relevant viruses such as influenza and HIV.

Here structure (28)

4. Brief note on BSAs from other sources

Plants and animals are also producing peptidic BSAs as part of their defenses against viral pathogens. Likewise, some BSAs are generated *de novo* by synthetic chemistry. While both groups of compounds are not the main topic of this review, we briefly mention some for completeness.

4.1 Host defense factors

Antiviral defense factors other than ISGs have been described. Defensins and cathelicidins are antimicrobial polypeptides that can be constitutively produced by the host or induced after innate immune recognition of pathogens [284]. Two excellent recent reviews refer to the BSA activities of these host defense factors [285, 286]. Wilson et al. have recently summarized the BSA effect of α- and β-defensins against various viruses including HIV, VSV, AAV, VV, RSV, HSV, and HPV [286]. Their proposed mechanisms of action are: interacting with lipid bilayers, binding to glycoproteins and blocking protein-protein or protein–DNA interactions. Thus, defensins can potentially block different steps in viral life cycles [286]. Interestingly, defensins seem to be conserved among different organisms. Indeed, mastoparan, a defense peptide found in the venom of wasps, has been described to have BSA activities against VSV, WNV, DENV, HSV, RSV, influenza virus and AdV mainly by disrupting the viral envelope structure [287]. Cathelicidins are another type of defense peptides that carry a conserved cathelin-like domain [288]. Barlow and colleagues have recently reviewed the BSA effect of cathelicidins [285]. In particular, the human cathelicidin LL-37 has been shown to affect several viruses including VV, RSV, influenza virus, HIV, HSV, DENV and AdV by distinct mechanisms such as envelope disruption and polymerase or protease inhibition [285]. However, the mere co-existence of cellular defense mechanisms and viruses already implies that there is an ongoing evolutionary race between the arming of cells with new antiviral weapons and the arming of viruses with new anti-host defense mechanisms to stay in place. Recent elegant studies emphasize this “arms race” as part of the evolution of the human innate immune system [289]. The extent to which this holds true for the interrelationships of defensins and cathelicidins with viruses has yet to be determined.

4.2 Non-natural synthetic ligands

Drug-like small synthetic compounds have also been reported to exhibit BSA activities. Still, most of these chemicals are only able to efficiently block the replication of certain viral groups such as RNA viruses. Examples are arbidol, an indole derivative (reviewed in [290]), T-705 (Favipavir) (reviewed in [291]) and more recently BCX4430, a novel nucleoside analog shown to have strong antiviral effects against filoviruses, and mild effects against bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses and flaviviruses [292]. Highly encouraging results *in vitro* and in cynomolgus macaques have yet to be confirmed by clinical studies.

5. Conclusions and perspectives

While humans depend on their immune system to repel microbial threats, simpler organisms like plants, bacteria and fungi produce a variety of metabolites for this purpose. These compounds are often targeting general cellular pathways and regulatory elements that are also exploited by viruses for their propagation. Given the intriguing conservation of some of these elements between species and their promiscuous use by divergent viruses, it is not too surprising to find a rich arsenal of antivirus-acting natural products when analyzing simpler organisms. Indeed, good examples are the cyclophilin inhibitors as mentioned above. More recent examples are the described overlapping hits from a myxobacterial library that inhibit both HIV and HCV as well as host factors involved in the processing machinery of cellular and viral RNA[55, 237, 238, 263].

Today, DAAs are the dominant class of antiviral drugs in use. They are highly successful against clinically important infections like HIV, HCV and several others. Nonetheless, obstacles like drug resistant viruses or emerging viruses with no available selective antivirals in the market call for utilization of the armament of simpler organisms that target host factors and show broad-spectrum antiviral activities. The observation that some host factors like the HIV co-receptor CCR5 can be targeted without major toxicities is encouraging for the overall concept of targeting the host to inhibit a virus. Compounds like Alisporivir with a potentially broader antiviral application range than CCR5 inhibitors are in clinical trials. With the (i) rapidly increasing knowledge of virus – host factor interactions via system-wide screening campaigns, (ii) the highly advanced techniques of natural product isolation, characterization and modification either via chemistry or genetic modifications of producer strains, and (iii) the advances of *in-silico* tools for dynamic molecule simulations and toxicity predictions, the usable antiviral drug space will significantly increase in the coming years. Thus, despite perpetual worrisome news of novel or re-emerging viral threats, there is a rich source of weaponry out in nature to appease.

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