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Antiviral strategies targeting host factors and mechanisms obliging +ssRNA viral pathogens

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ABSTRACT

The ongoing COVID-19 pandemic, periodic recurrence of viral infections, and the emergence of challenging variants has created an urgent need of alternative therapeutic approaches to combat the spread of viral infections, failing to which may pose a greater risk to mankind in future. Resilience against antiviral drugs or fast evolutionary rate of viruses is stressing the scientific community to identify new therapeutic approaches for timely control of disease. Host metabolic pathways are exquisite reservoir of energy to viruses and contribute a diverse array of functions for successful replication and pathogenesis of virus. Targeting the host factors rather than viral enzymes to cease viral infection, has emerged as an alternative antiviral strategy. This approach offers advantage in terms of increased threshold to viral resistance and can provide broad-spectrum antiviral action against different viruses. The article here provides substantial review of literature illuminating the host factors and molecular mechanisms involved in innate/adaptive responses to viral infection, hijacking of signalling pathways by viruses and the intracellular metabolic pathways required for viral replication. Host-targeted drugs acting on the pathways usurped by viruses are also addressed in this study. Host-directed antiviral therapeutics might prove to be a rewarding approach in controlling the unprecedented spread of viral infection, however the probability of cellular side effects or cytotoxicity on host cell should not be ignored at the time of clinical investigations.

1. Introduction

Viruses encompass a diverse group of pathogens that cause contagious infections. Viruses are generally simple, small, and non-cellular organisms containing single or double stranded nucleic acid genomes made up of DNA or RNA.[1] RNA viruses are further sub-divided into negative-sense and positive-sense viruses according to the sense or polarity of their genomic material. In case of positive-sense single-stranded RNA viruses (+ssRNA), the genomic mRNA can be translated directly by host cell to produce structural and non-structural (nsPs) viral proteins. For negative-sense RNA viruses, the viral RNA is converted to positive-sense RNA by RNA polymerase before proceeding with translation.[1] In the last 40 years, the world has witnessed frequent viral outbreaks including the Human Immunodeficiency Virus (HIV, 1981)[2], Middle East Respiratory Syndrome Coronavirus (MERS-CoV, 2012)[2], Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV, 2002)[2], Chikungunya virus (CHIKV, 2005)[3], Japanese Encephalitis virus (JEV, 2005)[4], Dengue virus (DENV, 1980–2010)[5], and presently, the ongoing pandemic caused by the novel SARS coronavirus-2 (SARS-CoV-2).[6] Therefore, detailed knowledge of viral characteristics, replication strategies, and their modes of action are imperative to identify new antiviral therapies for hampering the spread of viral disease.

Viruses have immense ability to modify physiological and metabolic pathways of the host. Comprehensive understanding of the molecular mechanisms involved in spread of viral infections has paved the way for discovering new antiviral therapies, either by targeting the viral proteins or by upregulation of host factors for alleviating host antiviral response.[7] Host innate immune system forms the first line of defence against viruses and is primarily responsible for recognizing pathogen-associated molecular patterns (PAMP) for initiating a strong antiviral response.[8,9] The second role is played by adaptive immune system which then kicks in to totally clear the virus infection and to build up prolonged memory response.[10]

Due to the small genomic size, viruses co-opt with host cell machinery in every step of their infectious cycle, starting from entry into the host cell to final transcription, translation, replication, and budding.

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Therefore, a continual interaction of host-viral proteins is maintained by viruses to hijack the complex cellular pathways for its own replication or to overcome host antiviral response for long-term persistence inside the host. Classical antiviral therapy imparts antiviral functions by inhibiting the biological activities of viral structural proteins[11] (capsid, nucleocapsid, envelope etc.), nsPs[3], and replication enzymes (RNA methyltransferase, capping enzyme[12], protease[13], RNA dependent RNA polymerase (RdRp), helicase etc.).[14] An alternative antiviral strategy for controlling virus infections is to design molecules targeting the host pathways hijacked by viruses for pathogenesis and immune evasion inside the host, such as the host metabolic pathways (lipid[15], glucose[16], and polyamine[17]), ubiquitin proteasome system[18], glycosylations[19], inflammatory cascades[20], programmed ribosomal frameshifting (PRF)[21] etc.[22,23,24] Advantages of this approach includes the broad spectrum inhibitory activity of antivirals against multiple viruses and an increased threshold to emergence of drug resistance.[23] Genetic variability and mutation rate of host is relatively low when compared to viruses, therefore the probability of host-directed antiviral agents to lose their efficiency against rapidly evolving and mutating virus is also quite low.

The present review aims to compare the available information pertaining to +ssRNA virus families (*Togaviridae*, *Flaviviridae*, *Coronaviridae*, *Astroviridae*, and *Picornaviridae*) in terms of the host traits hijacked by them for downregulating antiviral response and viral dependency on host metabolic pathways (Lipid synthesis/polyamine metabolism/glucose metabolism). The virus life cycle begins with the attachment of viral glycoproteins to the host cell receptor, and entry into host cell via receptor-mediated endocytosis.[14,25,26] Following entry, open reading frame (ORF) of viral genome is translated to generate polypeptide of nsPs.[14] Viral proteases, such as nsP2 of CHIKV, 3C-like protease (3CLpro) and papain like protease (PLpro) of SARS-CoV and SARS-CoV-2, NS2B/NS3 protease of DENV etc. further cleave polypeptide into individual nsPs by autoproteolytic activity.[3,14,27,28] The enzymatic activities of these nsPs further aid in the replication (RdRp) and capping [methyltransferase (MTase), and guanylyltransferase (GTase)] of the viral genomes.[29] The nsPs form the replication-transcription complexes (RTC), essential for carrying out the replication of viral genome. Through a negative-sense RNA intermediate, the genomic RNA is transcribed and translated to form the structural and accessory proteins.[14,27,30] For flaviviruses, the genomic RNA is initially transcribed to form negative-sense RNA resulting in a dsRNA replication intermediate which acts as a template for synthesis of large number of capped +ssRNA viral genomes. These newly generated viral genome further helps in translation of viral proteins and generation of sfRNA (subgenomic flaviviral RNA).[31] For coronaviruses and flaviviruses, translated structural proteins translocates through endoplasmic reticulum (ER) and Golgi body to encapsidate the newly produced genomic RNA and to bud off the virions by exocytosis.[27,32] E1 and E2 envelope proteins of alphaviruses undergoes translocation through ER-to-Golgi complex for processing and maturation of glycoproteins, whereas the genomic RNA gets surrounded by capsid protein in the cytoplasm itself. Ultimately, the virus with the capsid encapsulated genomic RNA buds out through the cell membrane after acquiring the lipid bilayer envelope composed of E1 and E2 proteins.[33,34]

The survival of virus in the host cells depends upon the host factors to render the infected cell amenable for the viral genome replication, and therefore, identification of these host-viral interactions is fundamental for development of host-targeted antiviral drugs. Some of the key approaches used for identifying host-viral interactions are RNAi-based methods[23,35], drug combination approach[36], transcriptome and proteomic analysis of virus infected cells[37], and CRISPR/Cas9 screens.[23,38] Small interfering RNA screens are used for high-throughput screening of host factors required for replication and pathogenesis of viruses.[39,40] Drug combination approach uses a suitable combination of drugs to target multiple host proteins and signalling enzymes that aids in viral pathogenesis.[36] CRISPR/Cas9 is an improved approach to identify exploitable host factors for the development of antivirals.[41] Major advantages of these approaches lie in the fact that the most of the drugs against host pathways are FDA approved for treatment of different diseases and can be instantly used to treat viral diseases (Table 1). Moreover, the targets of such drugs are well characterised, validated and pose

Table 1
List of FDA approved host-targeted antivirals.

Sr. No	Virus	FDA-approved host-directed antivirals	Host-factor targeted	Phase of clinical trials
1	ZIKV	Cabozantinib[53], R428[53], Nanchangmycin[54]	AXL Kinase	Preclinical
		Mycophenolic acid and Ribavirin[55]	IMPDH	Preclinical
		DFMO, Diethylnorspermine[56]	Host Polyamine synthesis pathway	Preclinical
		Suramin[57]	Glycosylation (Secretion pathway)	Preclinical
		Bortezomib[55]	Proteasome function	Preclinical
2	HCV	Ezetimibe[58]	Host cell receptor Niemann-Pick C1-like 1 (NPC1L1)	Preclinical
		Alisporivir[59]	Host cytosolic protein Cyclophilin A	Phase III
		Mycophenolic acid and Ribavirin[60]	IMPDH	Preclinical
3	SARS-CoV-2	IHVR-19029[61]	ER protein processing	Clinical trials
		Sanglifehrin A[61]	IMPDH	Preclinical
		PS3061[61]	ER protein processing	Preclinical
		Captopril, Lisinopril, Camostat, Nafamostat[61]	Cell entry	Approved
		Chloramphenicol, Tigecycline, Linezolid[61]	Mitochondria and ribosome	Approved
		Silmitasertib[61]	Casein Kinase 2 Alpha 2	Approved
		Ribavirin[61]	IMPDH	Approved
		Mycophenolic acid[61]	IMPDH	Approved
		Merimepodib[61]	IMPDH	Clinical trial
		ZINC95559591[61]	TBK1	Pre-clinical
		Loratadine[61]	Sodium-dependent neutral amino acid transporter B(0) AT2 from SLC6A15 gene	Approved
4	JEV	Curcumin[62]	Ubiquitin Proteasome system	Preclinical
5	CHIKV	Chloroquine[63]	Acidification of endosomes	Terminated
		Berberine[64]	MAPK signalling pathway	Not available
		Geldanamycin[65]	HSP-90	Clinical trials terminated due to *in vivo* toxicity
		Pimozide and TOFA[66]	Fatty acid synthesis and calmodulin signalling	Preclinical
		Ivermectin[67]	Importin (IMP) α/β1-heterodimer	Phase II of clinical trails
6	DENV	DFMO and Diethylnorspermine[56]	Host Polyamine synthesis pathway	Preclinical
		UV-4B[68]	ER Glycosylation pathway	Preclinical
		Ivermectin[69]	Importin (IMP) α/β1-heterodimer	Phase III of clinical trails
		Celgosivir[70]	Alpha-glucosidase I inhibitor (host-directed glycosylation)	Phase I of clinical trials
		Montelukast[71]	Leukotriene receptor antagonist	Phase II of clinical trials

no or very little safety risks.

Several pioneering studies have identified important host proteins exploited by viruses for prolonging their survival such as Hepatitis C virus (HCV) depends on the vesicle-associated membrane protein-associated protein, 33-kDa human homologue (hVAP-33), and HIV exploits C—C chemokine receptor type 5 (CCR5) to facilitate its successful infection.[42,43] Similarly, influenza virus also exploits host proteases and other important nuclear components to evade host antiviral responses and to successfully establish its infection.[44,45,46,47] Focusing primarily on +ssRNA viruses, lipid biosynthesis pathway, glycolytic pathway, the stress-granule formation machinery, polyamine metabolism/catabolism, cytokine based inflammatory response, and the proteasome based ubiquitination/deubiquitination steps are the key targets exploited by viruses.[48,49,50,51,52]

This article highlights various approaches for upregulating host-mediated antiviral action against viruses to prevent replication of viruses, how host factors of different metabolic pathways assist viral replication, as well as progress and achievements in the field of antiviral drug development using these approaches.

2. Host pathways exploited by +ssRNA viruses

2.1. Dependency of viruses on host lipid pathway for completing their infectious cycle

The cellular metabolism of the host cell is the power house for all required ATP (energy), biosynthetic building blocks and many other important molecules needed for replication of viruses. Viruses require an uninterrupted supply of all these essential building blocks from the host at various stages of their replication cycle. Besides nucleotides and amino acids, many viruses need constant supply of host's cellular fatty acids and lipids. +ssRNA viruses are known to remodel host membranes for their entry and genomic replication.[72] Recent research has highlighted that the host lipids, being major constituents of cellular membrane, plays crucial role in the replication of many +ssRNA viruses.[73] From viral entry, replication and translation of genome to assembly or budding of progeny virions, lipids from diverse lipid classes play significant role in viral life cycle to create an appropriate environment for thriving and surviving inside the host.

Lipids are a large diverse group of non-polar and amphipathic molecules that are necessary for all cellular life forms. Lipids serve three basic cellular functions: firstly acts as building blocks of cellular membranes such as phospholipids, sterols, and sphingolipids.[15] Secondly, some lipids such as triacylglycerol and steryl ester, function as energy sources in the form of lipid droplets.[74] Thirdly, some lipids such as phosphatidic acid, sterols, sphingolipids, and glycerolipids serve as signalling molecules in multiple cellular pathways.[75] Apart from these, many host lipids are also essential for virus replication. Lipids are the structural constituents of all enveloped virions. Lipid membranes act as platforms for viral gene expression, replication, assembly, and protection of these processes from host defense system by compartmentalizing them. Interestingly, specific viruses have a preference for a particular membrane lipid composition on which they replicate. For doing so, viruses need to manipulate host lipid metabolism pathways to ensure the availability of lipids to complete their life cycle. Host cell membranes undergo a process called membrane bending and deformation, which give rise to distinct morphological structures such as small spherules, vesicles, membranous webs, and reticular layers for viral replication. Some common routes for lipid biosynthesis and inhibitors targeted in downstream steps are depicted in Figure 1.

2.1.1. Crucial roles of lipids in genome replication of +ssRNA viruses:

Alphaviruses acquire envelope during budding from plasma membrane and the lipid envelope also plays an essential role of mediating entry of virus into the host cell. For alphaviruses, the lipid composition of the viral envelope is highly significant for improving stability of viral

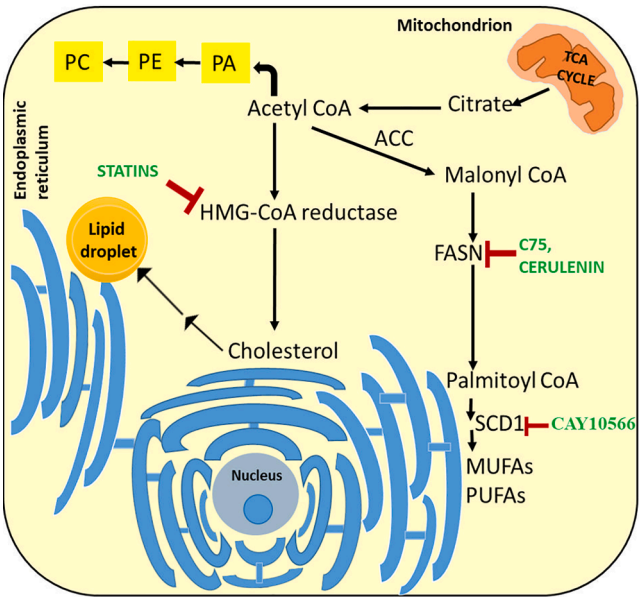

Figure 1. Common routes for the biosynthesis of major lipids in a host cell. Various key enzymes of the pathways that are recruited by the viruses are depicted. Inhibitors of the critical enzymes of these pathways are shown in green. ACC: Acetyl CoA carboxylase; SCD1: Stearoyl-CoA desaturase 1; FASN: Fatty acid synthase; PA: Phosphatidic acid; PUFAs: Polyunsaturated fatty acids; MUFAs: Monounsaturated fatty acids; PE: Phosphatidyl ethanolamine; PC: Phosphatidyl choline. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

genome and enhancing infectivity. Sphingolipids and cholesterol are essential components of host cell membranes liable for fusion of alphavirus envelope and for the viral exit.[76] Therefore, it could be a promising strategy to target host lipid synthesis pathways for inhibiting arthritogenic alphaviruses. Fatty acid synthase (FASN) is an important enzyme supporting *de novo* synthesis of long chain fatty acids and stearoyl-CoA desaturase (SCD1) enzyme, and is imperative for their early desaturation. Both these enzymes are reported to play important role in the replication of Mayaro virus (MAYV) and CHIKV.[77] Moreover, host transcription factors such as liver X receptors (LXR α and LXR β) of lipid synthesis pathway are vital for intracellular cholesterol homeostasis.[78] On the other hand, flaviviruses such as HCV, DENV, and West Nile virus (WNV) stimulates the lipid biosynthesis pathway for their membrane formation.[79] Fatty acids, sphingolipids, sterols, triglycerides, and many other lipid compositions of the host are used by flaviviruses for the formation of envelope. Apart from envelope formation, composition of membrane also plays an important role for prompting viral infection. In DENV, acetyl-coenzyme A (AcCoA) is required for the generation of distinct membrane lipids.[80] A variant of selective autophagy known as lipophagy, transports lipids for oxidation. The lipids get accumulated in auto-phagosomes and are transported to mitochondria which produces energy, playing an important part in lipophagy, thus facilitating DENV replication.[81] Moreover, NADPH formed as a result of oxidation, uses a cofactor of FASN and thus, assists fatty acid synthesis that is exploited by DENV for its replication.[82] Flaviviruses exploit host cell in such a way that both fatty acid synthesis and lipophagy occur at the same time, in contrast to healthy cells. DENV and JEV also modulates cholesterol synthesis and trafficking which assists viral entry and replication.[83] Cholesterol increases the expression of Angiotensin converting enzyme 2 (ACE2) receptor and hence potentiates the interaction between ACE2 and spike protein of SARS-CoV-2.[84] Intriguingly coronaviruses such as SARS-CoV and SARS-CoV-2 seize host membranes to form double membrane vesicles (DMVs) for their genomic amplification.[85,86] Cytosolic phospholipase A2α enzyme (cPLA2α), a lipid processing enzyme is crucial for DMV formation and replication of

coronaviruses.[87]

2.1.1.1. Targeting host lipid pathways and metabolism. Targeting host cellular lipid metabolism by blocking lipid biosynthesis pathways could potentially be a promising antiviral strategy but may be restricted due to host cell toxicity. To overcome this, knowledge of the structural and functional details of the lipids, their role in viral replication, their origin sites, and the sites where they are trafficked to, are prerequisites for identifying antivirals. Rational design of host-targeted antivirals can be achieved by identifying and targeting lipids that are non-essential for host cell or by targeting steps in lipid synthesis and metabolism that are extremely sensitive to viruses rather than host cell. This will allow host-targeted antiviral strategies with a reasonable therapeutic window without globally affecting the host cell.

In DENV, WNV, and Zika virus (ZIKV), it has been demonstrated that treating the host cells with the chemical inhibitors suppressing fatty acid biosynthesis has resulted in reduction of viral load.[88] FASN, ATP citrate lyase (ACLY), Acetyl coenzyme A carboxylase (ACC) are key enzymes responsible for regulating fatty acid biosynthesis in eukaryotic host cells. Previously published literature has suggested that targeting ACC with chemical fatty acid biosynthesis inhibitors MEDICA 16 (3,3,14,14-tetramethylhexadecanedioic acid) and TOFA (5-(tetradecyloxy)-2-furoic acid) reduced replication of flaviviruses such as WNV and Usutu virus (USUV).[89] The mode of action of these compounds is to act by reducing levels of multiple cellular lipids such as sphingolipids, glycerophospholipids, and cholesterol.[89] Additionally, TOFA exhibit broad spectrum activity against both ZIKV (Flaviviridae) and semliki forest virus (SFV, Togaviridae) by blocking the enzyme ACC.[90] Moreover, inhibition of FASN and mevalonate diphosphate decarboxylase enzymes required for cholesterol biosynthesis, reduced DENV titer in host cells.[91] Cerulenin, an antibiotic and inhibitor of lipid biosynthesis, and orlistat, an anti-obesity drug, both displayed broad spectrum antiviral activity by blocking FASN enzyme in ZIKV, SFV, CHIKV, and MAYV respectively.[77] Inhibition of SCD1 enzyme activity by CAY10566 (a potent, orally bioavailable and selective inhibitor of SCD1) reduced *in vitro* replication of both CHIKV and MAYV.[77] Antidepressant drug, imipramine, interferes in the cholesterol trafficking, resulting in the reduction of CHIKV replication in human skin fibroblast cells.[92] Liver X receptors such as LXR α and LXR β are one of the many potential targets in host lipid pathway. LXR-623, the LXR β selective agonist, has been demonstrated to inhibit replication of CHIKV in human fibroblasts.[93] Specific role of lipids and inhibitors reported to target host lipid pathway are listed in Table 2.

2.2. Targeting the host glycolytic pathway:

2.2.1. Dependency of viruses on host glycolytic pathway for their infectious cycle

In infected cells, many viruses rewire host cellular metabolism to enhance their genome replication for survival in host.[112] Reprogramming the host primary carbon metabolism cycle including glycolysis is one such aspect.[16,113] The precise changes in host metabolism depends upon virus to virus within the same family or on the type of host cell and is context-dependent. In glycolysis, ATP and pyruvate are the major metabolites formed from glucose.[114] The final step in the glycolytic pathway is the conversion of PEP (2-phosphoenolpyruvate) to pyruvate and ATP in the presence of pyruvate kinase (Figure 2).[16,113,115] Stress glycolysis is also the major contributing source of essential metabolites for many biosynthetic pathways such as amino acids, lipids, and nucleic acids.[114] Apart from this, glycolytic machinery is also important for the activation of immune cells.[116] To receive quick ATP supply, many

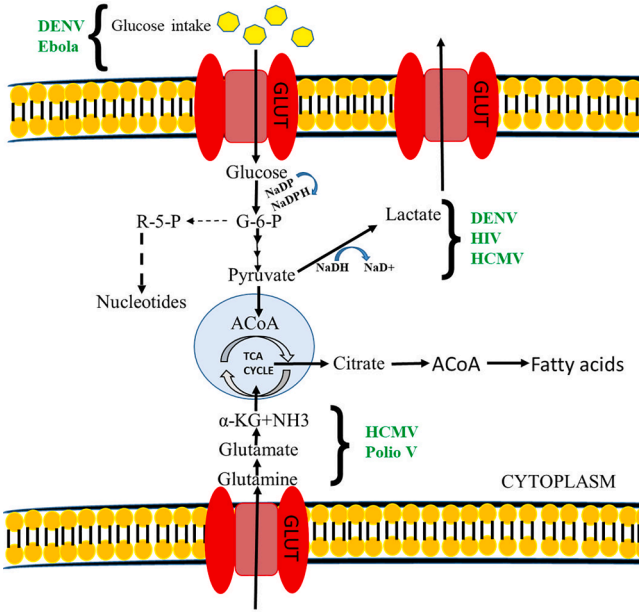

Figure 2. Host cell glycolytic pathway hijacked by viruses: The process starts with the intake of glucose into the cell, metabolism to G-6-P (glucose-6-phosphate) and then to pyruvate. Pyruvate is converted into lactate via glycolysis, which is then secreted out of the cell or Acetyl CoA (AcCoA) which is taken up by TCA cycle. Different viruses confiscating the glycolysis steps are shown in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Lipids required by +ssRNA viruses for completion of their life cycle and the inhibitors targeting this pathway.

Family	Virus	Lipids required	Host lipid function	Inhibitors
Flaviviridae	DENVWNVHCVZIKV	Phosphatidyl choline, Fatty acids, SterolSphingolipids, Fatty acids, SterolPhosphatidyl choline, Sphingolipids, sterol, Fatty acidsCeramide,Sphingomyelin	Viral entry and replicationVirion morphogenesis and releaseVirus replication and infectivityViral assembly, Viral pathogenesis	Fatty acid synthase inhibitors cerulenin[80], C75[94], pravastatin[95], U18666A[96]Medica 16, TOFA[97], GGTI (geranyl geranylationinhibitor), Lovastatin[98], 25-hydroxycholesterol[98,99]Fluvastatin with Peg-IFN/ribavirin[100]AM580[101], PF-429242[102]
Togaviridae	CHIKVSFVMAYVSindbis virus (SINV)	Sphingolipids, cholesterolSphingolipids, CholesterolSphingolipids, cholesterolSphingolipids, cholesterol	Viral entry and viral exitVirus entry, membrane formationViral replicationViral entry and viral exit	Fatty acid synthase inhibitors Cerulenin[77], Imipramine[92], Orlistat[103]TOFA[104], Cerulenin[104,105]Orlistat[106], Cerulenin[77]Valproic acid[107], AMPK[107]
Picornaviridae	Poliovirus	Phosphatidyl choline, sterol, PI4P	Virus entry	CAY10499[108], BafilomycinA1[109], Atglistatin[109]
Coronaviridae	SARS-CoV-2	Sphingolipids, cholesterol (lipid rafts), lipid droplet	Viral membrane fusion, viral replication, viral endocytosis, and exocytosis	cPLA2α, PCSK9[110], A939572, Fingolimod, C75, Cerulenin, Fibrates, Triacsin C[111]

viruses enhance the upregulation of aerobic glycolytic mechanism as well as glucose uptake.[117]

2.2.1.1. Targeting the host glycolytic pathways and metabolism. In DENV infection, a primary change occurs in central carbon metabolism that is glycolysis, where the consumption of glucose is increased along with upregulation of both glucose transporter 1 (GLUT1) and hexokinase II (HK-II) genes.[118] In order to meet viral metabolic requirements for completion of replication and life cycle, DENV activates glycolytic pathway. In healthy cells, glucose and glutamine serve as the primary carbon source and oxidation of glucose generates ATP via glycolysis in tricarboxylic acid (TCA) cycle (Figure 2).[112] However, in human cytomegalovirus (HCMV) infected cells, glutamine instead of glucose is used as carbon source for ATP generation in TCA cycle.[119] An elevated glycolysis or glucose level is also necessary for SARS-CoV-2 replication and for SARS-COV-2 induced monocyte immune response.[120] Various SARS-CoV-2 inhibitors that are designed against the host glycolytic pathway are fasentin, phloretin (GLUT 2 inhibitor), ritonavir (GLUT4 inhibitor), silybin/silibinin, and STF-31 (GLUT1 inhibitor).[121] It has been found that in the intestinal cells, coronavirus increases the glucose absorption through sodium ion-dependent glucose transporters known as SGLT1.[122] In DENV infected cells, it has been successfully demonstrated that treatment of infected cells with sodium oxamate and 2-deoxy-D-glucose (2DG) results in inhibition of glycolysis and thus, in DENV replication.[123,124]

Metabolically, ZIKV infection in human cells leads to increase in glycolysis. ZIKV-infected cells use increased glucose for the generation of TCA cycle intermediates.[125] Phloretin has been shown to be effective in ZIKV infected cells.[126] Moreover, inhibitor quercetin has been demonstrated to target GLUT1 in ZIKV, DENV-2, HCV, and Polio virus.[127] In COVID-19, lipogenesis (process of synthesis of fatty acids and triglycerides) is needed for virus packaging.[128,129] Hence, any intervention in glycolytic pathway of host will downregulate lipogenesis leading to an inhibition in pyruvate production and will eventually prevent it from entering into TCA cycle.[129] Various glycolytic inhibitors that are designed against AMPK (AMP-activated protein kinase, the ultimate energy-sensor in eukaryotic cells which shut down ATP-consuming processes) are metformine, lipoic acid, resveratrol, ivermectin and so on.[121] Some common inhibitors targeting the host glycolytic pathway of +ssRNA viruses are listed in Table 3.

2.3. Viral mimicry to usurp host ubiquitination pathways

2.3.1. Ubiquitin-proteasome system (UPS) in viral pathogenesis

Post-translational modifications of cellular proteins by attachment of ubiquitin or ubiquitin like modifiers leads to activation of innate and adaptive response. Protein ubiquitination is an enzymatic cascade involving covalent attachment of ubiquitin to target protein.[138] Ubiquitin is highly conserved protein composed of 76-amino acids, containing lysine residue at positions Lys6, Lys11, Lys27, Lys29, Lys33, Lys48, and Lys63.[48] Protein ubiquitination is a highly versatile and reversible event that controls the fate of the protein depending on the position of lysine in ubiquitin chain which is interacting with targeted protein. For instance, conjugation of ubiquitin at Lys48 classically designates the ubiquitinated protein as a target for proteasomal degradation, while Lys63 based ubiquitin chains primarily control protein trafficking among sub-cellular components and enzyme activity.[139,140] Ubiquitin mediated protein degradation is not only playing a role in regulation of protein turn-over but also regulates DNA-damage repair, apoptosis, cell-cycle, cellular growth, and signal transduction.[141]

Ubiquitination pathway comprises of three enzymes: ubiquitin-activating enzyme E1 responsible for forming an E1-ubiquitin thioester intermediate, ubiquitin-conjugating enzymes E2 responsible for transferring ubiquitin to targeted proteins, and ubiquitin ligases E3 usually involved in determining substrate specificity.[142] A reverse of the process of ubiquitination is deubiquitination, where ubiquitin residues are cleaved off from target protein by deubiquitinating enzymes (DUBs) or ubiquitin-specific proteases.[143] The ubiquitinated protein is recognized by 26S proteasome for degradation, and recycling of ubiquitin is carried out by DUBs.[139] Host-cells utilize UPS as a primary defense mechanism to counteract incoming pathogens such as viruses, by making them easily recognizable to *T*-cells.[142] As obligate intracellular pathogens, viruses have evolved strategies to antagonize host cell antiviral responses including molecular mimicry of key enzymes such as of ubiquitin, ubiquitin ligases, or action as DUBs to subvert the host cellular machinery for supporting their life cycle. Not only this, some viruses also use ubiquitin system to gain entry inside the host cell.[48] Therefore, a detailed understanding of virus-mediated suppression of host antiviral response by viral analogs infiltrating ubiquitin dependent pathways will deliver valuable information for antiviral drug discovery.

2.3.1.1. Viral avoidance and takeover of host UPS pathway. ZIKV envelope protein (E) is polyubiquitinated with the help of E3 ubiquitin ligase TRIM7 (Tripartite motif) that further drives entry, tropism, and pathogenesis of ZIKV.[144] Japanese Encephalitis virus (JEV), another example of +ssRNA virus, uses UPS for productive entry of virus into host cell by targeting a stage between virus internalization and initial translation of RNA genome after uncoating. A non-degradative ubiquitination step is utilized by DENV where ubiquitination of host protein TIM-1(receptor for DENV) at Lys338 and Lys346 is responsible for virus internalization and early entry step.[145] UBR-4, another E3-ubiquitin ligase of host cells, is specifically used by DENV non-structural (NS5) protein that inhibits Interferon-1 (IFN-I) signalling pathway after proteasomal degradation of the transcription factor STAT2, which is responsible for enhancing host IFN mediated antiviral response.[146]

Some virus families such as coronaviruses, codes their own deubiquitinating enzymes such as PLpro that not only possess proteolytic activity but is also responsible for hijacking host antiviral response after deubiquitination of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factor 3 (IRF3) of host cell resulting in downregulation of host innate immune response.[147] SARS-CoV-2 PLpro preferentially cleaves ubiquitin-like interferon-stimulated gene 15 protein (ISG15) from IRF3 resulting in attenuation of type I interferon responses, whereas SARS-CoV-PLpro predominantly targets cleavage of ubiquitin chains from targeted substrates.[148] Interestingly, nsP2 of CHIKV, SINV, and SFV ubiquitinates Rpb1 (a catalytic subunit of the RNA polymerase II complex) inducing its degradation, eventually hindering the activation of cellular genes and down-regulating cellular antiviral response.[149] In addition to it, Lys48-ubiquitination of capsid protein of VEEV (Venezuelan Equine Encephalitis Virus) orchestrates the UPS for capsid degradation to allow the release of viral RNA into the cytoplasm for replication and translation to

Table 3
Inhibitors against some +ssRNA viruses targeting host glycolytic pathway.

Virus	Target	Inhibitor
SARS-CoV-2	GLUT2	Fasentin[121], Phloretin[121]
	GLUT4	Ritonavir[121]
	GLUT1	Silybin/Silibinin[121], STF-31[121]
	SGLT1	Phloridzin[130]
	SGLT2	Dapagliflozin[130]
	AMPK activator	Metformine[131], Resveratrol[131], Ivermectin[131]
ZIKV	GLUT1	Phloretin[126], Quercetin[127]
DENV	GLUT1	Quercetin[132]
	GLUT4	Silibinin[132]
	HEK2	Luteolin[133]
CHIKV	GLUT4	Silymarin[134]
	Multikinase	Sorafenib[106]
	HEK2	Luteolin[133]
HCV	GLUT1	Quercetin[135]
	GLUT4	Silibinin[136]
	PI3K	LY294002[137]

occur.[18] UPS plays a critical role in initial stages of replication for both MAYV and Una virus (UNAV) as explicated from proteasome inhibition studies.[150]

Under these aspects, proteasome inhibitors have been reported as a therapeutic strategy to block UPS to inhibit replication of viruses as, coronaviruses[49], astrovirus[48], picornaviruses[151], and rotaviruses.[152] Studies suggest that a proteasome inhibitor MG132 played an inhibitory role against murine coronavirus by promoting accumulation of viral RNA in endosomes, thereby inhibiting its release into the cytoplasm.[49] Treatment with MG132, lactacystin, bortezomib etc., are reported to cause a significant virus inhibition for VEEV, MAYV, UNAV, and CHIKV.[149,150] The coronaviral protease PLpro is also an attractive antiviral drug target because of its deubiquitinating activity that is essential for coronaviral replication. Targeting coronaviral PLpro will not only suppress the deubiquitinating and deISGylating activities, but will also help in upregulation of cytokines and chemokines essentially required for the activation of the host innate immune response against viral infection. Based on this approach, inhibitors such as GRL0617, rac5c, VIR250, VIR251, flavonoids, naphthalene based compounds etc. are reported previously to dysregulate activity of PLpro of SARS-CoV-2, SARS, and MERS.[153,154,155] Understanding the mechanisms by which the UPS is involved in the process of viral life cycle will provide deeper insights into the key virus-host interactions during early infection and may provide novel targets for further therapeutic development.

2.4. Polyamine metabolic pathway and its role in virus infection

Polyamine are small, abundant, flexible, and positively charged molecules derived from ornithine and are involved in several cellular processes including proliferation, apoptosis, transcription, translation, DNA/RNA stabilization, and ion channel regulation in both mammalian and non-mammalian cells. In the metabolic pathway as summarized in Figure 3, arginine is first changed to ornithine, which is further decarboxylated to putrescine via ornithine decarboxylase 1 (ODC 1) (Figure 3). Putrescine is subsequently converted into spermidine and spermine with the help of their respective enzymes spermidine synthetase (SRM) and spermine synthetase (SMS) respectively (Figure 3). Steady-state levels of polyamines are maintained either by regulation of ODC1 activity to control polyamine synthesis or by reducing polyamine pools with the help of catalytic enzymes like spermine acetyltransferase (SAT1), spermine oxidase (SMOX), and polyamine oxidase (PAOX).[51] Spermidine and spermine can be catabolized back to putrescine after addition of an acetyl group by SAT1 enzyme (Figure 3). Polyamine

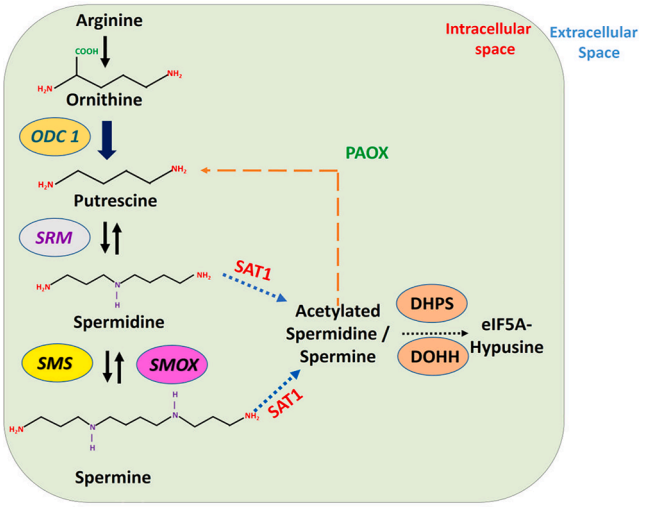

Figure 3. Schematic representation of host metabolic pathway for mammalian biogenic polyamine synthesis.

expression, synthesis, and degradation are highly regulated processes. For instance, ODC-1 activity is hindered by ODC-1 antizyme (OAZ1). Moreover OAZ1 translation is regulated by polyamine dependent translational frameshifting and also by antizyme inhibitor (AZIN1).[51] Furthermore, in eukaryotes spermidine acts as substrates for hypusination of a specific eukaryotic initiation factor 5A (eIF5A) with the help of two enzymes, deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH), facilitating transcription, translation, and protein synthesis.[17] Viruses rely on polyamines for numerous stages of their life cycle including genome packing, replication, and translation of proteins. Therefore, a thorough understanding of how viruses utilize host cell polyamines for their cycle would pave new path for discovery of novel strategies for combating viral infections.

NS5A and core proteins of HCV are reported to suppress level of ODC1 and SAT1 but elevates SMOX, which leads to diminished concentrations of spermine and spermidine, enhancing virus replication. Interestingly, polyamines are reported to facilitate binding and entry of coronavirus and flaviviruses.[17] It is also postulated in a study that the entry of DENV stimulates the overexpression of eIF5A, which prolongs survival of virus infected cell.[156] CHIKV has evolved with a unique strategy to prolong its survival against host antiviral response. CHIKV develops resistance to polyamine depletion through two mutations in the nsP1. These mutations ensued increase in viral replication in polyamine depleted cells.[17] Intriguingly, studies in SFV have shown that polyamines are not present in viral capsids, but are involved in promoting RNA synthesis. Conversely, polyamine depletion results in a marked decrease in activity of RNA polymerase in cells infected with SFV.[157] SAT1 is upregulated for CHIKV and ZIKV, in response to type I IFN stimulation, resulting in depletion of spermidine and spermine, ultimately restricting viral infection, since the depletion of polyamines limits the expression of nsPs, the viral polymerase and hence, the replication.[51] Reducing polyamine levels could, therefore, restrict the rate or even initiation of virus replication. Difluoromethornithine (DFMO), an inhibitor of ODC1 is documented to inhibit infections caused by CHIKV, ZIKV, MERS, SINV, JEV etc. by depleting levels of polyamine.[51] An offshoot of the polyamine metabolism is the cellular hypusination pathway, in which spermidine acts as a substrate molecule for enzyme DHPS to generate unique amino acid hypusine in eIF5A for activating it.[158] Hypusinated eIF5A facilitate mRNA nucleocytoplasmic transport and mRNA stability.[158] Therefore, ciclopirox (CPX), deferiprone (DEF), and GC7 inhibitors targeting DHPS/DOHH averting hypusination of eIF5A, have proven to be a great approach to impede MHV and HCV.[159] A concise list of polyamine inhibitors and their target is provided in Table 4.

2.5. Targeting the host stress granules machinery

Targeting the stress granules is a novel therapeutic strategy to treat viral diseases. Stress granules (SG) are stalled mRNA and protein assemblies that get accumulated during translation initiation in response to stress. SGs are formed in response to various biological functions such as inflammation, apoptosis, many signalling pathways and so on.[161] SGs play an important role in pathogenesis of viral infections, neurodegenerative diseases, aging, etc. Therefore, targeting the stress granules has become a potential therapeutic strategy to treat human diseases. In mammalian eukaryotic cells, most of the mRNA undergoes transcription inside the nucleus and after that, transported into the cytoplasm where it undergoes translation and expression. The mature mRNA is not translated into the proteins immediately in case of cell stimulation or disturbance. Hence, these temporarily-stalled mRNA complexes polymerize with RBPs (RNA-binding proteins) to form mRNP granules (messenger ribonucleoprotein) known as SGs, Cajal bodies, P-bodies (processing bodies), or germ granules. SGs are dynamic granules formed in the cytoplasm and their formation is stimulated by oxidative stress, viral infection, heat shock, hypoxia, etc. Stress granule formation mechanism is a type of adaptive regulatory process that protects the cells

Table 4
List of polyamine inhibitors reported to inhibit different molecules of polyamine pathway.

Name of inhibitor	Molecule targeted	Target	Virus
Difluoromethylornithine (DFMO)[51]	Inhibitor of ODC1	Causes reduction in infectious virus progenies	ZIKV, MERS, JEV, YFV, SARS-CoV-2, MHV, HCV, SINV
Diethylnor spermidine (DENspm)[51,17]	Enhances polyamine catabolism and rapidly depletes polyamines	Decreased viral translation, Decreased activity of viral RNA polymerase, reduction in production of infectious virions, upregulation of SAT1 to deplete polyamine	SFV, CHIKV, ZIKV, MHV, HCV, SINV
Ribavirin[160]	SAT1 upregulation	Polyamine depletion	ZIKV, Coxsackievirus B3
Ciclopirox (CPX), Deferiprone (DEF), and GC7[159]	Hypusination inhibitor	**GC7:**inhibits deoxyhypusine synthase [DHPS] to prevent eIF5A hypusination **DEF and CPX;** inhibit deoxyhypusine hydroxylase [DOHH])	MHV, HCV
AaNAT5b[17]	SAT1 upregulation	Depletion of polyamines and limit virus replication	CHIKV
nsP1-mutants[17]		Enhanced virus replication in polyamine depletion	CHIKV
RBM10[17]	SAT1 upregulation	Decreased SAT1 degradation and reduced polyamine levels and restrain virus replication	DENV
N79 ω-chloroacetyl-L-ornithine (NCAO)[157]	Competitive inhibitor of ODC	Decreases the biosynthesis of polyamines	CHIKV

from apoptosis during adverse conditions.

Virus invasion pose adverse stress conditions to the host. The viral interference with the host genome and antiviral responses to the same, drive SG formation in order to govern viral RNA replication and translation. These virus-induced SGs are called anti-viral SGs. Some cellular proteins like G3BP, T cell intracellular antigen-1 (TIA-1), and TIA-1-related protein (TIAR) were observed to be primarily involved in assembly of SG.[162] In coronaviruses, the significance of SG in viral infections is still not so clear. In SARS-CoV-2, it has been found that the nucleocapsid protein (N protein) is formed at high levels in infected cells and recruit the SG protein G3BP1 (GTPase-activating protein (SH3 domain)-binding protein), highlighting its potential role in SG inhibition.[163] Recent proteomic studies have also highlighted that *N*-protein of SARS-CoV-2 associates with host SG nucleating proteins G3BP1 and G3BP2, attenuating the formation of SGs, enhancing virus replication and packaging of new virions.[163,164] A previous study for WNV and DENV has emphasized the role of NS3 protein which interacted with TIA-1 or TIAR host proteins and resulted in down-regulation of SG formation in virus infected cells.[165] Furthermore, ZIKV proteins NS3 and NS4A are interrelated to translational repression whereas the capsid proteins NS3/NS2B-3 and NS4A were reported to inhibit the SG assembly. ZIKV RNA displays interactions with G3BP1 whereas the viral capsid proteins interacts with host G3BP1 and Caprin-1 proteins, suppressing the SG mediated antiviral response of the host cell.[166]

Many other viruses induce the formation of SGs such as CHIKV, SFV, SINV, picornavirus, SARS-CoV-2, poliovirus etc. by diverse modes of regulation of SGs. Stress response produced by the SGs is antiviral in nature and to counteract this antiviral response, many viruses like CHIKV have manipulated the host machinery for their own benefit. Such viruses block SG response by sequestering G3BP.[167] This sequestration occurs with the help of two conserved motifs namely FGDF motifs that are present in C-terminal of nsP3 in the viruses such as CHIKV, SFV, etc.[168] This viral nsP3 protein functions by disrupting the SGs and nsP3 facilitates this disruption process by recruiting this host G3BP protein via FGDF motifs.[169] Thus, targeting such host proteins like G3BP can actually induce the stress response which, in turn, can induce antiviral activity against such viruses. Studies regarding targeting the host protein G3BP are still carried out to initiate antiviral activity against viruses that facilitate stress granule mediated response.

2.6. Role of heat shock proteins (Hsp) in viral infections

Another promising broad-spectrum antiviral drug target is the cellular protein homeostasis pathway maintained by an array of molecular chaperones that control a number of processes such as protein translation, correct folding, degradation, apoptosis, cell cycle regulation, and intracellular trafficking.[170,171] Chaperones such as heat shock proteins (Hsp70 and Hsp90) are reported to play key roles in life cycle of many +ssRNA viruses such as DENV, HCV, ZIKV, CHIKV, YFV, WNV etc. Many viruses depend upon the chaperones to fold and assemble viral proteins. Hsp70 directly interacts with RdRp domain of JEV NS5 protein, stabilizes the RTC and positively regulates the genomic replication.[172] ZIKV requires Hsp70 to facilitate virus entry into host cell, formation of RTC, and egress from host cell.[173] Detailed role of recruitment of Hsp70 in entry and capsid maturation of flaviviruses is still not clear and is presumed to be linked with capsid uncoating and reduction in its stability.[174] Hsp70 isoforms are required for entry, replication, and virion biogenesis of DENV.[171] Chaperone proteins of Hsp70 participates in NS3/4A cleavage and replication of YFV.[175] In addition to these, Hsp70 interacts with NS5A protein of HCV that is essential for replication and virion assembly.[176] nsP3 and nsP4 proteins of CHIKV interacts with Hsp that promotes virus replication.[65] Quercitin, an inhibitor of Hsp, is reported to attenuate replication of HCV.[177] Geldanamycin and SNX-2112, inhibitors of Hsp, showed dramatic reduction in CHIKV viral titers and also abridged inflammation in a CHIKV mouse model of severe infection and musculopathy.[65] HS-72 inhibits entry of DENV by disrupting interaction of Hsp70 with DENV receptor complex.[178] However, the interplay between viruses and chaperones is still not characterized in depth and their roles in life cycle of many viruses are still unclear.

2.7. Role of programmed ribosomal frameshifting (PRF) in virus propagation

Among the repertoire of host mechanism that viruses use for regulating their gene expression, noncanonical translation such as − 1 programmed ribosomal frameshifting (−1 PRF) is another strategy used by viruses to increase coding capacity of their constrained genomes.[179,180,181] PRF is a translation recoding mechanism wherein the mRNA signal (frameshift signal) induces the translating ribosomes to

slip back 1 nucleotide in 5′ direction (-1 PRF) or in the 3′ direction (+1 PRF), so that the translation continues in a new reading frame by utilizing alternative start sites and bypassing termination codons.[21,181] This enables viruses to encode multiple proteins from a single mRNA and may confer selective advantage to viruses.[182] Typically a frameshift signal is comprised of three parts: a heptameric slippery site where frameshifting can occur while maintaining non wobble base pairing between tRNA and mRNA, a short spacer sequence between the slippery site and downstream secondary structural element, and a strong mRNA secondary structural element such as a pseudoknot to facilitate −1 PRF by transiently stopping the incoming ribosome and eventually letting the tRNAs to realign within the slippery sequence.[183,184] Sequence of this −1 PRF is conserved as it has to maintain structure while coding for overlapping regions, thus eliminating the possibility of development of mutations to become drug resistant and making it an attractive target for discovery of new antivirals.[185]

Alphaviruses are made up of two ORFs that encodes polyproteins that undergo proteolytic cleavage to produce structural and nsPs. Two recoding signals have been reported for alphaviruses: termination codon region (TCR) located at opal (UGA) termination codon at the boundary between nsP3 and nsP4 genes, and the −1 PRF signal located near the 3′ end of 6 K gene which leads to the production of *trans*-frame product that functions as an ion channel and is known to be important for neuropathogenesis in SINV.[181,186,187] NS1′ protein of flaviviruses (JEV and WNV), a larger-NS1 related protein involved in viral replication and regulation of innate immune response, is also a product of −1 PRF event that occurs near the start point of NS2A gene and is playing a role in viral neuroinvasiveness.[188] ORF1a and ORF1b of coronaviruses including SARS-CoV-2 are slightly overlapping, and since ORF1b lacks translation initiation site, proteins encoded by ORF1b are translated by −1 PRF mechanism leading to the production of fusion polypeptide proteolytically cleaved by viral proteases. The first protein produced after −1 PRF is the RdRp which is a key replicase protein of coronavirus required for genomic replication thus, highlighting the imperative role of −1 PRF in coronavirus infection cycle.[185,189] Studies revealed that −1 PRF machinery can be impeded or altered by small molecules interfering SARS-CoV-2 and SARS-CoV replication machinery, such as antisense peptide nucleic acids[185], 2-methylthiazol-4-ylmethyl)-[1,4]diazepane-1-carbonyl]amino}benzoic acid ethyl ester (MDTB)[190], merafloxacin, and ivermectin.[184] A host RNA binding protein, annexin A2 slows down the frameshifting efficiency after binding to pseudoknot of Infectious bronchitis virus (IBV). Host interferon stimulated protein shiftless, is a broad-spectrum suppressor of −1 PRF pathway in HIV, SARS-CoV-2, and SINV.[21,191]

2.8. Suppression of the host nucleoside synthesis pathway

Viruses dwell on host nucleosides for their genome replication. During infection, viruses discharge their cargo into the host and utilizes host cell's machinery to replicate their own genome, thus, producing progeny viral particles. Host proteins that are associated with synthesis of nucleosides can therefore be targeted as antiviral therapeutics. The inosine monophosphate dehydrogenase (IMPDH) is an essential enzyme which catalyses *de novo* synthesis of guanine nucleotides. Guanine biosynthesis can be inhibited by using a broad-spectrum antiviral called ribavirin. Ribavirin in combination with PEGylated interferon-a, has been used as a standard treatment for chronic HCV.[192] An immunosuppressant known as mycophenolic acid has also been shown to reduce CHIKV replication by depleting intracellular GTP pool.[164] Hence, nucleotide pool depletion (GTP more specifically), has emerged as a promising strategy for suppressing viruses particularly flaviviruses. Dihydroorotate dehydrogenase (DHODH) is an important enzyme of the *de novo* pyrimidine biosynthesis pathway. It can be inhibited using brequinar, an immune-suppressant and anti-metabolite in cancer.[193] It has been demonstrated to inhibit DENV serotypes 1, 2, and 3. A compound NITD-982 analogue has been shown to inhibit host DHODH but the compound didn't show efficacy in *in vivo* studies because of exogenous supply of pyrimidines in the diet. In addition, a uridine analog and other intracellular nucleotide-depleting compound called 6-azauridine functions as a competitive inhibitor of OMP (orotidine monophosphate decarboxylase enzyme) which results in the depletion of UTP pools.[194] Consequently, 6-azauridine has been shown to inhibit replication of some viruses like CHIKV and SFV.[195] Inhibition of *de novo* pyrimidine synthesis also occurs through an antiparasitic drug called atovaquone and has been shown to inhibit replication in CHIKV via dose dependent manner.[106]

2.9. Exploitation of host ER glycosylation pathway

Glycosylation is one of the many post translation modifications which is ubiquitous and contributes in multitude of important biological roles. During replication, viruses exploit this host glycosylation machinery for the production of their own glycosylated proteins in the secretory pathway.[196] Viral replication especially for +ssRNA viruses such as, SARS-CoV-2[19], ZIKV[197], DENV[198], and flaviviruses[199] occurs mostly in ER derived membranous structures that are induced by the nsPs of these RNA viruses. Viruses manipulate and exploit the functions of ER to promote their life cycle involving entry, translation, viral replication, morphogenesis, and egress.[200] Like other viruses, SARS-CoV-2 also follow this life cycle to promote its exponential growth which, in turn, offers opportunities to look for essential host proteins and pathways for SARS-CoV-2 that could act as hotspots to be targeted with therapeutic objectives.[201] The initial step of *N*-linked glycosylation starts from the membrane of ER on which precursor tetradecasaccharide gets assembled. In ER lumen, this precursor is attached via a covalent *en bloc* attachment of the asparagine residue to the nascent polypeptide.[202] From this point, these precursors are processed by series of processing enzymes that trim down and remould core oligosaccharide in ER and Golgi apparatus resulting in the formation of diverse classes of glycans (oligomannose, hybrid as well as complex-type-glycans).[196] In context of viruses, it is evident that some virus particles (such as HCV) bypass Golgi apparatus glycan maturation, therefore, bud off early and translocate in the glycosylation pathway from ER to plasma membrane or do not follow the secretion pathway because of some unusual glycans present on viral glycoproteins.[203] Depending on the type of virus, host glycans serve as primary receptors, co-receptors or attachment factors.[204] It has been observed that epitope masking occurs by glycosylation on coronavirus spike proteins. It appears that coronaviruses occlude receptor binding domains by using *N*-linked glycans.[201] In SARS-CoV-2, the genome encodes nsPs and accessory proteins which are responsible for virus assembly, virulence, and recruits components of host's secretory pathway. However, the coordination of assembly of viral structural proteins is still unclear. ZIKV has been reported to interact depending on major ER proteins such as SPC proteins (ER-associated signal peptidase complex), EMC (ER membrane complex), and ER translocon.[197] Apart from this, EMC proteins associate with ER translocon Sec61, and OST (oligosaccharyltransferase) complex proteins which promote ZIKV infection.[197]

2.9.0.1. Targeting the host glycosylation pathway

Understanding of ER glycosylation pathway gives an insight towards the active involvement of endoplasmic reticulum in viral infection, thus, bound to have therapeutic implications. Intriguingly another novel strategy to design inhibitors relies on ER-associated components, understanding glycans, their modes of function and viral glycobiology. In SARS-CoV-2 iminosugars have shown broad-spectrum antiviral activity in vivo and in vitro.[199] However, iminosugars are still to be approved for the treatment of viral infections and their potential use as host-targeted antiviral therapies is still to be investigated. Figure 4 provides a simplified presentation of *N*-Linked glycosylation pathway and Table 5 comprises a list of antivirals acting against glycosylation pathways.

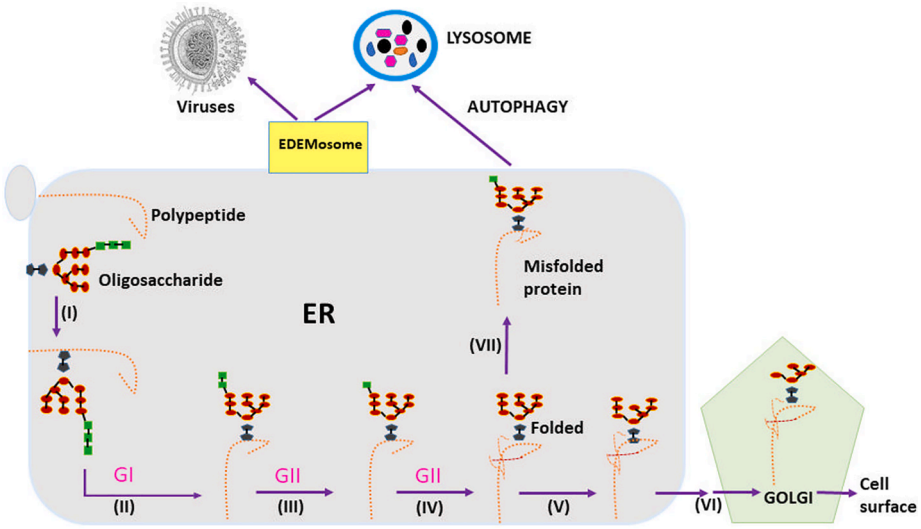

Figure 4. Simplified presentation of *N*-Linked glycosylation. The oligosaccharide core consists of two *N*-acetylglucosamine (GlcNAc, blue), nine mannose sugars (Man, red), and three glucose (Glc, green). Nascent polypeptide enters ER through Sec61 in which precursor core oligosaccharide gets transferred onto asparagine residues (I). Then the trimming of two terminal glucose moieties on the core oligosaccharide occurs in the presence of Glucosidase I (GI) (II) and GII (III), which leads to the folding of protein into native structure with the help of chaperones. The last trimming of glucose moiety occurs by GII and the glycoprotein finally attains a native conformation (IV). The glycoproteins that attain a native conformation pass gets their mannose residues removed (V) and pass through the canonical secretory pathway (VI). Eventually, misfolded glycoproteins are rapidly recycled through autophagy after demannosylated (VII). Viruses hijack EDEMosomes and form double membrane vesicles that act as a platform for viral replication. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Some of the glycosylation pathway inhibitors against various RNA viruses are shown.

Virus	Targets of ER Glycosylation pathway	Inhibitors
SARS-CoV-2[19,205]	*N*-Glycans	Peptide-*N*-Glycosidase F (PNGase-F)
	ER a-glucoside I	Iminosugars Miglustat, Celgosivir and NN-DNJ
	α-mannosidase inhibitors	Deoxymannojirimycin, mannostatin A
	α-glucosidase inhibitors	*N*-butyl deoxynojirimycin, *N*-nonyl deoxynojirimycin, castanospermine, celgosivir
ZIKV[197]	Sec61 α translocon	Myolactone treatment
DENV[198]	α- Glycosidase	Castanospermine (CST) and deoxynojirimycin (DNJ)

2.10. Cytokine signalling and inflammatory pathways critical in antiviral defense

2.10.0.1. Cytokine signalling cascade and immune regulation

The first line of defence against any viral infection comprises of pattern recognition receptors (PRR) such as RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs) that are primarily accountable for detection of viral RNA genome and its intermediates (Figure 5). Upon virus infection, the single-stranded or double-stranded viral RNA leads to activation of TLR/RIG-I/MDA-5, which transduces viral signal through adapter proteins MAVS (Mitochondrial activator of virus signalling) and MyD88, ultimately leading to initiation of downstream signalling cascades (Figure 5).[113] After virus recognition, a series of kinases belonging to IκB kinase (IKK) complexes including IKKα, IKKβ, IKKγ or TANK-binding kinase 1 (TBK1), and IKKε are activated subsequently leading to phosphorylation of transcription factors such as IRF3 and NF-κB.[206] Phosphorylation of these transcription factors consequently leads to their translocation to the nucleus cooperatively inducing formation and release of pro-inflammatory cytokines (G-CSF, IL-1β, IL-2, IL-8, IL-10, IL-17, TNFα, MCP-1, GMCSF, and CCL3), and antiviral type I IFNs (IFN-α and IFN-β) (Figure 5).[8] Type 1 IFN and pro-inflammatory cytokines mediates direct antiviral effects that subverts viral replication after binding to receptors present on infected cells or neighbouring cells and eventually activation of tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1).[10] Signal transducer and activator of transcription 1 and 2 (STAT 1 and STAT 2), the major substrates of JAK1 and

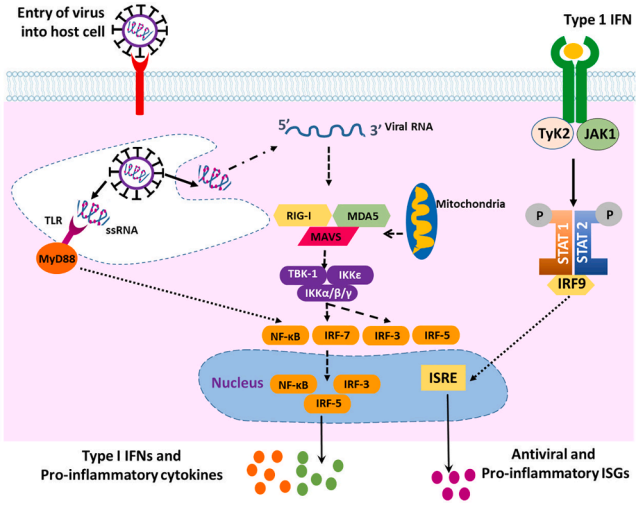

Figure 5. Schematic representation of inflammatory pathway used by host cell for antiviral response against viruses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

TYK2, after phosphorylation stimulates expression of ISG (Interferon stimulated genes) after migration to nucleus (Figure 5). While STAT1 is essentially required for IFN-λ and IFN-γ signalling, STAT 2 is crucial for IFNα and IFN-λ signalling.[207] Control of STAT signalling includes post-translation modifications such as methylation[208], acetylation[209], and ISGylation[210] that plays a role in promoting signalling whereas dephosphorylation and sumoylation pathways[211] are reported to inhibit it. Cytokines released by virus infected cells then plays a role in modulation of adaptive immune response by activating immune cells such as macrophages, B lymphocytes, and T lymphocytes that aids in elimination of virus.

2.10.0.2. Viral subversion of cytokine mediated innate antiviral immunity

The type I IFN system present in vertebrates epitomizes an important mechanism to block the intra-host growth of viruses across wide-ranging taxonomic classes. Conversely, viruses have co-evolved with humans and have developed multiple strategies to evade immune recognition and to suppress antiviral responses orchestrated by IFN. ORF 6 protein of SARS-CoV-2 inhibits IFN-β production by interacting with nuclear

importing factor karyopherins blocking IRF3 nuclear translocation.[212] SARS-CoV-2 is also highlighted to antagonize IFN signalling by using three approaches: i) ORF3a, ORF7b, M, ORF7b, nsP1, nsP6, and nsP13, proteins that are reported to suppress STAT1 phosphorylation; ii) ORF7a, nsP6, and nsP13 are reported to inhibit STAT2 phosphorylation; iii) and ORF-6 impedes STAT1 nuclear translocation.[212,213] SARS-COV-2 also provokes a fatal immune reaction after abnormal and uncontrolled production of pro-inflammatory cytokines, commonly termed as "cytokine storm".[20,86,129,213,214,215] SARS-CoV-2 activates T lymphocytes to produce GMCSF and IL6 which further leads to downstream activation of $CD14^+/CD16^+$ monocytes to produce bulk quantities of IL6, TNFα, IL-8, IL-10, CCL2, CCL3, and other cytokines, followed by infiltration of neutrophils and macrophages in lung tissue resulting in systematic inflammatory response and acute respiratory distress syndrome (ARDS).[20,214,215,216]

To avoid its recognition, SARS-CoV or MERS-CoV virus shields itself or its intermediates (dsRNA or ssRNA) within DMVs preventing its exposure to PRRs. To disguise host cell machinery, SARS-CoV is also reported to inhibit IRF3 by preventing its hyperphosphorylation, dimerization or its interaction with cofactor CREB-binding protein (CBP).[217] Not only this, SARS-CoV is also reported to inhibit nuclear import of transcription factor.[218] Interestingly it has also been reported that ORF3b, ORF 6, and N protein of SARS-CoV inhibits expression of IRF3 which further impedes expression of IFN-β.[219] In a similar context, PLpro of SARS-CoV and HCoV-NL63 are reported to interact with IRF3 preventing its activation. ORF9b protein of SARS-CoV is also responsible for proteasomal degradation of MAVS. Moreover ORF4a, ORF4b, ORF5, and M protein of MERS-CoV are identified to prevent IRF3 translocation. SARS-CoV ORF3b, ORF9b, ORF6, nsP1, nsP7, and nsP15 proteins are observed to disturb IFN induction, and most importantly anti-IFN function of nsP1 protein is based on its differential ability to degrade host mRNA to block host mRNA translation, sparing its own viral mRNA.[218] Several protein of MERS and SARS are documented to inhibit IFN signalling, for example ORF6 protein of SARS is documented to deter nuclear import of STAT1 by sequestering nuclear import factor karyopherin alpha 2 to intracellular membranes.[218]

CHIKV encoded proteins nsP2, E2, and E1 proteins are documented to inhibit MDA5/RIG-1 dependent activation of IFN-β promoter whereas MAVS-Mediated Induction of the IFN-β promoter is strongly impeded by nsP1, nsP2, E2, and E1 proteins. In addition to these, nsP4 and capsid protein of CHIKV is capable of antagonizing TBK1-medated induction of the IFN-β promoter and IKKε-Mediated Induction of the IFN-β Promoter is downregulated by nsP2, E2, and E1 proteins. nsP2 of CHIKV is also stated to strongly antagonize IRF3/IRF-5D mediated induction of the IFN-β promoter.[220] SINV and VEEV are described to disrupt IFNα/β signalling by inhibiting accumulation of tyrosine phosphorylated STAT1 and STAT2.[221] Flaviviruses have also evolved many counter-strike mechanisms to antagonize host's IFN response during infection by directly antagonizing activation of specific PRR or by inhibition of downstream signalling molecules of IFN pathway. A phosphomimetic motif within NS3 protein of DENV and WNV is reported to bind RIG-1 ultimately blocking its translocation to mitochondria.[222] Recent studies have uncovered that NS4A of DENV binds and sequesters MAVS, eventually hindering its interaction with RIG-1 and inhibiting downstream innate immune signalling cascade.[223] ZIKV NS4a interferes with RLR signalling by interrupting RLR-MAVS interaction, preventing induction and secretion of IFN and pro-inflammatory cytokines.[224] Recent work suggested that ZIKV is able to evade RIG-1 and MDA-mediated immunity by disrupting interactions with cellular scaffold proteins 14–3-3η and 14–3-3ε, where 14–3-3ε is responsible for cytosol-to-mitochondrial translocation of RIG-I and 14–3-3η expedites MDA5 translocation to mitochondria, thereby endorsing antiviral IFN induction.[225] Similar to DENV NS3, ZIKV NS3 binds to 14–3-3ε and prevents cytosol to mitochondrial translocation of RIG-1.[222] WNV induces expression of suppressors of cytokine signalling 1 and 3 (SOCS) after interacting and activation of TAM (Tyro3/Axl/Mer) receptors on dendritic cells, finally affecting JAK1 pathway and its downstream signalling. Many viruses antagonize STAT1 and STAT2 signalling functions with the help of their nsPs. NS4b of DENV is documented to reduce STAT1 phosphorylation and ISRE-dependent gene expression, in response to IFN-β.[226] Additionally, NS5 protein of DENV was shown to bind to human STAT2, which reportedly blocks its phosphorylation thereby, its ability to transcriptionally upregulate ISGs. NS5 protein of Yellow fever virus (YFV) interacted with STAT2-allowing downstream inhibition of ISRE activation.[227] A summarized list of host factors exploited by +ssRNA viruses to evade inflammatory antiviral response is provided in Table 6. Additionally, Table 7 provides a comprehensive list of antivirals targeting the host cytokine signalling pathway.

2.10.0.3. Antiviral response suppression by antibody dependent enhancement (ADE) of macrophage infection

It has also been observed that many +ssRNA viruses including DENV, CHIKV, SINV, WNV, JEV, Ross river virus, YFV etc. displays antibody dependent enhancement (ADE) of macrophages and monocytes to increase their overall replication.[228,229] ADE occurs when pre-existing antibodies (from first viral infection) in a body, binds to same virus (of different serotype) during second infection and this antibody-virus complex binds to circulating monocytes.[230] In contrast to normal antigen–antibody reaction, these antibodies will not neutralize virus but will result in an overall exacerbation in viral replication with the development of more severe disease. Paradoxically, ADE facilitates the upregulation of SOCS3 inhibits the JAK/STAT signalling pathway with an overall increase in expression of IL6 and IL10, enabling the virus to take full advantage of immune suppressive and anti-inflammatory environment generated by production of IL10, ultimately inhibiting the IFN α/β signalling cascade.[228,229,231] A more comprehensive knowledge of important virus-host interactions of ADE pathway is required to identify cell-targeting drugs against effectors of ADE, which can be used as a prophylactic treatment in severe cases.

2.11. Host-directed therapeutic monoclonal antibodies

In the recent times, monoclonal antibodies (mAbs) are being directed against the host factors instead of directing against viral proteins. Antiviral mAbs are immunoglobulins with a single isotope and defined specificity. These antibodies exhibit therapeutic effects with the help of antigen-binding fragment (Fab) and can be used against particular disease targets such as HCMV.[245] mAb therapy is just like passive immunotherapy which targets direct and rapid viral agent instead of developing a long-term immune response against that viral pathogen. In contrary, vaccine stimulates the host's endogenous cellular and humoral immune responses to deliver sustained defensive immunity. There has been accumulating evidences to show that antiviral mAbs can interact both directly and indirectly with different constituents of immune system.[246] It depends upon the type of virus, viral antigen that is being recognized and the antibody itself. Direct interaction includes ADCVI (antibody dependent, cell-mediated virus inhibition) while indirect methods include engagement of the immune response of the host, etc. Thus, antiviral mAbs treatment can also trigger endogenous immune response of the host. Few examples of mAbs designed and targeted against host proteins are shown in Table 8.

3. Conclusion

The widespread predominance of viral infections such as CHIKV, DENV, ZIKA, HCV, JEV SARS etc., and the re-emergence of viral infections in the form of outbreaks such as the ongoing pandemic caused by SARS-CoV-2 have led to an immediate demand for development of new therapeutic approaches to combat these deadly infections. Viruses, not only depend upon molecular machinery of the host cell for their replication, but also transcribes and translate their own proteins for enhancing their spread and infection. In order to counteract host

Table 6
List of host factors exploited by viruses to evade inflammatory response of host cell.

Virus	Protein involved	Target
SARS-CoV-2	ORF 6	Inhibits IFN-β production by interacting with nuclear importing factor Karyopherins blocking IRF3 nuclear translocation[212]
	nsP1, nsP6, nsP13, ORF3a, M, ORF7b, and ORF7b	Suppress STAT1 phosphorylation[212]
	ORF7a, ORF7a, nsP6, and nsP13	Inhibits STAT2 phosphorylation[212]
	ORF6	Impedes STAT1 nuclear translocation[212]
SARS-CoV	Not defined	Inhibit IRF3 by preventing its hyper phosphorylation, dimerization or its interaction with cofactor CREB-binding protein[217]
	ORF 3b, ORF 6, Nucleocapsid protein, and nsP3	Inhibits expression of IRF3 and thereby impedes IFN-β production[219]
ZIKV	NS1 and NS4b	Binds to TBK-1 and inhibits its Oligomerisation[232]
	NS5	MAVS and TBK1-mediated phosphorylation of IRF3[233]
	NS2a, NS2b, NS4a, and NS4b	Reduced RIG-I mediated phosphorylation of IRF3[50]
	NS5	Interacts with IRF3 via MTase domain and inhibits IRF3/5D mediated stimulation of IFN-β[50]
DENV	NS5	Proteasome and ubiquitin mediated degradation of STAT 2[234]
	NS2a, NS4a, and NS4b	Antagonize IFN signalling by preventing STAT1 phosphorylation[234]
	NS2B/3 complex	Subverts RIG-I mediated signalling pathway, hindering the nuclear translocation or phosphorylation of IRF3 by mediating an interaction of NS2B/3 with IKKε that permits masking of the protein kinase domain.[235]
	NS4b	Reduce ISRE-dependent gene expression and STAT1 phosphorylation, in response to IFN-β[226]
	NS3 and NS4a	Block RIG-I translocation to mitochondria[236]
	NS2a, NS4a, and NS4b	Inhibit the activation of TBK1, blocking the RIG-I/MAVS signalling pathway and IFNβ induction[236]
CHIKV	nsP2, E2, and E1	Documented to inhibit MDA5/RIG-1 induced activation of IFN-β promoter[220]
	nsP1, nsP2, E2, and E1 proteins	MAVS-mediated induction of the IFN-β promoter is strongly impeded [220]
	nsP4 and capsid protein	Capable of antagonizing TBK1-mediated induction of the IFN-β promoter and[220]
	nsP2, E2, and E1	IKKε-mediated induction of the IFN-β promoter is downregulated[220]
	nsP2	Strongly antagonize IRF3/IRF-5D mediated induction of the IFN-β promoter by inhibiting JAK/STAT pathway[220]
JEV	NS5	Blocking the Nuclear Translocation of NF-κB and IRF3, Blocks TYK2 phosphorylation[237,238]
WNV	NS5, NS4b	Antagonist of Type I Interferon-Mediated JAK-STAT signalling, inhibits STAT1 phosphorylation[239]
YFV	NS4b	Inhibition of JAK/STAT signalling pathway by decreasing STAT1 phosphorylation, blocks RIG-1 signalling[238]
	NS5	Binds and inhibits STAT2 following IFN-1 induced phosphorylation of STAT 1[238]

Table 7
List of inhibitors reported to target the host cytokine pathway to inhibit further spread of virus infection.

Name of inhibitor	Target	Virus
Intron A, Rebetron, Rebetol, pegintron/ Sylatron, and Pegasys,	IFN-mediated antiviral acitivity and Immunomodulators[240]	HCV
PF-04878691 or 852A	TLR7/8 agonist[240]	HCV
IFN-α, PegIFN-α, and Alferon N	TNF-α-mediated antiviral activity[241]	HCV
Quercetin	TNF-α-mediated antiviral activity[242,243]	JEV, HCV
Azithromycin	Binding to IFNAR1 complex and ISGF3, upregulating IFN type I Signalling[244]	ZIKV, SARS-CoV-2
Mycophenolic Acid	ISGs upregulation[244]	MERS
Ribavirin	Enhances IFN-α signalling, activates the IFN-α-JAK/STAT signalling pathway leading to alleviated expression of MxA, an antiviral protein[244]	HCV
Gefitinib	Could inhibit the NF-κB pathway[244]	DENV
Berberine	Stimulation of IL-12 secretion and conversely inhibition of IL-6 production, thereby enhancing the production of IFN-γ[244]	CHIKV, SARS-CoV, HCV

Table 8
Examples of mAbs that are designed against host factors:

Monoclonal Antibodies	Host target	Viral infection
Anti-claudin1 (CLDN1), Anti-occludin	Entry receptors- claudin and occludin	HCV infection[247,248]
tocilizumab, sarilumab, siltuximab, sirukumab, clazakizumab, olokizumab, and levilimab	IL-6	SARS-CoV-2[249]
Ly-CoV1404	Angiotensin-converting enzyme (ACE2) receptor of host cell	SARS-CoV-2[250]
Oral anti-CD3 antibody	CD3 T- cell receptor	HCV infection[251]
Anti-SR-BI MAb	Human scavenger receptor class B, type I (SR-BI)	HCV infection[252]

antiviral response generated after virus entry, specialized viral enzymes hijacks and manipulates critical cellular enzymes and signalling proteins. Presently, diverse antiviral drugs targeting the viral proteins are either clinically approved or are in later stages of trial. Conventionally, most of these drugs function by targeting viral proteins (polymerases and proteases) and this traditional therapeutic approach has also proven to be highly beneficial in combating several viral infections. However, rapid regeneration of drug-resistant viruses have been reported with the usage of antivirals drugs based on this strategy that has eventually resulted in failure of this novel approach for some chronic viral infections. Therefore based on the fact of development of antiviral resistance, and global spread of viral infections, a deeper understanding of mechanisms behind immune dysregulation and alternative antiviral approaches are necessarily required for clinical management of severe viral infections.

The present review focuses on comprehensive understanding of host antiviral responses, immune responses and the advances made in the development of host-targeted drugs, primarily for +ssRNA viruses. The article also summarizes the key host-cellular factors or mechanism hijacked by viruses for their replication, including detailed information of host-based antiviral therapeutics already available for upregulation of immune response of the host. Since the genetic variability of host is quite less in comparison to viruses, host-based antiviral drugs are less likely to become ineffective against virus or its variants. In concordance to it, a combination of virus-targeted and host-targeted antiviral drug combination can also be tested for synergistic effects, if any. Besides virus-targeting antiviral drugs acting against viral specific proteins, host-based antiviral drugs will have the potential to be broad-spectrum as well. High-throughput molecular profiling techniques and

computational biology are providing new hopes to treat the deadly viral infections and focusses on the importance of host in viral pathogenesis providing unparalleled opportunities for diagnostics, better therapeutics and vaccines.

A major pitfall of host-targeted antiviral drugs is related to cellular side effects and cytotoxicity as they targets the cellular pathways of host cell essential for host survival.[253,254] Alisporivir, an inhibitor of cyclophilin A, displayed mild to moderate hyperbilirubinemia and hypertriglyceridemia, in phase II of its clinical trials.[253,255,256] Not only this, for host-directed therapeutic approaches, there is a possibility that viruses may use an alternate host factor or can modify the affinity towards the existing host dependency factor. Pertinently, host-targeted drugs are also subjected to genetic polymorphisms of host that may alter their ability to block their target function.[256] For instance, 10–15% of patients displayed suboptimal response against HCV on treatment with alisporivir.[59] Another possible risk associated with use of host-targeted antivirals is poor translation of *in vitro* results to *in vivo* therapies. Drugs displaying excellent activities in cell-culture based assays might behave differently when studied *in vivo* because host systemic mechanisms may compensate the effect of blocked target.[257] For instance, VX-497, an inhibitor of IMPDH, potently inhibited HCV replication when tested *in vitro* but displayed poor activity when it was tested in patients.[100] A possible explanation for this could be the variations in the level and supply of nucleotides in *in vitro* and *in vivo* conditions that would have resulted in poor efficacy of inhibitors targeting the IMPDH pathway. Similarly, statins displayed good antiviral activity against HCV *in vitro* but poor efficacy was observed when tested in clinical trials, probably because the cellular level of cholesterol is different *in vitro* and in human subjects.[258] Moreover, the host pathways involve a complex signalling cascade activating multiple pathways to generate a strong antiviral response. Therefore, identification of the host target and tracing the mechanism of action of identified drug is another challenge for the host-targeted therapy.[253]

Hence, quick and detailed understanding of positive impacts and side effects of host-based antiviral drugs is necessarily required for development of an effective antiviral therapy against chronic viral infections. A better understanding of the innate/adaptive responses of the host, the steps of viral life cycle, the signalling cascades and the host factors confiscated by viruses is a prerequisite to provide molecular insights for development of broad-spectrum antiviral therapy against recurring viral infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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