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Review

All differential on the splicing front: Host alternative splicing alters the landscape of virus-host conflict

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A B S T R A C T

Alternative RNA splicing is a co-transcriptional process that richly increases proteome diversity, and is dynamically regulated based on cell species, lineage, and activation state. Virus infection in vertebrate hosts results in rapid host transcriptome-wide changes, and regulation of alternative splicing can direct a combinatorial effect on the host transcriptome. There has been a recent increase in genome-wide studies evaluating host alternative splicing during viral infection, which integrates well with prior knowledge on viral interactions with host splicing proteins. A critical challenge remains in linking how these individual events direct global changes, and whether alternative splicing is an overall favorable pathway for fending off or supporting viral infection. Here, we introduce the process of alternative splicing, discuss how to analyze splice regulation, and detail studies on genome-wide and splice factor changes during viral infection. We seek to highlight where the field can focus on moving forward, and how incorporation of a virus-host co-evolutionary perspective can benefit this burgeoning subject.

1. Introduction

Virus cellular tropism is broadly determined by the ability for a virus to enter and reprogram a host cell for the purpose of multiplication and escape. If a host is genetically compatible to infection, target cell lineage and activation state further determine susceptibility to virus infection, which are molecularly controlled by epigenetics, transcription, and post-transcriptional modification. Nearly 95% of human pre-mRNAs are modified by alternative splicing (AS), the co- transcriptional process by which exons are differentially ligated together depending on signals in *cis* or *trans*-acting factors [1–3]. Splice isoform differences for a single gene impact, for example, the abundance of mRNA or coding differences that can affect the ultimate protein's localization, interaction domains, or post-translational modifications [4–6]. AS is also a major determinant of cellular lineage specificity and cellular activation status [7,8]. Despite the combinatorial effect on the host proteome, the impact of dynamic (activation-induced) and static (steady-state) AS is often overlooked when evaluating virus-host interfaces.

Advances in RNA sequencing (RNA-seq) technology has led to breakthroughs in understanding global host AS in different species, tissue types, and activation states [9]. Newer long-read RNA-seq datasets can better resolve full-length transcriptomes, demonstrating the under-appreciated wealth of transcript complexity. There is work prior to the sequencing revolution that characterized the overlap between AS, viral infection, and innate immunity, showing that many viruses target specific splicing factors during their life cycles (for reviews, see [10–16]). In this review, we seek to synthesize the molecular and transcriptional studies to better understand how AS shapes the virus-host landscape in vertebrates. We provide an overview of AS, discuss how virus infection re-wires host splicing, and contextualize AS within the ongoing battle of virus and host to shed a light on where the field is going in its bright future.

2. mRNA splicing

Most nuclear-encoded genes in eukaryotes are divided into a series of coding exons that are interdigitated by primarily non-coding introns. The average mRNA is 3.5 kilobase pairs (kb), containing each on average 8.8 exons and 7.8 introns [17,18]. Splicing is the mechanism that stitches the exons together and can either be constitutive (all exons are linked end-to-end) or alternative (certain exons are partially or fully excluded), depending on *cis*-encoded signals and *trans*-acting factors (Fig. 1) [1,19,20]. This multi-layered regulatory process provides ample opportunity for a given gene to be expressed as different mature mRNA isoforms. The varied coding sequences assembled by AS drastically change polypeptide function, abundance, or localization [6,21].

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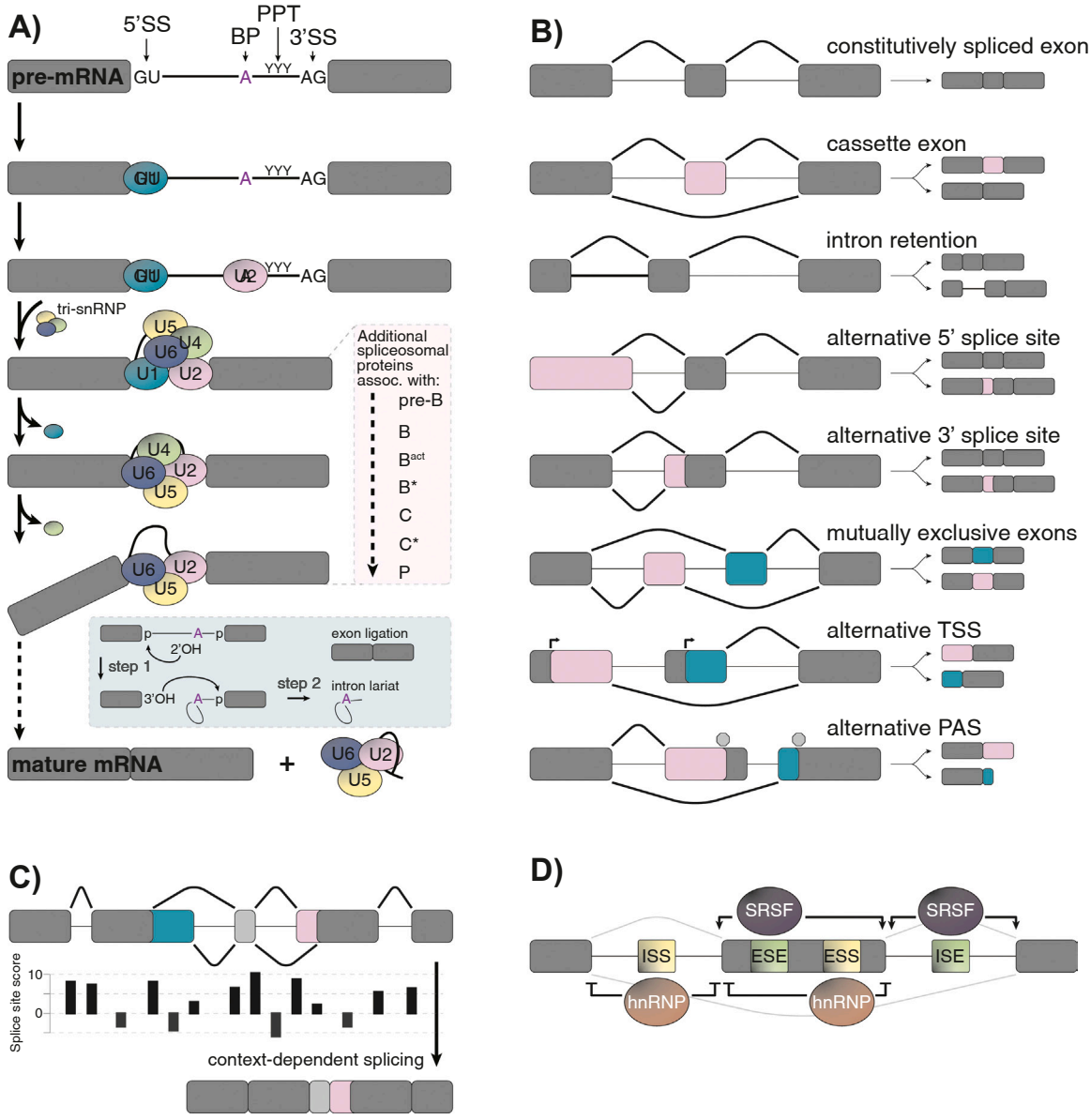

Fig. 1. Regulation and outcomes of alternative mRNA splicing. **A)** Step-wise snapshot of the splicing reaction carried out on mRNA exonic (gray boxes) and intronic (lines) sequences. U1 and U2 snRNP complexes bind canonical intronic sequences, and the tri-snRNP joins to form the catalytic spliceosome. Not shown are the dynamic shuffling of ~150 spliceosome subunits (those that interface with viruses are listed in Table 2). Magenta inset lists spliceosome complexes, blue inset shows the two-step enzymatic splicing reaction. 5'SS, 5' splice site; BP, branch point; PPT, poly-pyrimidine track; 3'SS, 3' splice site. **B)** Outcomes of alternative splicing. Curved lines indicate splice junctions. Arrows represent transcriptional start site (TSS); octagons represent polyadenylation sites (PAS) **C)** Context-dependent splicing takes into account splice site strength. Shown is a theoretical plot of splice site scores from MaxEnt that determines mRNA maturation [31]. **D)** Splicing regulatory factors SRSF and hnRNP proteins control alternative splicing by binding to intronic and exonic splice enhancer (ISE, ESE) and silencer regions (ISS, ESS), respectively.

2.1. Splicing by the spliceosome complex

Pre-mRNA splicing was first discovered by linking the genetic architecture of adenovirus to its mature transcription products [22,23]. It was later resolved that four conserved sequence motifs in introns served as signals for their removal: the 5' splice site (5'SS), the branch-point (BP) and polypyrimidine tract (PPT), and the 3' splice site (3'SS) (Fig. 1**A**) [1,19,20]. The canonical 5'SS is GU, and the downstream 3'SS is AG. Recent computational approaches continue to refine the motif and location of the BP sequence of (C/U)U(A/G)AC, where the penultimate A is of utmost importance, which are typically found 18–25 nucleotides upstream of the 3'SS [19,24,25]. These signals are cooperatively bound by the components of the major spliceosome comprising five small RNAs, U1, U2, U4, U5, U6, that together with over 100 additional proteins form five small ribonucleoprotein complexes (snRNP) [26]. For example, the U1 snRNP binds the 5'SS on pre-mRNA and subsequently the U2 snRNP binds to the BP [26,27]. The major spliceosome removes introns in a two-step transesterification reaction from nearly all pre-mRNAs [1,26–28]. The minor spliceosome is a functionally similar macromolecular complex that recognizes conserved, non-canonical splice sites – AU-AC as opposed to GU-AG – present in < 1% of introns but relevant in development and disease [29]. The assembly of the spliceosome relies on many protein-protein and protein-RNA interactions. As RNA polymerase II (Pol II) transcribes mRNA from DNA in humans, splicing occurs co-transcriptionally in the nucleus, and only fully spliced mature messenger RNAs are exported to the cytoplasm for translation [30].

2.2. Mechanism and consequence of alternative splicing

The consensus splice sequences are necessary but not sufficient for exonic splice inclusion. Splice site strength impacts alternative splicing and is determined largely by the accessibility and/or affinity of consensus sequences (5'SS, BP, PPT, 3'SS) to the spliceosomal machinery, which can be computationally predicted by evaluating entropies of RNA segments in a sliding window [31,32]. For example, a strong 5'SS and weak 3'SS within an intron may favor exon skipping for a stronger 3'SS in the neighboring downstream intron (Fig. 1**C**) [20,21]. Other than the canonical signals mentioned above, there are additional *cis*-encoded splicing regulatory elements that rely on *trans*-acting factors for their function. Namely, these are motifs recognized by RNA binding proteins (RBPs) that are categorized as follows: exonic splicing enhancer (ESE), exonic splicing silencer (ESS), intronic splicing enhancer (ISE), and intronic splicing silencer (ISS) (Fig. 1**D**) [19,20]. RBPs that bind silencing and enhancing motifs impact alternative splicing by recruiting or occluding spliceosomal proteins, or by changing the RNA structural availability for spliceosomal docking [21]. There are two main RBP families that coordinate AS by interacting with these motifs, the serine/arginine-rich splicing factor (SRSF) proteins and heterogenous nuclear ribonucleoproteins (hnRNPs) [33]. A simplified view categorizes SR proteins as splice enhancers that lead to exon inclusion, and hnRNPs as splice repressors. SR and hnRNP function is driven mainly by their propensity to bind ISE/ESE and ISS/ESS signals, respectively, but in practice is much more complex due to protein-protein and protein-RNA interactions between family members [19–21]. Outside of SR proteins and hnRNPs, AS is also controlled by genomic context, RNA structure, transcription speed, epigenetic status or other RBPs [19–21, 30]. Together these interactions result in AS events that can be categorized into the following: exon skipping, intron retention, alternative 5' or 3'SS, alternative transcription start site, or alternative polyadenylation (Fig. 1**B**).

Different isoforms of the same gene that vary in exonic inclusion can have vastly different functions [6]. For example, the immune modulating cell surface protein CD45 differs in exonic inclusion that alters the presence of homodimerization-inactivating glycosylated domains; dimerization turns off CD45 signaling, thus exon exclusion negatively regulates CD45 function [34]. AS provides a combinatorial advantage for proteome diversity, and splicing and evolutionary complexity are correlated [35,36]. Cellular lineage is a major determinant of the AS landscape during development [7]. Identical cells with the same lineage status can also have different AS expression patterns due to stimuli such as heat, ER stress, apoptosis, or signals that activate innate or adaptive immune transcriptional programs [12,34,37–39]. AS can also be influenced by rate of Pol II transcription or epigenetic context [40,41]. Under these scenarios, splicing can be relatively predictable, and splicing within species is highly conserved [35,36,42,43]. However, a major disruption in splicing networks occurs during cellular transformation [44–46]. This serves as both a driver and consequence of cancer formation, but it is equally relevant when studying AS in tissue culture models, since many cell lines are themselves cancerous (detailed further in 3.4). The magnitude of impact coupled to the multitude of contact points makes AS a predictable target for viruses.

3. Laboratory techniques to detect splicing

Unless studying prototypical splicing using in vitro reactions, AS is by definition heterogenous. In a cell, a single gene is expressed as many different transcript isoforms. Therefore, designing assays to enumerate isoform concentration will at best provide relative abundances. The following section discusses approaches to experimentally evaluate AS.

3.1. Targeted detection of alternative isoforms

There are several different approaches to evaluate AS of a single gene. These techniques rely on designing oligonucleotides complementary to the target mRNA, and will be influenced by where along the length of mRNA the oligonucleotides bind. Northern blotting involves hybridizing radiolabelled oligonucleotides to the target mRNA after the total mRNA is separated by gel electrophoresis [47]. This is advantageous because a single probe that recognizes transcripts of different lengths can be used to ascertain relative abundance of the different isoforms that have unique mobility in the gel. However, Northern blotting is limited by its relative difficulty and low throughput. It can be modified by using near-infrared or fluorescently labelled probes that span unique exon junctions to create a multiplex readout within a single lane, which is advantageous for detecting isoforms with minimal size differences [48]. This general principle can also be applied to RNA fluorescence in situ hybridization to visualize specific isoforms within fixed tissue or cells [49]. Reverse-transcription polymerase chain reaction (RT-PCR) is advantageous in its simplicity compared to these prior approaches. Mature mRNAs can first selectively be used to template cDNA synthesis using oligo dT primers during reverse transcription. Then primer sets that span the isoform of interest will amplify target isoforms. End-point PCR is only semi-quantitative, which can be overcome by using labelled probes for quantitative PCR (qPCR) or droplet digital PCR (ddPCR) for a more absolute AS measurement, with ddPCR more accurately quantifying transcripts at low levels [50,51]. These approaches are the gold-standard for demonstrating isoform presence, but cannot be used to broadly profile the transcriptome, and instead serve as a validation for already-determined transcripts of interest.

3.2. Transcriptome-wide detection of alternative isoforms

High throughput technologies allow unbiased analysis of genome-wide splice events [52]. The benefits and drawbacks of the most commonly used approaches – microarrays, short-read, and long-read RNA-seq – are described here. A common step for these approaches almost universally first involves a reverse transcription step, where cellular mRNA is enriched using poly(A) selection or primers and then converted to cDNA with additional depletion of ribosomal RNA. DNA microarrays were the first technology that allowed researchers to analyze the transcriptional profile of many genes in parallel [52]. Complimentary oligonucleotides to isoform targets are hybridized to DNA chips, then experimental cDNA binds these oligos and are quantified in a fluorescence-based reaction. Although many parallel targets can be quantified simultaneously, a major drawback of microarrays is that the targets need to be known prior to chip manufacturing, whereas RNA-seq collects all transcriptional expression information. For short-read RNA-seq (Illumina or Ion Torrent platforms), mRNA are sheared, converted to cDNA, ligated to adapters, and are then read in parallel on flow cells with fluorescently-labelled nucleotides. The resulting "short reads" are typically 50 – 200 base pairs (bp) in length, which are then computationally mapped to reference transcriptomes, providing coverage and depth that informs the identity and quantity of mRNA transcripts [9,53]. In a cross-platform comparison between microarray and Illumina for AS detection, Romero and colleagues found that RNA-seq was more sensitive and could better identify ambiguous transcript regions [54]. Short-read RNA-seq typically generates ~50 million reads per sample, but this unbiased approach is limited by the accuracy of the reference transcriptome, and the nature of the length of reads for isoform differentiation. For example, splice junction spanning reads can inform on the presence of particular pieces of isoforms, but without linkage to a full transcript the true isoform identity cannot be resolved. Long-read RNA-seq (Pacific Biosciences [PacBio] or Oxford Nanopore [ONT]) solves some of the problems for isoform identification [55,56]. For these technologies, full length mRNA is converted to cDNA and used for single molecule real-time analysis on a chip using fluorescence (PacBio) or ligated to adapters and flowed through pores for electrical current analysis (ONT). The PacBio Iso-seq protocol calls for cDNA size selection at 1 – 4 kb to avoid PCR length bias of smaller

transcripts, but transcripts up to 15 kb have been reported [9]. With direct cDNA sequencing of ONT such PCR bias is avoided, however, a PCR-amplification step is often performed to increase the overall number of reads. Additionally, ONT can be used for direct RNA sequencing bypassing these limitations altogether, albeit with reduced accuracy [57]. Because full transcripts are sequenced in long-read RNA-seq technologies, precise isoform identity can be resolved, and PacBio often results in > 10% novel full-length transcripts using the Iso-seq pipeline [58]. A drawback of long-read RNA-seq is the read depth, which is typically 50-fold lower than short-read RNA-seq. Thus, although isoform identity of moderate to highly expressed transcripts can be resolved, this approach is not ideal in quantifying differential expression.

The base technologies have provided limitations in adapting these systems for AS analysis, but ingenuity on the molecular or computational side has continually increased their utility for AS analysis [9,53]. Latest iterations of DNA microarrays have manufactured chips to detect AS by using splice junctions as targets, which has been shown to rival some short read RNA-seq experiments. As the most widely used technology for short-read RNA-seq, Illumina library prep can be modified to include unique molecular identifiers (UMIs), which links short reads to barcoded mRNAs to computationally create synthetic long reads [9]. Furthermore, modifications to library prep can also enrich for 3' mRNA ends to focus on alternative polyadenylation or the 5' mRNA end for transcriptional start-site identification [9]. There is also a litany of computational tools to differentially identify isoforms from short-read data [59–63]. It should be noted that using purely short-read RNA-seq maintains some of the limitations outlined above. Hybrid sequencing can overcome many of the aforementioned limitations, as this approach pairs matched RNA-seq data from short-read and long-read experiments to improve isoform identity and quantity over either approach alone [64]. Lastly, bulk RNA-seq has been used most commonly, but single-cell RNA-seq is becoming increasingly cost efficient. Microfluidics separate single cells into mini library prep manufacturing plants, where individual cell libraries are barcoded for downstream bulk RNA sequencing using short or long-read platforms [65]. Because the total sequencing read depth is distributed across cells, resolution for differential expression is lower in single cell than bulk RNA-seq. However, individual cells can be computationally clustered based on expression patterns to link AS of specific isoforms to other highly up or down-regulated genes. The rapid pace of technological development may make the intrepid experimentalist hesitate on when to start an experiment, but the nature of unbiased approaches allows for later re-analysis as reference transcriptomes or computational methods improve. The vast quantity of published data available on the Sequence Read Archive also allows the pioneering scientist access to an *in silico* pre-analysis for their experimental question [66].

3.3. Validation of AS events

After identifying the transcriptional signature for AS, it is crucial to demonstrate the phenomena experimentally. Typically, best practice is to demonstrate three criteria beyond transcriptomics: 1) transcript presence using targeted approaches, 2) impact on protein, and 3) selectively targeting transcripts via *cis* or *trans* regulation. RNA-seq is very reliable in capturing the transcriptional landscape within experimental cells, but it is desirable to demonstrate the quantifiable change of an alternatively spliced isoform using an orthogonal approach such as end-point or quantitative RT-PCR. Validating RNA-seq data with RT-PCR demonstrates proper data analysis and can further quantify the alternative transcript, report the full-length identity of the isoform, and test different cell types or stimulation conditions. After transcript identification hypothesis-driven experiments can evaluate changes in accumulation, size, localization, or function [4,5]. Functional experiments are often performed in overexpression settings, but it is also pertinent to characterize the endogenous isoform. Endogenous isoform analysis can often be a challenge because of low levels of expression or overlapping coding sequences among multiple isoforms. Both limited quantity and specificity of isoforms are particularly problematic for antibody-mediated detection approaches, which can be overcome by using mass spectrometry. One can also consider using targeted genome engineering to introduce protein fusions, epitope tags, or exon splice knock-out against their splice form of interest [67,68]. Additionally, anti-sense oligonucleotides or locked nucleic acid morpholinos can be used that target critical RNA signals for splicing [69]. One final step for validating an AS event is to demonstrate that splicing controls isoform expression, and not, for example protein degradation or leaky ribosomal scanning [21]. This can be achieved by modulating the RBPs that control the isoform; relevant RBPs can be identified computationally by motif scanning programs or using specific RNA co-immunoprecipitation and protein MS analysis [70,71]. Once identified, modulating the RBP (silencing, overexpression, retargeting) should have a consequent effect on isoform maturation. These approaches are often time and resource-consuming, but together can be used lock, stock, and barrel to demonstrate the impact of AS on phenotype.

Most studies have relied on using cell lines in culture to study AS differences. Although Martinez et al. found that many exons shared similar regulation in activating T cell lines compared to primary cells, there is not a thorough catalog of commonly used cell lines, their relevant primary cell type, and AS regulation overlap [72]. Furthermore, the AS profile of cancer cells is markedly different than pre-cancerous cells, giving credence to the caveat specifically in cancerous cell lines [44,45]. Observations made in common laboratory cell lines will benefit from validation in primary cells, and potentially in animal models.

4. Virus infection and changes in dynamic alternative splicing

Cells rapidly respond to diverse stimuli, typically manifesting as a transcriptional change that poises the cell to survive or altruistically assist in host survival. It is now understood that AS plays a large part in shaping this rapid change, as treatment with compounds mimicking environmental change, triggers of DNA damage or apoptosis, and even shifts in temperature all induce global splice changes [37,39,73,74]. It is not surprising then, that virus infection can similarly induce changes in host AS. However, mutual antagonism may exist: a host could use AS for pathogen elimination while a virus can evolve to selfishly re-wire the AS response for its own benefit. Evidence for the former phenomenon is lacking. Viruses indeed shape AS for their advantage (Section ***4.1***), but several studies have shown that the antiviral type I interferon (IFN) response is reduced via AS (reviewed in [8,12,34,75,76]). For example, the TLR signaling adaptor MyD88 typically amplifies innate immunity. However, MyD88 also encodes a negative regulatory isoform via AS, and the splicing factor that controls expression also controls many transcripts in the innate signaling pathway [77,78]. Such a mechanism to resolve the antiviral state may be beneficial for non-lytic latency-promoting viruses, which to date have been the most widely studied in terms of an AS response. Acute infection with lytic viruses, for example most respiratory RNA viruses, would only marginally benefit from late-stage IFN resolution. It is thus possible and worth studying if highly specialized AS responses occur during different viral infections.

Many different viruses rely on host spliceosome machinery to express their complete transcriptional repertoire. Host contribution to viral RNA splicing has been widely studied in the context of HPV, for example, where one of the hallmarks of active viral replication is the production of a spliced viral E1^E2 transcript [79]. Although important and evidence for the cross-talk between viruses and host AS, this topic is not detailed here. Further, this viral hijacking of host splice factors to aid in virus RNA biogenesis will also yield an effect on global host AS. The following section will focus on global host AS changes triggered by virus infection and host splice factors that may serve as lynchpins for this response.

Table 1
Studies evaluating host genome-wide alternative splicing during viral infection.

Host	Genome	Virus	Abbr.	Order, Family	Ref
Human	-ssRNA	Influenza A Virus	FLUAV	Articulavirales, Orthomyxoviridae	[88–94]
		Severe Fever with Thrombocytopenia Syndrome Virus	SFTSV	Bunyavirales, Phenuviridae	[98]
		Rift Valley Fever Virus	RVFV	Bunyavirales, Phenuviridae	[99]
		Respiratory Syncytial Virus	RSV	Mononegavirales, Pneumoviridae	[99]
	+ssRNA	Enterovirus 71	EV71	Picornavirales, Picornaviridae	[100]
		Foot-and-Mouth Disease Virus	FMDV	Picornavirales, Picornaviridae	[101]
		Hepatitis C Virus	HCV	Amarillovirales, Flaviviridae	[46,102]
		Dengue Virus	DENV	Amarillovirales, Flaviviridae	[103–105]
		Zika Virus	ZIKV	Amarillovirales, Flaviviridae	[105,106]
		Severe Acute Respiratory Syndrome Coronavirus 2	SARS-CoV-2	Nidovirales, Coronaviridae	[95–97,107]
	ssRNA-RT	Human Immunodeficiency Virus	HIV	Ortervirales, Retroviridae	[87,108]
		Human T-lymphotropic Virus	HTLV	Ortervirales, Retroviridae	[109–111]
		Lentiviral vector	LV	Ortervirales, Retroviridae	[85,86]
		Avian Reticuloendotheliosis Virus	AvREV	Ortervirales, Retroviridae	[112]
	dsRNA	Reovirus	ReV	Reovirales, Reoviridae	[102,113,114]
	dsDNA	Hepatitis B Virus	HBV	Blubervirales, Hepadnaviridae	[46,102]
		Herpes Simplex Virus	HSV	Herpesvirales, Herpesviridae	[81–83,114,115]
		Human Cytomegalovirus	HCMV	Herpesvirales, Herpesviridae	[81]
		Epstein Barr Virus	EBV	Herpesvirales, Herpesviridae	[84,116–120]
		Human Papilomavirus	HPV	Zurhausenvirales, Papillomaviridae	[121]
		Vaccinia Virus	VACV	Chitovirales, Poxviridae	[114]
Swine	+ssRNA	Porcine Reproductive and Respiratory Syndrome Virus	PRRSV	Nidovirales, Arteriviridae	[122]
	dsDNA	African Swine Fever Virus	ASFV	Asfuvirales, Asfaviridae	[123]
Chicken	-ssRNA	Influenza A Virus	FLUAV	Articulavirales, Orthomyxoviridae	[124]
		Newcastle Disease Virus	NDV	Mononegavirales, Paramyxoviridae	[124]
	ssRNA-RT	Avian Sarcoma Leukosis Virus	ASLV	Ortervirales, Retroviridae	[124]
	dsRNA	Infectious Bursal Disease Virus	IBDV	Family: Birnaviridae	[124]
	dsDNA	Marek's Disease Virus	MDV	Herpesvirales, Herpesviridae	[125]

4.1. Global host AS changes during viral infection

Vertebrate hosts respond to pathogen infection by upregulating 100s to 1000s of interferon stimulated genes tailored to fend off parasitic invasion [80]. However, viruses can in turn re-wire the transcriptome of infected cells to push them towards a different activation state, cell cycle step, or stage of differentiation. AS is altered at a similar, global scale by virus infection, where 100s of AS differences can be observed [13]. Differences in AS can drive phenotypic changes by modulating potential pro- or antiviral isoforms. Sections 4.1.1 and 4.1.2 highlight a few studies that leverage genome-wide analyses of host transcriptomes to query how viral infection impacts AS, see Table 1 for a complete list of studies arranged by virus.

4.1.1. DNA viruses

Several viruses with double-stranded DNA genomes trigger host AS changes (Table 1), with some changes favoring viral replication. Human cytomegalovirus (HCMV) infection for example, by inducing the expression of the host mRNA translation regulator *CPEB1*, leads to a global shortening of 3' UTRs and lengthening of poly(A)-tails [81]. This activity was shown to be necessary for efficient viral replication. Herpes simplex virus type-1 (HSV-1) and HSV-2 infection also change host AS to enhance virus replication. During infection, hosts display increased intron retention, a process that can have the byproduct of increased poly (A) signals [82,83]. A potential driver of this activity is that HSV expresses transcriptional products from overlapping reading frames that require such increased poly(A) signal incorporation. Lastly, Epstein-Barr virus (EBV) infects resting B cells, which on average have a much shorter lifespan than this long-lived infection. However, within one day post-infection, AS changes are induced that mirror B cell proliferation and activation [84]. These changes are beneficial for active infection and further spread of the virus. Because the outcomes of AS are so prolific, it's likely incorrect to infer that the global profiles triggered during infection en masse are proviral. More research is needed to find and link common mechanisms during viral infection, though the final outcome will be multifactorial with transcripts changing in both proviral and antiviral functions.

4.1.2. RNA viruses

Perhaps owing to more diverse lifecycles, the AS changes characterized by RNA virus infection thus far has been more varied. For example, viruses with ssRNA-RT genomes that integrate into DNA have been shown to induce alternatively spliced transcripts that contain chimeras of virus and host transcripts [85–87]. Similarly as observed for some dsDNA viruses, influenza A virus (FLUAV; -ssRNA genome) induces readthrough transcription or defective termination of Pol II [88–90]. Additionally, FLUAV can induce exon inclusion and less intron retention [91] or broad and heterogeneous global AS changes [92–94]. Lastly it has been shown that expression of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) NSP16 can increase intron retention [95,96] and decrease host splicing through its interaction with the U1 and U2 snRNAs [97]. Flaviviruses, Picornaviruses, and Reoviruses have also been shown to induce host AS changes, but a global mechanism has yet to be described.

4.2. Key host isoforms or splice regulatory mechanisms modulated by viruses

It has long been appreciated that viruses can trigger protective host gene expression changes, and indeed type I IFN was first isolated as a response agent in cells treated with influenza virus [126–128]. Understanding the nuance of IFN-stimulated AS requires analysis of the triggers (pathogen-associated molecular patterns), players (viral proteins that modulate splicing), and outcomes (host pre-mRNAs that undergo AS). Triggers are well-covered by Liao and Garcia-Blanco, and the players are discussed in Section ***4.3***, as follows will detail some of the outcomes of infection-stimulated AS [12].

Disabling the host antiviral state is a key contributor to virus genetic survival, and viral antagonism of host defense via modulation of host AS has occurred many different times and in unique ways. Early studies observed that FLUAV infection and the IFN antagonist protein, NS1, decreases the amount of host splicing events [129,130]. More recently this has been attributed to the intron-binding preference of NS1 [131], although the FLUAV endonuclease PA-X also preferentially targets host pre-mRNAs that are more abundantly spliced [132]. Human

Table 2
Host spliceosome components targeted during viral infection.

Sub-complex[a]	Host Gene	Virus [protein]; (VirHostNet2.0)[b]	Ref	ChIRP-MS[c]	BUSTED *P*-value[d]
Sm proteins	N/A	HSV [ORF57], KSHV [ICP27]	[159,160]	-	-
	SNRPB	(FLUAV)		yes	ns
	SNRPD1	HCV [NS3]	[161]	yes	1.95E-04
	SNRPD2	(EBV, HCV, FLUAV)		yes	ns
	SNRPD3	(HCV, FLUAV)		yes	ns
	SNRPG	(HIV, FLUAV)		yes	7.42E-04
	SNRPA	YFV [NS5]	[185]	yes	ns
	SNRPC	(HIV, FLUAV)		yes	ns
U2	SNRPA1	(FLUAV)		yes	ns
	SNRPB2	HSV [ICP27]; (EBV, FLUAV)	[165]	yes	ns
	SF3A1	(HIV, FLUAV)		yes	ns
	SF3A2	(HIV, FLUAV)		yes	ns
	SF3A3	(HIV, FLUAV, KSHV)		yes	ns
	SF3B1	ZIKV [sfRNA], DENV [sfRNA], HDV [genome]; (EBV, HCV, HSV, FLUAV)	[162,163]	yes	ns
	SF3B2	HSV [ICP27], HIV [Vpr]	[164,166]	yes	ns
	SF3B3	(HCV, HBV, HIV, HSV, FLUAV)		yes	ns
	SF3B4	(FLUAV)		yes	-
	SF3B5	(FLUAV)		yes	-
	SF3B6	(FLUAV)		yes	0.0125
	PHF5A	(FLUAV)		yes	-
U5	PRPF8	EV71 [$3D^{pol}$], ReV [μ2]	[167,168]	yes	-
	SNRNP200	HIV [virions], ReV [μ2]	[168,169]	yes	5.31E-05
	EFTUD2	HCV [downregulated], ReV [μ2]; (HCV, FLUAV)	[168,170]	yes	ns
	SNRNP40	(HIV, KSHV)		yes	ns
	PRPF6	(HIV)		yes	-
	DDX23	DENV [NS5]; (FLUAV)	[171]	yes	ns
	CD2B2	DENV [NS5]; (FLUAV)	[171]	yes	ns
U4/U6	LSM3	(KSHV)		yes	ns
	PRPF3	(KSHV)		yes	-
	PRPF4	HIV [gag]	[172]	yes	ns
	PRPF31	(HCV, HIV, FLUAV)		yes	-
	PPIH	SARS-CoV-1 [Nsp1]	[173]	yes	ns
	SNU13	(HIV)		yes	ns
	RNU6–1	FLUAV [NS1]	[174,175]	yes	-
tri-snRNP	SART1	(HIV)		yes	-
	USP39	(HIV)		yes	ns
	RBM42	(HIV)		yes	ns
B-specific	MFAP1	(HIV, FLUAV)		yes	ns
	IK (RED)	FLUAV [3pol]; (HIV)	[176]	yes	-
	SMU1	FLUAV [3pol]	[176]	yes	ns
PRP19-complex	PRPF19	FLUAV [NS1]; (HCV, HIV, FLUAV)	[180]	yes	ns
	CDC5L	(HIV, FLUAV)		yes	ns
	PLRG1	(HIV)		yes	ns
	BCAS2	(FLUAV)		yes	ns
IBC	AQR	(FLUAV)		yes	0.0224
	PPIE	FLUAV [NP]	[178]	yes	ns
NTR	CRNKL1	(FLUAV)		yes	2.48E-05
	SNW1	HPV [E7]	[181]	yes	ns
	PPIL1	(FLUAV)		yes	ns
	RMB22	(KSHV)		yes	ns
B^{act}	CWC22			-	0.00106
	SRRM2	HTLV [Tax], HIV [phosphoregulated]	[182,184]	yes	5.21E-06
	SRRM1	(EBV, FLUAV, KSHV)		yes	0.0155
RES	BUD13			-	1.14E-05
EJC	EIF4A3	FLUAV [PB2, PB1, NP]; (FLUAV)	[177]	yes	-
	RBM8A	(FLUAV)		yes	ns
	MAGOH	HSV [ORF57]	[183]	yes	-
	CASC3	(HIV, FLUAV)		yes	Ns
C proteins	PPIG	SARS-CoV-1 [Nsp1]	[173]	yes	0.00139
	PPIL4	(FLUAV)		yes	ns
Step II splice factors	DHX38	(FLUAV)		yes	ns
	DHX8	(FLUAV)		yes	ns
	PRPF18	FLUAV [NP]	[179]	-	ns
Putative C* proteins	STEEP	(KSHV)		yes	ns
	SDE	(HIV)		yes	ns
	PRKRIP1	(FLUAV)		yes	ns

[a] Table compiled based on Kastner et al., where only proteins that had viral interfaces are presented [26]. IBC, intron binding complex; NTR, nineteen related; RES, retention and splicing; EJC, exon junction complex

[b] VirHostNet2.0 is a database of viral-interacting proteins [155]

[c] ChIRP-MS compiles data from 3 viral RNA-protein interaction studies in +ssRNA viruses. -, no viral RNA binding; yes, binding [156–158]

[d] BUSTED *P*-Value is an indication of adaptation, where values < 0.05 are reported as significant. -, not available; ns, not significant [154,186]

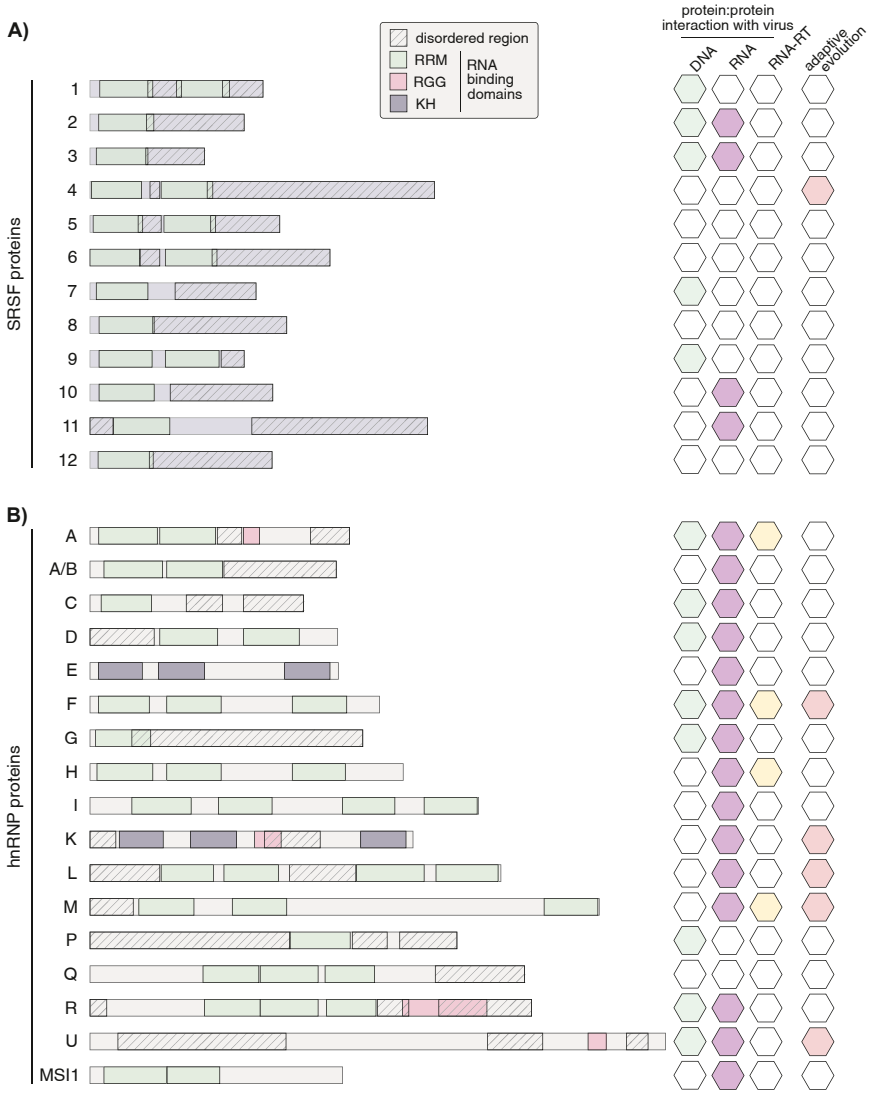

Fig. 2. Domain architecture and viral interface of splice regulatory factors. Protein secondary structure of **A)** SRSF and **B)** hnRNP family members. RNA binding domains indicated by colored boxes, and disordered regions indicated by diagonal lines. Filled hexagons (right) indicate virus families or adaptive evolutionary signatures where protein has been implicated. For a list of the viruses, references, and viral proteins, see Table 3.

Immunodeficiency Virus type 1 (HIV-1) Vpr can also decrease host RNA splicing [133]. ICP27 encoded by HSV-1 and HSV-2 similarly plays a master splice regulatory role by specifically inhibiting the spliceosome complex [134–137]. Limiting host splicing may be a general viral mechanism to decrease the host response to infection [12]. HSV-1-mediated host AS results in the expression of atypical isoforms of a proviral dynamin-like GTPase MxA, an interferon-repressive isoform of IKKε, a STING variant that blocks innate immune sensing, or reshaping PML bodies by isoform selection [137–140]. Antagonism of the cellular antiviral state is conserved among many viruses: Dengue virus (DENV) promotes intron retention of the polyamine regulator *SAT1*, EBV modulates the cytokine signaling adapter *STAT1*, Rift Valley fever virus (RVFV) modifies *TRA2B* to augment the IFN regulator RIOK3, Sendai virus (SeV) releases a RIG-I-MAVS inhibitory form of pro-inflammatory *TBK1*, and spring viremia of carp virus (SVCV) can degrade a spliceform of the broad antiviral ribonucleotide generating enzyme *RSAD2*, Viperin_sv1, that is uniquely turned on by viral infection and not poly(I:C) [141–145]. These findings provide corollary examples for how virus-triggered AS dampens immunity.

Another strong selection agent that controls successful virus replication and genetic survival is initiating infection in a permissive environment. Surprisingly, since viral replication is inherently downstream of entry, some virus entry factors show infection-induced isoform differences. Rhinovirus (RV) infection or interferon-induced spliceform of the host entry factor *ACE2* lacks the SARS-CoV-2 binding site [146]. In another observed impact on entry, infection with porcine reproductive and respiratory syndrome virus (PRRSV) affects Fc gamma receptor Ia (*FCGR1*) AS, producing isoforms that modulate antibody-dependent enhancement [147]. After establishing infection, some viruses utilize AS to affect ER stress response, T cell activation state, or expression of the cold stress response gene *CIRBP* isoforms, all which make for a better environment to generate progeny [148–150]. Lastly, keeping infected cells alive is critical to maximize progeny output, thus controlling the death-inducing signal receptor *FAS* and pro-survival tumor susceptibility gene *TSG101* by specific isoform expression also promotes virus infection [151–153]. Together these studies have demonstrated that viral infection results in AS that is beneficial to virus propagation. It should be noted that the majority of this research is performed in model systems that are generally permissive to viruses. Model systems with AS profiles that prevent or limit viral infection may be considered unsuitable for cell culture study. However, such restriction could have a major impact on exploring zoonotic potential and are discussed in more detail in Section 5.

Table 3
Host splice regulatory factors targeted during viral infection.

Protein Family[a]	Host Gene	Virus [protein]; (VirHostNet2.0)[b]	Ref	ChIRP-MS[c]	BUSTED *P*-value[d]
SRSF	SRSF1 (ASF)	AdV [E4-ORF4], EBV [SM, BMLF1], HPV [E2], VZV [IE4]	[191–195]	yes	ns
	SRSF2 (SC-35)	EBV [relocalize], HPV [E2], HSV [ICP27], HVS [ORF57], FLUAV [NS1]	[130,159,191,196, 200]	yes	-
	SRSF3 (SRp20)	CVB [2 A], EBV [BMLF1, SM, relocalize], HBV [genome], HPV [E2], HSV [ICP27], PV [2 A], VZV [IE4]	[192,193,195, 197–201]	yes	ns
	SRSFs 3–6	MDV [ICP27]	[190]	-	-
	SRSF4			yes	0.083
	SRSF7	EBV [BMLF1], VZV [IE4]	[193,195]	yes	ns
	SRSF9	AdV [E4-ORF4]	[194]	yes	ns
	SRSF10	(FLUAV)		yes	-
	SRSF11	(FLUAV)		yes	-
	Many	ReV [NSP2, NSP5]	[212]		
hnRNP A	HNRNPA0	(EBV, FLUAV)		yes	ns
	HNRNPA1	EV71 [relocalize], HIV [relocalize], SINV [relocalize], VSV [relocalize]	[205–207]	yes	ns
	HNRNPA3	(HIV, FLUAV)		yes	ns
	HNRNPA2B1	JEV [Core, NS5]	[208]	yes	ns
hnRNP C	HNRNPC	HDV [S-HDAg], FLUBV [NS1], PV [3CD], ReV [NSP2, NSP5], VSV [relocalize]	[207,209–212]	yes	ns
	HNRNPCL1	(EBV)		yes	-
hnRNP D	HNRNPAB	FLUAV [NP]	[213]	yes	ns
	HNRNPD (AUF1)	EBV [EBER1]; PV [3CD]; ReV [NSP2, NSP5]; RV [3CD]; (EBV, HIV, FLUAV, VACV)	[212,214,215]	yes	-
	HNRNPDL	ReV [NSP2, NSP5]; (HIV, FLUAV)	[212]	yes	ns
hnRNP E	PCBP1	CSFV [Npro], PV [3CD], ReV [NSP2, NSP5], RV [3CD]	[212,216,217]	yes	-
	PCBP2	PV [3CD], RV [3CD]	[216]	yes	-
	PCBP3	(FLUAV)		yes	ns
hnRNP F	GRSF1	(FLUAV)		yes	0.0154
	HNRNPF	PRRSV [relocalize]; (EBOV, HIV, HSV, FLUAV)	[218]	yes	ns
hnRNP G	RBMX	(FLUAV, VACV)		yes	ns
hnRNP H	HNRNPH1	HCV [Core], VSV [M]	[219,220]	yes	ns
	HNRNPH3	(EBOV, HCV, HIV, FLUAV)		yes	ns
hnRNP I	PTBP1	ReV [NSP2, NSP5]; (DENV, EBV, HCV, FLUAV)	[212]	yes	ns
	PTBP3	(FLUAV)		yes	ns
hnRNP K	HNRNPK	DENV [relocalize], FLUAV [NS1], JUNV [relocalize] SINV [nsp7]	[221–223,226]	yes	0.0026
hnRNP L	HNRNPL	HCV [NS5a]; (EBOV, FLUAV)	[232]	yes	3.22E-04
hnRNP M	MYEF2	(HIV, FLUAV)		yes	1.11E-04
	HNRNPM	CVB [3Cpro], EBV [EBNA5], FLUAV [NS1], PV [3Cpro]	[225–227]	yes	0.0121
hnRNP M	FUS	AAV [Rep]	[233]	yes	-
hnRNP R	HNRNPR	(EBV, HIV, HSV, FLUAV, VACV)		yes	ns
hnRNP U	HNRNPU	FLUAV [NS1]	[228]	yes	1.24E-06
	HNRNPUL1	AdV [E1B-55 K], FLUAV [NS1, PB2]	[229–231]	yes	ns
	HNRNPUL2	(FLUAV)		yes	ns
Musashi	MSI2	(HCV)		yes	-

[a] Table compiled based on Busch et al., where only proteins that had viral interfaces are presented [33]
[b] VirHostNet2.0 is a database of viral-interacting proteins [155]
[c] ChIRP-MS compiles data from 3 viral RNA-protein interaction studies in +ssRNA viruses. -, no viral RNA binding; yes, binding [156–158]
[d] BUSTED *P*-Value is an indication of adaptation, where values < 0.05 are reported as significant. -, not available; ns, not significant [151,183]

4.3. *Cis- or trans-splice factors targeted by viruses*

The compact size of viral genomes forces their encoded expressed products to be multifunctional, coordinating a massive set of host processes with limited tools. The complexity of host AS is altogether too genetically expensive for viruses to interface with in a similar way as the host (see Table 2 for a list of spliceosome components). Instead, viruses have derived thrifty means to interact with host splicing. For example, the major trans-acting splice regulatory factors (SR proteins and hnRNPs) have 50 members in humans, many that bind unique RNA motifs (Fig. 2). However, many domains are conserved across the proteins, which establishes a vulnerability for virus interaction. This allows viruses to, rather than encode the RNA binding proteins themselves, usurp the host's genomic redundancy to tap into and modify AS. Sections 4.3.1 and 4.3.2 highlight work that studies the interaction of viruses with host splicing factors of the spliceosome and SR and hnRNP proteins. Tables 2 and 3 compile sources from the literature from previous studies that compile virus-host interaction factors [154,155] and from correspondence with D. Enard cataloging host nucleic acid binding proteins with viral genomes from flaviviruses and SARS-CoV-2 [156–158]. Many other host proteins beyond spliceosome and SR and hnRNP proteins help coordinate AS, but they are not discussed here in detail.

4.3.1. *Virus interface with spliceosome components*

Many viruses modulate host splicing through interacting with the spliceosome. The spliceosome is a macromolecular complex that in humans comprises ~165 proteins that form various intermediate complexes to carry out the two major transesterification steps in splicing, predominantly by protein-protein and protein-RNA interactions [26]. A variety of host spliceosomal proteins are usurped by viruses and either modulate host splicing or coordinate viral splicing events. A comprehensive list of viral proteins that interface with spliceosomal factors towards potential host gene expression modulation is presented in Table 2. Recent structural insights have provided more clarity into how the sub-complexes of the spliceosome interact, which for purposes here are broadly divided into: 1) the five major snRNP complexes comprising Sm proteins, each of the eponymous snRNA (U1, U2, U4/U6, and U5), and additional snRNP-specific co-factors, and 2) auxiliary complexes that are required in a catalyticstep-dependent manner (ie. B activation complex [B^{act}] proteins, exon junction complex [EJC], etc.).

The majority of identified virus-host interactions have been

documented in the context of the snRNP complexes and their co-factors. Sandri-Goldin has done extensive work on the HSV-1 ICP27 protein and found that it interfaces with host spliceosomal machinery and specifically re-distributes spliceosomal Sm proteins and the splicing factor SRSF2 [159]. Both Kaposi's Sarcoma herpes virus (KSHV) ORF57 and hepatitis C virus (HCV) NS3 also bind and re-localize Sm proteins [160,161]. In addition to viral proteins, viral nucleic acid can also interact with snRNPs. For example, hepatitis delta virus (HDV) gRNA and flavivirus sfRNA are each bound by the U2 snRNP protein splicing factor 3b subunit 1 (SF3B1), which results in mis-splicing of host splicing factors RBM5, and SRSF7, respectively [162,163]. Vpr from HIV-1 binds to SF3B2 and alters host splicing [164]. HSV-1 ICP27 targets U2 snRNP by re-localizing Sm B'' or by binding to SF3B2 [165,166]. HSV-1 ICP27 expression results in decreased AS, making it difficult to ascertain whether the multitude of interactions is a redundancy or if each interface coordinates specific downstream effects. The U5 snRNP co-factors are also targeted frequently by viral proteins. The enterovirus 71 (EV71) viral polymerase 3Dpol interacts with the spliceosomal core component PRP8 and inhibits splicing of splice reporters in vitro (PIP85a) and in cells (b-globin; pSV40-CAT(In1)), and endogenous nucleolin (*NCL*) [167]. Reovirus (ReV) also attacks the U5 snRNP but through multiple mechanisms. In a follow-up study from global AS analysis in ReV-infected cells, Boudreault and colleagues show that the viral protein μ2 binds to and reduces the abundance of U5 snRNP proteins PRP8, SNRNP200, and EFTUD2 [102,168]. Interestingly, SNRNP200 has also been shown to be incorporated into HIV-1 virions [169]. Flaviviruses additionaly target U5 snRNP; EFTUD2 levels are decreased during HCV infection and DENV NS5 interacts with U5 snRNP proteins CD2BP2 and DDX23 to alter splicing of *ZNF35, CASP8,* and *MX1*, and *RIGI* [170,171]. Both the U4/U6 snRNP and U6 snRNA are also targeted by viral proteins [172–175]. Together, these studies indicate that viruses maintain a variety of mechanisms to interact with host snRNPs and effect AS.

Spliceosomal subcomplexes (Table 2), although not present for the entirety of the splicing reaction, are also integral for splicing. Virus products can interact with components of some of these complexes. In the context of FLUAV, the vRNP (3pol and NP) and NS1 have been most frequently identified as splice interactors. 3pol interacts with both RED and SMU1 components of the B-specific splice complex [176], and also interacts with the exon junction complex (EJC) component eIF4A3 [177]. Although in these scenarios host factor knockdown limits viral replication through diminishing viral splicing, these interactions also likely detract from normal host AS regulation. NP associates with PRP18 of the step II splicing factor complex and stimulates vRNA synthesis, but NP is also bound by IBC component PPIE to inhibit vRNP complex formation [178,179]. Additionally, NS1 associates with PRP19 and diminishes host AS [180]. Other viruses also interface with spliceosomal subcomplexes: human papillomavirus type 16 (HPV16) E7 binds NTR component SKIP, human T-lymphotropic virus (HTLV) Tax binds B^{act} protein SRRM2, and Herpesvirus saimiri (HVS) ORF57 binds EJC component MAGOH [181–183]. SRRM2 is also differentially phosphorylated upon HIV-1 receptor engagement, which is crucial for viral RNA splicing and replicative fitness [184]. Although these are numerous instances where viruses interfere with host spliceosomal components, these examples likely under-represent the complete swath of this interface.

4.3.2. Virus interface with SRSF and hnRNP splice regulatory factors

The splice regulatory factors from the SR and hnRNP families play a major role in exon choice by recognizing intronic and exonic splice enhancer and silencer sequences and coordinating downstream splicing. Pseudoexons, or appropriately-lengthed genomic stretches flanked by canonical splice sites, are predicted to outnumber real exons by an order of magnitude and nearly 15:1 in the human *HPRT* gene [187,188]. The mechanism by which eukaryotes differentiate real from pseudoexons is by additional exonic and intronic splice enhancer and silencer signals, all recognized by SR and hnRNPs, respectively [33]. During viral infection, differential levels, localization patterns, or posttranslational modifications of any of the SR and hnRNPs could result in broad changes to host AS. This is often achieved by viral proteins interacting with these host splice regulators, which can impact their normal function. Because SR and hnRNPs are RNA binding proteins, they are often associated with viral genomes or their intermediates. Fig. 2 and Table 3 show the SR and hnRNP proteins along with viruses that shift their function.

The SRSF family of proteins comprise 12 orthologs in humans that each contain one or two N-terminal RNA recognition motifs followed by serine/arginine dipeptides of at least 50 amino acids in length [33,189]. SR proteins are broadly characterized as splice enhancers that bind ESE and ISE sites on pre-mRNA, so viral perturbation could repress host splicing. Indeed, many dsDNA viruses interface with SR proteins particularly SRSF1–3, and infection often coincides with a reduction in host splicing. ICP27 from Marek's disease virus type-1 (MDV-1), for example, binds to SRSF proteins (either SRSF3–6) and inhibits splicing of viral vIL8 and host *chTERT* genes [190]. Alterations in the activity of SRSF1 (alias ASF/SF2) have been implicated in multiple dsDNA virus infections; SRSF1 is upregulated during HPV16 infection, and it interacts with EBV SM and BMLF1, Adenovirus (AdV) E4-ORF4, and Varicella Zoster virus (VZV) IE4 [191–195]. SRSF2 (alias SC-35) alterations have also been observed during viral infections, but interestingly, SRSF2 is often relocalized and its alterations generally correlate with reduced splicing. SRSF2 alterations has been attributed to the FLUAV NS1 protein, HVS ORF57, or HSV-1 ICP27 [130,159,196]. Lastly SRSF3 (alias SRp20) is also modulated during infection by either relocalization to virus-induced nodular structures during EBV infection or via Poliovirus (PV) 2A cleavage of Nups, or by interaction with EBV BMLF1, VZV IE4, Hepatitis B virus (HBV) HBx, or HSV-1 ICP27 [193,195,197–201]. The remaining SR proteins SRSF4–12 have been less commonly identified as impacted during viral infection, although SRSF4, SRSF7, and SRSF9 are interaction partners with some of the viral proteins above (Table 3).

Members of the hnRNP family of proteins were defined by their isolation properties as nuclear proteins that bind to nascent Pol II transcripts independent of other RNA-protein complexes [202]. In contrast to the SR proteins, hnRNPs are generally exonic splice repressors that act by binding to pre-mRNA ESS or ISS sites through their RNA recognition motifs (RRM, RGG, or KH domains) and recruiting homo or heterotypic protein interactions via their auxiliary domains containing acid-, glycine-, or proline-rich regions [33,203]. Like SR proteins, hnRNPs have commonly been identified as binding viral genomes or their intermediates, and nearly all members of both families were identified by ChiRP-MS during positive strand RNA virus infection (Table 3) [156–158]. Also like SR proteins, changes in hnRNP localization, abundance, or binding complexes mediated by viral infection or proteins can have major effects on host AS. Unlike SR proteins, however, the majority of hnRNP perturbations observed during virus infections thusfar have occurred during RNA virus infection, where most commonly the viral genome, replicase, or interferon-antagonizing proteins are involved [204]. hnRNP A1 is redistributed to the cytoplasm after infection with EV71, Sindbis virus (SINV), HIV-1, and Vesicular stomatitis virus (VSV), and in the case of the first three viruses is associated with vRNA [205–207]. hnRNP A2 also relocalizes to the cytoplasm upon infection, but this is driven by an interaction with the Japanese encephalitis virus (JEV) NS5a protein [208]. Viral proteins from FLUBV (NS1), PV (3CD), and HDV (S) all bind to hnRNP C, and its expression during the latter two infections enhances virus replication [209–211]. By contrast, hnRNP C plays an antiviral role during ReV infection, although viral NSP2 and NSP5, besides hnRNP C, also interact with antiviral hnRNP E1 and proviral hnRNP D, I, and L [212]. hnRNP AB is antiviral during FLUAV infection; the viral NP is bound by AB and viral mRNA export is inhibited [213]. hnRNP D (alias AUF1) interacts with viral RNA during EBV infection via EBER1 and PV or RV infection via the 5'UTR, although it is a target for degradation by the picornaviral 3CD protease [214,215]. 3CD also targets hnRNP E1 and E2 for

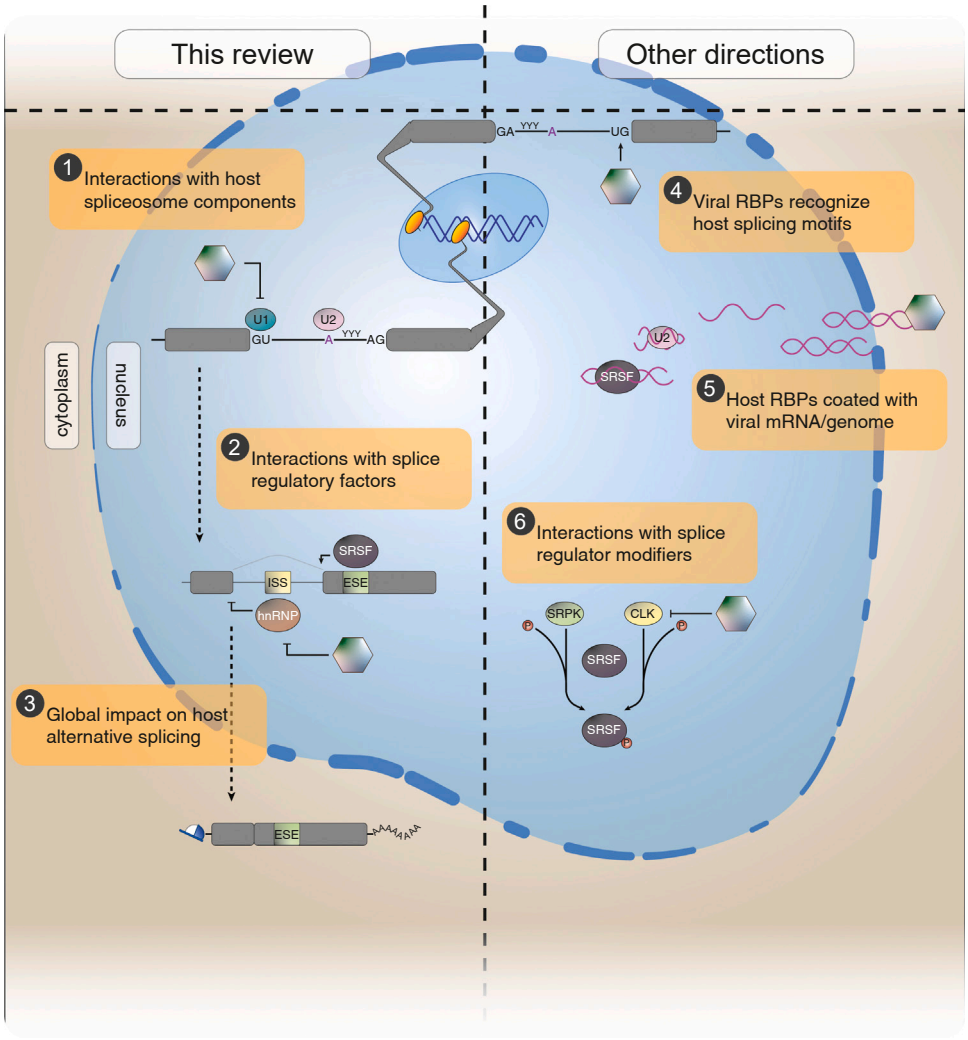

Fig. 3. Combinatorial impact on host gene expression by viral modulation of alternative splicing. The three major areas of literature covered in this review (*left*) focus on viral interface with the host spliceosome (**1**), splice regulatory factors (**2**), or transcriptome-wide studies of alternative splicing during viral infection (**3**). Viruses can also impact host splicing (*right*) by encoding RBPs that recognize host splice motifs (**4**), coating spliceosome or splice-regulatory factors with viral RNA products (**5**), or targeting the post-translational modifiers of splicing factors (**6**). Prismatic hexagon represents generic viral protein.

degradation, which leads to the switch of viral RNA translation to replication [216]. The protease of classical swine fever virus (CSFV) also interacts with hnRNP E1, although cleavage is not observed, and E1 serves a proviral role [217]. During infection with PRRSV, hnRNP F is relocalized and interacts with tandem G-tracts in the virus genome to stimulate virus infection [218]. VSV M and HCV Core proteins each bind to hnRNP H1, though the impact on virus infection was not addressed [219,220]. hnRNP K is relocalized to the cytoplasm and is proviral during FLUAV, DENV, or Junín virus (JUNV) infection, and has been shown to bind to FLUAV NS1 or SINV nsp7 [221–223]. hnRNP M has been shown to repress interferon-stimulated genes and interact with EBV EBNA5, relocalize during FLUAV infection, or be degraded by PV or Coxsackie virus B3 (CVB3) 3Cpro [224–227]. The hnRNP U group has been particularly targeted by FLUAV, where hnRNP U's antiviral function is antagonized by NS1 binding [228]. However, hnRNP UL1 is also bound by FLUAV NS1, and similarly by AdV E1B-55 K, which mediates a block in mRNA export, contrasting with PB2's observed interaction with hnRNP UL1 in a proviral manner [229–231]. These studies have shown that hnRNPs are differentially regulated during viral infection; future studies could benefit from an analysis of global splicing upon hnRNP or SRSF modulation in the absence of viral infection to isolate the role of infection on AS. By combining observations here and those discussed in Section ***4.1***, one can speculate whether viral protein interaction with or relocalization of specific hnRNP or SR proteins drives virus-induced AS.

5. Implications of AS on virus-host adaptation

Viruses vastly outpace their hosts in the speed of genomic replication. Paired with a substantially larger error rate during replication, especially for RNA viruses, spontaneous viral genomic mutations are continuously selected for should they carry advantageous properties. On the time scale of a single infection in vertebrate hosts, there is no opportunity for the host to counter viral adaptation with mutation of its own. However, along vertebrate evolutionary timescales, one can examine similar host species to identify genes that have undergone rapid evolution. Such iterative virus-host co-evolution is also known as the Red Queen hypothesis or a molecular arms race [234].

Enard and colleagues used the BUSTED algorithm to profile all human virus-interacting proteins for their propensity for rapid evolution, under the hypothesis that rapidly evolving genes may be viral targets [154,186]. Mapping these data points onto the genes within the spliceosome and the trans-acting regulators of splicing, most of these important regulators are very well conserved and undergoing purifying selection (BUSTED *P* value not significant; Tables 2 and 3). By contrast, the splicing factors that have BUSTED *P* values < 0.05 are rapidly evolving and are, at the time of this writing, almost all observed to be targeted by viruses as obtained from literature searches or from VirHostNet2.0 [155]. The major exceptions are spliceosome components *CWC22* and *BUD13*. Interestingly, BUD13 has been shown to repress intron retention of the interferon potentiating transcription factor *Irf7*, suggesting *BUD13* adaptation may be selected for by pathogen

infections [235]. This suggests that despite broad conservation of most splicing factors, virus interaction may drive evolution of these otherwise stable genes. Furthermore, it implies that genes with signatures of adaptation are worth future study in the context of virus infection.

Species-specific splicing events impact permissivity of viruses between hosts. For example, avian-adapted FLUAV 3pol is effectively non-functional in mammalian hosts due to the absence of an exonic insertion event [236]. However, not all birds equivalently splice this inserted exon, and we showed that alternative 3' splice site usage or cassette exon propensities across diverse birds differ and have dramatic impact on 3pol function [237]. It was then shown experimentally that specific splice isoforms can drive viral polymerases selection, and that in some birds SRSF10 controls this splice site usage [238,239]. The battle between SIV-like viruses and their primate hosts is the quintessential battlefront of molecular arms races [234], and these co-evolutionary struggles can also involve changes in host splicing. For example, Northern pig-tailed macaques contain an insertion in the antiviral gene *APOBEC3G* that introduces AS events and decreases function [240]. Additionally, the antiviral restriction factor TRIMCyp, a fusion protein that tethers the capsid-binding property of a retrotranspositionally inserted *CypA* to the effector activity of *TRIM5*, inhibits retroviruses in some primates [241]. Different primates create the TRIMCyp fusion through different ways, but it was shown that pig-tailed macaques have a mutation in a *TRIM5* consensus 3' splice site that leads to downstream fusion to CypA [242]. Notably only a subpopulation of the screened rhesus macaques contained this mutation, suggesting population-level heterogeneity of splicing could bolster antiviral defense.

Human genetic variation can often manifest as diseases caused by mis-splicing events [243,244]. Mutations in consensus splice sequences in antiviral proteins could similarly have a detrimental effect. The enzyme OAS1 plays a key role in cellular antiviral defense. OAS1 AS variants possess variable activity, which are present in humans due to single nucleotide polymorphisms [245–247]. Indeed it was shown that humans with OAS1 splice variants were more susceptible to severe COVID-19 caused by SARS-CoV-2 [248]. These examples highlight the importance of studying population-level AS variance in host genes involved in viral infection, with potential impact on species adaptation and antiviral factor selection.

6. Conclusions and perspectives

Viral genomes are a fraction the size of their hosts, yet they have found myriad ways to globally impact cellular homeostasis for selfish gain. Alternative splicing is a fixed feature of vertebrate host transcription, providing vast proteomic complexity through combinatorial assembling of unique isoforms under different stimuli. By tapping into this cascading network, viruses can encode factors of limited size that unleash profound host expression changes. The research covered in this review demonstrates the wealth of knowledge on viruses targeting central splicing factors and the increasing interest in profiling global AS. However, the full dynamics of virus infection and host splicing remains incompletely understood. Most pressing from a pandemic preparedness perspective, there is a gap in understanding how host-specific alternative splicing shapes protein-protein interfaces during zoonotic virus infections. Regardless of vertebrate host species, triggering innate immunity upregulates many conserved interferon stimulated genes, and focusing on interferon-regulated RBPs may prove fertile ground for understanding virus-induced AS. Another major shortcoming at this time lies in linking observed interactions, localization changes, and abundance differences of critical spliceosome or splice regulatory proteins in the face of viral proteins with global impact on host AS. This may be complicated by the recent advances in understanding disordered regions and their propensity to drive macromolecular complexes through phase separation since nearly all SRSF and hnRNP proteins may contain such characteristics (Fig. 2) [21]. In the near-term, it will be crucial to fully characterize how viral infection modulates SRSF and hnRNP kinases (SRPKs and CLKs) since transient and reversible post-translational modification can drive a multitude of effects (Fig. 3). Similarly, post-transcriptional modification may be a transient virus-induced switch that changes the fate of transcript splicing [128].

Taking an evolutionary perspective on virus-host interactions has been helpful in identifying protein:protein interfaces that are locked in a co-evolutionary struggle [234]. Might such an approach prove helpful for understanding the virus:splicing interface? Computational methods to discover rapid evolution rely on the degeneracy of codons to enumerate mutation rates that create non-synonymous (dN) changes relative to synonymous (dS) codon changes [249]. Without a denominator for dN/dS calculations, it is difficult to propose evolutionary adaptation at consensus splice motifs in non-coding introns. However, some central splicing proteins are indeed undergoing rapid evolution (Tables 2 and 3) providing evidence for host-parasite battles throughout evolutionary history. It remains to be observed if specific viral proteins will map to the rapidly evolving interfaces in these splice proteins, which could be a critical model system to further study adaptation at the virus:splicing interface. Regardless of approach, it is clear that virus interaction with host splicing is a convergent strategy that results in dramatic network-wide changes in host transcription, which could be targeted in the future for therapeutic and preventative strategies.

Declarations of interest

None.

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