



Shaping the Innate Immune Response Through Post-Transcriptional Regulation of Gene Expression Mediated by RNA-Binding Proteins

Anissa Guillemain¹, Anuj Kumar², Mélanie Wencker^{1,3} and Emiliano P. Ricci^{1*}

¹ LBMC, Laboratoire de Biologie et Modélisation de la Cellule, Université de Lyon, ENS de Lyon, Université Claude Bernard Lyon 1, CNRS, UMR 5239, INSERM, U1293, Lyon, France, ² CRCL, Centre de Recherche en Cancérologie de Lyon, INSERM U1052, CNRS UMR 5286, Lyon, France, ³ CIRI, Centre International de Recherche en Infectiologie, Université de Lyon, ENS de Lyon, CNRS, UMR 5308, INSERM, Lyon, France

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*Correspondence:

Emiliano P. Ricci
emiliano.ricci@ens-lyon.org

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Innate immunity is the frontline of defense against infections and tissue damage. It is a fast and semi-specific response involving a myriad of processes essential for protecting the organism. These reactions promote the clearance of danger by activating, among others, an inflammatory response, the complement cascade and by recruiting the adaptive immunity. Any disequilibrium in this functional balance can lead to either inflammation-mediated tissue damage or defense inefficiency. A dynamic and coordinated gene expression program lies at the heart of the innate immune response. This expression program varies depending on the cell-type and the specific danger signal encountered by the cell and involves multiple layers of regulation. While these are achieved mainly *via* transcriptional control of gene expression, numerous post-transcriptional regulatory pathways involving RNA-binding proteins (RBPs) and other effectors play a critical role in its fine-tuning. Alternative splicing, translational control and mRNA stability have been shown to be tightly regulated during the innate immune response and participate in modulating gene expression in a global or gene specific manner. More recently, microRNAs assisting RBPs and post-transcriptional modification of RNA bases are also emerging as essential players of the innate immune process. In this review, we highlight the numerous roles played by specific RNA-binding effectors in mediating post-transcriptional control of gene expression to shape innate immunity.

Keywords: innate immunity, RNA-binding proteins, RNA, virus, immune cells, post-transcriptional regulation, inflammation, pathogen

1 INTRODUCTION

Host's defense mechanisms form a complex interplay between molecular and cellular actors and require a plethora of processes to detect and eliminate pathogens or damage, such as loss of tissue integrity, irritants, or cancer. While infection or damage generally occur at barrier sites (at the interface between internal and external milieu), local cells are prone to rapidly sense any tissue dysregulation and to send signals of danger that initiate the innate arm of immune responses. Local

cellular sensors include epithelial cells, stromal cells and fibroblasts, whose role will be essential when being the initial target of infection (in case of strictly intracellular pathogens) or injury (1–4). In addition, resident immune cells, such as macrophages and dendritic cells (DC), if not directly affected, will be able to detect microbial components within the environment, or capture damaged cellular material leading to their subsequent activation (5). Sensing of damage leads to a cascade of events that generate a local inflammation, thus allowing the recruitment of circulating innate cells (e.g. neutrophils or circulating monocytes/macrophages), phagocytosis of infected/damaged cells and antigen presentation to T- and B- lymphocytes, the adaptive arm of immune response. In that regard, innate immune responses are crucial for the generation of a robust, antigen-specific adaptive response, and the maintenance of memory (6, 7).

At the molecular level, innate responses thus start with the recognition of danger. This is allowed by the expression of a set of receptors, called Pattern Recognition Receptors (PRRs), each being specific for classes of molecules known as Pathogen Associated Molecular Patterns (PAMPs) or Damage Associated Molecular Pattern (DAMPs) (8). Essentially all cells express a set of PRRs, the most common families being Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs) or cGAS (9). PRRs can be discriminated according to their specificity (e.g. double-stranded (ds) or single-stranded (ss) RNA, dsDNA, peptides...), or their location (e.g. cytosol, mitochondria, extracellular domains). Upon ligand binding, each family of PRRs recruits a specific adaptor such as myeloid differentiation primary response 88 (MyD88), mitochondrial antiviral signaling protein (MAVS) or stimulator of interferon genes (STING) for TLRs, RLRs or cGAS, respectively (**Figure 1A**). This initiates a signaling cascade, mostly involving IRF3/7, MAPK and NF κ B pathways, ultimately leading to the expression of type I and III IFN (10, 11) and/or the secretion of cytokines, that orchestrate the various events happening during the inflammation process (12, 13), or chemokines, that will attract immune cells to the affected tissue. Depending on many parameters such as the nature of the activating signals or the timing, cytokines produced are either pro-inflammatory (e.g. TNF- α , IL-6, IL-1 β , etc...), or anti-inflammatory (e.g. IL-4, IL-10, IL-13, IFN- α , etc...) (14, 15), even though this dichotomy has been shown to be realistically less simple (16).

Altogether, innate immunity plays an essential role during immune responses: guardian of tissue integrity, local cells act as a communication platform to detect, alert and, at least partially, eliminate infection or damage. However, the complex underlying program of innate responses has to be tightly regulated to avoid any hazardous effect. Indeed, overexpression of inflammatory components can damage the host (e.g. intolerance, auto-immunity), whereas their under-expression leads to an inefficient defense strategy (17, 18). This highlights the necessity of a rapid and efficient innate response, balanced with appropriate transcriptional and post-transcriptional regulations that finely tune the underlying gene expression program. While transcriptional regulation clearly plays a major

role during inflammation and has been widely studied as a model for cell stimulation (19, 20), post-transcriptional control more recently emerged as indispensable to properly tune the innate response (21–23).

RNA-Binding Proteins (RBPs) are key effectors of post-transcriptional regulatory processes (24–26) by targeting specific sequences, structures or post-transcriptional chemical modifications occurring on RNA bases, such as N⁶-methyladenosine (m⁶A). Altogether, RBPs act at all steps of the life of RNAs: pre-RNA processing (5' RNA capping, splicing, polyadenylation and base editing), mRNA transport, ribosome biogenesis, translation, and finally RNA decay (27–29). In line with this, recent system-wide analyses have revealed the importance of the RNA binding proteome (RBPome) during viral infections (30, 31) and activation of cells of the innate immune system (32). More recently, the global analysis of RNA-protein interactome has shown that a third of the RBPome is remodeled upon SARS-COV-2 infection in human cells, highlighting the importance of targeting RBPs for therapeutic strategies against COVID-19 (33, 34).

Here, we review the multiple roles played by RBPs in shaping the innate immune response, from pathogen and danger detection to the regulation of signal transduction and effector functions.

2 TECHNICAL APPROACHES TO STUDY RBPs

Advances in mass-spectrometry and high-throughput sequencing have substantially increased the list of cellular proteins which are known to interact with RNAs and allowed, for many of them, to identify their precise RNA binding sites. Depending on the biological questions to be addressed, RBP's studies can be performed *via* RNA-centric or protein-centric methods (35). One way to capture protein/RNA interactions is through cross-linking, which creates a covalent bond between the RNA molecule and its associated protein. Different RNA-Protein cross-linking methods exist, each with its own benefits and limitations. In order to identify proteins that interact directly with RNA, irradiation of cells with ultraviolet (UV) light (254nm) is the most commonly used approach, since it irreversibly cross-links amino acid residues to nucleic-acids, without inducing protein-protein covalent bonds. Additionally, the covalent bond created between the amino-acids and RNA bases can provide information related to precise binding site at single-nucleotide resolution (36). However, the efficiency of UV-crosslinking can differ depending on the nature of the amino acids involved in the interaction with RNA bases (37). Furthermore, RBPs that bind to dsRNA structures have been shown to cross-link poorly when exposed to UV radiation due to low accessibility of the RNA bases to the amino acids residues involved in RNA binding (38, 39). Finally, the overall efficiency of RNA/protein cross-linking induced by 254nm UV light is relatively low (5%) (40, 41) and UV light does not penetrate complex tissues or liquid cultures very efficiently, thus limiting its

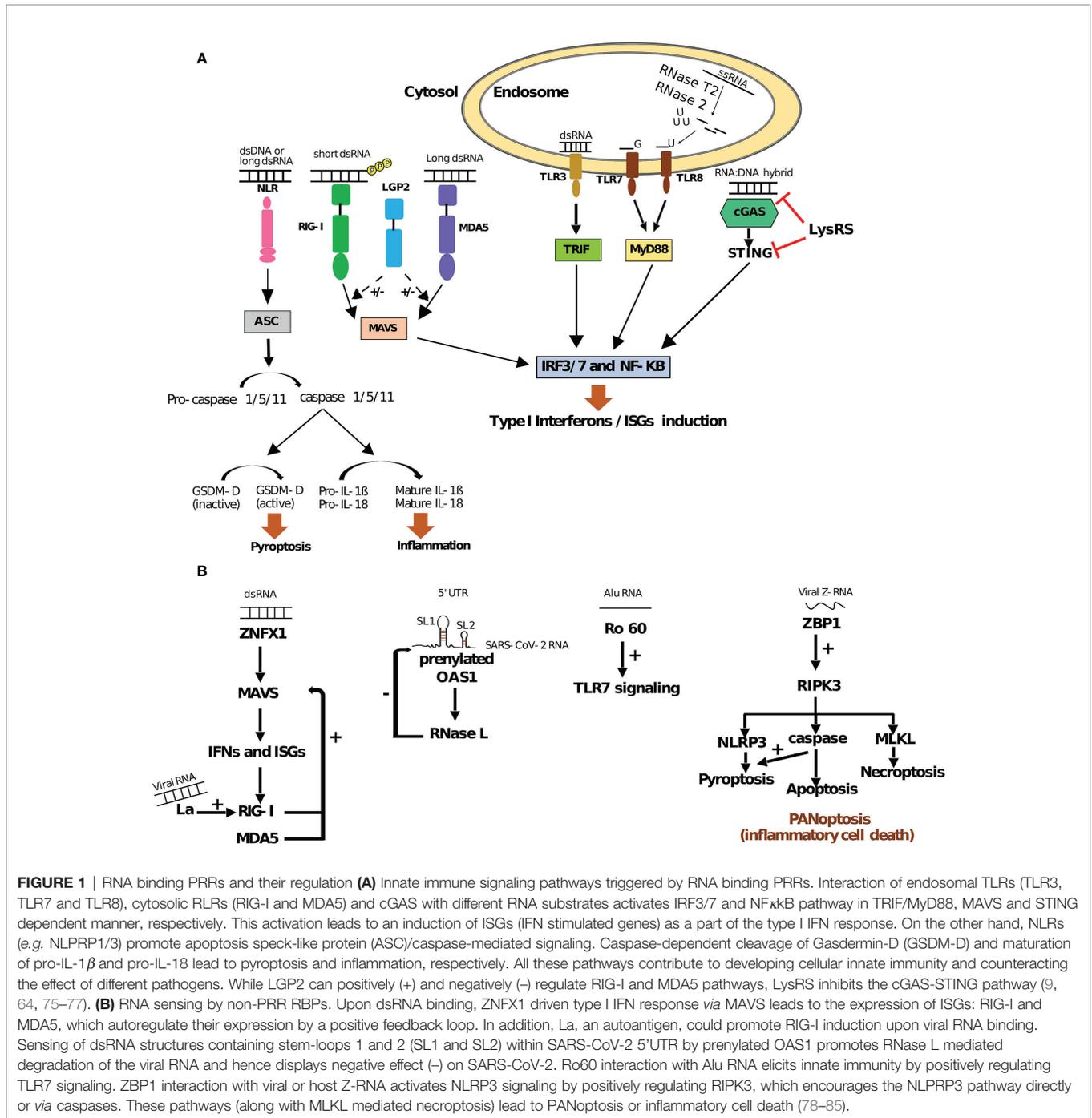


FIGURE 1 | RNA binding PRRs and their regulation (A) Innate immune signaling pathways triggered by RNA binding PRRs. Interaction of endosomal TLRs (TLR3, TLR7 and TLR8), cytosolic NLRs (RIG-I and MDA5) and cGAS with different RNA substrates activates IRF3/7 and NF κ B pathway in TRIF/MyD88, MAVS and STING dependent manner, respectively. This activation leads to an induction of ISGs (IFN stimulated genes) as a part of the type I IFN response. On the other hand, NLRs (e.g. NLPRP1/3) promote apoptosis speck-like protein (ASC)/caspase-mediated signaling. Caspase-dependent cleavage of Gasdermin-D (GSDM-D) and maturation of pro-IL-1 β and pro-IL-18 lead to pyroptosis and inflammation, respectively. All these pathways contribute to developing cellular innate immunity and counteracting the effect of different pathogens. While LGP2 can positively (+) and negatively (-) regulate RIG-I and MDA5 pathways, LysRS inhibits the cGAS-STING pathway (9, 64, 75–77). **(B)** RNA sensing by non-PRR RBPs. Upon dsRNA binding, ZNFX1 driven type I IFN response via MAVS leads to the expression of ISGs: RIG-I and MDA5, which autoregulate their expression by a positive feedback loop. In addition, La, an autoantigen, could promote RIG-I induction upon viral RNA binding. Sensing of dsRNA structures containing stem-loops 1 and 2 (SL1 and SL2) within SARS-CoV-2 5'UTR by prenylated OAS1 promotes RNase L mediated degradation of the viral RNA and hence displays negative effect (-) on SARS-CoV-2. Ro60 interaction with Alu RNA elicits innate immunity by positively regulating TLR7 signaling. ZBP1 interaction with viral or host Z-RNA activates NLRP3 signaling by positively regulating RIPK3, which encourages the NLPRP3 pathway directly or via caspases. These pathways (along with MLKL mediated necroptosis) lead to PANoptosis or inflammatory cell death (78–85).

use to cell monolayers or requiring dissociation of the tissue prior to UV irradiation (42). Some of the drawbacks of classical 254nm UV cross-linking can be overcome by the use of photoreactive ribonucleoside analogs 4-thiouridine (4SU), or 6-thioguanosine (6-SG). These ribonucleoside analogs are fed to cultured cells, incorporate into nascent transcripts and allow more efficient cross-linking of RNA to proteins following irradiation with long-wavelength UV light (365nm) that also penetrates samples more efficiently than the commonly used short-wavelength UVs (28). Moreover, this method, known as Photoactivatable-

Ribonucleoside-Enhanced Crosslinking (PAR-CL), is also able to score the transitions from thymidine (T) to cytidine (C) that occur at cross-linking sites upon reverse-transcription, which are used to identify precisely the RBP binding sites (43). Methylene blue can be an efficient alternative to UV irradiation when studying dsRBPs. It intercalates between RNA bases of a dsRNA structure and allow efficient dsRBP/RNA crosslinking through visible light, thus overcoming the poor cross-linking activity of UV (38, 44). Formaldehyde can also be used to cross-link single-strand and double-strand RBPs to their RNA targets

(39, 45–48). It also has the advantage to be reversible upon incubation of samples at high temperature, which can facilitate RNA recovery and downstream processing such as reverse-transcription. However, formaldehyde cross-linking is not restricted to RNA/proteins but also generates covalent bonds between proteins. As a consequence, ribonucleoprotein complexes can be cross-linked together, therefore making it impossible to discriminate between direct RBPs and non-RBPs that interact indirectly with RNA. Nevertheless, this drawback has been useful in determining the target sites of closely related RNP complexes such as different sub-types of the exon-junction complex (49).

Upon cross-linking, RNA-centric protocols rely on the purification of poly(A) mRNAs (corresponding to protein coding RNAs) (50), total RNA (that gives information on all RNAs including mRNAs and non-coding RNAs such as ribosomal RNA and microRNAs among other) (51), or specific RNA species (52). The RNA purification step is then followed by the identification and quantification of RBPs that were bound to the purified RNAs by mass spectrometry or western-blotting (53). Variations of these protocols combined with purification of poly(A) mRNAs with partial protease treatment have also enabled the characterization of the protein domains that are involved in RNA recognition (54). Altogether, these protocols have allowed the unbiased identification of RBPs in a wide-variety of organisms and biological contexts, but also of new types of RNA recognition domains within RBPs (55, 56). They have also been used to characterize the dynamics of RBP binding to RNA during a wide range of physiological and pathological processes (31, 32). For instance, comparison of the RBPome between resting and LPS-stimulated macrophages uncovered 91 RBPs not previously annotated to interact with RNA. Among identified RBPs, many displayed changes in their RNA-binding capacity upon LPS-stimulation (32). These include the HSP90 co-chaperone P23, which interacts with the mRNA coding for Kinesin 15 (KIF15) (32, 57). Upon macrophage activation, P23 binding to Kif15 mRNA decreases, leading to mRNA destabilization and down-regulation of KIF15 protein abundance, which stimulates macrophage migration (57).

In contrast to RNA-centric approaches, protein centric methods rely on the immuno-purification of a specific RNA-binding protein upon cross-linking (also known as cross-linking immuno-purification or CLIP) followed by RNA-sequencing in order to identify the RNA species bound to the RBP of interest. One can access to the precise RNA sequence where the RBP is binding by coupling immuno-purification with a RNase treatment and small-RNA sequencing (58). Several protocols exist, relying on UV or formaldehyde cross-linking, that allow either the characterization of the RNA-binding sites of isolated RBPs or protein complexes with RNA-binding capacity. Among these protocols, those relying on short and long wave UV crosslinking [such as iCLIP (59), eCLIP (60) and PAR-CLIP (43)] are largely the most frequently used in the literature thanks to their single-nucleotide resolution, availability of commercial kits for sample

preparation and development of many data analysis pipelines [some with intuitive graphic user interfaces (61)] that facilitate processing of the sequencing results for non-experts. Furthermore, UV-based CLIP-seq protocols [specifically eCLIP (60)] concentrate most of the efforts made by the Encyclopedia of DNA Elements (ENCODE) project to provide large-scale characterization of the RNA binding sites of hundreds of RBPs in a robust and reproducible manner, providing the scientific community with homogeneous datasets that can be compared across different RBPs and cell types (62). More recently, a CLIP-seq protocol using short laser pulses of UV-light through different time lengths has been able to uncover the *in vitro* kinetics of binding and dissociation of the RBP DAZL to a thousands of RNA targets (e.g. Thbs1 transcript) in a transcriptome-wide manner (63). Once applied to other RBPs, such a protocol could greatly improve our understanding of the biological roles of RBPs and the regulation of their binding and functional activity on their target RNAs.

Altogether, RNA-centric and protein-centric protocols have greatly participated in our understanding of RBPs and their functional role in a myriad of different cellular processes including the innate immune response.

3 RNA SENSING BY CANONICAL PRRs AND OTHER RBPs

While RNAs are essential components of cellular functions, they can also generate protective immune responses as it has been largely described following infection with RNA viruses (e.g. Influenza, SARS, Hepatitis, Measles, *etc.*). Although sensing of foreign RNA leads to a substantial and rapid antiviral response, it must be tightly controlled in order to avoid hazardous effects [for extensive review, see (64)]. Similarly, inappropriate host RNA recognition can also occur during several processes such as apoptosis (65) or cancer progression (66), leading to uncontrolled immune responses and/or auto-immunity. The capacity to discriminate between host and foreign RNAs is therefore essential to avoid unsuitable immune responses. PRRs that are specific for RNA components are well-known actors of innate immunity, especially in response to viral infections. They represent, as such, prototypic RBPs. However, several non-canonical PRR RBPs have been recently shown to participate in the sensing and/or regulation of RNA sensing and to have a significant role in modulating innate immunity, as examined below.

3.1 RNA Sensing by Canonical PRRs

Foreign RNAs can display specific features that distinguish them from endogenous RNAs and allow them to trigger an immune response through sensing by PRRs. These features can be linked to their structure, nucleotide composition and chemical modifications, or their subcellular location.

TLR3 was the first PRR described to interact with foreign RNA (67). Among all TLRs, TLR3, TLR7 and TLR8 are able to

recognize RNA substrates under different forms: TLR3 can recognize long dsRNAs, as well as short dsRNAs and structured ssRNAs (>35bp) (68, 69), while TLR7 and TLR8 rely on leucine-rich repeats to detect GU-rich ssRNA species (70) but also by-products of ssRNA degradation including endogenous microRNAs and exogenous siRNAs (71–73). TLR3/7/8 are transmembrane proteins localized within endosomal compartments. RNA sensing through these TLRs therefore requires uptake and endocytosis of extracellular RNAs which generally occurs during viral infection or phagocytosis of necrotic/apoptotic cells (67, 74). This allows a spatial compartmentalization of RNA-binding to TLRs, to avoid any activation by host cell RNAs. Upon activation of TLRs, Toll/IL-1 receptor (TIR) domain-containing adaptor inducing interferon- β (TRIF)-dependent pathway is activated, leading to the phosphorylation of transcription factors such as IFN regulatory factor 3 (IRF3) and IRF7 and their subsequent nuclear translocation. IRF3/7 thus turn on the antiviral response in infected host cells, through specific transactivation of type I IFN genes (see **Figure 1A**). In addition, both TLR7 and TLR8 contain two binding sites that synergize to induce TLR dimerization and activation. One binding site is for small ligands (including guanosine for TLR7 and uridine for TLR8) and one for short oligonucleotides (73, 86). For TLR8, the generation of those specific ligands requires both the endolysosomal endonucleases RNase T2 and RNase 2, each cleaving ssRNA upstream and downstream of uridines, respectively, to generate free uridine and short RNA oligonucleotides (71, 87). For TLR7, the source of guanosine and short nucleotides required for its activation are less well-characterized. RNase T2 is seemingly required for activation of TLR7 in macrophages (88) and crystallography studies suggest that successive U-containing ssRNA sequences are required for full binding to TLR7 (89). Studies in macrophages moreover suggested that accumulation of nucleosides in the lysosomal compartment upon inactivation of the lysosomal transmembrane protein SLC29A3 (a nucleoside transporter from lysosomes to the cytoplasm) leads to TLR7 activation following phagocytosis of necrotic cells (90). Interestingly, in monocytes, macrophages, and dendritic cells, the accumulation of nucleosides within lysosomes is responsible for inflammatory disorders like histiocytosis, further emphasizing the importance of a tight control of RNA mediated TLR activation (91).

Unlike TLRs, whose expression depends on TLR subtype and cellular subset, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are expressed in most cell types. Located in the cytosol, members of the RLR family include RIG-I, the melanoma differentiation-associated protein 5 (MDA5) and the laboratory of genetics and physiology 2 (LGP2) factors. All three RLRs share a central ATP-dependent helicase domain and a carboxy-terminal domain (CTD), both domains displaying RNA-binding activity. RIG-I and MDA5, but not LGP2, have two additional caspase activation and recruitment domains (CARDs) that are essential for downstream signal transduction through MAVS, upon RNA binding. RIG-I recognizes short dsRNA structures bearing a triphosphate or diphosphate group

at their 5' end (5'-PPP or 5'-PP) (92–94) and lacking a methyl group at the 2'-O position of the 5' terminal nucleotide (95). These structural features, present in many viral RNAs, but generally absent in endogenous cytosolic RNAs, allow RIG-I to discriminate between self and non-self RNAs. MDA5 on the other hand preferentially binds long dsRNAs molecules (including the synthetic poly(I:C) molecule), as shown by several reports (96–98).

However as opposed to RIG-I, the molecular determinants of MDA5 binding to foreign RNAs are less well understood. The presence of higher order RNA structures (combination of single-stranded and double-stranded RNA structures) appears to be important (97), as well as AU-rich sequences, although not specifically under the form of RNA duplex structures (99). Upon recognition of its target RNA, MDA5 oligomerizes into filaments in a cooperative manner and the CARDs domains allow the nucleation of MAVS leading to its activation (100). Interestingly, the ATP hydrolysis activity of MDA5 is stimulated by dsRNA binding and favors the dissociation of MDA5 at a rate that is inversely proportional to the length of the dsRNA substrate. This could explain the length requirement for dsRNAs to trigger MDA5-dependent signaling (101). Finally, the third member of the RLR family, LGP2, displays RNA-binding activity but lacks the CARDs domains required for downstream signal transduction. LGP2 recently emerged as both a positive and a negative regulator of RIG-I and MDA5 activities [for a recent review, see (75)], as supported by the fact that LGP2 deficient mice display disparate susceptibility to infection with RNA viruses (see **Figure 1A**) (102).

Finally, inflammasome-forming nucleotide-binding domain leucine-rich repeat (NLR) proteins are a group of cytosolic PRRs that assemble inflammasome in response to PAMP and DAMPs. Briefly, inflammatory ligand recognition by NLR leads to the recruitment of the apoptosis speck-like protein (ASC) adaptor, allowing the activation of caspase-1. Caspase-1 dependent cleavage of both Gasdermin-D and pro-IL-1 β or pro-IL-18, further induces cell death by pyroptosis or inflammation, respectively [**Figure 1A**, for a review, see (103)]. NLRs may rely on other PRRs and RBPs to trigger inflammasome activation and, for some of them, direct ligands remain to be characterized. For example, NLRP1 (nucleotide-binding domain leucine-rich repeat protein 1), was one of the first inflammasome-forming PRRs to be identified but its role in pathogen defense and its direct ligands were poorly understood. However, a recent report has shown that human NLRP1 can bind both dsDNA and dsRNA through its leucine-rich repeat domain, but only long dsRNAs [including poly(I:C)] are able to trigger NLRP1 activation (104). Interestingly, in several cell lines and primary cells tested (including primary human epidermal keratinocytes and immortalized human HBEC3-KT bronchial epithelial cells), the sensing of poly(I:C) or infection with Semliki Forest Virus (a positive-strand RNA virus) and its effect on cell viability are fully dependent on NLRP1 expression thus suggesting a non-redundant role of this NLR in sensing dsRNA and triggering activation of the inflammasome (104).

3.2 RNA Sensing and Regulation of PRR Activity by Non-PRR RBPs

PRRs are receptors of host defense mechanism that identify pathogens by sensing specific patterns (9). In addition to the layer that relies on canonical RNA-binding PRRs, numerous RBPs, that are not necessarily specific to immune cells, can interact with a large variety of RNAs in order to directly trigger an innate immune response or modulate the activity of canonical PRRs (see **Figure 1B**).

ZNFX1 (zinc finger NFX1-type containing 1) is a member of the helicase superfamily 1 (SF1) localized in the outer membrane of the mitochondria. Similar to RIG-I and MDA5, ZNFX1 can bind viral dsRNAs and interacts with MAVS, in order to promote IFN expression and IFN-stimulated genes (ISGs) (see **Figure 1B**) (78). However, ZNFX1 appears as an early sensor of dsRNA: as opposed to RIG-I and MDA5 whose expression and mitochondrial translocation is induced only following viral infection, ZNFX1 is constitutively localized within mitochondria and its expression, further increased by viral infection, reaches a peak much earlier than RIG-I and MDA5. ZNFX1 has further been shown to enhance the expression of RLRs, therefore priming the subsequent antiviral defense (78). As a consequence, mice deficient for ZNFX1 show increased susceptibility to viral infection (78) and those results have been recently confirmed in human with biallelic ZNFX1 deficiencies (105). Thus, ZNFX1 is seen as an early sensor for viral RNAs able to trigger a rapid antiviral response in two different manners: directly through IFN signaling pathway and indirectly through RLRs activation. Interestingly, deficiencies in ZNFX1 are also associated with uncontrolled inflammation following viral infection, in both humans and mice. Although the underlying mechanisms will need further investigation, it highlights the importance of a timely tune innate response, allowing proper elimination of viral spread, while preventing over inflammation. Another recent study involving an ISGs expression screening, has revealed that OAS1 (2'-5'-Oligoadenylate Synthetase 1), a dsRNA sensor, is able to inhibit SARS-CoV-2 through the action of RNase L (see **Figure 1B**) (80). Indeed, by performing iCLIP against OAS1, infection by SARS-CoV-2 was shown to enhance the RNA-binding activity of OAS1, which interacts primarily with highly structured host RNAs (e.g. snoRNAs, lncRNAs, intronic regions of mRNAs) as well as with specific stem loops (SL1 and SL2) located within the first 54 nucleotides of the 5'UTR of all positive-sense SARS-CoV-2 RNAs (80, 106). Importantly, the sensing of SARS-CoV-2 RNAs is dependent on the C-terminal prenylation of OAS1 (addition of hydrophobic molecules) (80), that leads at its translocation to membranous viral replicative organelles (107). The binding of SARS-CoV-2 dsRNAs by OAS1 activates RNase L, which in turn initiates the cleavage of viral and host RNAs harboring single-stranded UpU and UpA motifs (108).

In addition to dsRNA sensing in the cytoplasm, RBPs that are non-canonical PRRs can also act as sensors within the nucleus and potentiate robust immune responses. For instance, a nuclear matrix protein hnRNP U (also known as SAFA for scaffold attachment factor A) directly binds nuclear viral RNAs from DNA and RNA

viruses (109). The infection of mouse Bone Marrow-Derived macrophages (BMDMs) by HSV-1, a DNA virus, or by Vesicular Stomatitis Virus (VSV), a ssRNA virus, induced their recognition by hnRNP U in the nucleus. This sensing triggers its oligomerization, inducing its interaction with chromatin remodelers such as the DNA topoisomerase 1 (TOP1) and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5 (SMARCA5). This further activates distal and proximal enhancers of type I IFN and other host defense genes (e.g. Oasl1, IL-15, CXCL10, Irf1), therefore promoting robust antiviral responses (109). Thus, with its dual function as a viral RNA sensor and a transcriptional regulator, hnRNP U in the nucleus is an advantage against virus evasion strategy.

More recently, the role of the DEAD-box (Asp-Glu-Ala-Asp motif) or DEAH-box (Asp-Glu-Ala-His motif) helicase proteins during innate immune sensing has emerged in the literature [for a more detailed review, see (110)], with promising contribution in treatment of infectious diseases. They are categorized into two groups, based on their activity: (i) those which directly act as RNA sensors, independently of PRRs such as DDX1 or DHX9, and (ii) those which act as co-sensors of RLRs and NLRs, thus improving their activation such as DDX3 or DDX60. For instance, the first category involves proteins able to bind dsRNA. This is exemplified by DDX1, DHX9 and DHX33 that have been shown to directly interact with poly(I:C) or dsRNA from viruses such as Influenza A or reovirus, in myeloid DCs (111, 112). Thus, sensing by DDX1, DHX9 or DHX33 directly induces the production of IFN- α/β and/or pro-inflammatory cytokines responses, *via* MAVS (DHX9, DHX33) or TRIF (DDX1), independently of canonical PRRs. In addition, DHX9 (in murine intestinal cells) and DHX33 (in THP-1 macrophages cell line) are able to sense RNA and trigger NLRP9 and NLRP3 inflammasome, respectively (113, 114). The second category includes co-sensors such as DDX3 or DDX60. While DDX3 can directly associate with poly(I:C), it also form a complex with MAVS and RLRs to potentiate type I IFN responses, following stimulation (115). Similarly DDX60 interacts with RLRs to promote their downstream signaling (116).

Similarly, viral RNAs sensing are also modulated by several autoantigens such as La/SS-B (La). La has been recently shown to directly bind RIG-I once bound to a viral dsRNA (79), resulting in strengthened interaction between RIG-I and its RNA ligand and eventually empowered RIG-I-mediated type I and type III IFN production. In addition, La also promotes the activation of MAVS, a mitochondrial-associated adaptor downstream of RIG-I (79) (**Figure 1B**). Indeed, RNA recognition results in RIG-I exposing its activator CARD domains, which in turn binds the CARD domain of MAVS (117). The activation of MAVS leads to the formation of a complex with two other proteins (CARD9 and BCL-10) that eventually turn on the NF κ B signaling pathway (118). Therefore, upon infection, La reinforces the activation of MAVS through RIG-I and empowers the immune response. By contrast, Ro60, another viral RNA binding autoantigen, is known to negatively regulate the inflammatory response by buffering the recognition of viral RNAs by RNA sensors. Ro60 is a component of a ribonucleoprotein complex that targets misfolded cellular

RNAs (potentially foreign RNAs) for destruction, thus slowing down their detection by immune RNA sensors and delaying the alarm signal (81).

In addition to directly sensing or potentiating detection of viral RNAs, RBPs also modulate immune responses through the direct recognition of endogenous RNAs (119–122). This is for example the case for Alu transposable elements (TEs), which account for over 10% of the human genome (123, 124). Alu elements belong to the Short interspersed nuclear element (SINE) family of transposable elements (125). They are primate specific repeat sequences of around 280bp long, that can be found in intergenic regions but also embedded within introns and exons of protein coding genes and expressed together with the gene in which they are integrated. Functional Alu elements can be transcribed from their own promoter by RNA polymerase III and depend on the reverse transcriptase activity of the ORFp2 protein from LINE-1 elements to reverse transcribe and integrate into new genomic loci (125). Transcribed Alu elements can bind several cellular RBPs such as Ro60, which negatively regulates their abundance (81). In HeLa cells, infection with adenovirus type 5 and herpes simplex virus type 1 have been described to activate RNA polymerase III-dependent transcription of Alu TEs (122, 126). Alu TE are also strongly transcribed upon exposure to type I IFN and pro-inflammatory cytokines, both from their own promoter and as part of induced gene transcripts with embedded Alu elements (127). Interestingly, the high abundance of Alu transcripts induced upon IFN exposure has been shown to saturate Ro60 and allow their recognition by TLR7, to further amplify the IFN response through classical signaling pathways (MAPK, NF κ B) (81, 128) (**Figure 1B**). In line with this, auto-antibodies bound to Ro60-Alu RNA/protein complexes have been detected in the blood of Sjögren's Syndrome patients and have been proposed to mediate TLR7-dependent signaling in B cells (upon endosomal uptake), leading to their aberrant activation and production of inflammatory cytokines (81). Ro60 can therefore play a dual role in restricting Alu abundance to limit their recognition by PRRs under physiological conditions, while also being responsible for inducing a pathological innate immune response in the context of an autoimmune disease.

In addition to Alu RNAs transcribed from their own promoter, Alu elements embedded within mRNAs can act as scaffolds for the recruitment of RBPs in the context of innate immunity. Many cellular transcripts harbor two or more embedded Alu copies in inverted orientation (Alu inverted repeat, AIR) mostly located in their 3'UTRs (129). AIRs can base-pair with each other and the closer the inverted Alu sequences are, the more frequently they tend to base-pair with each other (39). The resulting dsRNA structure has been shown to form Z-RNA (a left handed dsRNA helix with Z-conformation) (130) that is recognized by the Z α domain of ADAR1 (131) and Z-DNA binding protein 1 (ZBP1) (83) with different outcomes. ZBP1 is a sensor for viral as well as endogenous Z-RNAs, promoting NLRP3 inflammasome and pyroptosis *via* Receptor Interacting Protein Kinase 3 (RIPK3) (83–85). More recently, ZBP1 has also been shown to induce

PANoptosis, a form of inflammatory cells death, through a large multi-protein complex named AIM2 PANoptosome (**Figure 1B**) (82). By contrast, ADAR1 appears more like a guardian of homeostasis, by limiting inflammation. Indeed, ADAR1 binding to Z-RNA mediates adenosine to inosine conversion (also known as A-to-I editing) within the dsRNA structure (132). A-to-I editing disrupts the continuity in the dsRNA structure avoiding its recognition by the dsRNA sensors MDA5 and PKR. Interestingly, gain of function mutations in MDA5 associated with human immune disorders such as Aicardi-Goutières syndrome, have been shown to render MDA5 more tolerant to the irregular AIRs dsRNA structures generated upon ADAR1 A-to-I editing and inducing an aberrant antiviral response (133). Similarly, a recent study has shown that ADAR1 could act as a negative regulator of ZBP1 mediated PANoptosis (134). Those results suggest that the specificity of MDA5 and ZBP1 in recognizing its RNA substrates is under strong selection to maintain a trade-off between efficient pathogen recognition and self-tolerance.

Another strategy to regulate immune responses through PRRs sensing is to physically mask host RNAs with RBPs. For instance, under physiological context, a host-derived RNA called 5S ribosomal RNA pseudogene 141 (RNA5SP141) is present in the nucleus. When RNA5SP141 translocates into the cytoplasm, it recruits different RBPs such as ribosomal protein L5 (RPL5) and mitochondrial ribosomal protein L18 (MRPL18), avoiding unwanted activation of the immune system by PRRs. Some DNA viruses [*e.g.* herpes simplex virus 1 (HSV-1), Epstein-Barr virus (EBV) and influenza A virus (IAV)] have been shown to disrupt the nucleus membrane and to induce a global downregulation of host proteins' synthesis. This leads to increased availability of RNA5SP141 in the cytoplasm and its unmasking from the RBPs (135). RIG-I thus recognizes the RBP-free RNA5SP141, inducing type I IFN stimulation and antiviral immunity. This study shows how RBPs protect host RNAs from PRR recognition and highlights a mechanism used by the host to induce PRR activation during infection by DNA viruses.

Finally, dsRNA or ssRNA are not the only molecules recognized by RBPs. RNAs can base-pair with DNA during different physiological processes (*e.g.* DNA transcription, DNA replication, dsDNA break repairs) or as intermediates of replication for certain viruses and endogenous retroelements (*e.g.* retroviruses, hepadnaviruses and LINE-1 retroelements). Viral RNA : DNA hybrids have been shown in mouse bone marrow-derived conventional DCs (cDCs) and human Peripheral Blood Mononuclear Cells (PBMCs), but not in BMDMs, to be recognized by TLR9, leading to the production of pro-inflammatory cytokines, such as IL-6 and IFN, in a Myd88-dependent manner (136). Similarly, the cyclic GMP-AMP synthase (cGAS), classically seen as a DNA sensor that activates inflammatory response *via* its adaptor STING (137) can also detect RNA : DNA hybrids and induce STING activation leading to IFN- β and ISG expression (138). However, this property appears highly regulated, probably to prevent over-inflammation following infection, or unwanted immune responses during biological processes involving RNA : DNA

hybrid intermediates. Indeed, the Lysyl tRNA synthetase (LysRS), a component of the cytosolic multi-tRNA synthetase complex (MSC) involved in mRNA translation (139–141), has recently been shown to directly interact with RNA : DNA hybrids and compete with cGAS to delay STING activation and downstream type I IFN response (142). In addition to competing with cGAS, binding of LysRS to RNA : DNA hybrids leads to LysRS-dependent production of diadenosine tetraphosphate (Ap4A), which is able to directly bind STING and prevent its interaction with 2'3'-cyclic GMP-AMP (cGAMP) and decreases downstream production of type I IFN (see **Figure 1A**) (142).

Altogether, RBPs are important players in the direct recognition and/or modulation of the recognition of foreign RNAs and in triggering a robust innate response against a wide-range of pathogens.

4 ROLE OF RBPs IN RNA PROCESSING DURING INNATE IMMUNITY

4.1 Mechanisms of Alternative Splicing

In eukaryotes, protein-coding genes contain sequences that are found in mature mRNAs (exons) and sequences that are removed during mRNA maturation (introns) through a process called splicing and catalyzed by the spliceosome (143–145). By skipping or retaining specific exonic sequences, pre-mRNA splicing can create various RNA isoforms from a single transcription unit in a process known as alternative splicing. The spliceosome is a megadalton machinery composed of small nuclear RNAs (snRNAs) and proteins that associate to form small nuclear ribonucleoprotein particles (snRNPs termed as U1, U2, U4, U5, and U6) (146). Each intron has specific conserved sequences, the splice donor site that defines the 5' exon/intron junction, the splice acceptor site that defines the 3' intron/exon junction and the branch site that is essential during the first step of the splicing reaction. These sequences are recognized by snRNPs that assemble in a chronological order to perform two transesterification reactions that lead to the cleavage and release of the intron, while performing phosphodiester bonds to ligate the exons (146). Selection of the splice donor and acceptor sites can be modulated by surrounding cis-acting sequences, such as exonic and intronic splicing enhancers or silencers, that recruit RBPs including serine/arginine-rich family of nuclear phosphoproteins (SR proteins) and heterogeneous nuclear ribonucleoproteins (hnRNPs) [for a short review, see (147)]. Differential recognition of splice donor and acceptor sites leads to the process of alternative splicing, creating multiple transcript isoforms with different coding sequences or alternative 5'UTRs. Alternative-splicing plays a critical role in numerous cellular processes such as the establishment of cell identity or sex selection (148, 149). In the context of immunity, alternative splicing has been shown to play an important role in the differentiation, homeostasis, and regulation of immune cells (150–153). Importantly, it appears as a major regulator of inflammation in innate immune cells. For instance, in mouse

macrophages isolated from the lung at different time-point following intra-tracheal injection of LPS, global changes in alternative splicing were observed at the pic of the inflammatory response. In that context, genes involved in cellular metabolism and chemotactism were shown to be highly regulated by alternative splicing. Moreover, alternative splicing appears to regulate different set of pre-mRNA in recruited macrophages (mostly pro-inflammatory) as compared to resident macrophages, likely explaining their different metabolic requirement (154). Similarly, in monocyte derived macrophages obtained from human blood, bacterial infection is associated with global changes in mRNA isoform usage, with increased cassette exon inclusion (155). Finally, numerous important immune molecules transcripts downstream of PRR signaling (e.g. MyD88, IL-1 receptor-associated kinase (IRAK)), and even some TLR mRNA themselves also see their expression regulated by alternative splicing to give rise to protein isoforms with differential biological activities (156–158). However, although alternative splicing is mainly modulated by RBPs such as SR and hnRNP proteins, their role in the context of innate immunity is still poorly understood at the molecular level.

4.2 Alternative Splicing of PRRs and Their Downstream Signaling Factors

As the key contact between the noxious molecule and the host cells, PRRs and their downstream factors, represent a central hub of regulation. Alternative splicing has been shown to regulate activation and/or functions of those receptors, in order to control the intensity of immune responses and their shutdown upon clearance of infection or damage, as well as to prevent inappropriate inflammatory responses and autoimmunity.

While PRRs play an essential role during innate immunity by sensing specific patterns and alarming the immune system, their activity needs to be downregulated upon activation, to avoid over-inflammation. In line with this, alternative splicing appears as an important mechanism to limit PRR signaling. For example, LPS recognition by TLR4 requires TLR4 interaction with Myeloid Differentiation Factor 2 (MD-2) and the subsequent signaling cascade will lead to the expression of an MD-2 spliced isoform (MD-2s) that will inhibit TLR4 signaling (158). *In vivo*, delivery of MD-2s in the lung substantially decreases LPS-induced inflammation (159). Such a negative feedback loop has also been observed for TLR3, which recognizes dsRNA. In human astrocytes cell lines, TLR3 activation leads to type I IFN production that, in turn, induces the expression of an alternative spliced TLR3 isoform that acts as a negative regulator of TLR3 downstream signaling pathways (160).

In a different context, alternative splicing has been shown to regulate the relative production of membrane-bound and soluble forms of immune receptors, with opposite effect on inflammation. This is the case for Siglec-14, a glycan recognition protein that can elicit pro-inflammatory responses, in response to bacterial pathogens. Siglec-14 is classically paired with Siglec-5, that acts as an inhibitory receptor for bacterial pathogens, providing a

first level of regulation in pro-inflammatory processes (161). Thus, in LPS-stimulated neutrophils, Siglec-14 has been found to be up-regulated and Siglec-5 down-regulated, suggesting a positive feedback loop that increases myeloid inflammatory responses (162). As an additional layer of regulation, it has been found that a soluble form of Siglec-14 (sSiglec14) is able to interfere with the interaction between TLR2 and the membrane-bound form of Siglec-14 (mSiglec-14), in myeloid cells (163). The soluble form of Siglec14 is due to the retention of intron 5 during pre-mRNA splicing, which contains a C-terminal hexapeptide before the translation termination codon (164). While sSiglec14 is involved in the suppression of pro-inflammatory cytokines production (164), these results suggest a negative feedback mechanism regulating the myeloid pro-inflammatory responses elicited by the engagement of mSiglec-14. Thus, the switching between sSiglec-14 and mSiglec-14 might be used by the innate system to control a potential unwanted inflammatory response that could damage the host tissues.

In addition to PRRs, the activity of immune receptor's adaptors such as MyD88 or TRIF has been shown to be dynamically modulated through alternative splicing (165). The cytoplasmic portion of most of the TLRs shows high similarities with the interleukin-1 (IL-1) receptors family and is thus called the TIR domain, for Toll/IL-1 receptor (165). TIR domain thus serves as a platform to recruit TIR domain-containing adapter, such as MyD88 (166). Upon stimulation, MyD88 recruits IL-1 receptor-associated kinase (IRAK), a serine/threonine kinase, also containing a TIR domain. IRAK is then activated by phosphorylation and interacts with TRAF6. Altogether, this signaling cascade leads to the activation of MAPK and NF κ B signaling pathways that are crucial for completion of innate immune response (165). Thus, the regulation of TLR's adaptors are critical for the control of immune defense. Interestingly, a MyD88 splice variant (MyD88s) induced upon LPS activation in monocytes codes for a protein isoform that lacks the IRAK-interacting domain, thus acting as a dominant negative by preventing IRAK phosphorylation and downstream NF κ B activation to inhibit the LPS induced signaling pathway (167, 168). In resting cells, MyD88s alternative splicing is regulated by SF3A, SF3B and EFTUD2 that specifically inhibits the generation of the MyD88s isoform (lacking the IRAK-interacting domain), thus ensuring a robust initial innate response (see **Figure 2A**) (169, 173). Interestingly, in macrophages, SF3A knockdown preferentially affects splicing events related to innate immunity, such as the TLR signaling pathway, highly suggesting a more global role of this splicing factor in controlling the intensity of inflammation (170).

4.3 ISG Control by RBP-Mediated Alternative Splicing

In the case of a viral infection, the innate immune system reacts by disrupting the functions and pathways vital for the pathogen's life cycle. Once PRRs are activated by viral components, antiviral cytokines are produced. Among the earliest cytokines to be produced are type I IFNs (*e.g.*, IFN- β , IFN- α , *etc.*) that trigger the JAK/STAT signaling pathway in order to induce expression

of ISGs (174). These ISGs (*e.g.*, IFIT1-3) generally act as antiviral effectors that control viral replication and spread (175, 176). Modulating ISG expression is critical to manage an efficient defense against pathogens while preventing detrimental adverse immune effects. RNA splicing is one way among others to ensure the proper timing and intensity of ISG expression. Splicing regulation involves one or more splicing factors acting like a regulatory node, as illustrated by heterogeneous nuclear RiboNucleoProteins (hnRNPs) (177). hnRNPs are complexes comprising typical RNA-binding and modular proteins mostly present in the nucleus (178). Using UV cross-linking followed by oligo(dT) purification of RNAs, about 20 species of hnRNPs have been identified (hnRNP A-U) (179). These 'RNA scaffolds' play various roles associated with the fate of the RNA such as the regulation of splicing or the transcriptional responses to DNA damage (180–183). It has been recently shown that a loss of hnRNP M results in overproduction of several innate immune transcripts such as antimicrobial factors as well as ISGs (171). In early stages of macrophage activation, the splicing factor hnRNP M associates with nascent IL-6 mRNA and slows down its initial ramping, acting probably as a safeguard of the inflammatory response. Once the macrophage is fully activated, hnRNP M is phosphorylated (downstream of the TLR pathway) and is then released from mRNA transcripts, promoting their splicing and full maturation (see **Figure 2B**) (171). Zinc finger RNA-binding protein, ZFR, is another example of alternative splicing regulation that has been shown to suppress the IFN response by regulating ISGs splicing (172). ZFR contains double-stranded RNA binding motifs as well as several Cys-Cys-His-His (CCHH) zinc finger domains (184). This zinc finger protein has been shown to prevent aberrant splicing of the histone variant macroH2A1 (mH2A1), which in turn binds and represses IFN- β activation and ISG expression (see **Figure 2C**) (172). Although the precise mechanisms of both ZFR impact on mH2A1 splicing and mH2A1 negative effect on type I IFN responses still remain to be determined, it again highlights the high level of regulation underlying type I IFN-responses.

4.4 Specialized Splicing in Non-Canonical Nuclear Bodies During Inflammation

The nucleus is highly organized into membrane-less structures called nuclear bodies. Different nuclear bodies have been described, endowed with specific proteins and RNA composition, and functional specificity. One example of such sub-nuclear compartments are Cajal Bodies (CB), that act as an organizer of spliceosomal small nuclear ribonucleoproteins (snRNP) biogenesis (185). On a mechanistic point of view, Coilin, a multivalent scaffold protein, has been shown to interact with small nuclear RNAs (snRNAs), targeting them to CB to achieve snRNP assembly (186, 187). Coilin interacts with U snRNPs and with a CB component called survival of motoneurons (SMN) in order to participate in the formation and integrity of CB themselves (188). In an inflammation context such as LPS-activated macrophages, Coilin interacts with higher affinity to SMN, leading to snRNA release and CB destabilization (**Figure 3**). Simultaneously, Tat-activating regulatory DNA-

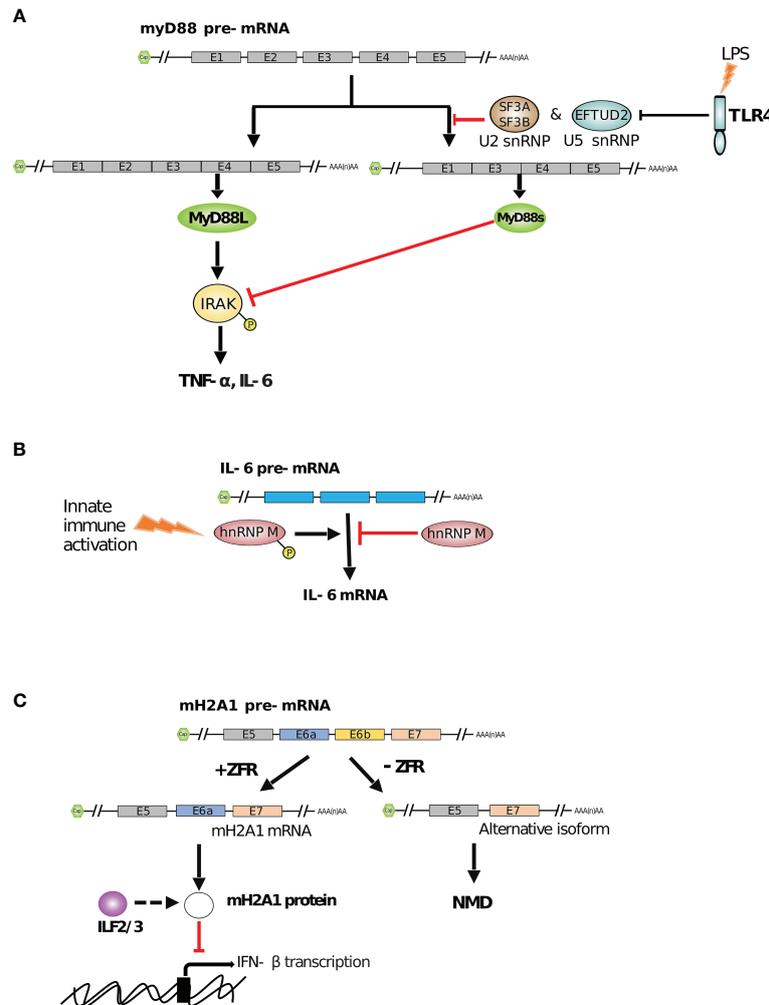


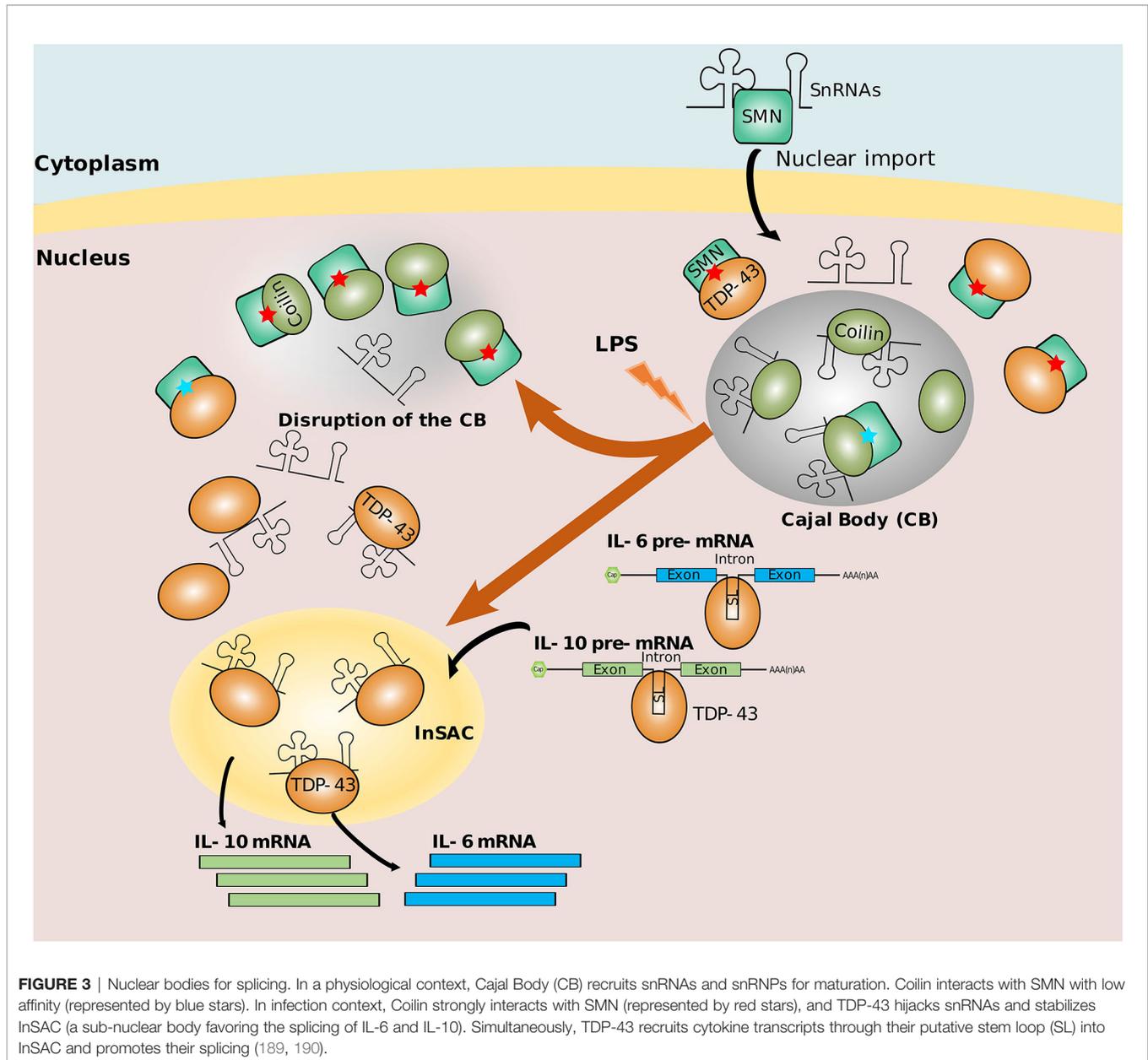
FIGURE 2 | RBP mediated regulation of innate immune functions by alternative splicing. **(A)** The smaller isoform (myD88s) of TLR4 signaling adaptor myD88 inhibits the production of cytokines (such as TNF- α and IL-6) by inhibiting myD88L mediated phosphorylation of IRAK. However, SF3A/3B and EFTUD2, in complexes with other snRNPs, reduce the production of myD88s to maintain cytokine expression (169, 170). **(B)** hnRNP M represses the splicing of IL-6 mRNA. However, innate immune activation in infected macrophages leads to phosphorylation of hnRNP M and relieves this splicing suppression (171). **(C)** ZFR facilitates correct splicing of mH2A1 transcript by exon inclusion which prevents the formation of an aberrantly spliced isoform. mH2A1 protein, which ILF2/3 possibly regulates, further promotes IFN- β mRNA expression to enhance type I IFN response (172).

binding protein-43 (TDP-43), a highly conserved hnRNP involved in RNA processing (*e.g.* splicing, trafficking, *etc.*), becomes ubiquitinated, decreases its binding to SMN and competitively recruits snRNAs and other components from spliceosomal snRNPs creating a novel sub-nuclear body different from CBs (189). TDP-43 also binds cytokine IL-6 and IL-10 pre-mRNAs in a sequence-specific manner (through short GC-rich palindromic repeats separated by a short spacer with a conserved 'ACU' sequence located in intron 2 of IL-6 and intron 1 of IL-10), thereby favoring their splicing within the sub-nuclear body dubbed InSAC (which stands for Interleukin-6 and -10 Splicing Activating Compartment) (see in **Figure 3**) (189). By hijacking components from CBs and controlling the distribution of subnuclear compartments, TDP-43 functions as a scaffold

protein within InSACs, which become a specific cytokine pre-mRNA splicing compartment and an important effector of the immune response during inflammation (190).

4.5 Polyadenylation

Most mRNAs, with the exception of those coding for canonical histones, bear a 3' poly(A) tail added during the maturation of mRNA, in a process called polyadenylation. Polyadenylation is a co-transcriptional process involving the recognition of a cleavage/polyadenylation site (typically "AAUAAA" in a GU or U-rich context) in the nascent pre-mRNA, followed by endonucleolytic cleavage of the pre-mRNA (35 nt downstream of the cleavage/polyadenylation signal) and addition of a poly(A) sequence (50-250 nt long) at the 3' end of the cleavage site (191).



An estimated 80% of mammalian genes contain multiple cleavage/polyadenylation sites generally leading to transcript isoforms with alternative 3' untranslated regions (3'UTRs) (192). Use of alternative polyadenylation (APA) sites is a dynamic process regulated by the abundance of the RNA-binding proteins involved in the polyadenylation process itself or by other RBPs, such as HuR, that can bind close to the cleavage/polyadenylation site and block its recognition (193). Ultimately, 3'UTR is the target of several RBP and/or antisense RNAs that regulate mRNA destiny. Modifications of mRNA 3'UTRs have thus important consequences on mRNA sub-cellular localization, translation efficiency or stability (194).

APA has been shown to also play an important role in innate immunity. For example, the sequencing of the human genome in

2001 helped to reveal that most TLRs have between two and four predicted APA sites (195). In line with this, several subsequent studies could underline that infected or inflamed macrophages display rapid and extensive changes in APA leading to a global shortening of 3'UTRs (155, 196). In LPS stimulated macrophages (BMDM and RAW 264.7 mouse cell line), this has been explained by the expression of Cstf-64, a 64kDa Cleavage stimulatory factor, that likely contributes to alternative polyadenylation of numerous genes associated with a global change in their expression (197). Similarly, macrophages derived from human blood monocytes infected by *Salmonella typhimurium* or *Listeria monocytogenes* show a near universal shift toward usage of more upstream polyadenylation sites, leading to shorter 3'UTR in genes where longer 3'UTR are targeted by miRNA negative regulation (155).

Altogether, those observations argue for a role of 3'UTR shortening in the escape from immune repression, allowing a rapid establishment of innate immune responses. Consistent with this, infection of primary human monocyte derived macrophages and mouse peritoneal macrophages with VSV leads to a gradual shortening of 3'UTRs through the use of proximal cleavage/polyadenylation sites. From 2 to 16 hours post infection, mRNA displaying altered APA are enriched in immune-related Gene Ontology categories and this is accompanied by increased levels of several innate-related proteins such as RIG-1, RIPK1 (a kinase involved in host defense) (198) or DDX3Y (a RNA helicase involved in type I IFN production) (199). In line with this, down-regulation of different RBPs involved in 3' mRNA processing prior to infection with VSV, promoted virus replication. Although it remains to be determined whether certain RBPs involved in 3'UTR processing are themselves regulated by APA and how viral infection modifies their expression/activity, this further validates the hypothesis about the important role of APA in regulating innate immunity (196). By contrast, Jia et al. study interestingly highlights a picture that is likely more sophisticated, where the impact of 3' UTR shortening does not necessarily correlate with increased protein output. Indeed, while APA usage leads to stabilization and increased translation of several mRNAs, other immune-related mRNAs were negatively impacted by the viral induction of 3'UTR shortening, including Fos, SOS1 [a negative regulator of TLR signaling (200)], TNFRSF10D [a TRAIL-receptor with a truncated death domain (201)], CASP6, PPSB1, N4BP1 [a suppressor of cytokine response (202)], (196). Although more extensive analysis should be performed in relevant models, the impact of APA and 3'UTR shortening in the context of infection overall appears as an additional regulator of protein output with a putative role in the interplay between positive and negative regulators of innate responses.

5 TRANSLATIONAL CONTROL DURING INNATE IMMUNITY

5.1 mRNA Translation Process

Once matured, mRNAs are transported from the nucleus to the cytoplasm, where they can recruit specific initiation factors and ribosomes to undergo translation. The control of this step plays a critical role in most cellular processes as it provides a rapid response to endogenous and exogenous cues without requiring *de novo* transcription. Furthermore, translational control is versatile as it can be exerted on a global scale or restricted to specific mRNA species. The translation process itself can be split into four phases: initiation, elongation, termination and ribosome recycling. Translation initiation is commonly assumed to be the rate limiting and the most regulated step of the process. However, the advent of high-throughput sequencing and protocols such as ribosome profiling (203), which allows to map the position of individual ribosomes across all expressed transcripts at a single-nucleotide resolution, has uncovered many additional layers of regulation taking place during elongation and termination of translation. Altogether, mRNA translation can thus be regulated by RBPs through multiple mechanisms involving binding to either specific RNA sequences or structures found in the 5'UTR, coding

sequence, 3'UTR or poly(A) tail of cellular and viral RNAs, or as a consequence of the detection of non-self RNAs.

5.2 Individual RBP-Mediated Translation Silencing

The nucleolysin TIA-1 (TIA1 Cytotoxic Granule Associated RNA Binding Protein) and its closely related homologue TIAR are both RBPs containing three RNA Recognition Motif (RRM) domains in their N-terminal (204–206). In response to stress-induced phosphorylation of the translation initiation factor eIF2 α , these proteins participate in the assembly of membrane-less cytosolic structures called stress granules (SGs). In cooperation with other RBPs, TIA-1 binds and sequesters untranslated mRNAs into the SGs, away from ribosomes (207). This occurs in five steps: (i) phosphorylation of eIF2 α results in abortive initiation complexes preventing ribosome elongation and resulting in the formation of 48S messenger RiboNucleoParticle (mRNPs); (ii) free 48S mRNP are aggregated by factors such as TIAR or TIA-1, initiating SG nucleation; (iii) secondary aggregation where mRNA transcripts bind to multiple proteins forming microscopically visible SGs; (iv) integration and signaling in which proteins that lack RNA-binding domains (RBDs), such as TIA-1 binding proteins (e.g. SRC3, FAST or PMR1), bind in a 'piggyback' manner proteins involved in SGs assembly; (v) mRNA triage: SGs are organized into compartments. In each compartment, transcripts are specifically selected for decay or stabilized for further export and integration into polysomes, or stored (208). In LPS-activated macrophages, it has been shown that TIA-1 and TIAR bind U-rich motifs of mRNAs and selectively induce the silencing of TNF- α translation, while other cytokines such as IL-1 β or IL-6, are largely unaffected (209, 210). Similarly, activated macrophages from TIA-1 $^{-/-}$ mice were shown to produce significantly more TNF- α as compared to macrophages from wild type mice (210). Although the direct link between TIA-dependent silencing of TNF- α and stress granules has not been formally shown in that cellular context, several lines of evidence suggest that TNF- α silencing is linked to a stress response. By contrast, stimulation of the integrated stress pathway, a cytoprotective response that regulates cellular homeostasis, can prevent the production of IL-1 β in LPS-activated macrophages. Indeed, incubation of murine macrophages with Arsenic, a known inducer of eIF2 α phosphorylation and stress granule formation, after LPS activation or bacterial infection, results in a decreased production of IL-1 β . Mechanistically, this decrease is explained by the formation of stress granules, through the interaction of IL-1 β mRNA with TIA-1/TIAR, that eventually leads to IL-1 β mRNA degradation (211).

Altogether, these studies suggest that TIA-1 and TIAR constitute specific translational silencers regulating the cellular response to environmental stress. The fact that, depending on the environmental context, such a stress-response targets specific cytokine-encoding mRNAs, further suggests the existence of additional elements of specificity, as exemplified in non-immune cellular context (212).

5.3 GAIT Complex-Mediated Translational Regulation

RBP-containing protein complexes such as the IFN- γ -activated inhibitor of translation (GAIT) complex play an important role

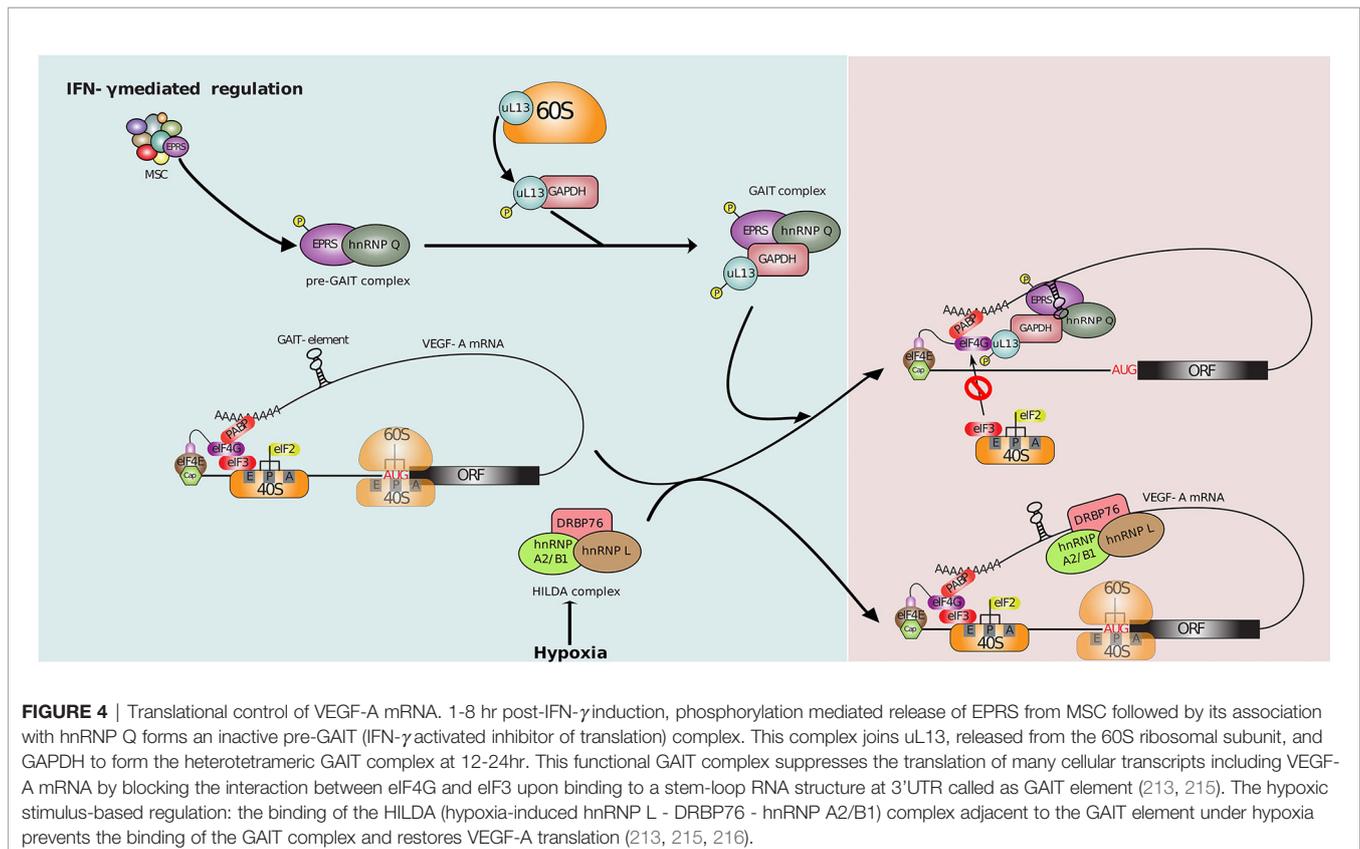
in regulating transcript-specific translation during innate immunity (213).

GAIT is a heterotetrameric complex formed by the glutamyl-prolyl tRNA synthetase (known as EPRS), heterogeneous nuclear ribonucleoprotein Q (known as hnRNP Q or NSAP1), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the ribosomal protein L13a [also known as uL13 in the new ribosomal protein naming system (214)]. Assembly of the GAIT complex in response to IFN- γ exposure occurs in two distinct stages that are temporally regulated (see **Figure 4**). The first stage, which occurs within 8 hours from IFN- γ exposure, is triggered by the phosphorylation of EPRS mediated by several kinases (*e.g.* CDK5, p35, mTORC1) (217, 218). This induces its release from the tRNA synthetase complex (MSC) and its interaction with hnRNP Q to form a 'pre-GAIT complex' that is not functional. The second stage occurs after 12-24h of IFN- γ exposure, when ribosomal protein uL13 is phosphorylated, and triggers its release from the 60S ribosomal subunit. uL13 then binds GAPDH and the 'pre-GAIT complex' formed by EPRS and hnRNP Q to generate a functional heterotetrameric GAIT complex (215, 219). Once functional, the GAIT complex becomes competent for binding transcripts containing specific RNA stem-loops in their 3'UTRs sequence (*i.e.* GAIT elements), that are present in numerous pro-inflammatory mRNAs. GAIT complex likewise represses their translation through a direct interaction between uL13 from the GAIT complex and the translation initiation factor eIF4G, which inhibits the association of eIF4G and eIF3 (217, 220). uL13 deficiency, however, does not

impair ribosome assembly in general or its global translation capacity, highlighting a non-essential role for uL13 as a regulator of specific mRNA translation (221).

Macrophage specific knockout of uL13 in mice has shown that translational control driven by the GAIT complex is an important player in the resolution of inflammation (219, 222, 223). Indeed, many cellular transcripts involved in the inflammatory response contain GAIT elements in their 3'UTR and are translationally regulated by the GAIT complex following stimulation with IFN- γ . These include transcripts coding for chemokines, chemokine receptors (219) and cytokines (222).

Similarly, treatment of human monocytic U937 cell line with IFN- γ induces strong expression of vascular endothelial growth factor A (VEGF-A that promotes angiogenesis during inflammation) mRNA after 8 and 24 hours. However, while VEGF-A protein levels are increased 8 hours post IFN- γ treatment, its level returns to baseline at 24 hours. Indeed, VEGF-A translation is repressed by the GAIT complex *via* the binding of GAIT to its GAIT element (224). Conversely, VEGF-A mRNA is positively regulated by the HILDA ribonucleoprotein complex composed of the RBPs, hnRNP L, DRBP76 (or ILF3, a dsRBP), and hnRNP A2/B1 that promotes angiogenesis under hypoxia conditions (216, 225). Interestingly, the GAIT element located in the 3'UTR of VEGF-A is in vicinity of an RNA binding site for HILDA complex (**Figure 4**). Binding of the GAIT or HILDA complex is mutually exclusive and results in a conformational switch of the RNA that impedes binding of the



other complex (216, 225). This conformational switch, dependent on normoxic or hypoxia cell condition, enables efficient VEGF-A regulation and tissue oxygenation following inflammation, through translational control. Altogether, this process highlights a translation-dependent mechanism by which monocytes/macrophages can handle conflicted clues in complex environment such as inflammation (216).

5.4 Viral RNA Translation Control

Many ISGs with RNA-binding capacity (*i.e.* ISG-RBPs) boost immune response by restricting viral replication through the regulation of mRNA translation (either self or foreign mRNA), some acting on bulk translation while other targeting specific transcripts (226, 227). Among these, the best characterized is the dsRNA-activated protein kinase (PKR). PKR contains two dsRBDs that recognizes dsRNA structures longer than 30 nucleotides through its N-terminal end, which are an abundant replication intermediate for RNA viruses (228). Binding of dsRNA by PKR induces homodimerization and autophosphorylation of PKR C-terminal kinase domain, leading to its activation. One major target of PKR is the translation initiation factor eIF2 α , which becomes phosphorylated upon PKR activation. Phosphorylated eIF2 α cannot be recycled and is no longer able to form a ternary complex with the initiating Met-tRNA and a molecule of GTP. This results in a global inhibition of translation initiation affecting both cap-dependent and most forms of IRES-dependent translation (IRES for internal ribosome entry site, an RNA element often located in 5' UTR that allows translation initiation in a cap-independent manner). However, certain cellular mRNAs are selectively translated in the presence of high levels of phosphorylated eIF2 α and many viruses are able to overcome this arrest (229). Additionally, PKR is also present in stress granules containing stalled 48S ribosomes (**Figure 5A**). The activation of the stress granule localized PKR contributes to amplifying the innate immunity without the need for viral dsRNA pattern recognition (231) highlighting another antiviral mechanism of PKR. In line with this, PARP12, an ISG-RBP phosphorylated by PKR, has been shown to localize into SGs and p62/SQSTM1 containing structures (an adaptor protein involved in innate signaling and autophagy). Regulated by type I IFN during LPS stimulation, PARP12 contributes to the cellular antiviral response by increasing the SG-mediated translational silencing of viral and cellular RNAs. PARP12 contains five Cys-Cys-Cys-His (CCCH) zinc finger domains, the N-terminal one being essential for its subcellular location and function (235, 236). ISG20, another ISG-RBP, contains an RNase I domain and displays antiviral activities (237). ISG20 is upregulated by the three types of IFN and appears to perturb both viral mRNA translation and stability either directly, or *via* host factors (238). At the opposite of PARP12, ISG20 has been shown to specifically inhibit translation of a large number of non-self RNAs but not that of host mRNAs, participating in the discrimination between self and non-self substrates, however its mechanism of action still remains elusive (239). This is also the case for ZAP, a zinc-finger antiviral protein, also known as ZC3HAV1 that promotes

translational repression of spliced viral mRNAs, by binding specific ZAP responsive element present in target viral RNAs. Once bound to viral RNAs, ZAP disrupts the interaction between the translational initiation factors (eIF4G, eIF4A) and the viral mRNAs, leading to their translational silencing (240, 241). ZAP also participates in maintaining the integrity of stress granules which could potentially be linked to its ability to restrict virus infection (230). More recently, the long isoform of ZAP has been shown to be essential for limiting translation of viral RNAs (242). At the opposite of the short isoform, the long isoform of ZAP contains a PARP domain and a CaaX motif (amino acids "CVIS") at its C-terminus. Because ZAP is known to lead to degradation or translational inhibition by binding CpG dinucleotides in viral RNAs (243), CpG-enriched viruses have been used to highlight the antiviral activity of ZAP RBP. First, it has been shown that not only the N-terminal RBD, but also the C-terminal PARP domain both contribute to the restriction of CpG-enriched HIV-1. Second, the presence of the well-conserved CVIS sequence of the CaaX box mediates S-farnesylation (addition of a hydrophobic group). This post-transcriptional modification combined with the presence of the PARP domain are required for a full antiviral activity, through the recruitment of important co-factors such as TRIM25 and KHNYN proteins and the localization of ZAP into intracellular membranes. The subcellular distribution of this RBP has been shown to be critical for the antiviral restriction of both CpG-enriched HIV-1 and SARS-CoV-2 viruses (242).

RBPs can also recognize specific RNA patterns carried by some viruses in order to restrict their translation. For example, IFIT1 (interferon-induced protein with tetratricopeptide repeats 1), induced by IFN- α/β upon viral infection, binds a triphosphate group on the 5' terminal of viral RNAs (PPP-RNA) (244) in a sequence-independent manner and form a complex with IFIT2 and IFIT3 (and other proteins from IFIT family) to physically sequester the viral RNA and limit the assembly of viral particles (see **Figure 5A**) (245, 246). IFIT1 also interacts with eIF3 thereby blocking its association with the ternary complex (eIF2-GTP-Met-tRNA) to further inhibit translation of viral RNAs (247). In addition, the lack of 2'-O methylation of viral RNAs increases the interaction with IFIT1 and therefore raises the translational silencing (248). However, host mRNAs lacking 2'-O-methylation can also be targeted by IFIT1-mediated silencing. Interestingly, one way to circumvent this issue is mediated by CMTR1, another ISG also known as ISG95. CMTR1 is responsible for the catalysis of 2'-O-methylation, which prevents IFIT1-mediated repression, especially for some ISG transcripts (see **Figure 5B**) (233). By doing so, CMTR1 promotes ISG protein expression in response to type I IFN. This example underlines the complex relation between (viral and host) RNA and RBPs and the requirement of several layers of regulation to optimize the antiviral response induced by the infection.

Altogether, a broad panel of RBPs exists, that regulate RNA dynamics through the modulation of translation. Their molecular and functional structure are divergent but they all converge into shaping the intensity and the efficiency of the innate immune response in time and space.

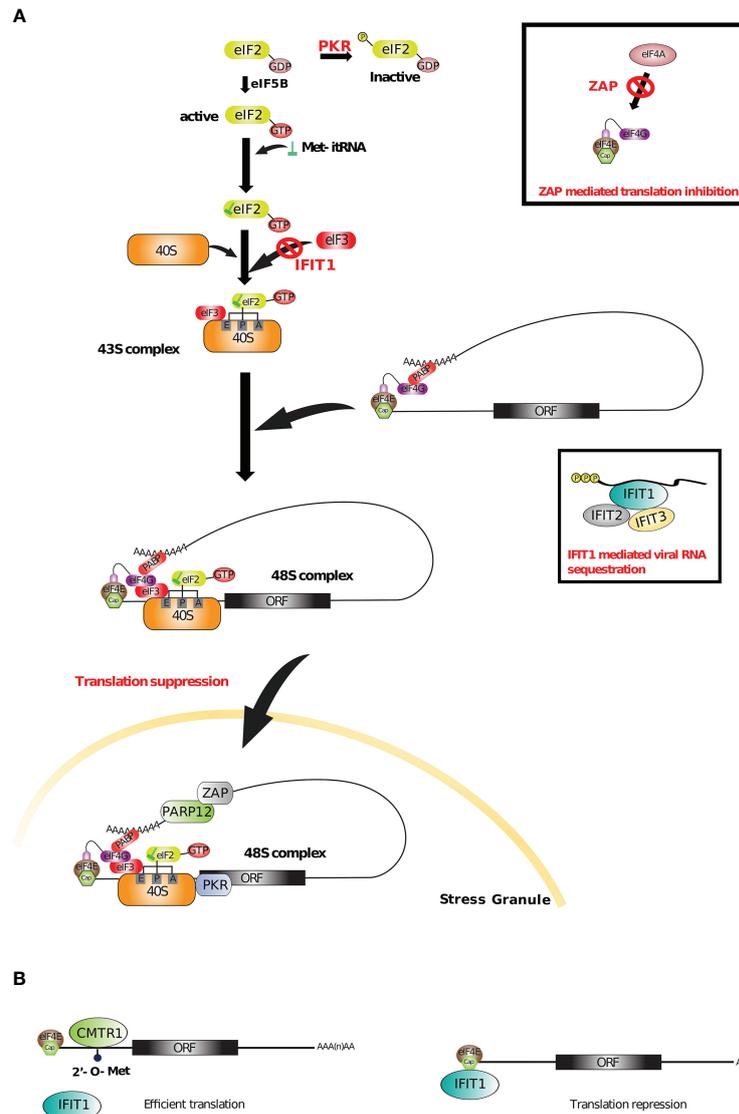


FIGURE 5 | Translational control by ISG-RBPs. **(A)** Upon viral infection, several ISGs (such as PKR, ZAP and IFIT1) suppress viral and/or cellular translation by recognizing different RNA sequences or structures and targeting important initiation and elongation factors. With PARP12, PKR and ZAP also participate in stress granule mediated antiviral response (227, 230–232). **(B)** 2'O methylation of cellular mRNAs recruits CMTR1 that inhibits IFIT1 mediated translation repression (233, 234).

6 mRNA STABILITY

6.1 mRNA Decay Process

The number of proteins synthesized from any given mRNA molecule is defined by its translation and degradation rates (249, 250). In eukaryotes, for most cellular transcripts, decay involves deadenylation and/or decapping. Deadenylation of the mRNA 3' end is mainly dependent on the CCR4-NOT complex among other deadenylases (251, 252), while decapping at the 5' end is performed by the mRNA decapping complex Dcp2-Dcp1 (253, 254). Each of these events is followed by exonucleolytic degradation from one or the other transcript extremity: from 5' to 3' by the exonuclease Xrn1 (255) and from 3' to 5' by the RNA exosome complex (256). Degradation of mRNAs by

decapping complexes is thought to occur in cytoplasmic processing bodies (P-bodies) that are cytosolic membraneless structures composed of aggregates of proteins involved in RNA metabolism (including the decapping complex and Xrn1 among many others) and untranslated mRNAs (257). However, this model has been challenged in the past few years by studies indicating that P-bodies can be sites of mRNA storage and “triage” before resuming translation or being degraded (258, 259). Furthermore, growing evidence points to a close link between mRNA translation and degradation, which can occur simultaneously, outside of P-bodies (249, 260–263). Finally, endonuclease-associated mRNA decay can also occur, initiated by internal cleavage and followed by bidirectional exonuclease degradation (264). However this mechanism is not involved in

bulk mRNA degradation and is usually restricted to a subset of mRNAs with specific features.

RNA-seq technology combined with metabolic labeling of nascent mRNA transcripts allows to measure transcriptome-wide mRNA degradation rates in different conditions (e.g. LPS, TNF- α in myeloid cells or fibroblast) (265–267). Even in the absence of metabolic labeling, recent mathematical models are able to estimate with accuracy mRNA degradation rates from total RNA-seq datasets (268, 269). These analyses showed that in cells stimulated with LPS or TNF- α , the raise of mRNA levels induced by pro-inflammatory stimuli is mainly due to a global increase at the transcriptional level, with a globally constant mRNA degradation rate (265, 266). However, following LPS stimulation of DCs, a small set of mRNA show a rapid increase in their degradation rate, following an initial increase in their translation, thus affecting their cellular level within the first 3 hours after stimulation. Interestingly, most of the concerned mRNA were immediate-early genes (e.g. Fos, Jun, Egr1, Tristetraprolin) suggesting that, in the context of a rapid and transient response, the rate of the mRNA decay is an important parameter controlling mRNA output (266).

Rapid mRNA degradation mechanisms are essential for shaping the innate immune responses and the binding by RBPs to transcripts happens in a sequence or structure dependent manner. The most widely targeted cis-elements are AU-rich elements (AREs), with RBPs stimulating the deadenylation of mRNA (270).

6.2 ARE-Mediated Regulation

ARE usually consists in several clusters of the AUUUA pentamer or UUAUUUA(U/A)(U/A) nonamer sequence located in the 3'UTR of protein-coding transcripts (271). Their sequence is specifically recognized by ARE-binding proteins that can compete against each-other for ARE binding and thus, depending on the relative expression of ARE-binding proteins as well as the nucleotide context in proximity of a given ARE, these elements can either lead to transcript destabilization (272), translational control (273) or stabilization (274) [for a review, see (275)]. Historically, AU-rich elements were discovered as cis-acting elements responsible for inducing mRNA degradation of transcripts coding for inflammatory mediators (276). Indeed, it has been shown that early and transient mRNA transcripts induced after LPS or TNF- α stimulation in macrophages are enriched in AREs in their 3'UTRs, which is in line with the essential control of the immune response duration by rapid mRNA decay (277, 278). Consequently, ARE-mediated regulation affects many pro- or anti-inflammatory cytokines such as IL-2, TNF- α , IL-1 β or Granulocyte Macrophages Colony Stimulating Factor (GM-CSF) (279). Their AU-rich sequence are recognized by over 20 different ARE-binding proteins with different roles in regulating mRNA metabolism (24, 279).

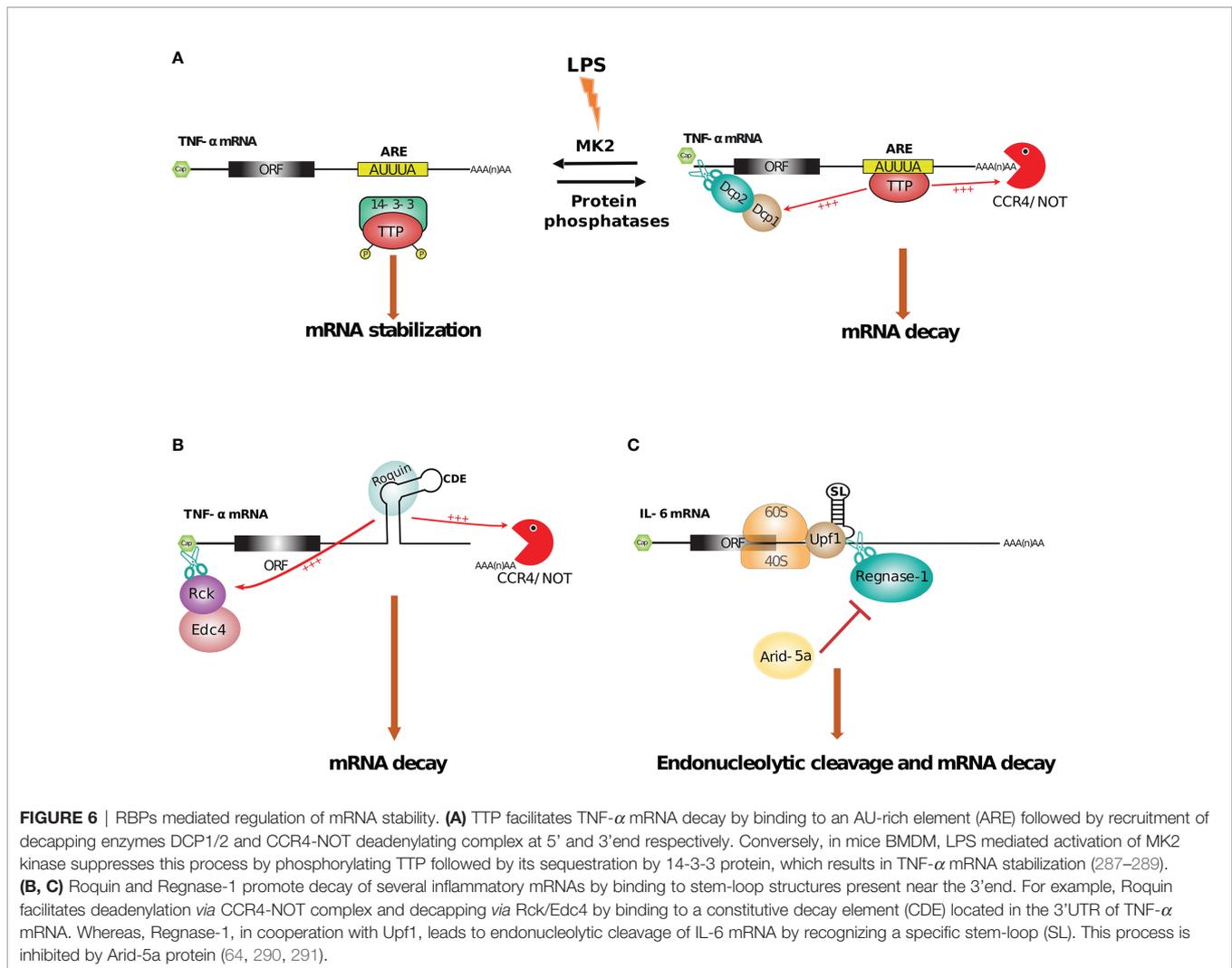
One of the most well-known examples of ARE binding proteins involved in inflammatory process is Tristetraprolin (TTP, a Cys-Cys-Cys-His (CCCH) zinc finger protein). It has been identified in various organisms from human to yeast

(280–282) and has been shown to bind to the ARE contained within the 3'UTR of targeted mRNAs *via* its zinc finger domain. Well known targets are mRNAs displaying high turnover rates such as cytokines and growth factors (283–285). Mechanistically, TTP recruits the CNOT1 subunit of the CCR4-NOT complex (286), leading to deadenylation which accelerates degradation of the target mRNA. In addition to inducing deadenylation, TTP has also been described to stimulate mRNA-decay by decapping through the involvement of decapping proteins (Dcp1/2) (see **Figure 6A**) (292). TTP is therefore highly controlled to maintain a proper innate response intensity and duration. In mouse BMDMs (Bone Marrow-Derived macrophages), TTP expression is ubiquitous and low in resting conditions but, during the first hours of inflammation, TTP is phosphorylated by MK2 and further sequestered by 14-3-3 proteins (293, 294), therefore leading to pro-inflammatory cytokines mRNAs stabilization and accumulation (see **Figure 6A**) (295). Following this, TTP expression is empowered both transcriptionally and post-transcriptionally by inflammatory stimuli [as described upon activation of TLR4 (296, 297)] leading to the destabilization of several inflammation-associated mRNAs, such as TNF- α (283, 298, 299). By alternating between sequestration and release, TTP is able to regulate the stability of important inflammation-related mRNAs in a temporal manner.

6.3 Non ARE-Mediated Regulation

Non ARE-mediated regulation refers to mRNA regulation (decay or stabilization) by RBPs, through the recognition of specific sequences and RNA structures in the 3'UTR of targeted mRNAs, that are not ARE. For example, Constitutive Decay Element (CDE) relates to a decay through deadenylation, that is mediated by a 3'UTR conserved sequence with a stem-loop structure specifically recognized by Roquin and Roquin2 (300–302).

Non ARE-mediated regulation thus further regulates RNA stability of pro- and anti-inflammatory elements. For example, in addition to an ARE element in its 3'UTR, TNF- α encoding mRNA contains a non-ARE CDE that tightly regulate its expression, and overall prevent excessive TNF- α production in inflamed macrophages (300). Following macrophages (mouse RAW 264.7 cell line and BMDMs) stimulation by LPS, the CDE (which corresponds to a conserved 37 nucleotide long RNA stem-loop structure) is recognized by Roquin and Roquin2 (see **Figure 6B**). Roquin proteins actively recruit the CCR4-Caf1-Not deadenylase complex (a major multi-subunit complex responsible for the deadenylation of a large number of eukaryotic transcripts) through their C-terminal domain, which mediates deadenylation of the TNF- α mRNA and its accelerated clearance (301). Within this complex, Caf1a was identified as the factor directly responsible for deadenylation, since expression of a dominant-negative mutant of Caf1a, completely abolished Roquin mediated mRNA decay of CDE-containing mRNAs (301). The binding of a decapping enzyme Edc 4 (enhancer of mRNA decapping protein 4) and the RNA helicase Rckat 5'end also contributes to this mRNA degradation process. In addition to TNF- α transcripts, conserved CDEs were



identified in more than 50 other cellular transcripts, enriched in T cell differentiation, nucleic acids metabolism and transcription factor functions, suggesting a wider role of Roquin proteins and their CDE target elements in modulating immune responses (301). In addition to AREs and CDEs, embryo deadenylation element (EDEN)-like sequences (rich in uridine–purine dinucleotides) present in immune related transcripts such as TNF- α and *c-fos* where they are scattered throughout the mRNA, are recognized by CUG-BP1 (CUG triplet repeat RNA-binding protein 1, also known as CELF1). In this case, CUG-BP1 is able to directly recruit the PARN deadenylase to induce target mRNA decay (303). Multiple mRNA decay pathways implicating different cis-acting RNA elements, specific adaptor proteins and leading to the recruitment of different effector proteins or complexes are responsible for modulating the stability of hundreds of transcripts during the inflammatory response. Some transcripts, such as those coding for TNF- α contain multiple different cis-acting RNA elements responsible for inducing mRNA destabilisation, allowing for complex regulatory networks responding to multiple inputs.

6.4 Translation-Dependent mRNA Decay

mRNA degradation can be strongly interconnected to other processes such as translation. For example, mRNA quality control pathways, such as nonsense-mediated decay (NMD), no-go decay (NGD) and non-stop decay (NSD) also rely on translation to induce degradation of aberrant mRNAs [for a review see (263)]. However, accumulating evidence indicates that functional mRNAs can be degraded co-translationally, and therefore the rate of translation can influence their degradation rate (262). Other mRNA degradation pathways such as the one mediated by microRNAs have been shown to occur co-translationally and in some cases to depend on target mRNA translation to trigger degradation (304–306). Finally, some target-specific mRNA degradation pathways driven by RBPs have been shown to require mRNA translation in order to license for degradation.

This is illustrated by Regnase-1 (also known as MCP1P1 or ZC3H12A), a RBP recognizing specific stem loop in 3'UTR and harboring an endoribonucleolytic activity thought to act as a negative regulator of pro-inflammatory processes (Figure 6C).

Regnase-1-deficient mice develop severe immune disorder and mostly die around 12 weeks old (307) [for an extensive review, see (308)]. In peritoneal macrophages from mice deficient for Regnase-1, TLR-stimulation induces increased levels of IL-6 and IL-12p40 secretion, while TNF- α remains unaffected (307). In line with this, stimulation of human monocytes derived macrophages with IL-1 β induces Regnase-1 expression that will, in turn, shorten IL-1 β mRNA half life (309). In both studies, the function of Regnase-1 has been linked to its ability to bind RNA stem-loops in the 3'UTR of target mRNAs and induce their rapid degradation through a putative amino-terminal nuclease domain (290). Interestingly, Regnase-1 not only plays its role of anti-inflammatory regulator in myeloid cells, but also in epithelial cells by exerting RNase activity towards the IL-8 mRNA, that stimulates immune cell migration and phagocytosis (310). More recently, Mino et al. could show that Regnase-1 mediated decay occurred in a translation-dependent manner. In this process, the stem-loop RNA structure is first recognized by Regnase-1 prior to the pioneer round of translation. However, this interaction alone is not sufficient for Regnase-1 to induce mRNA cleavage and decay. Instead, during the first round of mRNA translation, translation termination recruits the RNA helicase Upf1 to Regnase-1 which stimulates its RNA-helicase activity leading to unwinding of the stem-loop structure bound by Regnase-1 and allowing target mRNA cleavage (311). Remarkably, Regnase-1 and Roquin share multiple target sites in several transcripts, although not all [as shown for TNF- α whose decay depend on Roquin but not Regnase-1 (301, 307)]. This observation led to the conclusion that Regnase-1 and Roquin could, to some extent, act in concert for a spatio-temporal regulation of common immune-related genes. Indeed, Regnase-1 mediated mRNA decay occurs in the ribosome/endoplasmic reticulum and is translation-dependent, likely playing a role during the early acute phase of immune response. By contrast, Roquin is mainly localized within stress granule, targeting translationally inactive mRNA, in line with a role during the late phase of immune response (290).

MicroRNAs (miRNAs or miR) are other important modulators of mRNA decay and translation by interacting with the 3'UTR of the target transcripts. miRNAs are short (22 to 25 nt long) noncoding RNAs that regulate gene expression in numerous cellular processes. By targeting the 3'UTR of protein coding transcripts, they might directly regulate expression of about 60% of all mammalian genes (312, 313). miRNAs act by guiding the RNA-induced silencing complex (RISC) to interact with mRNAs, inducing translational repression followed by mRNA decay (314). miRNAs have been shown to be critical regulators of immune responses (315, 316). For instance, in hepatocytes, miR-122 is able to repress expression of several kinases involved in STAT3 phosphorylation and promote antiviral immunity by repressing STAT3 signaling pathway (317). Similarly, miR-155 is an important regulator of the innate and adaptive immune response. Its expression is induced in response to pathogen infection and several inflammatory stimuli, and repressed in response to anti-inflammatory cytokines (316, 318). Finally, it has been shown

that ISGs have more conserved miRNA target sites in their 3'UTRs than all other cellular mRNAs and are therefore more prone to regulation by the RISC complex (319). Interestingly, infection with viruses or synthetic ligands that activate an antiviral response result in a global inhibition of RISC that removes the negative effect of miRNAs on ISG transcripts to improve their expression and potentiate the antiviral response (319). Furthermore, in some contexts such as during Poxvirus infection, the host miRNA activity is ablated by the viral machinery to avoid direct translation silencing of its own transcripts (320). This action probably outweighs the costs of any possible increase of ISG toxicity. In addition to a direct role of miRNAs in the cell in which they were produced, horizontal transfer of miRNAs through specific vesicles such as exosomes might be a key factor in inflammatory response (321). For example, after binge or chronic alcohol consumption, the number of exosomes containing miR-122 drastically increases in circulation. They are transferred from hepatocytes to monocytes, sensitizing them to the inflammatory response (322). Similarly, alcohol-exposed monocytes communicate with naive monocytes *via* the release of extracellular vesicles containing high levels of miR-27a. These miR-27a cargos lead naive monocytes to differentiate into M2 macrophages (an alternative group of macrophages) (323). Furthermore, macrophages are not the only cell-type sensitive to horizontal transfer of miRNAs during innate responses. This process can also occur between DCs (324) or between T cells and DCs (325). miRNAs, by binding RNAs, regulating their expression, and being the communication support between immune cells, participate in modulating immune response in quantitative and qualitative ways.

6.5 Stabilization of RNA

Some RBPs, instead of promoting mRNA degradation, increase the stability of both cellular and viral mRNA, either by direct competition for mRNA binding with RBPs involved in mRNA degradation, or indirectly through the regulation of factors involved in mRNA decay. For example, the RBP Arid-5a is exported from the nucleus to the cytoplasm during LPS-mediated macrophage activation. Cytoplasmic Arid-5a thus promotes mRNA stabilization of cytokines such as IL-6, by suppressing the function of Upf1, which is essential for Regnase-1-mediated mRNA decay function (see **Figure 6C**) (326). Notably, these cytokines (*e.g.* IL-6 mRNA) can also be stabilized through the inactivation of miRNAs. Indeed, IL-6 mRNA can be targeted by miR-26 family members for degradation. However, miR-26 family members can be inactivated by TUT4 (Terminal uridylyltransferase 4, also called zcchc11), a ribonucleotidyltransferase (327) which adds uridine residues to the 3' ends of miRNAs, thereby inactivating them. Inactivation of miR-26, that act as inhibitors of IL-6 translation and, thus indirectly promoting IL-6 mRNA stability (328).

Another example of RBP-mediated stability relates to HuR, an ubiquitously expressed RNA binding protein, (also known as ELAV-like protein 1), which is known as one of the most

important AU-rich element (ARE)-containing mRNA stabilizing proteins (329). This RBP contains three RNA recognition motifs (RRMs) called RRM1-to-3. RRM1 & RRM2 domains bind to U/AU-rich RNA (330), whereas the RRM3 domain is able to interact with poly(A) tails of HuR's mRNA targets (331). HuR positively regulates antiviral responses by stabilizing diverse mRNAs in response to RLR or cGAS stimulation, including IFN- β (332), ISGs and regulators of host defense mechanism (332, 333). For example, following RLR stimulation, Polo-like kinase 2 (PLK2), regulates the nuclear translocation of IRF3. HuR has been found to stabilize the mRNA coding for PLK2 (334), increasing PLK2 levels and therefore assisting IRF3 transit into the nucleus in order to activate the transcription of IFNs and ISGs [for extensive review about IRF, see (335)]. Interestingly, HuR mode of action appears to be closely linked to its subcellular localization, that itself depends on the cell type, and the cellular context (*e.g.* naive versus activated cells). Initial studies performed in HEK293 cells, by combining data from different experimental systems such as PAR-CLIP, and whole-transcript expression profiling, have shown that HuR is involved in coupling pre-mRNA processing and mRNA stability, highlighting an important role of HuR within the nucleus through its binding at intronic sequences (336). However, further analysis using THP-1 cells (that, in their naive state, shared HuR properties observed in HEK293 cells) revealed that HuR dramatically modifies its binding properties upon activation. Indeed, cGAMP stimulation was associated with an accumulation of HuR in the cytoplasm, and a concomitant enrichment in cellular transcript 3'UTR binding (333). Those results underline a dynamic network in which RBP tightly regulate the complex changes that occur during immune activation.

RBP-mediated RNA stabilization is also important in the mechanism of action of specific therapeutic regimens or, by contrast, during viral immune escape. For example, under DNA-methyltransferase inhibitors (DNMTis) cancer therapy, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) patients are treated with decitabine or azacitidine. This induces the expression of dsRNAs from endogenous retroviruses (ERVs), that are normally silenced by epigenetic regulation. ERVs are in turn recognized by a specific PRR, MDA5, that stimulates an immune response, leading to the death of the cancer cell. Concomitantly, STAU1, which contains multiple dsRBDs, has been shown to cooperate with a long non coding RNA, TINCR, to bind ERV transcripts. The STAU1-TINCR-ERV complex stabilizes ERV transcripts and is required to promote the expected immune response and cell death (337). Therefore, by mediating the efficiency of the DNMTis treatments, levels of STAU1 and TINCR are important indicators of patient receiving DNMTis treatment. Following the same principle, STAU1 has been found to bind and stabilize infectious bursal disease virus (IBDV) dsRNAs, although with a different outcome. Indeed, as opposed to the previous example, binding of STAU1 allows IBDV to escape its recognition by MDA5 and favoring IBDV replication and escape from host antiviral response (*i.e.* IFN response) (338).

In combination, all these RBPs participate in a regulatory network that finely tune inflammation by controlling the fate of diverse mRNAs. RBPs deploy mRNA decay and/or stability mechanisms to maintain immune homeostasis. This is allowed through a timely regulation of RBP activity during immune responses. Indeed, RBPs participate in the positive regulation of rapid pro-inflammatory processes at the onset of immune response and, conversely, appear to play an even more important role in shutting down or reducing inflammation at later time points, thus preventing detrimental tissue damage. Interestingly, this tight regulation appears often regulated by the subcellular localization of RBPs, with RBP harboring different function depending on their local interacting environment. As the mechanisms behind these interactions are still not fully characterized, it will be important to further investigate the different roles and molecular mechanisms by which RBPs regulate mRNA stability during the course of innate immune responses.

7 EPITRANSCRIPTOMICS

In analogy to the epigenetics field, epitranscriptomics involves a biochemical modification of the ribonucleotide sequence. This field of RNA modification has been recently recognized as an important layer in post-transcriptional regulation of gene expression. The source of this emergence comes from the technical advances in the detection and mapping of chemically modified bases (339, 340). Transfer RNA (tRNAs) are the most modified RNA species, with up to 25% of their bases being post-transcriptionally modified (341, 342). tRNAs but also rRNA, snRNA, lncRNA, miRNA or mRNA, among others, can bear such modifications (341–343). These modifications can be simple methylations but also complex multistep transformation with incorporation of low-molecular-weight metabolites (341). A large number of modifications have thus been identified in coding and non-coding RNAs. While m⁶A is the most common mRNA reversible post-transcriptional modification (344), alternative reversible methylation can also occur on the carbon of the fifth position on cytosine (5-methylcytidine or m⁵C) or on the nitrogen of the first position on adenine (N¹-methyladenosine or m¹A). Other types of RNA modifications such as Cytidine-to-Uracil or Adenine-to-Inosine RNA editing (C-to-U or A-to-I, respectively) can lead to changes in the secondary structure of the edited RNA (345) and in the protein sequence encoded by the mRNAs in case of editing events taking place within the coding sequence (346). Pseudouridine, a C5-glycoside isomer of uridine, is necessary to support proper secondary and tertiary structures of rRNAs and tRNAs, thus affecting mRNA translation (347). Mechanistically, most of these RNA modifications involve writer and reader proteins. Others, such as m⁶A and m¹A, can involve additional eraser proteins allowing reversible and dynamic modifications (348). The writers are the RNA-modifying enzymes able to catalyze the transfer of the chemical group on the ribonucleotide targets (*e.g.*

methyltransferase), while the eraser proteins can reverse the modifications by specifically removing the chemical groups from the RNA targets. Finally, the readers are the RNA-binding proteins able to specifically bind the RNA bases bearing the chemical modification (see **Figure 7A**) (342, 358).

It is now well recognized that epitranscriptomics affects several molecular processes. In the immune system, while epitranscriptomics appears important during hematopoietic stem cell differentiation (359), it is currently viewed as a major mechanism that allows self- and non-self dsRNAs discrimination during innate responses (348, 360). Indeed, while dsRNA is a feature found in numerous viruses, endogenous dsRNAs are also found in healthy cells, originating from transcription of endogenous retroviruses, mitochondrial transcripts, or inverted-Alu repeat sequences (353, 361). This raises an important challenge for innate receptors (e.g. RIG-I or MDA5), since they need to discriminate between self and non-self dsRNA molecules. While evolutionary elimination of dsRNA sequences within cellular mRNAs has been observed, which should limit innate immune activation against host RNAs, dsRNAs remain frequent in pre-mRNAs (362). One way to circumvent this issue is through modification of dsRNAs in order to prevent their recognition by PRRs and downstream type I IFN responses. Such a mechanism is well illustrated by the Aicardi Goutieres Syndrom, an inflammatory disorder affecting mainly the brain and the skin and associated with aberrant type I IFN production. Aicardi Goutieres Syndrom is associated with mutations in ADAR1, a dsRNA specific adenosine deaminase responsible for the most common cellular RNA editing through hydrolytic deanylation of Adenosine to Inosine (A-I editing) (363, 364). In line with this, ADAR1 deficient human monocytes derived macrophages leads to increased RLR signaling and pro-inflammatory cytokines (e.g. IFNs, IL-1, IL-6) production.

Through A-I editing, ADAR1 appears to modify host dsRNAs, preventing their recognition by dsRNA innate sensors. Accordingly, mutant mice carrying an ADAR1 protein that is editing deficient (ADAR1^{E861A/E861A}) are embryonically lethal, and present over-activation of IFNs and dsRNA-sensing pathways. This deregulated innate responses are due to a lack of A-I editing in ADAR1 ADAR1^{E861A/E861A} embryos, as further shown by a decrease in A-I editing in a vast majority of RNA targets. Moreover, the phenotype of ADAR1 ADAR1^{E861A/E861A} can be rescued by a concurrent deletion of MDA5 (352). Similarly ADAR1^{-/-} mice are embryonically lethal and this phenotype can be rescued by crossing ADAR1^{-/-} to MAVS^{-/-} mice (348). In those double knock-out mice, the aberrant type I IFN response induced by ADAR deficiency is prevented by inhibiting the RLR pathway (348, 352). Likewise, ADAR1 deficiency confers A549 human lung epithelial cell lines with a lethal phenotype and MAVS ablation partially restores ADAR1^{-/-} cells' survival. However, in this cell type, full rescue of ADAR1^{-/-} lethality is obtained by an additional ablation of RNase L, an ISG induced upon dsRNA sensing that leads to translation arrest by cleaving rRNAs and mRNAs (see section *RNA Sensing and Regulation of PRR Activity by Non-PRR RBPs*). ADAR1 appears as an essential protein in protecting

host dsRNA from innate recognition, thus preventing aberrant innate responses against self (see **Figure 7B**) (348).

Altogether, these results led to the elegant hypothesis that editing of host RNAs by ADAR1 could prevent their recognition by innate sensors (e.g. RLR, RNase L) while viral RNAs, which are not edited, would trigger robust innate responses (348). However, in some contexts of infection, several studies have described ADAR1 as a proviral factor. This is notably the case following infection with Vesicular Stomatitis Virus (VSV) (365), Zika virus (366), HIV (367), HCV (364) or Measles Virus (368). One major mechanism by which ADAR1 promotes viral replication is through inhibition of PKR. As mentioned earlier (section *Viral RNA Translation Control*), PKR is an IFN-inducible protein that, following dsRNA recognition, phosphorylates eIF2 α , favors the formation of stress granules, and acts as a major inhibitor of global translation (for both cellular and viral mRNAs). ADAR1 mediated inhibition of PKR occurs in an editing-dependent or -independent way, and mostly requires direct interactions between ADAR1 and PKR (353, 369). ADAR1 is thus seen as an important inhibitor of self-recognition in homeostatic conditions, to prevent auto-immune disorder, but paradoxically might, in some context, favor viral replication following infection. Finally, two distinct isoforms have recently been described for ADAR1, a cytoplasmic isoform (p150) and a nuclear one (p110), endowed with pro- and anti-viral properties, respectively (370). This suggest additional levels for ADAR1 regulation, and further studies will be required to fully comprehend the overall impact of ADAR1 activity in homeostatic condition or following infection.

Other RNA modification mechanisms have been described, that allow induction of innate responses specifically towards viral RNAs, while protecting host RNA recognition by innate sensors. For example, PKR is able to recognize short stem loops in a 5' triphosphate dependent manner, knowing that 5' triphosphate are mostly present in viral or bacterial transcript (369). Likewise in DCs, RNA from bacteria that is devoid of nucleoside modifications, induces strong activation of TLR3, TLR7 and TLR8, while host RNAs carrying modified nucleosides (m⁵c, m⁶A, m⁵U, s²U or pseudo-uridine) induce little or no stimulation (371). Similarly, the presence of m⁶A modifications in host circular RNAs inhibits their recognition by PRR while unmodified circular RNAs, present mostly in viral genomes, are known to activate RIG-I leading to downstream stimulation of IFN gene expression (372). The latter example also emphasize the importance of nucleoside modification readers. Indeed, YTHDF2 reader allows the discrimination between host *versus* foreign circular RNAs through the binding and the sequestration of m⁶A containing host circular RNAs (372). m⁶A modification can have additional impact during innate immune responses, favoring the expression of important immune players. Thus, it has been shown in DCs that methyltransferase-like 3 (METTL3), a well know writer of m⁶A modification (373), catalyzes the m⁶A modification of membrane co-stimulatory molecules, CD40, CD80 and a TLR signaling adaptor Tirap, during DC maturation. These modifications are read by YTHDF1, which promotes their translation by associating with translation

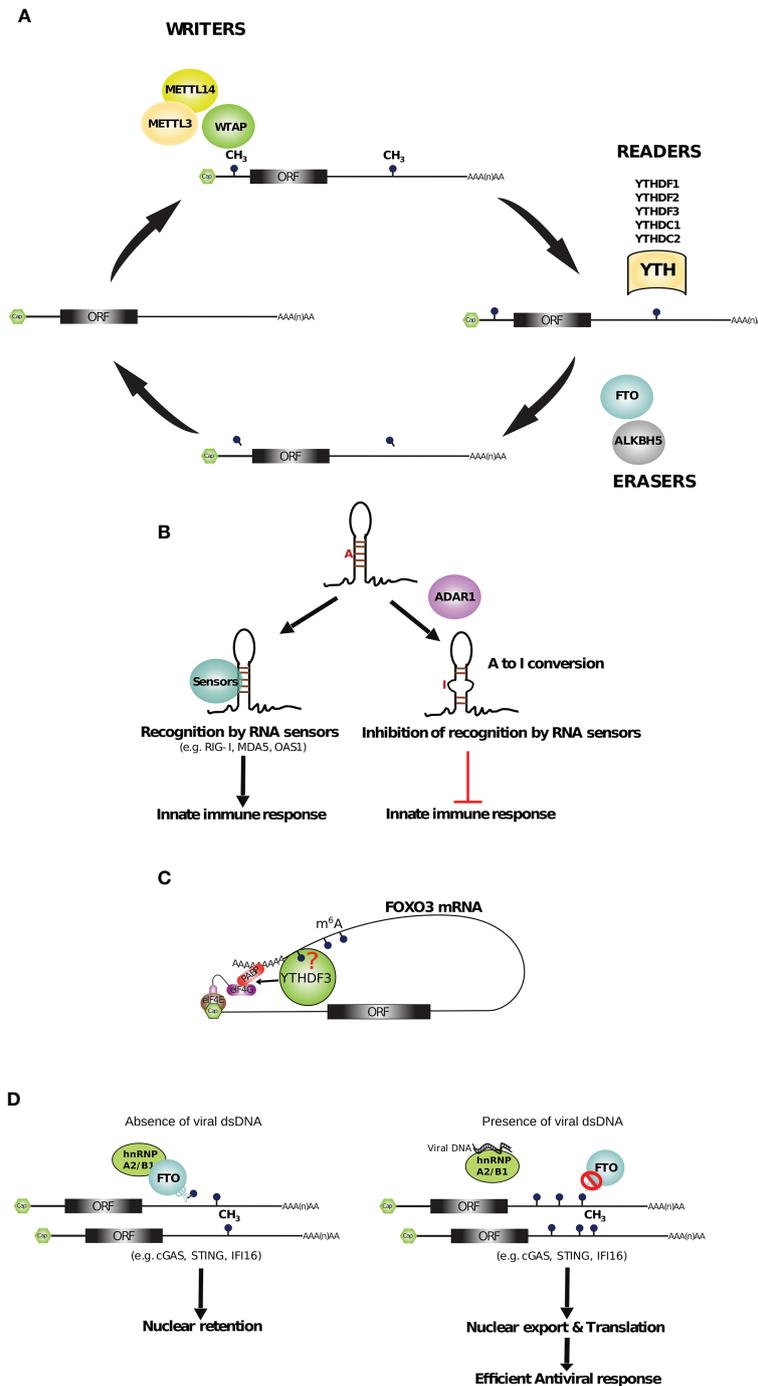


FIGURE 7 | RBPs mediated epitranscriptomic regulation of innate immunity. **(A)** m⁶A modifications, elicited by methyltransferases (METTL3, METTL14 and WTAP), are read by YTH domain-containing proteins (YTHDF1-3, YTHDC 1-2) and reversed by the erasers (FTO and ALKBH5) to dynamically control the gene expression at the post-transcriptional level (349–351). **(B)** Recognition of endogenous dsRNAs by RNA sensors (e.g. RIG-I, MDA5 and OAS1) induces an innate immune response. However, A-to-I mediated base editing mediated by adenosine deaminase ADAR1 inhibits this process (352–354). **(C)** YTHDF3 promotes FOXO3 mRNA translation by binding the 5'UTR and circularizing the mRNA. The requirement of m⁶A for YTHDF3 recruitment has not been elucidated yet (355). **(D)** On the left, hnRNP A2/B1 interacts with FTO, a m⁶A demethylase, to remove the m⁶A modifications from hnRNP A2/B1 mRNA targets. Thus, these mRNAs, important for the antiviral response, are retained into the nucleus. On the right, when viral DNA is sensed by hnRNP A2/B1, the interaction with FTO is disrupted and hnRNP A2/B1 targets, containing more m⁶A modifications, are exported to the cytoplasm to be translated and to activate an efficient antiviral response (356, 357).

initiation factors. m⁶A modifications thus lead to an increase of DC activation and function, promoting T-cell activation (360, 371, 374, 375). YTHDF3, another reader of m⁶A in RNAs has been shown to bind and promote translation of the transcription factor forkhead box protein O3 (FOXO3) RNA, a negative regulator of ISGs expression (355). By binding to the 5'UTR of FOXO3 transcript, YTHDF3 cooperates with PABP1 and eIF4G2 to stimulate its translation (see **Figure 7C**). Although YTHDF3 recognizes m⁶A modified RNA targets to regulate their translation, its recruitment to FOXO3 mRNAs appears independent of METTL3 mediated m⁶A addition. Nevertheless, the interaction depends on the hydrophobic pocket of YTHDF3 that is essential for m⁶A recognition thus suggesting that other methyltransferases could be involved in m⁶A addition on FOXO3 transcripts. Alternatively, YTHDF3 could interact with FOXO3 transcripts in a m⁶A-independent manner, or recognise other types of methylated bases (such as m¹A). Thus, YTHDF3 participates indirectly to the negative control of antiviral responses by promoting translation of ISG inhibitors to limit the risk of unnecessary inflammation (355). Similarly, upon viral infections, the nuclear RNA-helicase DDX46 has been shown to recruit the m⁶A demethylase protein ALKBH5 to the MAVS, Trif3 and Trif6 mRNAs inducing their nuclear retention to avoid their translation and prevent prolonged activation of the antiviral response (376). Dynamic m⁶A modification is also involved in the antiviral response against DNA viruses. For instance, the viral DNA sensor hnRNPA2B1, in addition to its role in inducing the IFN signaling pathway, has been shown to interact with mRNAs coding for many innate immunity factors such as cGAS, STING and IFI16 (an ISG) (356, 357). In the absence of infection, hnRNPA2B1 interacts with the m⁶A demethylase FTO to remove m⁶A from hnRNPA2B1 targets and induce their nuclear retention. Upon viral DNA sensing, the interaction between FTO and hnRNPA2B1 is disrupted, leading to increase m⁶A levels in hnRNPA2B1 target transcripts, therefore allowing their efficient nuclear export and translation to improve the antiviral response (**Figure 7D**).

Taken together, these results suggest that epitranscriptomics is a strategy used to prevent autoimmunity and balance the risk between an aberrant induction of innate response and self-tolerance (353, 362). However, more investigations are required to precisely apprehend the complex interplay between self-RNA and viral-RNA modifications, since factors involved in self-RNA disguise are not necessarily detrimental for viral RNA (and *vice versa*), suggesting that each of these factors is involved in several cellular mechanisms.

8 CONCLUSIONS AND PERSPECTIVES

Through their capacity to interact with specific RNA sequences, structural features or chemical modifications, RBPs orchestrate all steps of RNA metabolism from its synthesis, maturation and functional role, to its eventual decay. In the context of innate immunity, RBPs play multiple roles, acting at the first line of defense through their capacity to sense non-self RNAs and induce an immune response, being involved in the activation and effector

functions of innate immune cells by finely tuning the amplitude and temporal control of gene expression, and finally acting as key effectors of the antiviral response through their capacity to destroy foreign RNAs. The activity of RBPs is tightly regulated by numerous mechanisms that include control of their subcellular localization, competition with other RBPs for their RNA substrate, or post-translational modifications that modulate their activity. Working in a collaborative network with signal transducers, epigenetic modifiers, and canonical trans-acting factors, RBPs play important roles in developing a global and complex gene regulatory network. Illustrating their importance in finely tuning the innate immune response, numerous human pathologies, such as autoimmune diseases, are associated to mutations in genes coding for RBPs [for a review see (377)]. Technical developments such as the RNA interactome capture (RIC) (31) and CLIP-seq have facilitated the functional identification of new RBPs and the characterization of their exact RNA binding sites. To date, more than 1000 human encoded proteins have been shown to display RNA-binding capacity (378) and the precise RNA target sites for several hundreds of these RBPs have been mapped (62). Nevertheless, we are still far from understanding precisely the numerous roles of RBPs and their mechanisms of action in the context of innate immunity. The rapid development of efficient gene editing technologies coupled with new protocols to quantitatively monitor gene expression at multiple levels (transcription and degradation rates, splicing and translation) in bulk and single-cells, as well as methods to quantitatively assess the binding dynamics of RBPs in single-molecule or transcriptome-wide assays opens the door for new and exciting discoveries in the field of RBPs and innate immunity.

AUTHOR CONTRIBUTIONS

AG and ER determined the scope and focus of the review with feedback from AK and MW. AG drafted the manuscript with contributions from ER and MW. AK generated most figures with help from AG and ER. All authors contributed to the article and approved the submitted version.

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