Published in final edited form as:

Immunol Rev. 2013 May ; 253(1): 253–272. doi:10.1111/imr.12051.

Post-transcriptional regulatory networks in immunity

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Summary:

Post-transcriptional mechanisms that modulate global and/or transcript-specific mRNA stability and translation contribute to the rapid and flexible control of gene expression in immune effector cells. These mechanisms rely on RNA-binding proteins (RBPs) that direct regulatory complexes (e.g. exosomes, deadenylases, decapping complexes, RNA-induced silencing complexes) to the 3′-untranslated regions of specific immune transcripts. Here, we review the surprising variety of post-transcriptional control mechanisms that contribute to gene expression in the immune system and discuss how defects in these pathways can contribute to autoimmune disease.

Keywords

post-transcriptional regulation; RNA-binding proteins; mRNA decay; microRNAs; translational control; inflammation

Introduction

Transcription of mRNA is the first step in a complex process that leads to the production of protein. When activated, individual transcription factors induce the expression of a distinct set of genes (transcriptional regulons) that often encode components of a common functional program. This is accomplished by the recognition and activation of promoter elements to initiate target gene transcription. The directed production of distinct mRNA species leads to the synthesis of the proteins responsible for cellular growth, maturation, and effector function. In the immune system, this allows the production of specialized immune effector cells.

Although transcription is an essential step in the regulation of gene expression, post-transcriptional control mechanisms play an especially important role in regulating the expression of immune effector proteins. These mechanisms can re-program gene expression at a global level or modulate the stability and translation of specific immune transcripts. Although mechanisms of global control depend on the activity/availability of general factors involved in mRNA maturation or translation, transcript-specific regulation depends on action

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of individual trans-factors that can bind either individual mRNAs or subsets of related mRNAs. Because mRNAs that encode proteins involved in a common functional program (post-transcriptional regulons) often possess common regulatory elements, coordinate protein expression drives specific functional programs in the cell. This allows specific functional programs to be rapidly turned on or off in response to exogenous stimuli.

Eukaryotic mRNAs are born in the nucleus as capped, polyadenylated, and spliced transcripts that acquire distinctive protein ‘coats’. Every step of transcript processing is regulated by nuclear quality control mechanisms (reviewed in 1). Following these processing steps, mature mRNAs are transported from the nucleus into the cytoplasm as mRNPs (messenger ribonucleoprotein particles). The composition of the mRNP determines the functional fate of individual transcripts. Cytoplasmic mRNPs can be engaged by the translational machinery to initiate a ‘pioneer’ round of translation that ensures the presence of start and stop codons required for protein synthesis. Some mRNPs are rendered translationally silent for transport to sites where protein synthesis is required. Other transcripts are rapidly degraded before protein synthesis can occur. Each of these functional fates is determined by RNA-binding proteins (RBPs) or antisense RNAs (such as microRNAs [miRNAs]) that target specific mRNAs. These interactions typically occur within 5′- and 3′-untranslated regions (UTRs) of mRNAs. RNA-binding proteins can stabilize/destabilize their target transcripts and/or inhibit/stimulate their translation. In contrast, miRNAs typically repress translation and stimulate degradation of their target mRNAs. Molecular details of these processes, consequences of cross-talk between miRNAs and RBPs, and implications for immunity are discussed below.

Here, we review the post-transcriptional mechanisms known to modulate immune function. We focus on recent findings implicating general and transcript-specific aspects of mRNA metabolism in the regulation of the immune response, and discuss how mRNA quality control, subcellular localization, decay, and translation of cytokine transcripts contribute to immune function in health and disease.

mRNA turnover regulation in immunity

Cytoplasmic mRNA turnover plays a central role in the determination of mRNA fate. The mRNA decay machinery is the major effector of mRNA quality control and also determines the half-lives of individual transcripts. This machinery relies on protein constituents possessing distinct ribonucleolytic activities that mediate mRNA deadenylation [shortening or removal of the poly(A) tail at the mRNA’s 3′-end], decapping [hydrolysis of the 5′-cap structure (m^7G)], 5′-3′ or 3′-5′ exoribonucleolytic decay, and in some cases endoribonucleolytic cleavage. Since the 5′-cap and poly(A)-tail play important roles in mRNA translation, these unique *cis*-elements are regulated both by translation and mRNA decay machineries.

Deadenylation is the first step in the canonical mRNA decay process. Deadenylases are often associated with regulatory proteins that reside in multi-subunit complexes (reviewed in 2, 3). These multi-subunit complexes can homodimerize and heterodimerize to assemble unique higher order complexes with diverse enzymatic and regulatory functions (2). Three different

deadenylases are capable of shortening poly(A) tails: (i) a homodimer of poly(A) ribonuclease (PARN), (ii) a multi-subunit complex CCR4-POP2-NOT1 containing CCR4a (CNOT6), CCR4B (CNOT6L), CAF1A (CNOT7), and POP2 (CNOT8, CAF1B) deadenylases associated with regulatory NOT factors, and (iii) a complex of PAB-specific ribonuclease 2 and 3 (PAN2/3). Proteins associated with specific mRNAs determine which deadenylase complex is recruited to which transcript. By removing the poly(A) tail from targeted transcripts, these deadenylase complexes displace polyadenylate-binding protein (PABP) to eliminate communication between poly(A) tail and the cap structure that is pivotal for efficient translation.

Removal of PABP allows the activation of the decapping enzymes that remove m^7G from the 5′-ends of mRNAs (4). A decapping complex consisting of DCP1A and DCP2 decapping enzymes in association with the regulatory factors EDC3 and Hedls (also referred to as Ge-1 and Edc4) are responsible for hydrolysis of the cap structure (5). Under steady-state conditions, the cap is protected from these decapping enzymes by bound cap-binding eIF4F complex (consisting of translation initiation factors eIF4E, eIF4A, and eIF4G), which communicates with the poly(A) tail through direct binding to PABP molecules. As a consequence of deadenylation, the PABP-eIF4F connection is disrupted, allowing the decapping complex to bind to and hydrolyze the cap structure.

Following deadenylation/decapping, the mRNA body is degraded by exonucleases that act in 5′-3′ (XRN1 exonuclease) or 3′-5′ (exosome-associated exonucleases RRP44 [hDIS3] or PM-SCL75 [RRP45, EXOSC10]) directions. In some cases, decay of specific mRNAs is initiated by endoribonucleolytic cleavage within its body followed by degradation in both 5′-3′ and 3′-5′ directions. This alternative decay mechanism plays important roles in the elimination of transcripts bearing premature stop codons (nonsense-mediated mRNA decay [NMD]) and in the regulation of specific mRNA transcripts by endoribonuclease ZC3H12A (see below).

ARE-mediated mRNA decay

Twenty-five years ago, clusters of adenine and uridine-rich elements (AREs), were found in 3′-UTRs of short-lived cytokines and were proposed to regulate some aspects of their metabolism (6, 7). Multiple subsequent studies confirmed the significance of these motifs in the regulation of cytokine mRNA stability and translation. ARE-mediated mRNA decay (AMD) was first demonstrated by inserting an ARE derived from granulocyte-macrophage colony-stimulating factor (GM-CSF) transcripts into a stable heterologous reporter transcript, a modification that strongly destabilizes the reporter mRNA (7). At the same time, deletion of AREs from the 3′ UTRs of tumor necrosis factor-α (TNF-α) or interleukin-3 (IL-3) transcripts was shown to inhibit AMD and enhance mRNA and protein expression (8, 9).

Although AUUUA pentamers and UUAUUUAUU nonamers are considered to be canonical AREs, large clusters of overlapping and scattered AU-rich motifs are typical for many cytokines. AREs have been classified into different classes according to their sequence composition and deadenylation (poly-A tail shortening) kinetics (10, 11). Class II AREs

(e.g. TNF-α, GM-CSF, and IL-3) contain several partially overlapping AUUUA pentamers within 50–150 nucleotides with U-rich context (10), while class I AREs (e.g. c-fos, c-myc) have fewer non-overlapping AUUUA pentamers (11). Interestingly, class III AREs (e.g. c-Jun) completely lack the AUUUA pentamer (11). Typical AREs are 50–150 nucleotides long, with the UUAUUUAUU nonamer acting as the minimal sequence element that can induce modest mRNA degradation (12, 13). Mutations within AUUUA pentamers inhibit AMD. As for the difference in the deadenylation kinetics, class II AREs trigger efficient and rapid shortening of the poly-A tail, while class I and III AREs trigger less rapid decay (10, 11). As a unifying feature, a general high content of uridylate residues within the ARE is absolutely required for its destabilizing activity.

AMD is an evolutionarily conserved regulatory mechanism that functions in a variety of mammalian cell types and different species. First discovered in cytokine transcripts, AREs are also found in mRNAs encoding growth factors, nuclear transcription factors, and proto-oncogenes. Although the presence or absence of an ARE is not an absolute reflection of mRNA stability, it has been estimated that 5–10% of all human mRNAs contain functional AREs (14), making this element the most common determinant of RNA stability in mammalian cells.

AREs recruit numerous ARE-binding proteins (ARE-BPs) that determine the stability of target transcripts. To date, more than 20 different ARE-BPs have been identified; well-known members include the tristetraprolin (TTP or Zfp36) family members TTP (15), BRF1, and BRF2 (butyrate response factors 1 and 2) (16), the ELAV family members (HuR, HuB, HuC, HuD) (17), AUF1 (hnRNP D), and its isoforms (18), TIA-1 (19), TIAR (19), KSRP (the KH splicing regulatory protein) (20), FXR1P (21), YB1 (22), and CUGBP2 (23). Depending on the ARE-containing 3′-UTR sequence and ARE-containing mRNA (ARE-mRNA) localization in the cell, the composition of individual ARE-containing mRNPs can vary significantly. Each ARE-BP has distinct regulatory function(s): TIA-1, TIAR, CUGBP2, and FXR1P inhibit the translation of ARE- mRNAs (19, 21, 24); KSRP, TTP, BRF1, and BRF2 destabilize ARE-mRNAs (15, 16, 25); AUF1 isoforms either promote or inhibit mRNA decay (26-28); YB1 and HuR stabilize ARE-mRNAs (22, 29, 30); and HuR can both promote (31) and inhibit translation (32). Although sequence specificities of many ARE-BPs have been identified, distinct ARE-BPs physically interact with each other and can have redundant, additive, or competitive functions on the same target transcript (33-37). As ARE-mRNPs can be composed of several ARE-BPs, the functional outcome is determined by the combined effect of these ARE-BPs on target ARE-mRNA stability and translation. Table 1 gives an overview of immunity-related genes whose expression is regulated by RBPs including ARE-BPs.

TTP is one of the best-characterized ARE-BPs. It is an endotoxin-inducible zinc finger protein and early response factor that destabilizes several pro-inflammatory cytokine mRNAs such as TNF-α, GM-CSF, IL-1β, and IL-2 (15, 64, 75, 80, 115). TTP is part of a negative feedback loop that controls excessive pro-inflammatory cytokine production in response to endotoxin action and prevents the development of septic shock (116). Mice lacking TTP develop a severe autoimmune syndrome characterized by arthritis, cachexia, dermatitis, myeloid hyperplasia, and formation of autoantibodies due to the excessive release

of TNF-α and GM-CSF by macrophages and neutrophils (116). The administration of TNF antibodies significantly alleviates this systemic inflammatory syndrome (116, 117). This phenotype is similar to that of genetic knockin mice that lack the ARE region of TNF-α (8), suggesting that control of TNF-α mRNA stability plays a critical role in modulating the inflammatory response in general and synovial inflammation in particular. In human T cells, TTP also regulates production of IL-17, a cytokine involved in the innate immune response and pathogenesis of inflammatory diseases. TTP binds to the 3′-UTR of IL-17 transcripts in a region that contains eight ARE/ARE-like motifs. TTP overexpression enhances and TTP depletion inhibits IL-17 mRNA decay (97), suggesting that IL-17 is a physiological TTP target.

Other members of the TTP family, BRF1 and BRF2, are close homologues of TTP that share a high degree of sequence identity in their tandem C_3H zinc finger domains, but differ in their C- and N-terminal domains (118). Genetic studies in mutant cell lines lacking expression of BRF1 or overexpressing BRF1/BRF2 suggest, similarly to TTP, that these proteins induce AMD of various cytokine mRNAs including TNF-α and GM-CSF (16, 84, 119, 120). In contrast to TTP knockout mice, BRF1-deficient mice are embryonically lethal (121) and BRF2 knockout mice die within 2 weeks of birth (122). Interestingly, mice expressing N-terminally truncated BRF2 are viable but exhibit complete female infertility (123). All these data suggest that although TTP/BRF1/BRF2 share common functions in AMD and immunity, these proteins also have non-redundant roles in embryonic development, fertility, and haematopoiesis.

Similarly to TTP, AUF1 is part of the negative feedback loop of the innate response to endotoxin (27). This protein binds with high affinity to AREs of many short-lived mRNAs including cytokines (18, 124). Several splice isoforms of AUF1 (p37, p40, p42 and p45) have been described (125), and individual AUF1 isoforms differ biochemically in their affinity toward AU-rich elements, target specificity, and effect on target mRNA stability (18). AUF1-knockout mice display symptoms of severe endotoxic shock as a result of excessive production of TNF-α and IL-1β (27). This is due both to the absence of AUF1 isoforms (p37, p42, and p45) that degrade selected ARE-mRNAs (27) and to the absence of the p40 isoform that selectively stabilizes IL-10 transcripts (126) that play a critical role in the suppression of inflammatory responses. Moreover, mice lacking AUF1 exhibit an altered size and proportion of splenic B-cell subsets due to the increased apoptosis in splenic B-cell follicles. AUF1 knockout mice develop spleens of reduced size that contain approximately half as many lymphocytes as wildtype spleens. This observation suggests that AUF1 plays an important role in regulating splenic lymphocyte cellularity and splenic follicular B-cell maintenance (127). Moreover, AUF1-deficient mice develop chronic pruritic inflammatory skin disease that has clinical and histological features of human atopic dermatitis. Histological analysis of chronic skin lesions demonstrates marked epidermal acanthosis with spongiosis and prominent dermal and epidermal leukocyte infiltration. AUF1 knockout mice display elevated serum IgE levels and increased contact sensitivity. Macrophages and T cells from AUF1-deficient mice demonstrate a number of abnormalities associated with dermatitis including T-cell hyperproliferation, increased ability of macrophages to be recruited to sites of inflammation, and increased production of TNF-α, IL-2, and IL-1β (128). AUF1 does not directly target degradation of mRNAs (129). Rather, it modulates decay by complexing with

different co-factors such as heat shock proteins HSC70 and HSP70, translation initiation factor eIF4G, and poly(A)-binding protein (130-132). Interestingly, AUF1-mediated mRNA decay is associated with physical displacement of eIF4G from AUF1 followed by ubiquitination of AUF1, and degradation of ubiquitinated AUF1 by the proteosome (26). These results imply a functional coupling of AUF1 mRNA decay with the translation initiation machinery, stress response (heat shock pathway), and the ubiquitin-proteosomal degradative network. The peptidyl-prolyl isomerase PIN1 is another binding partner of AUF1 in eosinophils and T lymphocytes. In these cells, PIN1 associates with AUF1 to destabilize GM-CSF mRNA (65, 133).

KSRP is another protein that binds to selected AREs through its KH domains and destabilizes selected ARE-mRNAs (25). Overexpression of KSRP markedly downregulates while siRNA-mediated knockdown upregulates expression levels of more than 100 related mRNAs encoding inflammatory proteins such as IL-8, TNF-α, and inducible nitric oxide synthase (iNOS) (93). Interestingly, KSRP knockout mice are viable and do not exhibit obvious abnormalities (68). Mouse embryonic fibroblasts (MEFs) derived from KSRP$^{-/-}$ mice exhibit higher levels of ARE-containing type I interferon (IFN) transcripts, and the increased levels of type I IFN provides resistance against vesicular stomatitis virus (VSV) and herpes simplex virus 1 (HSV-1) infection (68). These findings highlight the function of KSRP in innate immunity as a negative regulator of IFN production.

In contrast to TTP/BRF1/BRF2, AUF1, and KSRP that promote ARE-mRNA destabilization, HuR stabilizes target ARE-mRNAs (reviewed in 134). Recent studies have identified HuR-binding sites in more than 7,000 transcripts, and many of these binding sites are found in U-rich regions within the 3′-UTR (135). In macrophages and T cells, HuR associates with several mRNAs encoding pro-inflammatory proteins such TNF-α, GM-CSF, IL-6, IL-8, cyclooxygenase-2 (COX-2), and iNOS (35, 53, 73, 136-138). Peritoneal macrophages isolated from mouse strains expressing TNF-α mRNA containing a trinucleotide mutation/insertion in an HuR-binding site produce lower amounts of TNF-α protein upon stimulation with lipopolysaccharide (LPS) or IFNγ (139). These mice also develop an autoimmune syndrome that resembles systemic lupus erythematosus in humans (140, 141); the onset of this syndrome can be delayed by injecting recombinant TNF-α (142), suggesting a positive role for HuR in TNF-α expression. Although the genetic deletion of HuR in mice leads to embryonic lethality (143), genetic studies using approaches of conditional manipulation of HuR expression further illuminate the importance of this protein in immunity. Mice with a conditional knockout of HuR in thymocytes have defects in T-cell development, proliferation, and migration (144), demonstrating the importance of HuR for adaptive immunity. Surprising results came from studies in transgenic mice conditionally overexpressing HuR in myeloid cells, where HuR appeared to function as a negative modulator of inflammation *in vivo* (32). Contrary to expectations, LPS-induced macrophages derived from these mice express lower levels of key inflammatory mediators such as TNF-α and COX-2. Moreover, HuR overexpressing mice clearly reduce concanavalin A-induced hepatic inflammation and damage. Further analysis suggested that although HuR stabilizes TNF-α and COX-2 mRNAs, it suppresses their translation by cooperation with TIA-1, a known translational silencer (32). The complexity of HuR functions was further demonstrated in studies using mice lacking HuR in myeloid lineage

cells. Myeloid loss of HuR sensitizes mice to systemic pathologic inflammation, manifest by a polarized proinflammatory response that enhances progression and maintenance of inflammatory colitis and colitis-associated cancer. Bone marrow-derived macrophages from these mice demonstrate normal macrophage activation and function in terms of Toll-like receptor (TLR) signaling engagement, pinocytosis, and phagocytosis, expression of markers and pattern recognition receptors. At the same time, macrophages exhibit exacerbations in the balance of proinflammatory and homeostatic states governing the extent of the inflammatory response including increased accumulation of IL-6 mRNA and IL-6 protein secretion, a key acute-phase protein and mediator of colitis-associated cancer. HuR-deficient macrophages exhibit enhanced chemotaxis to CCR2 signals. Surprisingly, and in contrast to the role of HuR as general mRNA stabilizer, this is due to mRNA stabilization of the chemokines CCL2 and CCL7 and their receptors (CCR2 and CCR3), which mediate macrophage chemotaxis in acute inflammation and cancer (145). Moreover, the classical ARE-containing transcripts TNF-α and COX-2 appear unaffected by the loss of HuR (145), despite their increased stability when HuR is overexpressed (32). As HuR is known to interact with other ARE-BPs such as CUGBP2, KSRP, and AUF1 (reviewed in 146, 147), it is suggested that HuR acts in a pleiotropic fashion through multiple physical and functional interactions with different ARE-BPs and ARE-mRNAs.

How do ARE-BPs modulate mRNA stability? Experiments in which ARE-BPs (such as TTP) are directly tethered to non-ARE-containing mRNA reporters show that physical interaction of an ARE-BP to mRNA is sufficient to induce rapid reporter decay. Although purified recombinant ARE-BPs do not possess exoribonuclease activities, they function by recruiting components of the mRNA decay machinery, including the exosome complex, the deadenylases PARN, PAN2/PAN3, and/or CCR1-POP2-NOT1 complexes, the decapping enzymes DCP1A and DCP2, and the 5′-3′ exoribonuclease XRN1. For example, TTP family members bind the exosome, XRN1, and decapping enzymes (148-150), and KSRP binds to the exosome, PARN, DCP2, and XRN1 (25, 151). Similarly, HuR competes with mRNA destabilizing ARE-BPs for binding to selected AREs, thus displacing them from mRNA and blocking the action of deadenylases.

Non-ARE-mediated mRNA turnover

Although the ARE is the most common sequence (besides microRNA-binding sites) that regulates mRNA stability, other regulatory elements have been described in transcripts encoding proteins implicated in immunity. A single mRNA often contains several different regulatory elements that coordinately determine rates of mRNA stability and translation. For example, the 3′-UTR of TNF-α mRNA encodes both an ARE and a downstream constitutive decay element (CDE) (107). In macrophages, CDE-mediated decay is refractory to stimulation with LPS and serves as a fail-safe mechanism that prevents the pathological overexpression of TNF-α under conditions when the ARE is inactive. Similarly, in addition to its ARE, G-CSF (granulocyte colony-stimulating factor) mRNA contains a stem-loop destabilizing element (SLDE) in its 3′-UTR. The SLDE prevents stabilization of G-CSF mRNA under conditions in which AMD is inhibited to maintain stringent control over G-CSF production (62).

Regulation of IL-2 mRNA decay is a complex process. In unstimulated T cells, an ARE in the 3′-UTR of IL-2 transcript mediates rapid degradation via AMD. In stimulated cells, IL-2 mRNA is stabilized by simultaneous inhibition of AMD and the c-Jun N-terminal kinase (JNK)-dependent recruitment of nucleolin and YB-1 proteins to a specific *cis*-element in 5′-UTR called the JNK-responsive element (JRE) (22, 152). Besides binding of these proteins to JRE, binding of nuclear factor 90 (NF90) to the ARE-containing subregion of the 3′-UTR further slows down the degradation of IL-2 mRNA (82).

Vascular endothelial growth factor (VEGF) functions to link angiogenesis and inflammation in an oxygen-dependent manner. Under normoxic conditions, VEGF mRNA is intrinsically labile but in response to hypoxia the mRNA is stabilized. Three distinct and independent destabilizing elements contribute to the rapid decay of VEGF mRNA: an element in 5′-UTR, an ARE in the 3′-UTR and a coding region determinant of instability (110-112). Although each of these elements can cause rapid decay of mRNA reporters, their cooperative action is required for mRNA stabilization in response to hypoxia. As in the case of IL-2 mRNA, cooperative binding of distinct factors is required for VEGF mRNA stabilization: HuR binding to the 3′-UTR (112), and binding of a complex containing polypyrimidine tract-binding protein (PTB) and YB-1 to two sites in the 5′- and one site at the 3′-UTR (110). Interestingly, YB-1 and PTB are also implicated in mRNA turnover of other short-lived transcripts, suggesting a general role for these factors in mRNA turnover. YB-1 directly binds to the ARE of GM-CSF mRNA to enhance its stability (153), while a complex containing PTB and nucleolin binds to a CU-rich region in the 3′-UTR of CD154 (CD40L) mRNA to stabilize this transcript during T-cell activation (44, 48, 50). In B cells, a PTB-containing complex also stabilizes Rab8A mRNA upon TLR9 activation by unmethylated CpG DNA (105).

The GU-rich (GRE) consensus sequence, UGUUUGUUUGU, was identified as a sequence that is highly overrepresented in the 3′-UTR of short-lived transcripts expressed in human T cells (such as TNF receptor 2, c-jun, and CD9) (43). Insertion of a GRE into the 3′-UTR of a heterologous mRNA reporter promotes mRNA decay (154). In human cells, the GRE is a target of CUG-binding protein 1 (CUGBP1, CELF1), an RNA-binding protein that mediates mRNA decay by recruiting PARN to stimulate poly(A) tail shortening (155).

Mast cells play a number of different functions in immune responses (156). Although all mast cells are derived from a common progenitor, they exhibit differential expression of the chymase family of serine proteases in a tissue-specific manner. While mouse mast cells residing in the intestinal mucosa abundantly express mouse mast cell protease-1 (mMCP-1) and mMCP-2, those in the peritoneal cavity and skin preferentially express mMCP-4 and mMCP-5. Interestingly, immature bone marrow-derived mast cells efficiently transcribe all four of these mMCP genes, but exhibit high steady-state mRNA levels of mMCP-5 and not of mMCP-1, mMCP-2, and mMCP-4. In response to IL-10, mMCP-2 mRNA levels are increased due to a prolongation of their half-life, suggesting that mMCP-2 mRNA is regulated primarily post-transcriptionally. Analysis of the 3′-UTRs of mMCPs does not reveal the presence of AREs or other known destabilizing *cis*-elements. A repetitive C-rich sequence (CRS: UGXCCCC where X is any nucleotide) was identified in the 3′-UTRs of mMCP-1, mMCP-2, and mMCP-4 but not in the mMCP-5 transcripts (102). Although the

functional importance of CRS motifs remains to be determined, it is likely that this element is responsible for the constitutive decay of CRS-containing transcripts through the action of unknown *trans*-factors.

ZCCHC11-mediated stabilization of IL-6 mRNA

The zinc finger protein ZCCHC11 (terminal uridyltransferase 4) has uridyltransferase activity allowing addition of nongenome-encoded uridine to the 3′-ends of target RNAs (88). Analogous uridylation of histone transcripts is used to promote their degradation (157). Knockdown of ZCCHC11 in A549 human alveolar epithelial cells inhibits TNF-induced secretion of inflammatory cytokines (such as IL-6, CCL5, VEGF, and TGFβ). Depletion of ZCCHC11 reduces IL-6 mRNA levels, a consequence of increased IL-6 transcript decay (88). Remarkably, ZCCHC11 uridylates members of the miRNA-26 family, which represses the expression of IL-6 mRNAs by promoting their decay, and targets them for degradation (88). By eliminating miRNA-26 species, ZCCHC11 stabilizes IL-6 transcripts.

ZC3H12A-mediated cleavage of cytokine mRNAs

ZC3H12A (MCPIP1, CCL2-induced ribonuclease) is a protein containing a single C_3H zinc finger and a characteristic PIN (PilT N-terminus) endoribonuclease domain (89, 158). Mice lacking the *Zc3h12a* gene die within 12 weeks due to severe anemia and the development of a systemic autoimmune syndrome characterized by severe splenomegaly, augmented serum immunoglobulin levels, autoantibody production, expansion of plasma cells, and infiltration of plasma cells in the lung. In response to TLR ligands, macrophages from ZC3H12A knockout mice show highly increased levels of IL-6 and IL12b (IL-12p40) but not TNF-α (89). While the activation of TLR signaling pathways is normal, IL-6 mRNA decay is severely impaired (89). Overexpression of ZC3H12A promotes IL-6 mRNA degradation by direct cleavage of putative destabilizing elements within the 3′-UTR of IL-6 transcripts (89, 91). Recently, IL-1β transcripts were identified as another target of the MCPIP1 endoribonuclease (77). Altogether, these data demonstrate that ZC3H12A is an important negative regulator of the inflammatory response.

Nonsense-mediated mRNA decay

Newly synthesized mRNAs are delivered to the cytoplasm in the form of mRNPs whose composition reflects their ‘nuclear history’ of mRNA processing (e.g. splicing, capping, and polyadenylation). These proteins provide information that is decoded by mRNA quality control mechanisms used to determine cytoplasmic fate. NMD is an mRNA surveillance mechanism that detects and eliminates mRNAs with premature termination codons (PTCs) (reviewed in 159, 160). Such transcripts encode C-terminally truncated proteins that may be non-functional or toxic or could act as dominant-negative inhibitors of normal cell function. The sources of PTC-containing transcripts are genomic DNA mutations, errors of DNA replication and DNA repair, DNA recombination events, and errors of RNA transcription/processing. Moreover, genome-wide studies showed that NMD also regulates the abundance of up to 5% of properly processed mRNAs (non-PTC mRNAs) (161), suggesting a role for NMD in cellular processes in addition to mRNA quality controls.

NMD is a splicing- and translation-dependent mechanism. UPF proteins (UPF1-3) play important roles in this process in all organisms. During splicing, protein complexes [so-called exon junction complexes (EJCs)] are deposited 20–24 nucleotides upstream of every exon-exon junction (162). During the first (or pioneer) round of translation, EJCs located upstream of the stop codon are ‘stripped off’ by translating ribosomes (163). If the translating ribosome is terminated at a PTC, the ribosome may not remove all of the EJCs from the mRNA. In this case, the transcript is targeted for degradation. Although the molecular mechanisms of this process are not fully understood, physical interactions between the terminating ribosome, UPF proteins, the EJC, and PABP determine whether the stop codon is physiological or premature (164-166). PTC-containing transcripts are marked for degradation by interactions between UPF1 protein and the SMG5-SMG6-SMG7 complex that directs mRNAs for decay through two pathways: (i) SMG6-mediated endonucleolytic cleavage followed by exonucleolytic degradation of fragments by 5′-3′- and 3′-5′ exonucleases; (ii) decapping/deadenylation followed by exonucleolytic decay (167, 168).

The immunoglobulin (Ig) and T-cell receptor (TCR) genes require programmed rearrangements and other ‘nontemplate’ mechanisms to generate a diverse set of functional receptors that recognize different antigens. An important consequence of such manipulations is the increased receptor repertoire. However, such rearrangements often change the reading frame to generate PTCs. The resulting truncated non-functional TCRs and Igs may cause defects in the development and function of T and B lymphocytes (169). The mRNA levels of PTC-containing mRNAs encoding these non-functional receptors are much lower than mRNAs encoding functional TCRs and Igs (170-176). The observed difference is not due to different rates of transcription but rather to the preferential degradation of PTC-bearing transcripts. Although detailed molecular mechanisms of this downregulation are not clear, this RNA surveillance is translation-dependent and at least partially relies on the action of the classical NMD machinery (177-179).

Presentation of endogenous peptides on major histocompatibility complex (MHC) class I molecules allows the immune system to distinguish between self and nonself. These peptides are mainly derived from proteosome-mediated protein turnover. Recently, translation of PTC-containing transcripts has been proposed to be an alternative source of peptides that are loaded into MHC class I for antigen presentation (180). While newly synthesized mRNA is undergoing the pioneer round of translation, PTC-containing transcripts synthesize C-terminally truncated proteins. These truncated proteins are then processed into peptides by the proteosome to eliminate potentially deleterious effects on cell physiology. The same peptides are also selected for antigen presentation by the MHC class I pathway (180).

Cross-talk between RNA-binding proteins and microRNAs

Mature miRNAs are produced by sequential processing of pre- and pri-miRNAs by the ribonucleases Drosha and Dicer. The resulting short double-stranded RNA binds to argonaute proteins (AGOs) and is incorporated into the RNA-induced silencing complex (RISC) that uses the AGO-associated guide RNA strand as a template for recognizing

complementary mRNA targets. Upon binding its target transcript, miRNA/RISC then causes inhibition of mRNA translation and/or degradation. miRNAs are known to contribute significantly to the post-transcriptional regulation of genes involved in immune functions (reviewed in 147, 181, 182). For example, conditional knockout of DICER in B-cell progenitors causes a developmental block at the pro- to pre-B-cell transition, and Dicer deletion in cortical thymocytes affects iNKT cell differentiation (183, 184).

Even more abundant than AREs, miRNA-binding sites are estimated to be present in 30% of the human protein-coding genome (185). Interestingly, compared to the rest of the genome, predicted miRNA-binding sites are more frequent in immune genes. Within immune genes, transcription factors, co-factors, and chromatin modifiers are major targets, while upstream signaling factors such as ligands and receptors are in general non-targets of 'immuno-miRNAs'. About 10% of the predicted miRNA-regulated immune genes are targeted by eight or more different miRNAs and they include key immune regulatory genes such as SMAD7, BCL6, and NFAT5 (186). Factors involved in the regulation of ARE-containing transcripts such as HuR, TTP, AUF1, and KSRP are also heavily regulated by one or more miRNAs (186, 187). Taking into consideration that single ARE-BPs simultaneously regulate expression of many mRNAs, a single miRNA controlling ARE-BP expression may indirectly regulate multiple immunomodulatory genes.

While certain miRNAs regulate expression of ARE-BPs, ARE-BPs can also regulate expression of miRNAs. For example, KSRP participates in the processing of multiple miRNAs including let-7 and miR-155 that control TLR signaling (188, 189) and HuR downregulates processing of miR-7 (190). AUF1 directly binds to the coding region and 3′-UTR of DICER mRNA causing its destabilization. AUF1 overexpression downregulates while AUF1 depletion upregulates DICER protein levels. Since DICER is indispensable for miRNA maturation, AUF1 indirectly suppresses the miRNAome by reducing Dicer production (191).

miRNAs and ARE-BPs can interact with each other to regulate the expression of selected transcripts. The first report linking AMD and miRNA-mediated decay came from studies of reporter genes bearing the TNF-α ARE: knockdown of DICER, AGO1, or AGO2 also inhibited AMD of reporter transcripts in *Drosophila melanogaster* S2 cells and human HeLa cells (192). In addition, TTP associates with AGO proteins providing a mechanistic link between miRNA- and ARE-mediated machineries. Moreover, miR-16, a human miRNA containing an UAAAUAUU sequence that is partially complementary to the ARE sequence, is required for turnover of a TNF-α ARE-reporter transcript. These data suggest that miRNAs with appropriate sequence complementarity can recruit RISC to the ARE and thus mediate part of the repressive effect (192), although a recent report strongly argues that AREs can function independently of miRNAs (193). Another study shows that HuR, which typically promotes translation of its target transcripts, cooperates with let-7 miRNAs to repress the expression of MYC transcripts. HuR-mediated inhibition requires both HuR and AGO2-let-7 complexes to bind adjacent sites in the 3′-UTR of MYC mRNAs (194). In response to environmental stress, HuR translocates from the nucleus to the cytoplasm to regulate the expression of specific transcripts. One of them, cationic amino acid transporter 1 (CAT-1), is repressed by miR-122 under normal conditions. In response to amino acid

starvation, miR-122-mediated repression is relieved by the binding of HuR to CAT-1 transcripts or mRNA reporters possessing the CAT-1 3′-UTR (195). Similarly, the translational silencer FXR1 paradoxically converts the TNF-α ARE from a repressor of translation to an activator of translation. Stress recruits FXR1 and AGO2 to a TNF-α ARE-containing mRNA reporter and increases translation of the reporter protein. This stress-induced translational activation requires miR-369-3, a miRNA with a 5′-seed region complementary to the TNF-α ARE. Mutations in the ARE of TNF-α that disrupt complementarity to miR-369-3 or knockdown of miR369-3 precursor RNA abolish stress-induced translational activation of this TNF-α ARE reporter (196, 197), suggesting that under some conditions, miRNAs can specifically enhance protein translation.

Translational control of immunity

Post-transcriptional control mechanisms often target the initiation step of translation, a complex multistep process requiring the action of more than a dozen initiation factors (eIFs) (198, 199). Two steps of the translation initiation process are under particularly stringent control: (i) the initiation factor eIF2 (eIF2$\alpha/\beta/\gamma$) -dependent recruitment of the initiator tRNA ($tRNA_i^{Met}$) to the ribosome, and (ii) binding of the major cap-binding protein eIF4E (which combines with eIF4G and eIF4A to assemble the eIF4F complex) to the 5′ cap structure of mRNA. In the first step, ternary complex consisting of eIF2$\alpha/\beta/\gamma$/$tRNA_i^{Met}$/GTP joins with other early initiation factors and the 40S ribosomal subunit to assemble the 43S pre-initiation complex. This complex allows $tRNA_t^{Met}$ to recognize the AUG start codon to initiate protein synthesis. Start codon recognition results in hydrolysis of GTP to GDP and release of eIF2-GDP from the translating ribosome. The initiation factor eIF2B then exchanges GTP for GDP to re-charge the ternary complex, allowing another round of initiation. The activity of eIF2B is regulated by the phosphorylation state of eIF2α: when eIF2α is phosphorylated, it converts eIF2 from a substrate to a competitive inhibitor of eIF2B. Consequently, inhibition in eIF2B activity results in a decrease in eIF2$\alpha/\beta/\gamma$/$tRNA_i^{Met}$/GTP levels to decrease translation initiation. The second step is the recruitment of the eIF4F complex to mRNA through interactions with the cap structure. The mRNA-bound eIF4F complex recruits the 43S pre-initiation complex which scans the 5′-UTR until initiator tRNA recognizes the AUG start codon. Upon recognition of the start codon, the 60S large ribosomal subunit joins the 40S ribosomal subunit, and the complete ribosome (80S) then commences translation elongation. Interference with eIF4F function inhibits the initiation of capped mRNAs. This occurs when eIF4E-binding proteins (4E-BPs) interact with eIF4E and prevent assembly of the translation-competent eIF4F complex on capped transcripts. The eIF4E/4E-BPs binding is regulated by mammalian target of rapamycin (mTOR), a central integrator of signals playing critical roles in the metabolism, differentiation, activation, and function of a diverse set of immune cells (200). Examples of translational control mechanisms governing immune system functions are discussed below.

Translational silencing of ARE-containing transcripts

Besides contributing to AMD, some ARE-BPs also control translation of ARE-containing transcripts. Quantitative analysis of inflammatory mediator production showed that the

actual levels of protein often reflect the integration of combined effects of ARE-BP(s) on mRNA decay and translation.

TIA-1 and TIAR proteins are closely related members of the RNA-recognition motif (RRM) family of RBPs. They share a very similar domain architecture comprised of three RRMs and a C-terminal glutamine/asparagine-rich prion-related domain. Macrophages obtained from mice lacking TIA-1 or TIAR overexpress pro-inflammatory proteins such as TNF-α, IL-1β, IL-6, matrix metalloproteinase, and COX-2. Initial studies revealed that these proteins do not affect the stability of their target transcripts but rather inhibit their translation (19, 201-203). Specifically, upon LPS stimulation, macrophages derived from TIA knockout mice showed significantly increased association of TNF-α transcripts with polysomes, which represent the most actively translating fraction of ribosomes, in comparison to wildtype macrophages. Consequently, macrophages lacking TIA-1 produce significantly more TNF-α protein than wildtype controls, despite having comparable TNF-α mRNA steady-state levels and half-lives. As a consequence of the overexpression of selected cytokines, mutant mice lacking TIA-1 or TIAR have a hyperinflammatory phenotype and develop mild arthritis in a strain-dependent manner (reviewed in 146, 204). Mice lacking both proteins die before embryonic day 7, suggesting that at least one of these proteins must be present for normal embryonic development (19).

Gene array studies revealed a subset of mRNAs that are regulated by both TIA-1 and TTP (205), and mice lacking both TTP and TIA-1 develop severe spontaneous inflammatory arthritis that is more prominent than that observed in mice with ablation of TTP or TIA-1 alone (206) suggesting an overlapping regulatory network for these proteins. Mechanistically, tethering of TIA-1 to mRNA reporters not only promotes translation inhibition, but also stimulates transcript decay. This TIA-1-mediated decay relies on the action of both 5′-3′ and 3′-5′ degradation pathways (DCP2 decapping enzyme and the exosome complex) and requires polysome disassembly (drugs stabilizing polysomes inhibit this decay) (205). Whether or not TIA-1 cooperates with TTP (for example to recruit degradation enzymes) to promote TIA-1-mediated decay of transcripts simultaneously regulated by these proteins remains to be determined.

How do TIA-1 and TIAR inhibit translation? A hint of the mechanism of TIA-1/TIAR-mediated translational silencing comes from studies of the global translational arrest triggered by environmental stress. In stressed cells (e.g. upon nutrient and energy deprivation, heat shock, or oxidative conditions), eIF2α becomes phosphorylated by one or more members of a family of serine/threonine kinases. These kinases are activated by viral infection, endoplasmic reticulum stress, amino acid deprivation (GCN2), and hemin deficiency. In some cases, their dimerization and autophosphorylation greatly increases their ability to phosphorylate eIF2α. As a consequence of eIF2α phosphorylation, the availability of the ternary complex is reduced and translation initiation is inhibited. Under these conditions, TIA-1/TIAR promote the assembly of non-canonical, translationally stalled 48S* pre-initiation complexes that lack selected initiation factors (eIF2 and eIF5). The 48S* complexes are then assembled into stress granules (SGs), discrete cytoplasmic foci where untranslated mRNAs are stored. Transiently overexpressed TIA-1/TIAR proteins inhibit translation initiation, disassemble polysomes, and promote SG assembly, but these effects

are blocked in mutant cells expressing only nonphosphorylatable eIF2α. TIA-1 and TIAR as well as other RBPs (FXR1, FMRP, YB-1, HuR, etc.) are concentrated in SGs, suggesting that these proteins may work together to promote stress-induced translational silencing. Moreover, recruitment of mRNA transcripts into SGs is a selective process that depends on mRNA structure, cytoplasmic levels of specific SG-associated mRNA-binding proteins, and the nature/severity of the stress. It is possible that the reduced translation of selected ARE-mRNAs mediated by TIA-1/TIAR also requires assembly of 48S* complexes as observed during stress-induced global translation inhibition.

Stress granules have also been linked to post-transcription control pathways that regulate the immune response. T lymphocytes mediate adaptive immunity through differentiation of naive precursors into cytokine-secreting effector cells. After initial priming of naive T cells, the transcription of effector cytokines (such as IFN-γ and IL-4) is turned on, but the production of IFN and IL-4 proteins is not detected until these cells undergo antigen-specific re-stimulation (207). These results suggest that transcription and translation are uncoupled in naive T cells. Mechanistically, primed T cells readily demonstrate increased levels of eIF2α phosphorylation that positively correlates with polysome disassembly/assembly of TIA-1-positive SGs and translation attenuation (207). However, after antigen-specific restimulation, these effector cytokines are abundantly secreted as a consequence of rapid eIF2α dephosphorylation, disassembly of SGs, and translation of their mRNAs. Significantly, introduction of dominant-negative TIA-1 or interference with eIF2α phosphorylation reversed this phenomenon, allowing IL-4 protein secretion in response to the initial priming of T-helper 2 cells (207).

SGs have also been linked to the etiology of an autoimmune syndrome similar to systemic lupus erythematosus and caused by a point mutation in *Rc3h1*, the gene that encodes the zinc finger protein roquin (67). In $CD4^+$ T cells, roquin promotes the decay of mRNA encoding inducible T-cell costimulator (ICOS), and in cells expressing mutant roquin, ICOS mRNA is stabilized leading to enhanced T-cell activation, a common trigger of autoimmunity. Roquin directly binds to a region within the 3′-UTR of ICOS mRNA, and both roquin and ICOS mRNA colocalize in SGs and P-bodies (another RNA granule putatively involved in mRNA storage/decay) (67, 208, 209). Although roquin associates with the decapping machinery to degrade ICOS transcripts (208), it remains to be determined whether or not roquin also influences ICOS mRNA translation.

The IFN-γ-activated inhibitor of translation

The IFN-γ-activated inhibitor of translation (GAIT) element (210) is a 29-nucleotide hairpin structure found in the 3′-UTRs of a distinct group of inflammation-related transcripts [both pro- and anti-inflammatory (211)] such as ceruloplasmin, VEGF, diverse chemokines, and chemokine receptors (210, 212, 213). In human myeloid cells, IFN-γ triggers formation of a heterotetrameric GAIT complex consisting of glutamyl-prolyl tRNA synthetase (EPRS), NS1-associated protein 1, ribosomal protein L13a (RPL13a), and glyceraldehyde-3-phosphate dehydrogenase (213). The GAIT complex binds GAIT-containing transcripts, targets components of the translation initiation machinery, and inhibits mRNA translation. Specifically, IFNγ triggers phosphorylation of EPRS and RPL13a and their subsequent

release from the tRNA multisynthetase complex and 60S subunit, respectively (214, 215). Upon GAIT complex assembly and its binding to mRNA, RPL13a binds to the eIF3-binding site of eIF4G to remodel the cap-binding eIF4F complex and to inhibit 43S pre-initiation complex recruitment (216). Interestingly, although binding of the GAIT complex to target transcripts is mediated by EPRS, the ability of EPRS to bind GAIT elements is repressed until the holocomplex is assembled (213, 216, 217). An interesting aspect of GAIT complex regulation is the dynamics of its assembly: after IFNγ stimulation, it takes 14–16 h to terminate the production of inflammatory mediators. This 'delay' between IFNγ activation and actual translational silencing of GAIT-transcripts is thought to balance other IFNγ-mediated effects on expression of inflammatory mediators (mostly at the transcriptional level) by suppressing mRNAs that avoid early IFNγ-induced transcriptional blocks (213).

HNRNPL-mediated translation modulation

The activity of the GAIT complex can be regulated by changes in environmental conditions. VEGF (VEGF-A) mRNA contains a GAIT element in its 3′-UTR that is regulated by cross-talk between heterogeneous nuclear ribonucleoprotein L (hnRNP L) and the GAIT complex (114). In macrophages, IFNγ simultaneously activates the transcription of VEGF transcripts and activates the GAIT complex to allow a tightly regulated production of VEGF protein. Under hypoxia, while transcription of VEGF is stimulated, the GAIT-mediated translational repression is inhibited to greatly stimulate VEGF protein production (113). The hypoxia-induced override of the GAIT system is mediated by HNRNPL binding to a cytosine- and adenine-rich instability element (CARE) that lies adjacent to the GAIT element in the 3′-UTR of VEGF transcripts (113, 114). While under normoxia, IFNγ promotes the proteosomal degradation of HNRNPL, hypoxia prevents this degradation. HNRNPL binding to the CARE alters the secondary structure of the 3′-UTR to eliminate the GAIT element hairpin preventing GAIT complex binding and translational repression.

HNRNPL also regulates translation of CD154 (CD40L) transcripts encoding a transmembrane glycoprotein expressed on the surface of activated T cells that regulates B-cell functions. CD154 protein is overexpressed in some autoimmune diseases like systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. In addition to the nucleolin/PTB-mediated mechanisms regulating stability of CD154 mRNA (44, 48, 50), HNRNPL regulates its translation. A 100-nucleotide cytosine- and uridine-rich instability element (CURE) found in the 3′-UTR of CD154 mRNA (47) recruits alternative splice variants of PTB that differentially modulate CD154 mRNA stability: whereas full length PTB stabilizes this transcript, a splice variant lacking exons 3–10 (PTB-T) destabilizes CD154 mRNA (46). A CARE element (similar to the one found in VEGF transcripts) located downstream of the CURE recruits HNRNPL to inhibit CD154 translation (47). Although the molecular details of CARE-mediated HNRNPL recruitment and translation inhibition are not known, CARE-bound HNRNPL might unwind local secondary structure to remodel an element that recruits a translational enhancer. In humans, the CARE in CD154 is polymorphic with the number of cytosine-adenine (CA) repeats ranging from 20 to 30 (218). Case-association studies demonstrate that larger numbers of CA repeats (>24 repeats) are found in systemic lupus erythematosus patients than in healthy controls (24 repeats), and a group of patients with shorter numbers of CA repeats (<24 CA) present with more *livedo*

reticularis, anti-Sm, and anti-RNP autoantibodies, suggesting that CA repeat polymorphism contributes to the development of systemic lupus erythematosus (218). While molecular details explaining how the number of CA repeats regulates CD154 expression remains to be deciphered, we speculate that changes in CA repeat number influence the relative contribution of CARE and CURE elements to modulate CD154 mRNA stability and translation.

Steroid receptor co-activator 3-mediated inhibition of cytokine translation

Steroid receptor co-activator 3 (SRC3) (NCOA3) is a transcriptional co-activator that can either promote or inhibit inflammation by regulating rates of transcription (219). $Src3^{-/-}$ mice are hypersensitive to LPS challenge and overexpress pro-inflammatory TNF-α, IL-6, and IL-1β cytokines (108). Polysome profiling experiments on LPS-activated peritoneal macrophages from wildtype and SRC3 knockout mice demonstrated that translation of TNF-α and IL-1β transcripts is higher in $Src3^{-/-}$ macrophages. Mechanistically, SRC3 was shown to associate with TIA-1 and to increase affinity of TIA-1 for the ARE of TNF-α, thus cooperatively repressing translation of TNF-α mRNA (108). These studies show that SRC3 functions as both a transcriptional co-activator and a translational co-repressor.

Translational control of production of lipid mediators

Lipid mediators play essential roles in both the initiation (prostaglandins and leukotrienes) and resolution (lipoxins and resolvins) of inflammation. Their production is indirectly controlled by post-transcriptional mechanisms that regulate expression of cyclooxygenases and lipoxygenases, principal enzymes that produce lipid mediators from arachidonic acid. The 3′-UTRs of mRNAs encoding these enzymes contain regulatory elements that modulate their translation and stability. For example, expression of COX-2, an enzyme that metabolizes arachidonic acid to produce pro- and anti-inflammatory prostaglandins, is regulated on the level of translation by TIA-1 (54) in a manner similar to the TIA-1-mediated TNF-α mRNA translation regulation (19). TIA-1 binds to the ARE in the 3′-UTR of COX-2 mRNA to inhibit its translation, and TIA-1 null fibroblasts produce significantly more COX-2 protein than wildtype fibroblasts, but have no differences in the COX-2 mRNA turnover and levels (54).

The 12, 15-lipoxygenases participate in the conversion of arachidonic acid into a number of important lipid mediators. The mRNAs encoding these enzymes contain cytosine- and uridine-rich repeats similar to the differentiation control element (DICE) found in the 3′-UTR of 15-LO (15-lipoxygenase) mRNA (100, 101). Although 15-LO mRNAs are detected at early stages of erythropoiesis, 15-LO proteins are only expressed in erythroid cells just before they become mature erythrocytes (220). This developmental stage-restricted expression of 15-LO is achieved by translational inhibition through HNRNPE1 and HNRNPK binding to the DICE. DICE-bound HNRNPE1/HNRNPK complex inhibits translation initiation by preventing 60S ribosomal subunit joining to the 48S pre-initiation complex (100).

Some lipid mediators can directly function as inhibitors of protein translation. Cyclopentenone 15d-PGJ2 is an anti-inflammatory prostaglandin produced by mast cells, T cells, platelets, and macrophages (221). 15d-PGJ2 works as a PPARγ agonist and inhibitor of NF-κB to repress transcription of mRNAs encoding pro-inflammatory mediators (222, 223). In addition to targeting the transcriptional machinery, 15d-PGJ2 directly binds to the eIF4A helicase, inhibits its activity, and interferes with the ability of the 48S pre-initiation complex to scan the 5′-UTR of mRNAs in search of the AUG start codon (224). As a consequence of 15d-PGJ2-mediated translation inhibition, untranslated mRNAs accumulate in SGs allowing dynamic reprogramming of gene expression in response to external insults such as inflammation (224). Although the inhibition of eIF4A is expected to cause global repression of translation, selected mRNAs with structured guanine- and cytosine-rich (GC-rich) 5′-UTRs might be preferentially targeted by 15d-PGJ2, since 48S scanning through these structured regions is particularly dependent on the unwinding activity of the eIF4A helicase. For example, the mRNAs encoding inflammatory cytokines IL-4, IL-10, and IFNγ have structured GU-rich 5′-UTRs. In CD3/CD28-activated lymphocytes lacking PDCD4 (programmed cell death protein 4, which inhibits eIF4A functions), expression of these cytokines is selectively higher than that in wildtype cells (225). Proteomic approaches will be required to determine whether or not 15d-PGJ2, similarly to PDCD4, targets mRNAs with structured GU-rich 5′-UTRs encoding inflammatory mediators.

Indoleamine 2,3-dioxygease/GCN2-mediated metabolic control of immune responses

Indoleamine 2,3-dioxygease (IDO) is a potent immunoregulatory enzyme that catabolizes the essential amino acid tryptophan (TRP) into kynurenine (KYN) (reviewed in 226, 227). IDO is expressed in professional antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), and its expression is tightly regulated by exogenous signals. Although IDO enzymes are intracellular and not secreted, neighboring cells can respond to metabolic effects of IDO by sensing secreted KYN as well as reduced access to TRP. Thus, ‘IDO-competent’ APCs can affect both the APC itself and the neighboring T cell in a paracrine fashion (226, 227).

KYN and its metabolites (KYN-pathway metabolites) are natural ligands for the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor. In T cells, binding of KYN-pathway metabolites to AhR has immunosuppressive effects mediated by promoting the differentiation of forkhead box protein 3 $(Foxp3)^+$ T-regulatory cells (Tregs) and in decreasing the immunogenicity of DCs (228-230).

By depleting TRP, IDO activates the GCN2 kinase to trigger an evolutionarily conserved stress-response program, the integrated stress response (ISR) (231). GCN2 contains a regulatory domain that binds the uncharged form of transfer RNA (tRNA) and a kinase domain that phosphorylates eIF2α (232). As a reflection of TRP depletion by IDO, levels of uncharged tRNAs are elevated leading to GCN2 activation and eIF2α phosphorylation. Phosphorylation of eIF2α, a central checkpoint in the ISR, causes profound changes in the level of global translation leading to rapid re-programming of gene expression. For example,

expression of IDO by professional APCs causes *trans*-effects in neighboring T cells by modulation of their gene expression. Functionally, IDO-induced GCN2 activation leads to functional anergy and cell cycle arrest in $CD8^+$ T cells (233). In $CD4^+$ T cells, GCN2 activation blocks T-helper 17 (Th17) differentiation (234, 235) and promotes activation of functional suppressor activity in mature Tregs and *de novo* Treg differentiation (236, 237). In summary, IDO-induced GCN2 activation seems to inhibit T-effector cells and enhance Treg activity. The precise molecular events governed by this GCN2/eIF2α pathway remain to be determined.

Translational control of type I IFNs

Type I IFN, which includes IFN-α and IFN-β, is the first line of innate immunity defense against viruses. Type I IFNs are transcriptionally and translationally regulated and are induced following recognition of pathogen components during infection by various host pattern recognition receptors. Rapid synthesis and secretion of these cytokines is critical for a potent antiviral response; IFN-α/β-induced transcription of a large group of genes plays an important role in host resistance to viral infections and in activation of key components of the innate and adaptive immune systems.

Plasmacytoid DCs (pDCs) are the most potent producers of type I IFN. These cells sense virus infection using endosomal TLR family members TLR7 and TLR9. Activated TLR7/TLR9 interacts with the adapter protein myeloid differentiation factor 88 (MyD88) to activate the transcription factor IFN-response factor 7 (IRF7), which in turn transcribes type I IFN genes. Interestingly, mTOR signaling has recently emerged as key regulator of type I IFN production. Treatment of pDCs with rapamycin, an inhibitor of mTOR, as well as siRNA-mediated knockdown of mTOR selectively blocks production of type I IFN (238). Mechanistically, inhibition of mTOR activity leads to dephosphorylation of downstream targets 4E-BP1 and 4E-BP2. In pDCs, hypophosphorylated 4E-BPs bind to the cap-binding eIF4E protein with high affinity to decrease translation of a subset of mRNAs including transcripts encoding IRF7 (238, 239). Decreased IRF7 mRNA translation leads to decreased type I IFN production and, in pDCs from mice lacking 4E-BP1/2, translation of IRF7 transcripts is upregulated. Furthermore, 4E-BP1/2 knockout mice are resistant to vesicular stomatitis virus infection in agreement with an enhanced type-I IFN production in pDCs (239).

Production of type I IFN appears to be regulated by another translation-dependent mechanism that relies on the phosphorylation of the cap-binding factor eIF4E (240). Mitogen-activated protein kinase-interacting kinases Mnk1 and Mnk2 phosphorylate eIF4E at Ser209 to modulate translation of certain mRNAs that encode inflammation-and cancer-associated proteins (241, 242). One of these mRNAs (*Nfkbia* mRNA) encodes IκBα protein, the short-lived inhibitor of NF-κB, which is a key transcriptional activator of type I IFN production (243, 244). Mice and MEFs in which eIF4E cannot be phosphorylated (S209A) produce less IκBα due to decreased translation of *Nfkbia* mRNA. Reduced IκBα protein levels result in enhanced activity of NF-κB and, consequently, elevated production of NF-κB-regulated genes such as IFNβ. Finally, S209A knockin mice were less susceptible to

virus infection suggesting that eIF4E phosphorylation contributes to the host defense against viral infections (240).

These findings together suggest that modulations of eIF4E function (through its interaction with 4E-BPs and/or its dephosphorylation) regulate the production of type I IFN, a fundamental aspect of innate immunity. Further dissection of translation-control mechanisms involved in the regulation of type I interferon production may provide important insights into the development of novel antiviral and immunomodulatory therapies.

Conclusions and perspectives

In this review, we highlight the role that post-transcriptional regulatory mechanisms play in the immune system. The multitude of post-transcriptional mechanisms that contribute to the regulation of immune function is remarkable. RBPs and miRNAs are *trans*-factors that bind mRNAs, regulate their stability and translation in immune cells, and thus influence immunity. In this regard, further potential intersections between different regulatory mechanisms and regulatory factors have yet to be defined.

Several aspects of the post-transcriptional regulation of immune system functions warrant future investigation in both pre-clinical and clinical arenas. First, RBPs, like miRNAs, can regulate a large number of mRNA targets, thus affecting several aspects of immune function simultaneously. Identification of mRNA target networks requires the development of high-throughput systems able to identify target transcripts whose stability and translation is modulated by individual RBPs and miRNAs. Second, key mRNA transcripts can be combinatorially regulated by different RBPs and miRNAs, which can lead to greater complexity and have unexpected physiological and disease implications. Third, current information about post-transcriptional regulatory networks has come from *in vitro* studies. Relevant *in vivo* models will need to be developed. Fourth, the diversity and differentiation of immune cell types complicates the analysis of post-transcriptional modulation of immune function. Finally, future challenges in this emerging field will require the identification of novel RBPs regulating mRNA stability and translation, characterization of new interactions between RBPs and miRNAs, and deciphering how these interconnected networks modulate immune function. A more detailed understanding of the post-transcriptional pathways that turn on and turn off immune functions is important for the development of new therapies for infectious, inflammatory, autoimmune diseases, and cancer.

Acknowledgements

The authors have no conflicts of interest to declare.

References

1. Schmid M, Jensen TH. Nuclear quality control of RNA polymerase II transcripts. Wiley Interdiscip Rev RNA 2010;1:474–485. [PubMed: 21956943]
2. Goldstrohm AC, Wickens M. Multifunctional deadenylase complexes diversify mRNA control. Nat Rev Mol Cell Biol 2008;9:337–344. [PubMed: 18334997]
3. Chen CY, Shyu AB. Mechanisms of deadenylation-dependent decay. Wiley Interdiscip Rev RNA 2011;2:167–183. [PubMed: 21957004]

4. Yamashita A, et al. Concerted action of poly(A) nucleases and decapping enzyme in mammalian mRNA turnover. Nat Struct Mol Biol 2005;12:1054–1063. [PubMed: 16284618]
5. Ling SH, Qamra R, Song H. Structural and functional insights into eukaryotic mRNA decapping. Wiley Interdiscip Rev RNA 2011;2:193–208. [PubMed: 21957006]
6. Caput D, Beutler B, Hartog K, Thayer R, Brown-Shimer S, Cerami A. Identification of a common nucleotide sequence in the 3′-untranslated region of mRNA molecules specifying inflammatory mediators. Proc Natl Acad Sci USA 1986;83:1670–1674. [PubMed: 2419912]
7. Shaw G, Kamen R. A conserved AU sequence from the 3′ untranslated region of GM-CSF mRNA mediates selective mRNA degradation. Cell 1986;46:659–667. [PubMed: 3488815]
8. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. Immunity 1999;10:387–398. [PubMed: 10204494]
9. Stoecklin G, Hahn S, Moroni C. Functional hierarchy of AUUUA motifs in mediating rapid interleukin-3 mRNA decay. J Biol Chem 1994;269:28591–28597. [PubMed: 7961806]
10. Chen CY, Shyu AB. AU-rich elements: characterization and importance in mRNA degradation. Trends Biochem Sci 1995;20:465–470. [PubMed: 8578590]
11. Chen CY, Xu N, Shyu AB. mRNA decay mediated by two distinct AU-rich elements from c-fos and granulocyte-macrophage colony-stimulating factor transcripts: different deadenylation kinetics and uncoupling from translation. Mol Cell Biol 1995;15:5777–5788. [PubMed: 7565731]
12. Lagnado CA, Brown CY, Goodall GJ. AUUUA is not sufficient to promote poly(A) shortening and degradation of an mRNA: the functional sequence within AU-rich elements may be UUAUUUA(U/A)(U/A). Mol Cell Biol 1994;14:7984–7995. [PubMed: 7969138]
13. Zubiaga AM, Belasco JG, Greenberg ME. The nonamer UUAUUUAUU is the key AU-rich sequence motif that mediates mRNA degradation. Mol Cell Biol 1995;15:2219–2230. [PubMed: 7891716]
14. Bakheet T, Williams BR, Khabar KS. ARED 3.0: the large and diverse AU-rich transcriptome. Nucleic Acids Res 2006;34:D111–D114. [PubMed: 16381826]
15. Carballo E, Lai WS, Blackshear PJ. Feedback inhibition of macrophage tumor necrosis factor-alpha production by tristetraprolin. Science 1998;281:1001–1005. [PubMed: 9703499]
16. Stoecklin G, et al. Functional cloning of BRF1, a regulator of ARE-dependent mRNA turnover. EMBO J 2002;21:4709–4718. [PubMed: 12198173]
17. Hinman MN, Lou H. Diverse molecular functions of Hu proteins. Cell Mol Life Sci 2008;65:3168–3181. [PubMed: 18581050]
18. Gratacos FM, Brewer G. The role of AUF1 in regulated mRNA decay. Wiley Interdiscip Rev RNA 2010;1:457–473. [PubMed: 21956942]
19. Piecyk M, et al. TIA-1 is a translational silencer that selectively regulates the expression of TNF-alpha. EMBO J 2000;19:4154–4163. [PubMed: 10921895]
20. Briata P, et al. KSRP, many functions for a single protein. Front Biosci 2011;16:1787–1796.
21. Garnon J, et al. Fragile X-related protein FXR1P regulates proinflammatory cytokine tumor necrosis factor expression at the post-transcriptional level. J Biol Chem 2005;280:5750–5763. [PubMed: 15548538]
22. Chen CY, et al. Nucleolin and YB-1 are required for JNK-mediated interleukin-2 mRNA stabilization during T-cell activation. Genes Dev 2000;14:1236–1248. [PubMed: 10817758]
23. Mukhopadhyay D, Houchen CW, Kennedy S, Dieckgraefe BK, Anant S. Coupled mRNA stabilization and translational silencing of cyclooxygenase-2 by a novel RNA binding protein, CUGBP2. Mol Cell 2003;11:113–126. [PubMed: 12535526]
24. Mukhopadhyay D, Jung J, Murmu N, Houchen CW, Dieckgraefe BK, Anant S. CUGBP2 plays a critical role in apoptosis of breast cancer cells in response to genotoxic injury. Ann NY Acad Sci USA 2003;1010:504–509.
25. Gherzi R, et al. A KH domain RNA binding protein, KSRP, promotes ARE-directed mRNA turnover by recruiting the degradation machinery. Mol Cell 2004;14:571–583. [PubMed: 15175153]

26. Laroia G, Cuesta R, Brewer G, Schneider RJ. Control of mRNA decay by heat shock-ubiquitin-proteasome pathway. Science 1999;284:499–502. [PubMed: 10205060]
27. Lu JY, Sadri N, Schneider RJ. Endotoxic shock in AUF1 knockout mice mediated by failure to degrade proinflammatory cytokine mRNAs. Genes Dev 2006;20:3174–3184. [PubMed: 17085481]
28. Sarkar B, Xi Q, He C, Schneider RJ. Selective degradation of AU-rich mRNAs promoted by the p37 AUF1 protein isoform. Mol Cell Biol 2003;23:6685–6693. [PubMed: 12944492]
29. Fan XC, Steitz JA. Overexpression of HuR, a nuclear-cytoplasmic shuttling protein, increases the in vivo stability of ARE-containing mRNAs. EMBO J 1998;17:3448–3460. [PubMed: 9628880]
30. Peng SS, Chen CY, Xu N, Shyu AB. RNA stabilization by the AU-rich element binding protein, HuR, an ELAV protein. EMBO J 1998;17:3461–3470. [PubMed: 9628881]
31. Galban S, et al. RNA-binding proteins HuR and PTB promote the translation of hypoxia-inducible factor 1alpha. Mol Cell Biol 2008;28:93–107. [PubMed: 17967866]
32. Katsanou V, et al. HuR as a negative posttranscriptional modulator in inflammation. Mol Cell 2005;19:777–789. [PubMed: 16168373]
33. David PS, Tanveer R, Port JD. FRET-detectable interactions between the ARE binding proteins, HuR and p37AUF1. RNA 2007;13:1453–1468. [PubMed: 17626845]
34. Kawai T, Lal A, Yang X, Galban S, Mazan-Mamczarz K, Gorospe M. Translational control of cytochrome c by RNA-binding proteins TIA-1 and HuR. Mol Cell Biol 2006;26:3295–3307. [PubMed: 16581801]
35. Linker K, Pautz A, Fechir M, Hubrich T, Greeve J, Kleinert H. Involvement of KSRP in the post-transcriptional regulation of human iNOS expression-complex interplay of KSRP with TTP and HuR. Nucleic Acids Res 2005;33:4813–4827. [PubMed: 16126846]
36. Pan YX, Chen H, Kilberg MS. Interaction of RNA-binding proteins HuR and AUF1 with the human ATF3 mRNA 3′-untranslated region regulates its amino acid limitation-induced stabilization. J Biol Chem 2005;280:34609–34616. [PubMed: 16109718]
37. Sureban SM, et al. Functional antagonism between RNA binding proteins HuR and CUGBP2 determines the fate of COX-2 mRNA translation. Gastroenterology 2007;132:1055–1065. [PubMed: 17383427]
38. Pastore S, Mascia F, Mariotti F, Dattilo C, Mariani V, Girolomoni G. ERK1/2 regulates epidermal chemokine expression and skin inflammation. J Immunol 2005;174:5047–5056. [PubMed: 15814736]
39. Sauer I, et al. Interferons limit inflammatory responses by induction of tristetraprolin. Blood 2006;107:4790–4797. [PubMed: 16514065]
40. Marcais A, Tomkowiak M, Walzer T, Coupet CA, Ravel-Chapuis A, Marvel J. Maintenance of CCL5 mRNA stores by post-effector and memory CD8 T cells is dependent on transcription and is coupled to increased mRNA stability. Eur J Immunol 2006;36:2745–2754. [PubMed: 16983723]
41. Atasoy U, et al. Regulation of eotaxin gene expression by TNF-alpha and IL-4 through mRNA stabilization: involvement of the RNA-binding protein HuR. J Immunol 2003;171:4369–4378. [PubMed: 14530362]
42. Arif A, Jia J, Mukhopadhyay R, Willard B, Kinter M, Fox PL. Two-site phosphorylation of EPRS coordinates multimodal regulation of noncanonical translational control activity. Mol Cell 2009;35:164–180. [PubMed: 19647514]
43. Vlasova IA, et al. Conserved GU-rich elements mediate mRNA decay by binding to CUG-binding protein 1. Mol Cell 2008;29:263–270. [PubMed: 18243120]
44. Barnhart B, Kosinski PA, Wang Z, Ford GS, Kiledjian M, Covey LR. Identification of a complex that binds to the CD154 3′ untranslated region: implications for a role in message stability during T cell activation. J Immunol 2000;165:4478–4486. [PubMed: 11035087]
45. Ford GS, Barnhart B, Shone S, Covey LR. Regulation of CD154 (CD40 ligand) mRNA stability during T cell activation. J Immunol 1999;162:4037–4044. [PubMed: 10201926]
46. Hamilton BJ, Genin A, Cron RQ, Rigby WF. Delineation of a novel pathway that regulates CD154 (CD40 ligand) expression. Mol Cell Biol 2003;23:510–525. [PubMed: 12509450]
47. Hamilton BJ, et al. Separate cis-trans pathways post-transcriptionally regulate murine CD154 (CD40 ligand) expression: a novel function for CA repeats in the 3′-untranslated region. J Biol Chem 2008;283:25606–25616. [PubMed: 18640985]

48. Kosinski PA, Laughlin J, Singh K, Covey LR. A complex containing polypyrimidine tract-binding protein is involved in regulating the stability of CD40 ligand (CD154) mRNA. J Immunol 2003;170:979–988. [PubMed: 12517964]
49. Rigby WF, Waugh MG, Hamilton BJ. Characterization of RNA binding proteins associated with CD40 ligand (CD154) mRNA turnover in human T lymphocytes. J Immunol 1999;163:4199–4206. [PubMed: 10510356]
50. Singh K, Laughlin J, Kosinski PA, Covey LR. Nucleolin is a second component of the CD154 mRNA stability complex that regulates mRNA turnover in activated T cells. J Immunol 2004;173:976–985. [PubMed: 15240685]
51. Vavassori S, Shi Y, Chen CC, Ron Y, Covey LR. In vivo post-transcriptional regulation of CD154 in mouse CD4 + T cells. Eur J Immunol 2009;39:2224–2232. [PubMed: 19572319]
52. Mazumder B, Fox PL. Delayed translational silencing of ceruloplasmin transcript in gamma interferon-activated U937 monocytic cells: role of the 3′ untranslated region. Mol Cell Biol 1999;19:6898–6905. [PubMed: 10490627]
53. Cok SJ, Acton SJ, Morrison AR. The proximal region of the 3′-untranslated region of cyclooxygenase-2 is recognized by a multimeric protein complex containing HuR, TIA-1, TIAR, and the heterogeneous nuclear ribonucleoprotein U. J Biol Chem 2003;278:36157–36162. [PubMed: 12855701]
54. Dixon DA, et al. Regulation of cyclooxygenase-2 expression by the translational silencer TIA-1. J Exp Med 2003;198:475–481. [PubMed: 12885872]
55. Datta S, et al. Tristetraprolin regulates CXCL1 (KC) mRNA stability. J Immunol 2008;180:2545–2552. [PubMed: 18250465]
56. Rousseau S, Morrice N, Peggie M, Campbell DG, Gaestel M, Cohen P. Inhibition of SAPK2a/p38 prevents hnRNP A0 phosphorylation by MAPKAP-K2 and its interaction with cytokine mRNAs. EMBO J 2002;21:6505–6514. [PubMed: 12456657]
57. Stoeckle MY. Post-transcriptional regulation of gro alpha, beta, gamma, and IL-8 mRNAs by IL-1 beta. Nucleic Acids Res 1991;19:917–920. [PubMed: 2017372]
58. Vockerodt M, et al. The Epstein-Barr virus oncoprotein latent membrane protein 1 induces expression of the chemokine IP-10: importance of mRNA half-life regulation. Int J Cancer 2005;114:598–605. [PubMed: 15578697]
59. Frasca D, Landin AM, Alvarez JP, Blackshear PJ, Riley RL, Blomberg BB. Tristetraprolin, a negative regulator of mRNA stability, is increased in old B cells and is involved in the degradation of E47 mRNA. J Immunol 2007;179:918–927. [PubMed: 17617583]
60. Brown CY, Lagnado CA, Goodall GJ. A cytokine mRNA-destabilizing element that is structurally and functionally distinct from A+U-rich elements. Proc Natl Acad Sci USA 1996;93:13721–13725. [PubMed: 8943001]
61. Koeffler HP, Gasson J, Tobler A. Transcriptional and posttranscriptional modulation of myeloid colony-stimulating factor expression by tumor necrosis factor and other agents. Mol Cell Biol 1988;8:3432–3438. [PubMed: 2463477]
62. Putland RA, et al. RNA destabilization by the granulocyte colony-stimulating factor stem-loop destabilizing element involves a single stem-loop that promotes deadenylation. Mol Cell Biol 2002;22:1664–1673. [PubMed: 11865046]
63. Bickel M, Cohen RB, Pluznik DH. Post-transcriptional regulation of granulocyte-macrophage colony-stimulating factor synthesis in murine T cells. J Immunol 1990;145:840–845. [PubMed: 2197329]
64. Carballo E, Lai WS, Blackshear PJ. Evidence that tristetraprolin is a physiological regulator of granulocyte-macrophage colony-stimulating factor messenger RNA deadenylation and stability. Blood 2000;95:1891–1899. [PubMed: 10706852]
65. Esnault S, Shen ZJ, Whitesel E, Malter JS. The peptidyl-prolyl isomerase Pin1 regulates granulocyte-macrophage colony-stimulating factor mRNA stability in T lymphocytes. J Immunol 2006;177:6999–7006. [PubMed: 17082615]
66. Grosset C, Boniface R, Duchez P, Solanilla A, Cosson B, Ripoche J. In vivo studies of translational repression mediated by the granulocyte-macrophage colony-stimulating factor AU-rich element. J Biol Chem 2004;279:13354–13362. [PubMed: 14726527]

67. Yu D, et al. Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA. Nature 2007;450:299–303. [PubMed: 18172933]
68. Lin WJ, et al. Posttranscriptional control of type I interferon genes by KSRP in the innate immune response against viral infection. Mol Cell Biol 2011;31:3196–3207. [PubMed: 21690298]
69. Raj NB, Pitha PM. Two levels of regulation of beta-interferon gene expression in human cells. Proc Natl Acad Sci USA 1983;80:3923–3927. [PubMed: 6575385]
70. Whittemore LA, Maniatis T. Postinduction repression of the beta-interferon gene is mediated through two positive regulatory domains. Proc Natl Acad Sci USA 1990;87:7799–7803. [PubMed: 2172963]
71. Hodge DL, Martinez A, Julias JG, Taylor LS, Young HA. Regulation of nuclear gamma interferon gene expression by interleukin 12 (IL-12) and IL-2 represents a novel form of posttranscriptional control. Mol Cell Biol 2002;22:1742–1753. [PubMed: 11865054]
72. Mavropoulos A, Sully G, Cope AP, Clark AR. Stabilization of IFN-gamma mRNA by MAPK p38 in IL-12- and IL-18-stimulated human NK cells. Blood 2005;105:282–288. [PubMed: 15345584]
73. Wang JG, et al. LFA-1-dependent HuR nuclear export and cytokine mRNA stabilization in T cell activation. J Immunol 2006;176:2105–2113. [PubMed: 16455966]
74. Hao S, Baltimore D. The stability of mRNA influences the temporal order of the induction of genes encoding inflammatory molecules. Nat Immunol 2009;10:281–288. [PubMed: 19198593]
75. Chen YL, Huang YL, Lin NY, Chen HC, Chiu WC, Chang CJ. Differential regulation of ARE-mediated TNFalpha and IL-1beta mRNA stability by lipopolysaccharide in RAW264.7 cells. Biochem Biophys Res Commun 2006;346:160–168. [PubMed: 16759646]
76. Fenton MJ, Vermeulen MW, Clark BD, Webb AC, Auron PE. Human pro-IL-1 beta gene expression in monocytic cells is regulated by two distinct pathways. J Immunol 1988;140:2267–2273. [PubMed: 3258333]
77. Mizgalska D, et al. Interleukin-1-inducible MCPIP protein has structural and functional properties of RNase and participates in degradation of IL-1beta mRNA. FEBS J 2009;276:7386–7399. [PubMed: 19909337]
78. Sirenko OI, Lofquist AK, DeMaria CT, Morris JS, Brewer G, Haskill JS. Adhesion-dependent regulation of an A+U-rich element-binding activity associated with AUF1. Mol Cell Biol 1997;17:3898–3906. [PubMed: 9199324]
79. Bufler P, Gamboni-Robertson F, Azam T, Kim SH, Dinarello CA. Interleukin-1 homologues IL-1F7b and IL-18 contain functional mRNA instability elements within the coding region responsive to lipopolysaccharide. Biochem J 2004;381:503–510. [PubMed: 15046617]
80. Ogilvie RL, Abelson M, Hau HH, Vlasova I, Blackshear PJ, Bohjanen PR. Tristetraprolin down-regulates IL-2 gene expression through AU-rich element-mediated mRNA decay. J Immunol 2005;174:953–961. [PubMed: 15634918]
81. Shi L, Godfrey WR, Lin J, Zhao G, Kao PN. NF90 regulates inducible IL-2 gene expression in T cells. J Exp Med 2007;204:971–977. [PubMed: 17470640]
82. Shim J, Lim H. J RY, Karin M. Nuclear export of NF90 is required for interleukin-2 mRNA stabilization. Mol Cell 2002;10:1331–1344. [PubMed: 12504009]
83. Nair AP, Hahn S, Banholzer R, Hirsch HH, Moroni C. Cyclosporin A inhibits growth of autocrine tumour cell lines by destabilizing interleukin-3 mRNA. Nature 1994;369:239–242. [PubMed: 8183344]
84. Stoecklin G, Ming XF, Looser R, Moroni C. Somatic mRNA turnover mutants implicate tristetraprolin in the interleukin-3 mRNA degradation pathway. Mol Cell Biol 2000;20:3753–3763. [PubMed: 10805719]
85. Wodnar-Filipowicz A, Moroni C. Regulation of interleukin 3 mRNA expression in mast cells occurs at the posttranscriptional level and is mediated by calcium ions. Proc Natl Acad Sci USA 1990;87:777–781. [PubMed: 2105489]
86. Yarovinsky TO, Butler NS, Monick MM, Hunninghake GW. Early exposure to IL-4 stabilizes IL-4 mRNA in CD4 + T cells via RNA-binding protein HuR. J Immunol 2006;177:4426–4435. [PubMed: 16982877]

87. Akashi M, Loussararian AH, Adelman DC, Saito M, Koeffler HP. Role of lymphotoxin in expression of interleukin 6 in human fibroblasts. Stimulation and regulation. J Clin Invest 1990;85:121–129. [PubMed: 1688564]

88. Jones MR, et al. Zcchc11-dependent uridylation of microRNA directs cytokine expression. Nat Cell Biol 2009;11:1157–1163. [PubMed: 19701194]

89. Matsushita K, et al. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Nature 2009;458:1185–1190. [PubMed: 19322177]

90. Neininger A, et al. MK2 targets AU-rich elements and regulates biosynthesis of tumor necrosis factor and interleukin-6 independently at different post-transcriptional levels. J Biol Chem 2002;277:3065–3068. [PubMed: 11741878]

91. Paschoud S, Dogar AM, Kuntz C, Grisoni-Neupert B, Richman L, Kuhn LC. Destabilization of interleukin-6 mRNA requires a putative RNA stem-loop structure, an AU-rich element, and the RNA-binding protein AUF1. Mol Cell Biol 2006;26:8228–8241. [PubMed: 16954375]

92. Winzen R, et al. The p38 MAP kinase pathway signals for cytokine-induced mRNA stabilization via MAP kinase-activated protein kinase 2 and an AU-rich region-targeted mechanism. EMBO J 1999;18:4969–4980. [PubMed: 10487749]

93. Winzen R, et al. Functional analysis of KSRP interaction with the AU-rich element of interleukin-8 and identification of inflammatory mRNA targets. Mol Cell Biol 2007;27:8388–8400. [PubMed: 17908789]

94. Stoecklin G, et al. Genome-wide analysis identifies interleukin-10 mRNA as target of tristetraprolin. J Biol Chem 2008;283:11689–11699. [PubMed: 18256032]

95. Bamba S, Andoh A, Yasui H, Makino J, Kim S, Fujiyama Y. Regulation of IL-11 expression in intestinal myofibroblasts: role of c-Jun AP-1- and MAPK-dependent pathways. Am J Physiol Gastrointest Liver Physiol 2003;285:G529–G538. [PubMed: 12760902]

96. Casolaro V, et al. Posttranscriptional regulation of IL-13 in T cells: role of the RNA-binding protein HuR. J Allergy Clin Immunol 2008;121:853–859. e4. [PubMed: 18279945]

97. Lee HH, et al. Tristetraprolin down-regulates IL-17 through mRNA destabilization. FEBS Lett 2012;586:41–46. [PubMed: 22138182]

98. Di Marco S, et al. NF-kappa B-mediated MyoD decay during muscle wasting requires nitric oxide synthase mRNA stabilization, HuR protein, and nitric oxide release. Mol Cell Biol 2005;25:6533–6545. [PubMed: 16024790]

99. Soderberg M, Raffalli-Mathieu F, Lang MA. Identification of a regulatory cis-element within the 3′-untranslated region of the murine inducible nitric oxide synthase (iNOS) mRNA; interaction with heterogeneous nuclear ribonucleoproteins I and L and role in the iNOS gene expression. Mol Immunol 2007;44:434–442. [PubMed: 16584775]

100. Ostareck DH, Ostareck-Lederer A, Shatsky IN, Hentze MW. Lipoxygenase mRNA silencing in erythroid differentiation: the 3′UTR regulatory complex controls 60S ribosomal subunit joining. Cell 2001;104:281–290. [PubMed: 11207368]

101. Ostareck DH, Ostareck-Lederer A, Wilm M, Thiele BJ, Mann M, Hentze MW. mRNA silencing in erythroid differentiation: hnRNP K and hnRNP E1 regulate 15-lipoxygenase translation from the 3′ end. Cell 1997;89:597–606. [PubMed: 9160751]

102. Xia Z, Ghildyal N, Austen KF, Stevens RL. Post-transcriptional regulation of chymase expression in mast cells. A cytokine-dependent mechanism for controlling the expression of granule neutral proteases of hematopoietic cells. J Biol Chem 1996;271:8747–8753. [PubMed: 8621509]

103. Huwiler A, el Akool S, Aschrafi A, Hamada FM, Pfeilschifter J, Eberhardt W. ATP potentiates interleukin-1 beta-induced MMP-9 expression in mesangial cells via recruitment of the ELAV protein HuR. J Biol Chem 2003;278:51758–51769. [PubMed: 14523003]

104. Yu Q, Cok SJ, Zeng C, Morrison AR. Translational repression of human matrix metalloproteinases-13 by an alternatively spliced form of T-cell-restricted intracellular antigen-related protein (TIAR). J Biol Chem 2003;278:1579–1584. [PubMed: 12426321]

105. Porter JF, Vavassori S, Covey LR. A polypyrimidine tract-binding protein-dependent pathway of mRNA stability initiates with CpG activation of primary B cells. J Immunol 2008;181:3336–3345. [PubMed: 18714005]

106. Han J, Brown T, Beutler B. Endotoxin-responsive sequences control cachectin/tumor necrosis factor biosynthesis at the translational level. J Exp Med 1990;171:465–475. [PubMed: 2303781]

107. Stoecklin G, Lu M, Rattenbacher B, Moroni C. A constitutive decay element promotes tumor necrosis factor alpha mRNA degradation via an AU-rich element-independent pathway. Mol Cell Biol 2003;23:3506–3515. [PubMed: 12724409]

108. Yu C, York B, Wang S, Feng Q, Xu J, O'Malley BW. An essential function of the SRC-3 coactivator in suppression of cytokine mRNA translation and inflammatory response. Mol Cell 2007;25:765–778. [PubMed: 17349961]

109. Croft D, McIntyre P, Wibulswas A, Kramer I. Sustained elevated levels of VCAM-1 in cultured fibroblast-like synoviocytes can be achieved by TNF-alpha in combination with either IL-4 or IL-13 through increased mRNA stability. Am J Pathol 1999;154:1149–1158. [PubMed: 10233853]

110. Coles LS, et al. A multi-protein complex containing cold shock domain (Y-box) and polypyrimidine tract binding proteins forms on the vascular endothelial growth factor mRNA. Potential role in mRNA stabilization. Eur J Biochem 2004;271:648–660. [PubMed: 14728692]

111. Dibbens JA, Miller DL, Damert A, Risau W, Vadas MA, Goodall GJ. Hypoxic regulation of vascular endothelial growth factor mRNA stability requires the cooperation of multiple RNA elements. Mol Biol Cell 1999;10:907–919. [PubMed: 10198046]

112. Levy NS, Chung S, Furneaux H, Levy AP. Hypoxic stabilization of vascular endothelial growth factor mRNA by the RNA-binding protein HuR. J Biol Chem 1998;273:6417–6423. [PubMed: 9497373]

113. Ray PS, Fox PL. A post-transcriptional pathway represses monocyte VEGF-A expression and angiogenic activity. EMBO J 2007;26:3360–3372. [PubMed: 17611605]

114. Ray PS, Jia J, Yao P, Majumder M, Hatzoglou M, Fox PL. A stress-responsive RNA switch regulates VEGFA expression. Nature 2009;457:915–919. [PubMed: 19098893]

115. Carballo E, Gilkeson GS, Blackshear PJ. Bone marrow transplantation reproduces the tristetraprolin-deficiency syndrome in recombination activating gene-2 (−/−) mice. Evidence that monocyte/macrophage progenitors may be responsible for TNFalpha overproduction. J Clin Invest 1997;100:986–995. [PubMed: 9276715]

116. Taylor GA, et al. A pathogenetic role for TNF alpha in the syndrome of cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency. Immunity 1996;4:445–454. [PubMed: 8630730]

117. Carballo E, Blackshear PJ. Roles of tumor necrosis factor-alpha receptor subtypes in the pathogenesis of the tristetraprolin-deficiency syndrome. Blood 2001;98:2389–2395. [PubMed: 11588035]

118. Varnum BC, Ma QF, Chi TH, Fletcher B, Herschman HR. The TIS11 primary response gene is a member of a gene family that encodes proteins with a highly conserved sequence containing an unusual Cys-His repeat. Mol Cell Biol 1991;11:1754–1758. [PubMed: 1996120]

119. Lai WS, Carballo E, Thorn JM, Kennington EA, Blackshear PJ. Interactions of CCCH zinc finger proteins with mRNA. Binding of tristetraprolin-related zinc finger proteins to Au-rich elements and destabilization of mRNA. J Biol Chem 2000;275:17827–17837. [PubMed: 10751406]

120. Stoecklin G, Stoeckle P, Lu M, Muehlemann O, Moroni C. Cellular mutants define a common mRNA degradation pathway targeting cytokine AU-rich elements. RNA 2001;7:1578–1588. [PubMed: 11720287]

121. Stumpo DJ, et al. Chorioallantoic fusion defects and embryonic lethality resulting from disruption of Zfp36L1, a gene encoding a CCCH tandem zinc finger protein of the Tristetraprolin family. Mol Cell Biol 2004;24:6445–6455. [PubMed: 15226444]

122. Stumpo DJ, et al. Targeted disruption of Zfp36 l2, encoding a CCCH tandem zinc finger RNA-binding protein, results in defective hematopoiesis. Blood 2009;114:2401–2410. [PubMed: 19633199]

123. Ramos SB, et al. The CCCH tandem zinc-finger protein Zfp36 l2 is crucial for female fertility and early embryonic development. Development 2004;131:4883–4893. [PubMed: 15342461]

124. Brewer G, An A. + U-rich element RNA-binding factor regulates c-myc mRNA stability in vitro. Mol Cell Biol 1991;11:2460–2466. [PubMed: 1901943]

125. Wagner BJ, DeMaria CT, Sun Y, Wilson GM, Brewer G. Structure and genomic organization of the human AUF1 gene: alternative pre-mRNA splicing generates four protein isoforms. Genomics 1998;48:195–202. [PubMed: 9521873]

126. Sarkar S, Sinsimer KS, Foster RL, Brewer G, Pestka S. AUF1 isoform-specific regulation of anti-inflammatory IL10 expression in monocytes. J Interferon Cytokine Res 2008;28:679–691. [PubMed: 18844578]

127. Sadri N, Lu JY, Badura ML, Schneider RJ. AUF1 is involved in splenic follicular B cell maintenance. BMC Immunol 2010;11:1. [PubMed: 20064252]

128. Sadri N, Schneider RJ. Auf1/Hnrnpd-deficient mice develop pruritic inflammatory skin disease. J Invest Dermatol 2009;129:657–670. [PubMed: 18830269]

129. Moraes KC, Quaresma AJ, Maehnss K, Kobarg J. Identification and characterization of proteins that selectively interact with isoforms of the mRNA binding protein AUF1 (hnRNP D). Biol Chem 2003;384:25–37. [PubMed: 12674497]

130. Knapinska AM, et al. Chaperone Hsp27 modulates AUF1 proteolysis and AU-rich element-mediated mRNA degradation. Mol Cell Biol 2011;31:1419–1431. [PubMed: 21245386]

131. Laroia G, Schneider RJ. Alternate exon insertion controls selective ubiquitination and degradation of different AUF1 protein isoforms. Nucleic Acids Res 2002;30:3052–3058. [PubMed: 12136087]

132. Lu JY, Bergman N, Sadri N, Schneider RJ. Assembly of AUF1 with eIF4G-poly(A) binding protein complex suggests a translation function in AU-rich mRNA decay. RNA 2006;12:883–893. [PubMed: 16556936]

133. Shen ZJ, Esnault S, Malter JS. The peptidyl-prolyl isomerase Pin1 regulates the stability of granulocyte-macrophage colony-stimulating factor mRNA in activated eosinophils. Nat Immunol 2005;6:1280–1287. [PubMed: 16273101]

134. Srikantan S, Gorospe M. HuR function in disease. Front Biosci 2012;17:189–205.

135. Mukherjee N, et al. Integrative regulatory mapping indicates that the RNA-binding protein HuR couples pre-mRNA processing and mRNA stability. Mol Cell 2011;43:327–339. [PubMed: 21723170]

136. Dixon DA, et al. Altered expression of the mRNA stability factor HuR promotes cyclooxygenase-2 expression in colon cancer cells. J Clin Invest. 2001;108:1657–1665. [PubMed: 11733561]

137. Nabors LB, Gillespie GY, Harkins L, King PH. HuR, a RNA stability factor, is expressed in malignant brain tumors and binds to adenine- and uridine-rich elements within the 3′ untranslated regions of cytokine and angiogenic factor mRNAs. Cancer Res 2001;61:2154–2161. [PubMed: 11280780]

138. Sung SC, et al. 7-Ketocholesterol upregulates interleukin-6 via mechanisms that are distinct from those of tumor necrosis factor-alpha, in vascular smooth muscle cells. J Vasc Res 2009;46:36–44. [PubMed: 18515973]

139. Jacob CO, Tashman NB. Disruption in the AU motif of the mouse TNF-alpha 3′ UTR correlates with reduced TNF production by macrophages in vitro. Nucleic Acids Res 1993;21:2761–2766. [PubMed: 8332472]

140. Jacob CO, McDevitt HO. Tumour necrosis factor-alpha in murine autoimmune ‘lupus’ nephritis. Nature 1988;331:356–358. [PubMed: 2893286]

141. Jacob CO, Hwang F, Lewis GD, Stall AM. Tumor necrosis factor alpha in murine systemic lupus erythematosus disease models: implications for genetic predisposition and immune regulation. Cytokine 1991;3:551–561. [PubMed: 1686413]

142. Gordon C, Ranges GE, Greenspan JS, Wofsy D. Chronic therapy with recombinant tumor necrosis factor-alpha in autoimmune NZB/NZW F1 mice. Clin Immunol Immunopathol 1989;52:421–434. [PubMed: 2758698]

143. Katsanou V, et al. The RNA-binding protein Elavl1/HuR is essential for placental branching morphogenesis and embryonic development. Mol Cell Biol 2009;29:2762–2776. [PubMed: 19307312]

144. Papadaki O, Milatos S, Grammenoudi S, Mukherjee N, Keene JD, Kontoyiannis DL. Control of thymic T cell maturation, deletion and egress by the RNA-binding protein HuR. J Immunol 2009;182:6779–6788. [PubMed: 19454673]

145. Yiakouvaki A, Dimitriou M, Karakasiliotis I, Eftychi C, Theocharis S, Kontoyiannis DL. Myeloid cell expression of the RNA-binding protein HuR protects mice from pathologic inflammation and colorectal carcinogenesis. J Clin Invest 2012;122:48–61. [PubMed: 22201685]

146. Anderson P Post-transcriptional control of cytokine production. Nat Immunol 2008;9:353–359. [PubMed: 18349815]

147. Schott J, Stoecklin G. Networks controlling mRNA decay in the immune system. Wiley Interdiscip Rev RNA 2010;1:432–456. [PubMed: 21956941]

148. Hau HH, Walsh RJ, Ogilvie RL, Williams DA, Reilly CS, Bohjanen PR. Tristetraprolin recruits functional mRNA decay complexes to ARE sequences. J Cell Biochem 2007;100:1477–1492. [PubMed: 17133347]

149. Lykke-Andersen J, Wagner E. Recruitment and activation of mRNA decay enzymes by two ARE-mediated decay activation domains in the proteins TTP and BRF-1. Genes Dev 2005;19:351–361. [PubMed: 15687258]

150. Sandler H, Stoecklin G. Control of mRNA decay by phosphorylation of tristetraprolin. Biochem Soc Trans 2008;36:491–496. [PubMed: 18481987]

151. Chou CF, et al. Tethering KSRP, a decay-promoting AU-rich element-binding protein, to mRNAs elicits mRNA decay. Mol Cell Biol 2006;26:3695–3706. [PubMed: 16648466]

152. Chen CY, Del Gatto-Konczak F, Wu Z, Karin M. Stabilization of interleukin-2 mRNA by the c-Jun NH2-terminal kinase pathway. Science 1998;280:1945–1949. [PubMed: 9632395]

153. Capowski EE, Esnault S, Bhattacharya S, Malter JS. Y box-binding factor promotes eosinophil survival by stabilizing granulocyte-macrophage colony-stimulating factor mRNA. J Immunol 2001;167:5970–5976. [PubMed: 11698476]

154. Rattenbacher B, et al. Analysis of CUGBP1 targets identifies GU-repeat sequences that mediate rapid mRNA decay. Mol Cell Biol 2010;30:3970–3980. [PubMed: 20547756]

155. Moraes KC, Wilusz CJ, Wilusz J. CUG-BP binds to RNA substrates and recruits PARN deadenylase. RNA 2006;12:1084–1091. [PubMed: 16601207]

156. Gurish MF, Austen KF. Developmental origin and functional specialization of mast cell subsets. Immunity 2012;37:25–33. [PubMed: 22840841]

157. Mullen TE, Marzluff WF. Degradation of histone mRNA requires oligouridylation followed by decapping and simultaneous degradation of the mRNA both 5′ to 3′ and 3′ to 5′. Genes Dev 2008;22:50–65. [PubMed: 18172165]

158. Xu J, et al. Structural study of MCPIP1 N-terminal conserved domain reveals a PIN-like RNase. Nucleic Acids Res 2012;40:6957–6965. [PubMed: 22561375]

159. Nicholson P, Yepiskoposyan H, Metze S. Zamudio Orozco R, Kleinschmidt N, Muhlemann O. Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. Cell Mol Life Sci 2010;67:677–700. [PubMed: 19859661]

160. Rebbapragada I, Lykke-Andersen J. Execution of nonsense-mediated mRNA decay: what defines a substrate? Curr Opin Cell Biol 2009;21:394–402. [PubMed: 19359157]

161. Mendell JT, Sharifi NA, Meyers JL, Martinez-Murillo F, Dietz HC. Nonsense surveillance regulates expression of diverse classes of mammalian transcripts and mutes genomic noise. Nat Genet 2004;36:1073–1078. [PubMed: 15448691]

162. Le Hir H, Gatfield D, Izaurralde E, Moore MJ. The exon-exon junction complex provides a binding platform for factors involved in mRNA export and nonsense-mediated mRNA decay. EMBO J 2001;20:4987. [PubMed: 11532962]

163. Maquat LE, Tarn WY, Isken O. The pioneer round of translation: features and functions. Cell 2010;142:368–374. [PubMed: 20691898]

164. Eberle AB, Stalder L, Mathys H, Orozco RZ, Muhlemann O. Posttranscriptional gene regulation by spatial rearrangement of the 3′ untranslated region. PLoS Biol 2008;6:e92. [PubMed: 18447580]

165. Ivanov PV, Gehring NH, Kunz JB, Hentze MW, Kulozik AE. Interactions between UPF1, eRFs, PABP and the exon junction complex suggest an integrated model for mammalian NMD pathways. EMBO J 2008;27:736–747. [PubMed: 18256688]
166. Singh G, Rebbapragada I, Lykke-Andersen J. A competition between stimulators and antagonists of Upf complex recruitment governs human nonsense-mediated mRNA decay. PLoS Biol 2008;6:e111. [PubMed: 18447585]
167. Eberle AB, Lykke-Andersen S, Muhlemann O, Jensen TH. SMG6 promotes endonucleolytic cleavage of nonsense mRNA in human cells. Nat Struct Mol Biol 2009;16:49–55. [PubMed: 19060897]
168. Lykke-Andersen J Identification of a human decapping complex associated with hUpf proteins in nonsense-mediated decay. Mol Cell Biol 2002;22:8114–8121. [PubMed: 12417715]
169. Li S, Wilkinson MF. Nonsense surveillance in lymphocytes? Immunity 1998;8:135–141. [PubMed: 9491995]
170. Baumann B, Potash MJ, Kohler G. Consequences of frameshift mutations at the immunoglobulin heavy chain locus of the mouse. EMBO J 1985;4:351–359. [PubMed: 3926482]
171. Jack HM, Berg J, Wabl M. Translation affects immunoglobulin mRNA stability. Eur J Immunol 1989;19:843–847. [PubMed: 2500347]
172. Connor A, Wiersma E, Shulman MJ. On the linkage between RNA processing and RNA translatability. J Biol Chem 1994;269:25178–25184. [PubMed: 7523380]
173. Lozano F, Maertzdorf B, Pannell R, Milstein C. Low cytoplasmic mRNA levels of immunoglobulin kappa light chain genes containing nonsense codons correlate with inefficient splicing. EMBO J 1994;13:4617–4622. [PubMed: 7925302]
174. Aoufouchi S, Yelamos J, Milstein C. Nonsense mutations inhibit RNA splicing in a cell-free system: recognition of mutant codon is independent of protein synthesis. Cell 1996;85:415–422. [PubMed: 8616896]
175. Carter MS, Li S, Wilkinson MF. A splicing-dependent regulatory mechanism that detects translation signals. EMBO J 1996;15:5965–5975. [PubMed: 8918474]
176. Carter MS, et al. A regulatory mechanism that detects premature nonsense codons in T-cell receptor transcripts in vivo is reversed by protein synthesis inhibitors in vitro. J Biol Chem 1995;270:28995–29003. [PubMed: 7499432]
177. Chemin G, et al. Multiple RNA surveillance mechanisms cooperate to reduce the amount of nonfunctional Ig kappa transcripts. J Immunol 2010;184:5009–5017. [PubMed: 20357261]
178. Tinguely A, et al. Cross talk between immunoglobulin heavy-chain transcription and RNA surveillance during B cell development. Mol Cell Biol 2012;32:107–117. [PubMed: 22037763]
179. Wang J, Vock VM, Li S, Olivas OR, Wilkinson MF. A quality control pathway that down-regulates aberrant T-cell receptor (TCR) transcripts by a mechanism requiring UPF2 and translation. J Biol Chem 2002;277:18489–18493. [PubMed: 11889124]
180. Apcher S, et al. Major source of antigenic peptides for the MHC class I pathway is produced during the pioneer round of mRNA translation. Proc Natl Acad Sci USA 2011;108:11572–11577. [PubMed: 21709220]
181. Gracias DT, Katsikis PD. MicroRNAs: key components of immune regulation. Adv Exp Med Biol 2012;780:15–26.
182. O'Connell RM, Rao DS, Baltimore D. microRNA regulation of inflammatory responses. Annu Rev Immunol 2012;30:295–312. [PubMed: 22224773]
183. Koralov SB, et al. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. Cell 2008;132:860–874. [PubMed: 18329371]
184. Fedeli M, et al. Dicer-dependent microRNA pathway controls invariant NKT cell development. J Immunol 2009;183:2506–2512. [PubMed: 19625646]
185. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005;120:15–20. [PubMed: 15652477]
186. Asirvatham AJ, Gregorie CJ, Hu Z, Magner WJ, Tomasi TB. MicroRNA targets in immune genes and the Dicer/Argonaute and ARE machinery components. Mol Immunol 2008;45:1995–2006. [PubMed: 18061676]

187. Zhou R, Gong AY, Eischeid AN, Chen XM. miR-27b targets KSRP to coordinate TLR4-mediated epithelial defense against Cryptosporidium parvum infection. PLoS Pathog 2012;8: e1002702. [PubMed: 22615562]

188. Ruggiero T, et al. LPS induces KH-type splicing regulatory protein-dependent processing of microRNA-155 precursors in macrophages. FASEB J 2009;23:2898–2908. [PubMed: 19423639]

189. Trabucchi M, et al. The RNA-binding protein KSRP promotes the biogenesis of a subset of microRNAs. Nature 2009;459:1010–1014. [PubMed: 19458619]

190. Lebedeva S, et al. Transcriptome-wide analysis of regulatory interactions of the RNA-binding protein HuR. Mol Cell 2011;43:340–352. [PubMed: 21723171]

191. Abdelmohsen K, Tominaga-Yamanaka K, Srikantan S, Yoon JH, Kang MJ, Gorospe M. RNA-binding protein AUF1 represses Dicer expression. Nucleic Acids Res 2012;40:11531–11544. [PubMed: 23066106]

192. Jing Q, et al. Involvement of microRNA in AU-rich element-mediated mRNA instability. Cell 2005;120:623–634. [PubMed: 15766526]

193. Helfer S, Schott J, Stoecklin G, Forstemann K. AU-rich element-mediated mRNA decay can occur independently of the miRNA machinery in mouse embryonic fibroblasts and Drosophila S2-cells. PLoS ONE 2012;7:e28907. [PubMed: 22253700]

194. Kim HH, Kuwano Y, Srikantan S, Lee EK, Martindale JL, Gorospe M. HuR recruits let-7/RISC to repress c-Myc expression. Genes Dev 2009;23:1743–1748. [PubMed: 19574298]

195. Bhattacharyya SN, Habermacher R, Martine U, Closs EI, Filipowicz W. Relief of microRNA-mediated translational repression in human cells subjected to stress. Cell 2006;125:1111–1124. [PubMed: 16777601]

196. Vasudevan S, Steitz JA. AU-rich-element-mediated upregulation of translation by FXR1 and Argonaute 2. Cell 2007;128:1105–1118. [PubMed: 17382880]

197. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can upregulate translation. Science 2007;318:1931–1934. [PubMed: 18048652]

198. Holcik M, Sonenberg N. Translational control in stress and apoptosis. Nat Rev Mol Cell Biol 2005;6:318–327. [PubMed: 15803138]

199. Pestova TV, et al. Molecular mechanisms of translation initiation in eukaryotes. Proc Natl Acad Sci USA 2001;98:7029–7036. [PubMed: 11416183]

200. Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. Nat Rev Immunol 2009;9:324–337. [PubMed: 19390566]

201. Cok SJ, Acton SJ, Sexton AE, Morrison AR. Identification of RNA-binding proteins in RAW 264.7 cells that recognize a lipopolysaccharide-responsive element in the 3-untranslated region of the murine cyclooxygenase-2 mRNA. J Biol Chem 2004;279:8196–8205. [PubMed: 14662769]

202. Mazan-Mamczarz K, Lal A, Martindale JL, Kawai T, Gorospe M. Translational repression by RNA-binding protein TIAR. Mol Cell Biol 2006;26:2716–2727. [PubMed: 16537914]

203. Tong X, Van Dross RT, Abu-Yousif A, Morrison AR, Pelling JC. Apigenin prevents UVB-induced cyclooxygenase 2 expression: coupled mRNA stabilization and translational inhibition. Mol Cell Biol 2007;27:283–296. [PubMed: 17074806]

204. Ivanov P, Kedersha N, Anderson P. Stress puts TIA on TOP. Genes Dev 2011;25:2119–2124. [PubMed: 22012617]

205. Yamasaki S, Stoecklin G, Kedersha N, Simarro M, Anderson P. T-cell intracellular antigen-1 (TIA-1)-induced translational silencing promotes the decay of selected mRNAs. J Biol Chem 2007;282:30070–30077. [PubMed: 17711853]

206. Phillips K, Kedersha N, Shen L, Blackshear PJ, Anderson P. Arthritis suppressor genes TIA-1 and TTP dampen the expression of tumor necrosis factor alpha, cyclooxygenase 2, and inflammatory arthritis. Proc Natl Acad Sci USA 2004;101:2011–2016. [PubMed: 14769925]

207. Scheu S, Stetson DB, Reinhardt RL, Leber JH, Mohrs M, Locksley RM. Activation of the integrated stress response during T helper cell differentiation. Nat Immunol 2006;7:644–651. [PubMed: 16680145]

208. Glasmacher E, et al. Roquin binds inducible costimulator mRNA and effectors of mRNA decay to induce microRNA-independent post-transcriptional repression. Nat Immunol 2010;11:725–733. [PubMed: 20639877]

209. Athanasopoulos V, et al. The ROQUIN family of proteins localizes to stress granules via the ROQ domain and binds target mRNAs. FEBS J 2010;277:2109–2127. [PubMed: 20412057]

210. Sampath P, Mazumder B, Seshadri V, Fox PL. Transcript-selective translational silencing by gamma interferon is directed by a novel structural element in the ceruloplasmin mRNA 3′ untranslated region. Mol Cell Biol 2003;23:1509–1519. [PubMed: 12588972]

211. Muhl H, Pfeilschifter J. Anti-inflammatory properties of pro-inflammatory interferon-gamma. Int Immunopharmacol 2003;3:1247–1255. [PubMed: 12890422]

212. Vyas K, et al. Genome-wide polysome profiling reveals an inflammation-responsive posttranscriptional operon in gamma interferon-activated monocytes. Mol Cell Biol 2009;29:458–470. [PubMed: 19001086]

213. Mukhopadhyay R, Jia J, Arif A, Ray PS, Fox PL. The GAIT system: a gatekeeper of inflammatory gene expression. Trends Biochem Sci 2009;34:324–331. [PubMed: 19535251]

214. Mazumder B, Sampath P, Seshadri V, Maitra RK, DiCorleto PE, Fox PL. Regulated release of L13a from the 60S ribosomal subunit as a mechanism of transcript-specific translational control. Cell 2003;115:187–198. [PubMed: 14567916]

215. Sampath P, et al. Noncanonical function of glutamyl-prolyl-tRNA synthetase: gene-specific silencing of translation. Cell 2004;119:195–208. [PubMed: 15479637]

216. Kapasi P, et al. L13a blocks 48S assembly: role of a general initiation factor in mRNA-specific translational control. Mol Cell 2007;25:113–126. [PubMed: 17218275]

217. Mazumder B, Seshadri V, Imataka H, Sonenberg N, Fox PL. Translational silencing of ceruloplasmin requires the essential elements of mRNA circularization: poly(A) tail, poly(A)-binding protein, and eukaryotic translation initiation factor 4G. Mol Cell Biol 2001;21:6440–6449. [PubMed: 11533233]

218. Citores MJ, et al. The dinucleotide repeat polymorphism in the 3′UTR of the CD154 gene has a functional role on protein expression and is associated with systemic lupus erythematosus. Ann Rheum Dis 2004;63:310–317. [PubMed: 14962968]

219. Glass CK, Ogawa S. Combinatorial roles of nuclear receptors in inflammation and immunity. Nat Rev Immunol 2006;6:44–55. [PubMed: 16493426]

220. Rapoport SM, Schewe T. The maturational breakdown of mitochondria in reticulocytes. Biochim Biophys Acta 1986;864:471–495. [PubMed: 3098292]

221. Straus DS, Glass CK. Cyclopentenone prostaglandins: new insights on biological activities and cellular targets. Med Res Rev 2001;21:185–210. [PubMed: 11301410]

222. Straus DS, et al. 15-deoxy-delta 12,14-prostaglandin J2 inhibits multiple steps in the NF-kappa B signaling pathway. Proc Natl Acad Sci USA 2000;97:4844–4849. [PubMed: 10781090]

223. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. Trends Immunol 2007;28:551–558. [PubMed: 17981503]

224. Kim WJ, Kim JH, Jang SK. Anti-inflammatory lipid mediator 15d-PGJ2 inhibits translation through inactivation of eIF4A. EMBO J 2007;26:5020–5032. [PubMed: 18034160]

225. Hilliard A, et al. Translational regulation of autoimmune inflammation and lymphoma genesis by programmed cell death 4. J Immunol 2006;177:8095–8102. [PubMed: 17114484]

226. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. Trends Immunol 2012; doi: 10.1016/j.it.2012.10.001

227. Katz JB, Muller AJ, Prendergast GC. Indoleamine dioxygenase in T-cell tolerance and tumoral immune escape. Immunol Rev 2008;222:206–221. [PubMed: 18364004]

228. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 2010;185:3190–3198. [PubMed: 20720200]

229. Nguyen NT, et al. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. Proc Natl Acad Sci USA 2010;107:19961–19966. [PubMed: 21041655]

230. Stockinger B, Hirota K, Duarte J, Veldhoen M. External influences on the immune system via activation of the aryl hydrocarbon receptor. Semin Immunol 2011;23:99–105. [PubMed: 21288737]

231. Baird TD, Wek RC. Eukaryotic initiation factor 2 phosphorylation and translational control in metabolism. Adv Nutr 2012;3:307–321. [PubMed: 22585904]

232. Dong J, Qiu H, Garcia-Barrio M, Anderson J, Hinnebusch AG. Uncharged tRNA activates GCN2 by displacing the protein kinase moiety from a bipartite tRNA-binding domain. Mol Cell 2000;6:269–279. [PubMed: 10983975]

233. Munn DH, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity 2005;22:633–642. [PubMed: 15894280]

234. Sundrud MS, et al. Halofuginone inhibits TH17 cell differentiation by activating the amino acid starvation response. Science 2009;324:1334–1338. [PubMed: 19498172]

235. Keller TL, et al. Halofuginone and other febrifugine derivatives inhibit prolyl-tRNA synthetase. Nat Chem Biol 2012;8:311–317. [PubMed: 22327401]

236. Fallarino F, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells. J Immunol 2006;176:6752–6761. [PubMed: 16709834]

237. Sharma MD, et al. Plasmacytoid dendritic cells from mouse tumor-draining lymph nodes directly activate mature Tregs via indoleamine dioxygenase. J Clin Invest 2007;117:2570–2582. [PubMed: 17710230]

238. Cao W, et al. Toll-like receptor-mediated induction of type I interferon in plasmacytoid dendritic cells requires the rapamycin-sensitive PI (3)K-mTOR-p70S6K pathway. Nat Immunol 2008;9:1157–1164. [PubMed: 18758466]

239. Colina R, et al. Translational control of the innate immune response through IRF-7. Nature 2008;452:323–328. [PubMed: 18272964]

240. Herdy B, et al. Translational control of the activation of transcription factor NF-kappaB and production of type I interferon by phosphorylation of the translation factor eIF4E. Nat Immunol 2012;13:543–550. [PubMed: 22544393]

241. Joshi B, et al. Phosphorylation of eukaryotic protein synthesis initiation factor 4E at Ser-209. J Biol Chem 1995;270:14597–14603. [PubMed: 7782323]

242. Furic L, et al. eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression. Proc Natl Acad Sci USA 2010;107:14134–14139. [PubMed: 20679199]

243. Silverman N, Maniatis T. NF-kappaB signaling pathways in mammalian and insect innate immunity. Genes Dev 2001;15:2321–2342. [PubMed: 11562344]

244. Hoffmann A, Levchenko A, Scott ML, Baltimore D. The IkappaB-NF-kappaB signaling module: temporal control and selective gene activation. Science 2002;298:1241–1245. [PubMed: 12424381]

Table 1.

Examples of immune mRNAs subject to post-transcriptional control

mRNA	Encoded protein function	RNA-binding Protein	RNA element	Mechanism of control	References
CCL2 (MCP-1)	Chemokine	TTP	ARE	mRNA stability	(38)
CCL3	Chemokine	TTP	ARE	mRNA stability	(39)
CCL5 (RANTES)	Chemokine	n.d.	n.d.	mRNA stability	(40)
CCL11 (Eotaxin)	Chemokine	HuR	ARE	mRNA stability	(41)
CCL22	Chemokine	GAIT complex	GAIT	Translation	(42)
CCR2	Chemokine receptor	HuR	n.d.	mRNA stability	(40)
CCR3	Chemokine receptor	GAIT complex	GAIT	Translation	(42)
CCR4	Chemokine receptor	GAIT complex	GAIT	Translation	(42)
CCR6	Chemokine receptor	GAIT complex	GAIT	Translation	(42)
CD9	Platelet activation	CUGBP1	GRE	mRNA stability	(43)
CD154 (CD40L)	Ligand for CD40	PTB, PTB-T, nucleolin, HNRNPL	CURE, CARE	mRNA stability	(44-51)
Ceruloplasmin	Inflammatory mediator	GAIT complex	GAIT	Translation	(52)
COX-2	Lipoxygenase, prostaglandin synthesis	TTP, HuR, TIA1, TIAR	ARE	mRNA stability,	(37, 53, 54)
CXCL1 (GROα, KC)	Chemokine	TTP	ARE	mRNA stability	(55)
CXCL2 (GROβ)	Chemokine	n.d.	ARE	mRNA stability	(56, 57)
CXCL3 (GROγ)	Chemokine	n.d.	ARE	mRNA stability	(57)
CXCL10 (IP-10)	Chemokine	n.d.	n.d.	mRNA stability	(58)
E47	Class switch recombination	TTP	ARE	mRNA stability	(59)
G-CSF	Cytokine, neutrophil development	n.d.	ARE, SLDE	mRNA stability	(60-62)
GM-CSF	Cytokine	TTP, YB-1, AUF1, PIN1	ARE	mRNA stability, translation	(7, 61, 63-66)
ICOS	Co-stimulatory molecule	Roquin	Roquin-b.s.	mRNA stability	(67)
IFNβ	Cytokine, antiviral	n.d., KSRP	ARE, CRD	mRNA stability	(68-70)
IFNγ	Cytokine, macrophage stimulation	TTP, HuR	ARE	mRNA stability	(71-73)
IκBα	Inhibitor of NF-κB	n.d.	ARE	mRNA stability	(74)
IL1 β	Pro-inflammatory cytokine	TTP, AUF1, MCPIP1	ARE, endo	mRNA stability	(27, 75-78)
IL-1F7b	Cytokine	n.d.	CRD	mRNA stability	(79)
IL-2	Cytokine, T-cell growth factor	TTP, NF90	ARE, JRE	mRNA stability	(80-82)
IL-3	Cytokine, haematopoiesis	TTP	ARE	mRNA stability	(83-85)

mRNA	Encoded protein function	RNA-binding Protein	RNA element	Mechanism of control	References
IL-4	Cytokine, Th2 response	HuR	CRD	mRNA stability	(86)
IL-6	Proinflammatory cytokine	TTP, AUF1	ARE, SLDE, endo	mRNA stability	(84, 87-92)
IL-8 (CXCL8)	Chemokine	KSRP	ARE	mRNA stability	(93)
IL-10	Cytokine, anti-inflammatory	TTP	ARE	mRNA stability	(94)
IL-11	Cytokine, haematopoiesis	n.d.	ARE	mRNA stability	(95)
IL-12b	Cytokine, Th1 response, NK	MCPIP1	endo	mRNA stability	(89)
IL-13	Cytokine, Th2 response	HuR	ARE	mRNA stability	(96)
IL-17	IL-17, pro-inflammatory	TTP	ARE	mRNA stability	(97)
IL-18	Cytokine, Th1 response, NK	n.d.	n.d.	mRNA stability	(79)
iNOS	NO synthase	PTB, HuR, HNRNPL, HNRNPI, KSRP, TTP	ARE	mRNA stability	(35, 98, 99)
IRF1	Transcription factor, cytokine expression	n.d.	ARE	mRNA stability	(74)
15-Lipoxygenase	Erythropoiesis	HNRNPE1, HNRNPK	DICE	Translation	(100, 101)
mMCP-1	Mast cell protease	n.d.	CRS	mRNA stability	(102)
mMCP-2	Mast cell protease	n.d.	CRS	mRNA stability	(102)
mMCP-4	Mast cell protease	n.d.	CRS	mRNA stability	(102)
MMP9	Matrix metalloproteinase	n.d.	ARE	mRNA stability	(103)
MMP13	Matrix metalloproteinase	TIAR	ARE	Translation	(104)
Neuropilin-1	VEGF receptor, T-cell-APC interaction	Roquin	Roquin-b.s.	mRNA stability	(67)
Rab8a	RAS GTPase family member	PTB	CURE	mRNA stability	(105)
TNFα	Cytokine, pro-inflammatory	TTP, HuR, TIA1,TIAR, FXR1, SRC3	ARE, CDE	mRNA stability, translation	(15, 19, 21, 73, 106-108)
TNFR2	TNF receptor	CUGBP1	GRE	mRNA stability	(43)
TNFAIP3 (A20)	Inhibitor of NF-κB	n.d.	ARE	mRNA stability	(74)
VCAM-1	Adhesion molecule	n.d.	ARE	mRNA stability	(109)
VEGF-A	Growth factor, angiogenic	GAIT complex, HNRNPL, NF90, HuR, PTB, YB-1	GAIT, CARE, ARE, CRD, 5′-UTR	mRNA stability, translation	(110-114)

ARE, AU-rich element; n.d., not determined; GAIT, IFNγ-activated inhibitor of translation; GRE, GU-rich element; CURE, CU-rich element; CARE, cytosine- and adenine-rich instability element; SLDE, stem-loop destabilizing element; b.s., binding site; CRD, coding region determinant of instability; JRE, JNK-responsive element; endo; endoribonuclease cleavage site; DICE, differentiation control element; CRS, repetitive C-rich sequence; CDE, constitutive decay element.