

Review

Extending the reach of transcription factors to mRNA stability

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Transcription factors (TFs) are traditionally viewed as DNA-binding proteins that regulate gene expression at the level of transcription. While their roles in cotranscriptional RNA processing are well established, their contribution to downstream post-transcriptional events has remained comparatively underexplored. In this article, we review emerging evidence that TFs can directly regulate mRNA stability in a gene-specific manner, thereby extending their regulatory influence across the mRNA life cycle. We highlight diverse mechanisms, including cotranscriptional mRNA imprinting, modulation of RNA modification pathways, recruitment of mRNA decay factors, and direct binding to *cis*-acting mRNA elements. These findings reveal an unexpected convergence between TFs and RNA-binding proteins, expand current models of gene regulation, and establish mRNA stability as an important yet underappreciated dimension of TF function.

Significance

Transcription factors are traditionally viewed as regulators of transcription, yet growing evidence shows that they can also directly control mRNA stability. This review synthesizes recent mechanistic insights demonstrating how transcription factors influence mRNA stability through distinct pathways. By revealing an unexpected layer of gene regulation, this work provides a new perspective on how gene expression outputs and transcriptomic data are interpreted.

Transcription factors across the mRNA life cycle

Gene expression is tightly regulated to ensure that gene products are synthesized with the spatial and temporal precision required for cellular identity and function. Disruption of these regulatory networks can lead to developmental defects, metabolic disorders, and diseases such as cancer. Gene expression begins in the nucleus, where the RNA polymerase II (RNAPII) complex, general **transcription factors (TFs)** (see [Glossary](#)), sequence-specific TFs, and diverse coactivators assemble at promoters to initiate transcription. During transcription, the nascent precursor messenger RNA (mRNA) undergoes extensive cotranscriptional processing, including the addition of a 7-methylguanosine (m⁷G) cap at the 5' end, the removal of introns through splicing, and the addition of a polyadenosine [poly(A)] tail at the 3' end following cleavage. The mature mRNA is exported to the cytoplasm, where it can be translated, stored, or degraded, depending on cellular needs.

All stages of the mRNA life cycle are functionally interconnected, forming an integrated network that ensures robust and adaptable control of gene expression [1,2]. Within this network, TFs play central roles. By binding specific DNA motifs within promoters or enhancers, TFs recruit or stabilize RNAPII and the basal transcriptional machinery to regulate transcription initiation [3]. They also modulate chromatin accessibility through interactions with coactivators, chromatin remodelers, and histone-modifying enzymes [4] and contribute to 3D genome organization that shapes transcriptional states [5]. Beyond initiation, TFs further influence promoter-proximal pausing and elongation dynamics [6,7], thereby affecting cotranscriptional processes such as capping [8], splicing [9], and 3'-end processing [10].

Among these processes, splicing is one of the best-characterized examples of direct TF involvement. In addition to regulating the expression of splicing factors, TFs can directly influence splice-site selection through kinetic and spatial coupling mechanisms [11,12]. While TFs are recognized as multifunctional regulators of early gene expression, their roles in later stages of the mRNA life cycle, particularly mRNA decay, have only recently emerged. In this article, we review the growing

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evidence that TFs can directly regulate **mRNA stability**, the final stage of the mRNA life cycle, beyond their indirect effects on decay factor expression. After summarizing the core mechanisms governing mRNA turnover, we discuss examples of TF-mediated regulation of mRNA stability through direct molecular interactions with RNA or *trans*-acting decay factors. Collectively, these studies support TF-mediated control of mRNA decay as an emerging and potentially widespread layer of gene expression regulation.

Principles and pathways of mRNA decay

mRNA decay is not merely a waste-disposal process for defective or obsolete transcripts but a tightly regulated component of gene expression networks [13,14]. Transcript half-lives vary widely across genes, cell types, developmental stages, and environmental conditions, enabling rapid and reversible control of gene expression [15,16]. Accordingly, modulation of mRNA stability plays key roles in development [17,18], stress adaptation [19,20], cell cycle progression [21], and aging [22].

Eukaryotic cells use multiple mRNA decay pathways, including both general turnover mechanisms and specialized quality-control systems targeting aberrant transcripts [23]. In the nucleus, surveillance factors such as the 5'–3' exoribonuclease 2 (XRN2) and the RNA exosome eliminate improperly processed transcripts and are closely coupled to transcription and RNA processing [24]. In the cytoplasm, quality-control decay pathways are linked to translation and are triggered by aberrant translational events [25]. These include nonsense-mediated decay (NMD) [26], nonstop decay (NSD) [27], no-go decay (NGD) [28], and codon optimality-mediated decay [29]. Outside these specialized surveillance pathways, most constitutive mRNA turnover occurs through deadenylation-dependent mechanisms in the cytoplasm.

Deadenylation as the entry point to mRNA decay

Most mRNAs are exported to the cytoplasm with a 5' m⁷G cap and a 3' poly(A) tail bound by poly(A)-binding proteins (PABPs) [30]. Interactions between these structures promote a protective 'closed-loop' conformation that enhances translation and shields transcripts from exonucleolytic degradation [31]. Consequently, productive mRNA decay typically requires the disruption of this protective configuration and begins with shortening of the poly(A) tail, a step known as deadenylation [32].

Deadenylation is generally considered the first committed and rate-limiting step of cytoplasmic mRNA decay [33]. It is mediated primarily by two deadenylase complexes: poly(A)-nuclease (PAN) 2 and 3, or PAN2–PAN3 and Carbon Catabolite Repression 4-Negative On TATA-less, or CCR4–NOT [34]. PAN2–PAN3, consisting of a PAN3 homodimer and a single PAN2 exonuclease, preferentially shortens long poly(A) tails [35]. CCR4–NOT is a large multifunctional complex organized around the scaffold protein CNOT1 and comprising two catalytic subunits, CCR4-associated factor 1 (CAF1 also known as CNOT7 or CNOT8 in mammals) and CCR4 (also known as CNOT6 or CNOT6L in mammals), together with the noncatalytic subunits CNOT2, CNOT3, CNOT9, CNOT10, and CNOT11 [36]. While CNOT10/11 may facilitate RNA binding, CNOT9 and the CNOT2/3 (NOT) module contribute to transcript-specific recruitment through protein–protein interactions [37].

The classical biphasic model proposes that PAN2–PAN3 initiates deadenylation by trimming long poly(A) tails, after which CCR4–NOT completes tail removal [33]. However, more recent studies suggest that CCR4–NOT acts as the dominant regulator of global mRNA stability, whereas PAN2–PAN3 may operate on specific transcripts or in defined contexts [38,39]. CCR4–NOT can be recruited broadly through interactions with PABPC [poly(A)-binding protein cytoplasmic] and ribosomes, or selectively through **RNA-binding proteins (RBPs)** and the microRNA (miRNA) machinery [36]. Once the poly(A) tail is shortened below the protective PABPC footprint (~30 nt), transcripts become susceptible to decapping and exonucleolytic degradation by XRN1

Glossary

Cotranscriptional mRNA imprinting: mechanism by which promoter-associated factors or transcriptional regulators 'imprint' nascent mRNAs with proteins that subsequently determine their cytoplasmic fate, including stability, thereby coupling transcription to mRNA turnover.

Epitranscriptome: collection of chemical modifications present on RNA molecules that influence RNA metabolism without altering the underlying nucleotide sequence. These modifications regulate diverse processes, including mRNA stability, translation, localization, and RNA–protein interactions, through the coordinated action of writer, reader, and eraser proteins.

Intrinsically disordered region (IDR): protein region that lacks a stable three-dimensional structure under physiological conditions. They frequently mediate multivalent interactions with proteins, RNA, and DNA and promote the assembly of dynamic biomolecular condensates involved in gene regulation.

Messenger ribonucleoprotein

(mRNP): dynamic complex formed by an mRNA molecule and its associated proteins. Its composition changes throughout the mRNA life cycle and determines transcript processing, localization, translation, and stability.

mRNA stability: persistence of an mRNA molecule before degradation, commonly expressed as its half-life. It is determined by the interplay between *cis*-acting transcript features and *trans*-acting regulatory factors, and it constitutes a major determinant of steady-state transcript abundance and gene expression dynamics.

RNA-binding protein (RBP): protein that directly binds RNA to regulate one or more aspects of RNA metabolism, including splicing, 5'- and 3'-end processing, localization, translation, and stability. Although RBPs are traditionally distinguished from TFs, an increasing number of proteins exhibit both DNA- and RNA-binding activities.

Transcription factor (TF): protein that binds specific DNA sequences, typically within promoters or enhancers, to regulate transcription by modulating the recruitment of, or processing by, the transcriptional machinery. Although traditionally viewed as DNA-binding regulators of transcription, an increasing number of TFs have also been shown to

(5'–3' exoribonuclease 1) in the 5'–3' direction or by the RNA exosome in the 3'–5' direction [40, 41]. Although poly(A) tail shortening is generally a prerequisite for decapping, deadenylation-independent decapping pathways can also operate under specific conditions [42,43].

participate in cotranscriptional and post-transcriptional regulation of gene expression.

The 5'–3' and 3'–5' decay pathways

Following deadenylation, cytoplasmic mRNA decay most commonly proceeds through 5' decapping. This reaction is catalyzed by the mRNA-decapping enzyme 2 (DCP2) in complex with its cofactor DCP1 [44]. The assembly and activity of the DCP1–DCP2 complex are regulated by numerous accessory factors, including enhancers of decapping (EDC1–4), the Like-Sm proteins (LSM1–7) complex, the mRNA processing body assembly factors LSM14A and Protein associated with topoisomerase II homolog 1 (PATL1), and the DEAD-box RNA helicase 6 (DDX6) [45]. Notably, the PATL1/LSM1–7 complex preferentially binds oligoadenylated transcripts, linking completion of CCR4–NOT-mediated deadenylation to decapping initiation [46]. Decapped mRNAs are subsequently degraded in the 5'–3' direction by the exonuclease XRN1, which interacts with components of the decapping machinery to coordinate cap removal and exonucleolytic decay [47]. Together with reported interactions between PATL1 and the CCR4–NOT complex, these findings support a coordinated model in which deadenylation, decapping, and 5'–3' degradation are functionally coupled [48].

Alternatively, deadenylated transcripts can be degraded from the 3' end by the cytoplasmic RNA exosome. In metazoans, exosome-mediated mRNA decay depends on the DIS3-like exonuclease 1 (DIS3L1) and the associated RNA helicase Superkiller complex protein 2 (SKI2) [41]. Although this pathway contributes to mRNA turnover, it appears less prominent in bulk cytoplasmic decay than the decapping–XRN1 pathway, potentially because 3'–5' degradation is less compatible with cotranslational mRNA decay [49].

The molecular determinants of mRNA stability

mRNA stability is governed by the interplay between intrinsic *cis*-acting features and *trans*-acting factors that interpret them. Together, they regulate the recruitment and activity of decay machineries on specific transcripts (Figure 1).

Cis-acting features include sequence and structural elements recognized by RBPs, miRNAs, and long noncoding RNAs (lncRNAs), as well as epitranscriptomic modifications, premature termination codons, codon optimality, and overall nucleotide composition [50–52]. These features are distributed across coding sequences and untranslated regions (UTRs). Binding sites for stability-related RBPs and miRNA target sites are often enriched in 3' UTRs, whereas RNA modifications, such as *N*⁶-methyladenosine (m⁶A) and 5-methylcytosine (m⁵C), are preferentially located around stop codons and translation initiation sites, respectively [53–55]. The outcome of mRNA stability regulation reflects the combinatorial action of multiple stabilizing and destabilizing factors bound to the same transcript [56]. Such combinatorial control can arise through direct protein–protein interactions or through RNA structural cooperativity that exposes or occludes regulatory binding sites [57–59]. The CCR4–NOT complex serves as a hub within this regulatory network [36]. Nevertheless, alternative pathways, including direct decapping and endonucleolytic cleavage, can initiate mRNA degradation independently of deadenylation, underscoring the mechanistic versatility of mRNA decay.

RNA sequence motifs and structures

Sequence motifs, particularly within 3' UTRs, serve as docking platforms for RBPs and ncRNAs [54]. Among these, AU-rich elements (AREs) are some of the best-characterized *cis*-regulatory motifs and are especially enriched in short-lived transcripts encoding early-response genes, cytokines, growth factors, and proto-oncogenes [60,61]. AREs are recognized by ARE-binding proteins (ARE-BPs), many of which contain multiple RNA-binding domains that enable

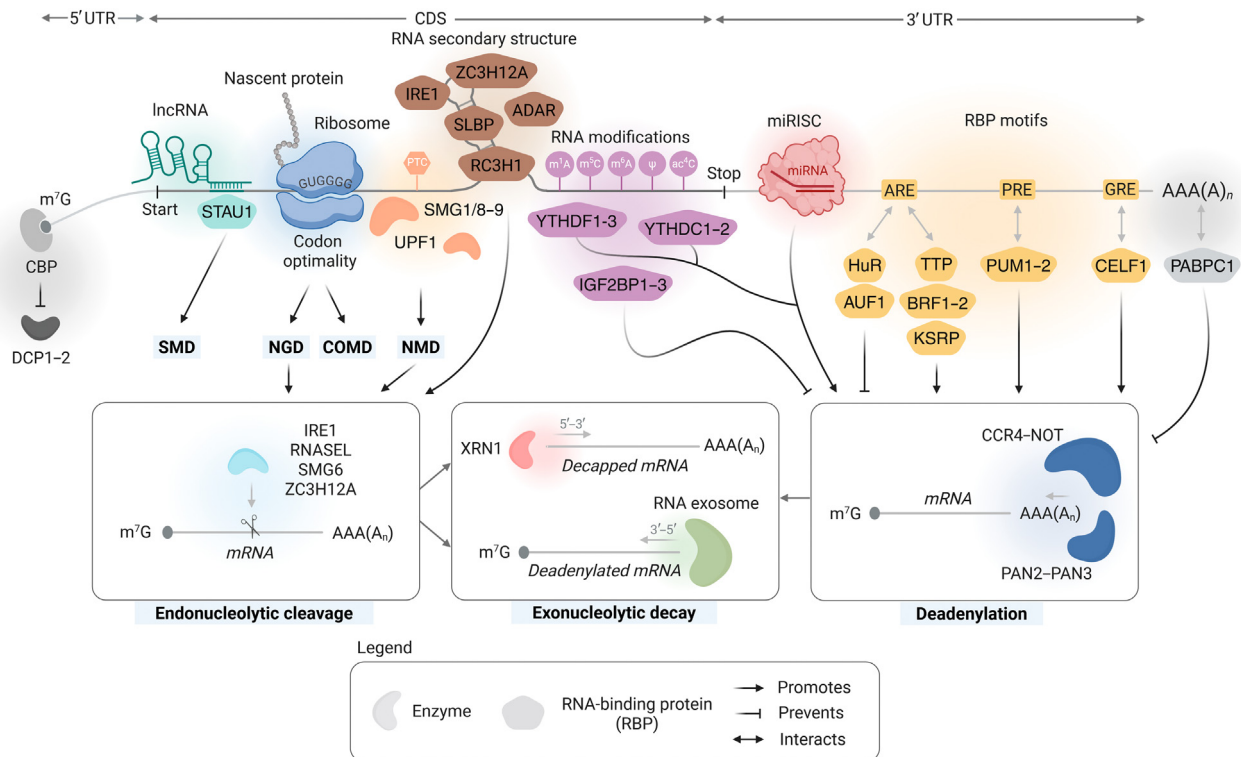


Figure 1. Major determinants of mRNA stability and mechanisms of cytoplasmic mRNA turnover. The figure summarizes the principal *cis*-acting features and *trans*-acting factors that regulate the stability of cytoplasmic mRNA. The transcript is shown schematically from the 5' cap to the poly(A) tail, highlighting representative regulatory features, RNA secondary structures, codon optimality, premature termination codons (PTCs), epitranscriptomic modifications (e.g., m⁶A, m⁵C, m¹A, Ψ, and ac⁴C), miRNA-binding sites, and RNA-binding protein (RBP) recognition motifs. These features are recognized by RBPs, noncoding RNAs (miRNAs or lncRNAs), epitranscriptomic reader proteins, and RNA surveillance factors, which promote or inhibit transcript degradation. Downstream, major routes of cytoplasmic mRNA turnover are illustrated: deadenylation mediated by the PAN2–PAN3 and CCR4–NOT complexes is followed by exonucleolytic decay involving decapping and 5'→3' degradation by XRN1 or 3'→5' degradation by the RNA exosome. Independently of deadenylation, transcripts can be degraded by endonucleolytic cleavage mediated by specialized endoribonucleases. Representative specialized decay pathways, including Staufen-mediated decay (SMD), nonsense-mediated decay (NMD), no-go decay (NGD), and codon optimality-mediated decay (COMD), are also shown. AAA(A)_n: poly(A) tail; ac⁴C: N⁴-acetylcytidine; ADAR: adenosine deaminase RNA specific; ARE: AU-rich element; AUF1: AU-rich element RNA-binding protein 1; BRF1–2: butyrate response factor 1–2; CBP: cap binding protein; CCR4–NOT: carbon catabolite repression 4-negative on TATA-less; CDS: coding sequence; CELF1: CUGBP Elav-like family member 1; DCP1–2: decapping protein 1–2; GRE: glucocorticoid response element; HuR: human antigen R; IGF2BP1–3: insulin-like growth factor 2 mRNA-binding protein 1–3; IRE1: inositol-requiring enzyme 1; KSRP: KH-type splicing regulatory protein; lncRNAs: long noncoding RNAs; m¹A: N¹-methyladenosine; m⁵C: 5-methylcytosine; m⁶A: N⁶-methyladenosine; m⁷G: 7-methylguanosine; miRISC: miRNA-induced silencing complex; PABPC1: poly(A)-binding protein cytoplasmic 1; PAN2–PAN3: poly(A)-specific ribonuclease subunit 2–3; PRE: progesterone response element; CDS: Coding sequence; PUM1–2: pumilio RNA-binding family member 1–2; RC3H1: ring finger and CCH-type domains 1; RNASEL: ribonuclease L; SLBP: stem-loop binding protein; SMG1: SMG1 nonsense mediated mRNA decay associated PI3K related kinase; SMG6/8–9: SMG6/8–9 nonsense mediated mRNA decay factor; STAU1: Staufen double-stranded RNA-binding protein 1; TTP: tristetraprolin; UPF1: UPF1 RNA helicase and ATPase; UTR: untranslated region; XRN1: 5'→3' exoribonuclease 1; YTHDC1–2: YTH N⁶-methyladenosine RNA-binding protein C1–2; YTHDF1–3: YTH N⁶-methyladenosine RNA-binding protein F1–3; ZC3H12A: zinc finger CCH-type containing 12A; Ψ: pseudouridine.

multivalent, high-affinity interactions with clustered or degenerate AREs [62]. Most ARE-BPs promote transcript decay by recruiting the CCR4–NOT complex, the 5'→3' and 3'→5' decay machineries, or components of the miRNA pathway [63,64]. Tristetraprolin (TTP; also known as ZFP36) is a prototypical destabilizing ARE-BP that recruits CCR4–NOT through multiple interaction surfaces to initiate deadenylation, followed by decapping and 5'→3' degradation [65]. Conversely, ARE-BPs such as AU-rich element binding protein 1 (AUF1, also known as hnRNP D) and Human antigen R (HuR, also known as ELAVL1) frequently stabilize target mRNAs by competing with destabilizing ARE-BPs or masking miRNA-binding sites, although both also promote decay depending on the protein isoform, post-translational modification, cellular context, and target transcript identity [66–69].

Sequence-dependent regulation of mRNA stability also occurs through miRNAs, which guide the miRNA-induced silencing complex (miRISC) to complementary target sites. The miRISC promotes degradation of target transcripts through GW182 (Glycine-tryptophan protein of 182 kDa)-mediated recruitment of the PAN2–PAN3 and CCR4–NOT complexes [70].

Many RBPs recognize RNA through a combination of primary sequence and local structures rather than linear motifs alone. Accordingly, RNA secondary and tertiary structures constitute bona fide *cis*-regulatory elements that can either recruit structure-specific RBPs or modulate the accessibility of nearby regulatory motifs, thereby influencing transcript stability [71]. A central mediator of structure-dependent mRNA decay is the RNA helicase UPF1 (Up-frameshift protein 1), which is best known for its role in NMD. Beyond NMD, UPF1 functions in multiple pathways involving structure-recognizing factors, including Staufen proteins (STAU1 and STAU2), stem-loop binding protein (SLBP), Ras GTPase-activating protein-binding protein 1 (G3BP1), Zinc finger CCCH-type containing 12a (ZC3H12A, also known as Regnase-1), and Tripartite Motif containing 71 (TRIM71) [72,73]. Staufen-mediated decay (SMD) is the best-characterized example of this principle, in which Staufen proteins bind double-stranded RNA structures generated by intramolecular folding or intermolecular base pairing, including interactions between Alu elements and lncRNAs [74]. Biochemical studies initially established UPF1 as a central component of SMD, but recent transcriptome-wide analyses suggest that at least some forms of SMD can occur independently of UPF1, revealing an unexpected mechanistic diversity within this pathway [75,76]. Consistent with this view, the lncRNA *Terminal Differentiation-Induced Non-Coding RNA* (*TINCR*) recruits STAU1 to target transcripts through RNA–RNA base-pairing, resulting in either transcript degradation or stabilization depending on context [77,78]. These findings suggest that STAU1-dependent RNA regulation is mechanistically versatile and may adapt to the structural and functional properties of individual RNA targets, although the molecular determinants governing pathway selection remain to be established.

RNA modifications

Beyond primary sequence and structure, chemical modifications introduce an additional layer of regulation collectively known as the **epitranscriptome**. More than 150 ribonucleoside modifications have been identified, many of which influence mRNA fate by reshaping RNA structure, modulating RNA–protein interactions, and ultimately altering transcript stability [79]. Among these, m⁶A is the most abundant internal modification in protein-coding transcripts and a major determinant of mRNA stability [80]. m⁶A is deposited cotranscriptionally by the METTL3 (Methyltransferase-like 3)–METTL14 (Methyltransferase-like 14)–WTAP (Wilms tumor 1-associating protein) methyltransferase complex, interpreted by dedicated reader proteins, and removed by the demethylases ALKBH5 (AlkB homolog 5) or FTO (Fat mass and obesity-associated protein) [81]. The functional outcome of m⁶A largely depends on its recognition by YTH (YT521-B homology)-domain proteins (YTHDC1, YTHDC2, and YTHDF1–3), the principal class of m⁶A readers [81]. YTHDF proteins generally promote transcript degradation by coupling methylated mRNAs to CCR4–NOT-dependent deadenylation, endonucleolytic cleavage, or XRN1-mediated decay [82–85]. In contrast with YTH-domain proteins, insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1–3) stabilize transcripts through recognition of GG(m⁶A)C motifs [86]. Additional RNA modifications, including m⁵C, N⁶,2'-O-dimethyladenosine (m⁶Am), pseudouridine, and 8-oxo-7,8-dihydroguanosine, have been implicated in mRNA stability, although their mechanisms remain less well understood [87].

TFs as emerging regulators of mRNA stability

The idea that TFs might directly influence mRNA stability emerged from the unexpected observation that promoter identity can determine the cytoplasmic fate of the transcripts it produces. First hinted at in 1993, this concept gained strong support nearly 2 decades later when two seminal

studies from the Singer and Choder laboratories independently demonstrated that promoter sequences dictate the stability of specific yeast mRNAs [88–90]. Singer and colleagues showed that the half-lives of the yeast *SWI5* (*mating-type switching 5*) and *CLB2* (*Cycling B2*) mRNAs are specified by their promoters independently of transcript-encoded *cis*-elements, whereas the Choder laboratory demonstrated that exchanging the upstream activating sequence of the *RPL30* (*Ribosomal Protein of the Large subunit 30*) promoter was sufficient to alter reporter mRNA stability. Together with subsequent studies, these findings established the concept of **cotranscriptional mRNA imprinting**, whereby factors deposited onto nascent transcripts during transcription influence their cytoplasmic fate [91–93].

A central question raised by the mRNA imprinting model is the identity of the imprinted factors. In yeast, the strongest candidates include the RNAPII subunit dimer Rpb4/7 and the CCR4–NOT complex. Rpb4/7 associates with nascent transcripts during elongation before shuttling to the cytoplasm, where it interacts with multiple decay factors and participates in both major mRNA decay pathways [94–96]. These observations support a model in which Rpb4/7 accompanies transcripts from synthesis to degradation, although whether this imprinting mechanism operates in higher eukaryotes remains unresolved. CCR4–NOT provides a second potential link, as it functions in both transcription and cytoplasmic deadenylation, with several of its subunits localizing to promoters [97]. In yeast, CCR4–NOT physically interacts with Rpb4/7, suggesting that these factors may cooperate to couple transcription with cytoplasmic mRNA turnover [98]. Additional shuttling factors, including the 5′–3′ exonuclease Xrn1, may also contribute to this coupling [99,100].

Although these factors provide plausible molecular links between transcription and mRNA decay, they are generally considered global regulators and therefore do not readily explain the transcript- and condition-specific nature of mRNA turnover. A compelling possibility is that promoter-bound TFs provide the missing layer of specificity. Consistent with this idea, many TFs shuttle between the nucleus and the cytoplasm, and an increasing number have been shown to bind RNA directly [100,101]. These findings further blur the distinction between TFs and classical RBPs, with many factors operating at both transcriptional and post-transcriptional levels (Box 1).

Box 1. Transcription factors and RNA-binding proteins: evolutionary convergence or ancestral multifunctionality?

TFs and RBPs have traditionally been viewed as distinct classes of gene expression regulators. TFs recognize specific DNA sequences to control transcription, whereas RBPs bind RNA to regulate post-transcriptional processes, such as splicing, localization, translation, and mRNA decay [3,102]. Increasing evidence, however, suggests that this distinction is less clear-cut than previously anticipated.

Over the past decades, the repertoire of proteins with RNA-binding activity has expanded considerably, while numerous RBPs have been implicated in transcriptional regulation, chromatin organization, and genome architecture [103,104]. Conversely, an increasing number of canonical TFs have been shown to bind RNA directly and participate in diverse post-transcriptional processes [101,105]. Moreover, both TFs and RBPs are frequently enriched in IDRs that mediate multivalent interactions, regulate subcellular localization, and promote assembly into biomolecular condensates [106]. These shared structural, biophysical, and functional properties suggest that TFs and RBPs may exist along a continuum of multifunctional nucleic acid-binding regulators rather than representing entirely distinct protein classes.

These observations raise an important evolutionary question. Did TFs independently acquire RNA-binding and post-transcriptional activities during evolution, or do modern TFs and RBPs descend from ancestral multifunctional nucleic acid-binding proteins that subsequently specialized? Under the latter model, TF-mediated regulation of mRNA stability would not represent a recently acquired function but rather the retention of an ancient regulatory property. The diversity of TF families implicated in mRNA stability regulation argues against a lineage-specific innovation, yet current evidence does not distinguish between these evolutionary scenarios. Resolving this question will require comparative analyses of the post-transcriptional functions of TFs across diverse eukaryotic lineages.

The following sections focus on direct mechanisms by which TFs regulate mRNA stability, excluding indirect effects arising from the transcriptional control of RBPs, miRNAs, or decay factors. Current evidence supports four nonmutually exclusive modes of regulation: (i) cotranscriptional mRNA imprinting, (ii) modulation of RNA modification pathways, (iii) recruitment of mRNA decay machinery, and (iv) direct interactions with *cis*-acting mRNA elements (Figure 2).

TFs controlling mRNA stability through cotranscriptional mRNA imprinting

Despite growing evidence linking transcription and mRNA decay, convincing examples of TFs functioning within the mRNA imprinting model remain rare. The best-characterized example is the yeast split-finger protein 1 (Sfp1), which coordinates transcription and mRNA stability of genes involved in protein biosynthesis, particularly ribosomal protein and ribosome biogenesis genes [107]. Sfp1 is recruited to promoters before traveling with elongating RNAPII in an Rpb4-dependent manner. By promoting RNAPII backtracking, Sfp1 is transferred from the polymerase to the nascent transcript, where it subsequently promotes transcript stabilization. Collectively, these findings establish Sfp1 as the first 'bona fide' TF shown to directly mediate cotranscriptional mRNA imprinting. Similar mechanisms have been proposed for other RNA-binding zinc finger (ZnF) proteins, but these remain considerably less well characterized [93].

Although Sfp1 establishes an important conceptual precedent, several questions remain. Sfp1-dependent imprinting affects only a subset of its transcriptional targets, indicating that additional determinants contribute to transcript selectivity. Moreover, although Sfp1 limits deadenylation, it is still unclear whether it remains associated with target mRNAs in the cytoplasm and how it interfaces with the core deadenylation machinery.

Interestingly, RNAPII backtracking has previously been linked to mRNA decay through a distinct mechanism. Slower elongation promotes cotranscriptional association of CCR4–NOT with nascent transcripts, particularly those encoding ribosomal proteins [108]. As CCR4–NOT is recruited to elongating RNAPII via an Rpb4/7-dependent mechanism [98], these findings suggest a unifying model in which Sfp1-mediated modulation of Rpb4 stoichiometry within the elongating polymerase complex influences CCR4–NOT recruitment. By limiting CCR4–NOT loading onto nascent transcripts, Sfp1 could favor transcript stabilization and thereby couple transcriptional activation to prolonged mRNA stability. Although Sfp1 remains the only well-characterized example of TF-dependent mRNA imprinting, it provides a compelling proof of principle that promoter-bound TFs can coordinate transcription with cytoplasmic mRNA fate. Whether similar mechanisms operate in higher eukaryotes remains an important open question [93].

TFs controlling mRNA stability via the epitranscriptome

SMAD2 and SMAD3 belong to the SMAD family of TFs and act downstream of Transforming Growth factor (TGF)- β signaling, governing cell-fate decisions during development and tissue homeostasis [109]. In human embryonic stem cells, SMAD2/3 physically associate with the METTL3–METTL14–WTAP m⁶A methyltransferase complex [110]. Inhibition of Activin/Nodal signaling reduces m⁶A deposition on a subset of transcripts, many of which (~40%) are SMAD2/3 transcriptional targets, including the pluripotency factors *NANOG*, *NODAL*, and *LEFTY1* (*Left-Right Determination Factor 1*). Under active signaling, SMAD2/3 promote WTAP recruitment and cotranscriptional m⁶A deposition on these transcripts, priming them for subsequent cytoplasmic degradation. This m⁶A-dependent destabilization facilitates exit from pluripotency. These findings establish SMAD2/3 as gene-specific regulators of cotranscriptional m⁶A deposition, illustrating how TFs can directly modulate mRNA stability through epitranscriptomic mechanisms.

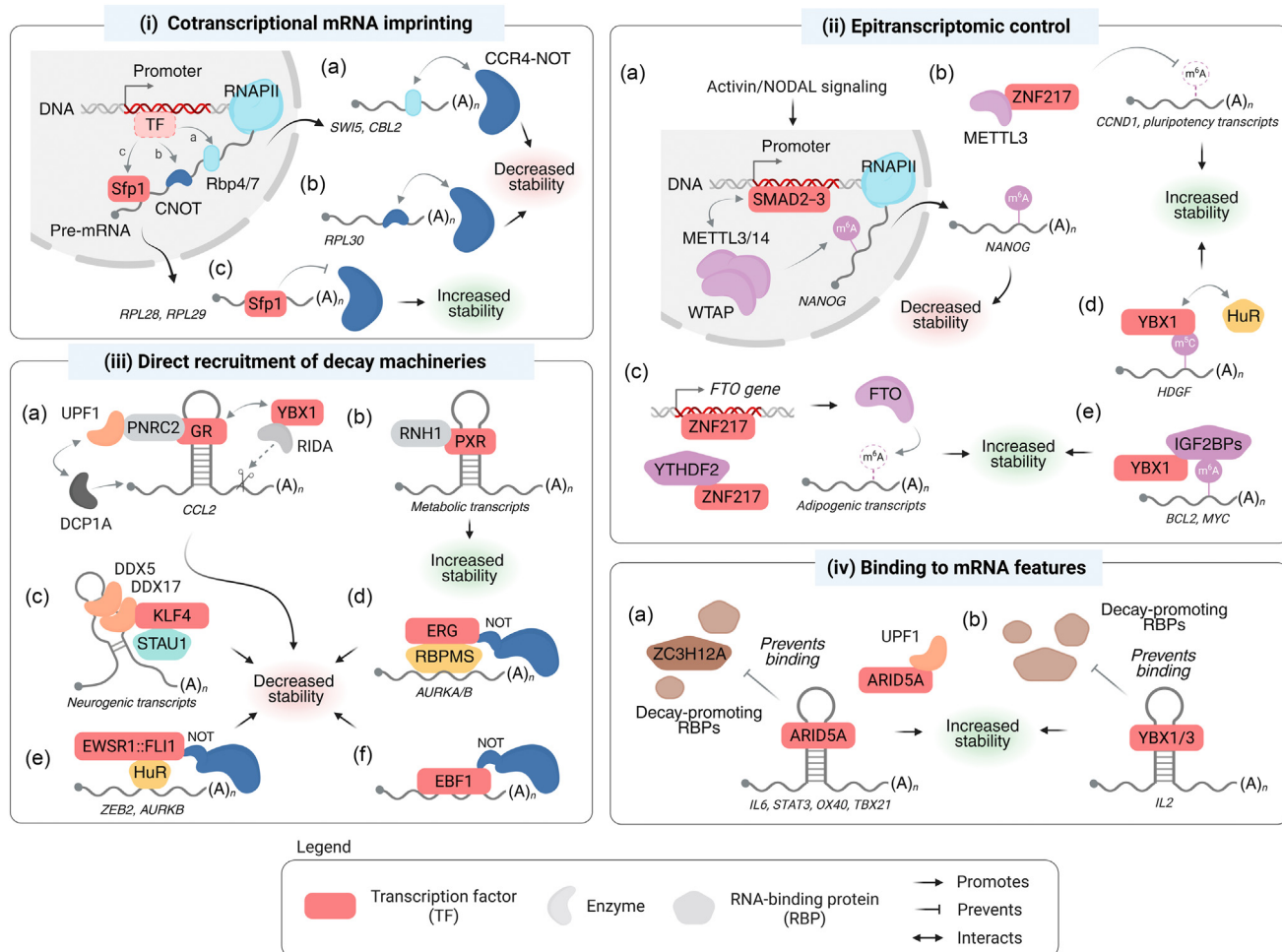


Figure 2. Mechanisms of transcription factor-mediated regulation of mRNA stability. Transcription factors (TFs; red) regulate mRNA stability through four principal mechanisms. Depending on the target transcript and cellular context, these mechanisms either promote mRNA degradation or enhance transcript stability. Representative target mRNAs are shown in italics. (i) Cotranscriptional mRNA imprinting. General factors, including Rbp4/7 (a) and CCR4-NOT (b), associate with nascent transcripts and influence their subsequent cytoplasmic degradation. Sfp1 (c) represents the best-characterized example of a TF directly mediating mRNA imprinting by limiting CCR4-NOT-dependent deadenylation. (ii) Epitranscriptomic control. TFs regulate mRNA stability by promoting m⁶A deposition through recruitment of the METTL3-METTL14-WTAP methyltransferase complex (a), limiting m⁶A deposition through inhibition of FTO (b and c), or acting as readers of RNA modifications (d and e). Filled and open circles denote high and low m⁶A levels, respectively. (iii) Direct recruitment of mRNA decay or stabilization machinery. TFs recruit UPF1-dependent decay factors (a), stabilizing proteins such as RNH1 (b), STAU1-associated decay factors (c), or the CCR4-NOT complex through its NOT module (d-f). Recruitment may occur through direct RNA binding or via intermediary RBPs. (iv) Direct recognition of mRNA features. TFs bind RNA structures or sequence elements and regulate transcript stability by controlling the access of decay-promoting or stabilizing factors to the transcript. ARID5A (a) stabilizes target transcripts by antagonizing ZC3H12A-dependent decay, whereas YBX proteins (b) stabilize target mRNAs by limiting the access of destabilizing RBPs. ARID5A: AT-rich interaction domain 5A; AURKA/B: aurora kinase A/B; BCL2: BCL2 apoptosis regulator; CBL2: Cbl proto-oncogene 2; CCL2: C-C motif chemokine ligand 2; CCND1: cyclin D1; CCR4-NOT: carbon catabolite repression 4-negative on TATA-less; CNOT: CCR4-NOT transcription complex subunit; DCP1A: decapping enzyme 1A; DDX5/17: DEAD-box helicase 5/17; EBF1: early B-cell factor 1; ERG: ETS transcription factor ERG; EWSR1::FLI1: EWS RNA-binding protein 1::Friend leukemia integration 1; FTO: FTO alpha-ketoglutarate dependent dioxygenase; GR: glucocorticoid receptor; HDGF: heparin binding growth factor; HuR: human antigen R; IGF2BPs: insulin-like growth factor 2 mRNA-binding proteins; IL2: interleukin 2; IL6: interleukin 6; KLF4: Krüppel-like factor 4; m⁶A: N⁶-methyladenosine; METTL3: methyltransferase 3, N⁶-adenosine-methyltransferase complex catalytic subunit; METTL14: methyltransferase 14, N⁶-adenosine-methyltransferase complex non-catalytic subunit; MYC: MYC proto-oncogene, bHLH transcription factor; NANOG: Nanog homeobox; NODAL: Nodal growth differentiation factor; NOT: negative on TATA; OX40: tumor necrosis factor receptor superfamily member 4; PNRC2: proline rich nuclear receptor coactivator 2; PXR: pregnane X receptor; RBPs: RNA-binding proteins; RBPMS: RNA binding protein, mRNA processing factor; RIDA: reactive intermediate imine deaminase A; Rbp4/7: RNA polymerase II subunits Rpb4/7; RNAPII: RNA polymerase II; RNH1: ribonuclease/angiogenin inhibitor 1; RPL28, 29, and 30: ribosomal protein L28, L29, and L30; Sfp1: split-finger protein 1; SMAD2-3: SMAD family member 2-3; STAT3: signal transducer and activator of transcription 3; STAU1: Staufen double-stranded RNA-binding protein 1; SWI5: SWI5 homologous recombination repair protein; TBX21: T-box transcription factor 21; UPF1: UPF1 RNA helicase and ATPase; WTAP: Wilms tumor 1-associated protein; YBX1/3: Y-box-binding protein 1/3; YTHDF2: YTH N⁶-methyladenosine RNA-binding protein F2; ZC3H12A: zinc finger CCCH-type containing 12A; ZEB2: zinc finger E-box-binding homeobox 2; ZNF217: zinc finger protein 217.

In contrast to SMAD2/3, which promote m⁶A deposition to stabilize target mRNAs, ZnF protein 217 (ZNF217; ZFP217 in mice) limits m⁶A deposition to stabilize selected transcripts. In embryonic stem cells, this C2H2 ZnF TF maintains pluripotency by interacting with METTL3 at the promoters of m⁶A-regulated genes, where it sequesters the methyltransferase in a catalytically inactive complex [111]. This inhibits cotranscriptional m⁶A deposition, thereby stabilizing transcripts and preventing differentiation. Consistent with this mechanism, ZNF217 reduces m⁶A levels and stabilizes transcripts such as *SOX2* ('SRY-box transcription factor 2'), *KLF4* ('Krüppel-like factor 4'), *NANOG* ('homeobox transcription factor NANOG'), *MYC* ('MYC proto-oncogene'), and the cell cycle regulator *CCND1* ('Cyclin D1') across multiple cellular contexts [111–113]. Additional studies suggest that ZNF217 may also promote transcript stabilization indirectly by inducing expression of the m⁶A demethylase FTO while preventing YTHDF2-mediated restriction of its activity, although the physiologically relevant target mRNAs remain to be identified [114].

Beyond regulating the deposition of RNA modifications, some TFs can function as readers of epitranscriptomic marks. Y-box-binding proteins (YBX proteins), originally identified as DNA-binding TFs, are now regarded as multifunctional regulators of transcription and RNA metabolism [115]. YBX1 binds m⁵C-modified RNAs through its conserved cold shock domain and promotes their stabilization by recruiting protective RBPs such as HuR [116,117]. This activity has been demonstrated in mammalian cells, where YBX1 stabilizes transcripts, including *HDGF* (*Hepatoma-Derived Growth Factor*), as well as in zebrafish and *Drosophila*, where YBX family proteins preserve developmentally important mRNAs [116–118].

YBX1 also stabilizes several oncogenic m⁶A-modified transcripts, including *c-MYC* and *BCL2* (*B-cell Lymphoma 2*) [119,120]. Unlike its recognition of m⁵C, this activity does not involve direct recognition of m⁶A. Instead, YBX1 cooperates with IGF2BP proteins and additional RBPs, including HuR, hnRNP U (heterogeneous nuclear ribonucleoprotein U), SYNCRIP (synaptotagmin-binding, cytoplasmic RNA-interacting protein), and DHX9 (DEXH-box helicase 9), to assemble stabilizing **messenger ribonucleoprotein (mRNP)** complexes that protect target transcripts from degradation [119,121]. Importantly, YBX1 depletion accelerates degradation of *c-MYC* and *BCL2* mRNAs without affecting their transcription, suggesting a mechanism independent of cotranscriptional imprinting. Additional studies suggest that YBX1 modulates transcript stability by competing with destabilizing RBPs and influencing interactions with m⁶A readers such as YTHDF and YTHDC proteins [122,123]. Collectively, these findings illustrate that TFs can regulate mRNA stability not only by shaping the epitranscriptome but also by directly interpreting its regulatory marks.

TFs controlling mRNA stability via direct recruitment of the mRNA decay machinery

By associating with RNA or RBPs, some TFs directly recruit mRNA decay machinery to selected transcripts, thereby promoting transcript-specific degradation. A well-characterized example is the glucocorticoid receptor (GR), a steroid nuclear receptor TF that controls inflammation, proliferation, and stress responses [124]. Beyond its transcriptional function, GR binds with high affinity to GC-rich RNA hairpins located predominantly within 5' UTRs via its DNA-binding domain (DBD) [125]. This RNA-binding activity enables GR to promote degradation of a subset of transcripts through a UPF1-dependent pathway termed GR-mediated decay (GMD) [126–128]. Unlike NMD and SMD, GMD is independent of translation and the exon–junction complexes [127]. Mechanistically, GR associates with target transcripts prior to ligand activation. Ligand binding induces a conformational change in mRNA-bound GR that promotes recruitment of the adaptor PNRC2 (proline-rich nuclear receptor coactivator 2), which assembles a decay complex containing UPF1 and DCP1A. Efficient decay also requires YBX1 and ribonuclease UK114 (RIDA) [129]. GMD regulates diverse biological processes,

including monocyte chemotaxis through control of *CCL2* (*C-C motif chemokine ligand 2*) mRNA stability and cellular mechanotransduction in cooperation with the lncRNA *LINC01569* (*long intergenic non-protein coding RNA 1569*) [130,131].

Interestingly, other nuclear receptors may possess related activities. For example, estrogen receptor alpha associates with mRNAs and interacts with several decay factors [132,133], although a direct role in mRNA turnover remains to be demonstrated. Similarly, the pregnane X receptor (PXR, also known as NR1I2) binds GC-rich stem-loop structures within transcripts involved in metabolic reprogramming and lipid metabolism and stabilizes them by recruiting the RNase inhibitor RNH1 (Ribonuclease/Angiogenin inhibitor 1) [134]. Together, these findings suggest that regulation of mRNA stability may represent a broader, yet still underexplored, function of steroid nuclear receptors.

Direct recruitment of decay machinery has also been reported by other ZnF TFs. KLF4, a key regulator of stem cell identity, promotes degradation of transcripts encoding neuronal differentiation factors, including *Distal-Less Homeobox 1 and 2* (*DLX1* and *DLX2*), and *TUJ1*, in neuronal progenitor cells [135]. Mechanistically, KLF4 interacts with STAU1 via its ZnF, enhancing STAU1 recruitment to target mRNAs and triggering degradation through a noncanonical SMD-like pathway that depends on DDX5 and DDX17 rather than UPF1. However, direct binding of KLF4 to these transcripts has not been demonstrated, and how KLF4 promotes STAU1-mediated decay of neurogenic transcripts remains unclear.

A second major strategy employed by TFs is the direct recruitment of the CCR4–NOT deadenylase complex to selected transcripts. We showed that the E26 transformation-specific (ETS) family TF ERG (ETS-related gene), a key developmental regulator frequently deregulated in cancer, promotes mRNA decay in addition to its well-established transcriptional activity [136]. ERG-mediated decay depends on a tripartite interaction involving the RBP with multiple splicing (RBPMS) and CCR4–NOT. RBPMS recruits ERG to target transcripts, whereas ERG engages the NOT-module subunit CNOT2 to trigger degradation. ERG decay targets are enriched for mitotic regulators such as *Aurora kinases A and B* (*AURKA* and *AURKB*), whose timely degradation is required for proper cell cycle progression. Notably, ERG's transcriptional and decay targets overlap extensively, suggesting that ERG may coordinate transcription and mRNA turnover of a subset of the same genes. However, RBPMS accounts for only part of ERG's target specificity, implying the involvement of additional RBPs in transcript selectivity.

We have recently reported a closely related mechanism involving the fusion oncoprotein EWSR1::FLI1 (Ewing sarcoma RNA binding protein 1::Friend leukemia integration 1), the primary driver of Ewing sarcoma [137]. Although best known for its roles in the regulation of transcription and chromatin organization [138], EWSR1::FLI1 also directly modulates mRNA turnover. This activity depends on the recruitment of CCR4–NOT through the EWSR1-derived **intrinsically disordered region (IDR)** and of HuR through the FLI1-derived region. By bridging HuR to CCR4–NOT, EWSR1::FLI1 converts HuR from a stabilizing factor into a promoter of mRNA decay. Ewing sarcoma cells are highly dependent on this pathway and are markedly sensitive to HuR inhibition. Most EWSR1::FLI1 decay targets are not transcriptionally regulated by the fusion protein, indicating that this decay activity operates largely independently of promoter-mediated imprinting. Similar to ERG, EWSR1::FLI1 engages the NOT-module-associated region of CNOT2, further implicating the NOT module as a key entry point for TF-mediated recruitment of CCR4–NOT.

A related interaction has also been described for early B cell factor 1 (EBF1), an essential TF for B cell lineage commitment [139]. EBF1 interacts with the CCR4–NOT subunit CNOT3 via its DBD

[140]. Disruption of this interaction alters both the transcription and mRNA stability of a subset of EBF1-regulated genes, suggesting partial coupling between EBF1's transcriptional and mRNA decay activities. Whether EBF1 directly recruits CCR4–NOT to target mRNAs or acts through cotranscriptional mechanisms remains unresolved.

Collectively, these studies reveal that TFs regulate mRNA stability by co-opting canonical decay effectors. Although the molecular mechanisms differ, many converge on a limited set of core machinery, particularly UPF1-dependent pathways and the CCR4–NOT complex, highlighting the direct recruitment of RNA decay factors as a recurrent mode of TF function.

TFs control mRNA stability through direct recognition of mRNA features

ARID5A is a dual-function member of the AT-rich interactive domain (ARID) family that acts as both a TF and an RBP [141]. Consistent with these dual activities, ARID5A localizes to both the nucleus and cytoplasm, enabling coordinated transcriptional and post-transcriptional regulation. In the cytoplasm, ARID5A stabilizes selected transcripts by binding structured elements within their 3' UTRs and preventing access of decay-promoting factors. It was initially shown to bind a stem-loop structure in the *Interleukine 6* (*IL6*) 3' UTR, thereby blocking recruitment of the endoribonuclease ZC3H12A and stabilizing the transcript [142]. Similar mechanisms have subsequently been described for the immune-related transcripts *STAT3* (*Signal Transducer and Activator of Transcription 3*), *NFKBIZ* (*Nuclear factor of Kappa Light Polypeptide Gene Enhancer in B-cell inhibitor Zeta*), *CXCL1* (*C-X-C motif chemokine ligand 1*), and *CXCL5* (*C-X-C motif chemokine ligand 5*) [143,144]. Additional targets, including *OX40* (*Oxford 40*) and *TBX21* (*T-box transcription factor 21*), may also be regulated by ARID5A, although whether this likewise depends on antagonizing ZC3H12A remains unclear [145,146]. Beyond directly competing with ZC3H12A, ARID5A also interacts with UPF1, raising the possibility that it further stabilizes transcripts by functionally inhibiting components of the ZC3H12A decay pathway [147]. Thus, unlike TFs such as GR, ERG, or EWSR1::FLI1, which promote transcript degradation by recruiting decay machinery, ARID5A primarily functions as an mRNA-stabilizing factor that protects transcripts from decay-promoting RBPs.

Transcript stabilization has also been reported for YBX1 and YBX3 [115]. Beyond their role as readers of epitranscriptomic marks, YBX proteins bind mRNAs independently of RNA modifications. Consistent with a broader role in post-transcriptional regulation, cross-linking and Immunoprecipitation followed by sequencing (CLIP-seq) analyses revealed that YBX1 associates with a large fraction of the transcriptome, with a modest preference for a CAUC motif located mainly within coding regions and 3' UTRs [148]. YBX proteins are thought to stabilize transcripts by limiting access of decay-promoting RBPs. For example, YBX1 cooperates with nucleolin and polypyrimidine tract-binding proteins to bind c-Jun N-terminal kinase (JNK)-responsive elements in the 5' UTR of the *IL2* (*Interleukin 2*) and *VEGF* (*Vascular endothelial growth factor*) mRNAs [122,149]. By contrast, stabilization of *CSF2* (*Colony-stimulating factor 2*) mRNA involves JNK-independent binding of YBX1 to AREs within the 3' UTR [150]. Although the underlying molecular mechanisms remain incompletely understood, these findings indicate that YBX1 stabilizes transcripts through distinct mechanisms depending on transcript architecture and cellular context.

A similar function has been described for YBX3, which binds 3' UTRs and stabilizes transcripts, including *CDKN1A* (*Cyclin-dependent kinase inhibitor 1A*), *SLC7A5* (*Solute carrier family 7 member 5*), and *SLC3A2* (*Solute carrier family 3 member 2*) [151–153]. However, the molecular basis of YBX3-mediated mRNA stabilization remains poorly understood and appears to be independent of its transcriptional activity. Collectively, these examples define a distinct mode of TF-mediated regulation in which TFs directly recognize *cis*-acting mRNA features and promote transcript stability by shielding target mRNAs from decay-promoting factors.

Table 1. Transcription factors reported to directly regulate mRNA stability

Transcription factor	DBD family	RNA binding	Biological context	Mechanism of mRNA stability regulation	Effect on mRNA stability	Representative human disease associations	Refs
Sfp1	C2H2 ZnF	Direct	Yeast growth control	Cotranscriptional mRNA imprinting	Stabilization	Endometrial stromal sarcoma (JAZF1, closest functional homolog in humans)	[107]
SMAD2/3	SMAD	Not demonstrated	Stem cell pluripotency and differentiation	Cotranscriptional recruitment of the METTL3/14–WTAP m ⁶ A methyltransferase complex	Destabilization	Loeys–Dietz syndrome, cancer, fibrosis, cardiovascular, and immune disorders	[110]
ZNF217	C2H2 ZnF	Not demonstrated	Stem cell pluripotency and differentiation	Inhibits m ⁶ A deposition by sequestering METTL3 in an inactive complex	Stabilization	Breast, ovarian, colorectal, and other cancers	[111,112]
			Adipogenesis	Transcriptional activation of FTO and inhibition of YTHDF2-mediated repression of FTO			[113,114]
YBX1	CSD	Direct	Bladder cancer	Recognizes m ⁵ C-modified transcripts and recruits HuR	Stabilization	Various cancers, cardiovascular diseases, and immune/inflammatory disorders	[116–118]
			Myeloid leukemia	Cooperation with IGF2BP and other RBPs to assemble stabilizing mRNP complexes			[119,120]
			T-cell activation	Competition with destabilizing RBPs			[122,123]
YBX3		Direct	Cell proliferation, stress adaptation, and metabolism	Binds specific 3' UTR sequence elements and promotes transcript stabilization through incompletely understood mechanisms			[151–153]
GR	Nuclear receptor	Direct	Immune regulation (monocytes chemotaxis)	Binding to RNA stem loops and recruitment of the GMD machinery (PNRC2, UPF1, YBX1, RIDA, and decapping factors)	Destabilization	Generalized glucocorticoid resistance, psychiatric and stress-related disorders, inflammatory and autoimmune diseases, and cancer	[126–129]
PXR		Direct	Glucose metabolism and metabolic reprogramming	Binding to C + G-rich RNA sequences and interaction with RNH1	Stabilization	Inflammatory bowel disease, metabolic disorders, and cancer	[134]
KLF4	C2H2 ZnF	Unknown	Cortical neurogenesis	Recruitment of STAU1 to target transcripts, promoting SMD through associated RNA helicases (DDX5/DDX17)	Destabilization	Cancer and vascular disease	[135]
ERG	ETS	Indirect (via RBPs)	Cell cycle progression	Recruitment to target mRNAs via RBPMS and recruitment of CCR4–NOT via CNOT2	Destabilization	Leukemia, prostate cancer, and sarcoma	[136]
EWSR1::FLI1		Indirect (via RBPs)	Ewing sarcoma	Recruitment to target mRNAs via HuR and recruitment of CCR4–NOT via CNOT2	Destabilization	Ewing sarcoma	[137]
EBF1	EBF	Unknown	B lymphopoiesis	Recruitment of CCR4–NOT via CNOT3	Destabilization	Cancer (especially hematologic malignancies), immunodeficiency, and metabolic disorders	[140]
ARID5A	ARID/BRIGHT	Direct	Immune regulation	Competes with ZC3H12A for binding to RNA stem loops and prevents ZC3H12A-mediated decay	Stabilization	Autoimmune and inflammatory diseases and cancer	[142–144]

CSD: cold shock domain; JAZF1: JAZF zinc finger 1.

Concluding remarks and perspectives

Although TFs are increasingly recognized as post-transcriptional regulators, this role has so far largely been confined to cotranscriptional RNA processing events. The studies discussed here extend this view, demonstrating that TFs can also directly regulate mRNA stability in a gene-specific manner. Together, these findings expand the functional repertoire of TFs beyond transcription, positioning them as integrative regulators that operate across multiple stages of the mRNA life cycle.

A central conclusion of this review is that TF-mediated control of mRNA stability is mechanistically diverse and highly context-dependent. Different TFs, and even the same TF in distinct contexts (e.g., YBX1 or ZFP217), can engage multiple, mechanistically independent pathways to either stabilize or destabilize target transcripts. The breadth of these mechanisms argues that regulation of mRNA stability is unlikely to represent a specialized property of only a few TFs, but rather an underappreciated dimension of TF function.

The molecular basis of TF-mediated regulation of mRNA stability nevertheless remains incompletely understood (see [Outstanding questions](#)). At a minimum, this function does not appear to be restricted to a particular TF family, as exemplified by the diversity of DBD families implicated to date ([Table 1](#)). Although TFs regulating mRNA stability lack obvious conserved sequence or structural features, they are typically enriched in IDRs or low-complexity regions that are also found in many RBPs and promote multivalent functional interactions with other biomolecules. This raises the possibility that TFs regulate mRNA stability through higher-order mRNP assemblies and the promotion of liquid–liquid phase separation, analogous to mechanisms described for transcriptional condensates and post-transcriptional mRNP assemblies [154]. Recent work on PABPC1, TTP, and CCR4–NOT illustrates how multivalent interactions between IDRs participate in the assembly of decay-competent mRNPs [65]. Whether TF-mediated regulation of mRNA stability similarly relies on higher-order condensates or common organizational principles remains an important open question that will require systematic mapping of TF–RNA interaction networks across diverse cellular and physiological contexts.

Another important unresolved question concerns the extent to which transcriptional and post-transcriptional regulation are coordinated by the same TF. Promoter-coupled imprinting models predict coordinated control of mRNA synthesis and stability, yet convincing evidence for such coupling remains limited in higher eukaryotes. If this mode of regulation proves to be widespread, it would provide a powerful mechanism for controlling both the amplitude and kinetics of gene expression. Transcription and mRNA stability could act in concert to amplify or prolong expression output, or antagonistically to generate rapid and transient responses. Defining the prevalence and logic of this coordinated regulation will require integrated measurements of transcriptional activity and RNA turnover following TF perturbation.

Several additional questions remain unresolved. Most TFs characterized to date promote mRNA degradation rather than stabilization. Whether this reflects a genuine biological preference or simply a bias in experimental detection is unknown. Likewise, the subcellular location of TF-mediated regulation remains poorly defined. Although most examples implicate cytoplasmic decay pathways, it is conceivable that some TFs regulate transcript stability within the nucleus or in specialized ribonucleoprotein compartments. Furthermore, there is remarkably little evidence linking TFs to canonical RNA surveillance pathways. Whether TFs function independently of these surveillance systems or instead engage them under specific physiological conditions has yet to be determined.

Outstanding questions

How widespread is direct regulation of mRNA stability among TFs?

Did TF-mediated regulation of mRNA stability arise through repeated functional innovation during evolution, or does it reflect an ancestral property of multifunctional DNA- and RNA-binding proteins?

Do TFs regulate mRNA stability through common mechanistic principles, or have distinct TF families evolved fundamentally different post-transcriptional strategies?

How is transcript specificity achieved during TF-mediated regulation of mRNA stability? Is specificity primarily determined by intermediary RBPs, direct RNA recognition, or cotranscriptional mRNA imprinting?

Do TFs coordinate transcription and mRNA stability of the same target genes, and how frequently are these regulatory layers coupled?

Do IDRs and biomolecular condensates contribute to TF-mediated regulation of mRNA stability?

Do TFs regulate mRNA stability predominantly in the nucleus, the cytoplasm, or both?

Why do most TFs identified to date promote mRNA decay rather than transcript stabilization?

Is TF-mediated regulation of mRNA stability combinatorial, with multiple TFs cooperating to control the stability of shared target transcripts?

What is the contribution of TF-mediated regulation of mRNA stability to human disease, and can this regulatory layer be therapeutically exploited?

Box 2. Cancer relevance of transcription factor-mediated control of mRNA stability

TFs are among the most frequently dysregulated proteins in human disease, particularly cancer [155]. Their pathogenic effects are traditionally attributed to aberrant transcriptional regulation. The emerging recognition that TFs can also directly regulate mRNA stability substantially broadens this view and suggests that altered RNA turnover may represent an overlooked layer of oncogenic gene regulation.

By simultaneously controlling transcription and mRNA stability, TFs could amplify, attenuate, or fine-tune gene expression programs beyond what is achieved through transcription alone. Oncogenic TFs may reinforce malignant phenotypes by stabilizing transcripts involved in proliferation, survival, or metastasis, or by promoting degradation of tumor suppressor mRNAs. Conversely, tumor suppressor TFs may restrain tumor progression by destabilizing pro-oncogenic transcripts.

Dynamic regulation of mRNA stability may also contribute to cancer cell plasticity. Modulation of transcript turnover enables cells to adapt their gene expression programs in response to oncogenic signaling, metabolic stress, or therapeutic pressure, processes central to epithelial–mesenchymal transition, metastatic dissemination, metabolic rewiring, and drug resistance [156]. Consistent with this idea, global alterations in mRNA stability accompany many human cancers and contribute to tumor-specific post-transcriptional regulatory programs [157].

This additional regulatory layer may also expose new therapeutic opportunities. Because TFs remain difficult pharmacological targets, disrupting RBPs or the RNA decay machinery that mediates TF-dependent mRNA stability may provide alternative strategies to interfere with oncogenic TF function. Several TFs discussed in this review, including ERG, EWSR1::FLI1, and KLF4, play well-established roles in human malignancies [138,158,159], yet their activities in mRNA stability regulation have largely been characterized under physiological conditions (see Table 1 in the main text). Determining the prevalence and functional significance of TF-mediated mRNA stability in cancer will therefore require systematic integration of transcriptional profiling, RNA stability measurements, and RNA–protein interaction analyses following TF perturbation.

Finally, TF-mediated regulation of mRNA stability has already been implicated in diverse biological processes, including stem cell differentiation, cell cycle progression, lipid metabolism, and immune regulation (Table 1). However, its contribution to human disease is only beginning to emerge (Box 2). In cancer and other disorders in which TF activity is frequently altered, disruption of TF-mediated mRNA stability control may reshape gene expression programs in ways that cannot be explained by transcriptional regulation alone. Recognizing this additional regulatory layer, therefore, expands our understanding of TF biology and may uncover new therapeutic opportunities while redefining the role of TFs across the entire mRNA life cycle.

Author contributions

F.D., B.G., L.O., and M.C. jointly developed the conceptualization for this review. B.G., L.O., M.C., and E.M. wrote the original draft of the manuscript. F.D. wrote the final version of the manuscript. B.G. designed the figures. F.D., B.G., and L.O. contributed to the critical review and editing of the final version. All authors have read and approved the final manuscript.

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Declaration of interests

The authors declare no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPT-5.2 for language editing and stylistic refinement of the text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Key references

1. Bregman, A. *et al.* (2011) Promoter elements regulate cytoplasmic mRNA decay. *Cell* 147, 1473–1483. 10.1016/j.cell.2011.12.005

This study, published back-to-back with Trcek *et al.* (2011), demonstrated that promoter identity influences cytoplasmic mRNA stability independently of transcript-encoded *cis*-elements. Together, these studies established the conceptual basis for the cotranscriptional mRNA imprinting model, linking transcription to the cytoplasmic fate of mRNAs.

2. Kelbert, M. *et al.* (2024) The zinc-finger transcription factor Sfp1 imprints specific classes of mRNAs and links their synthesis to cytoplasmic decay. *Elife* 12, RP90766. 10.7554/eLife.90766

This study provides the first direct mechanistic evidence that a bona fide TF regulates mRNA stability through cotranscriptional mRNA imprinting. The authors show that the yeast TF Sfp1 associates with nascent transcripts during transcription, remains associated following nuclear export, and promotes transcript stabilization by limiting deadenylation, thereby establishing a direct mechanistic link between transcription and cytoplasmic mRNA decay.

3. Bertero, A. *et al.* (2018) The SMAD2/3 interactome reveals that TGF β controls m⁶A mRNA methylation in pluripotency. *Nature* 555, 256–259. 10.1038/nature25784

This study provides the first evidence that a TF directly regulates mRNA stability through the epitranscriptome. The authors demonstrate that SMAD2/3 recruit the METTL3–METTL14–WTAP methyltransferase complex to selected target genes, promoting cotranscriptional m⁶A deposition and subsequent transcript destabilization during stem cell differentiation.

4. Cho, H. *et al.* (2015) Glucocorticoid receptor interacts with PNR2 in a ligand-dependent manner to recruit UPF1 for rapid mRNA degradation. *Proc. Natl. Acad. Sci. U S A* 112, E1540–E1549. 10.1073/pnas.1409612112

Author biographies



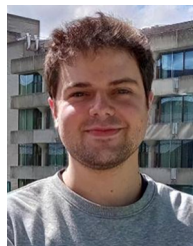
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tion in cancer, with particular emphasis on transcription factors, chromatin regulation, and RNA biology. His laboratory has recently uncovered unexpected post-transcriptional functions of developmental transcription factors, including roles in mRNA splicing and degradation, providing new insights into gene regulatory mechanisms and potential therapeutic vulnerabilities in cancer.

This study identifies GMD, revealing a direct post-transcriptional function of the GR. The authors show that ligand-bound GR recruits PNRC2, UPF1, and decapping factors to target mRNAs, triggering their selective degradation.

5. Rambout, X. *et al.* (2016) The transcription factor ERG recruits CCR4–NOT to control mRNA decay and mitotic progression. *Nat. Struct. Mol. Biol.* 23, 663–672. 10.1038/nsmb.3243

This study provides the first mechanistic evidence that a TF directly promotes mRNA decay through recruitment of the CCR4–NOT deadenylase complex. The authors show that ERG is recruited to target transcripts by the RBPMS, while engaging the CNOT2 subunit of CCR4–NOT to trigger their degradation, establishing RBP-mediated CCR4–NOT recruitment as a direct mechanism of TF-mediated mRNA decay.

References

- Maniatis, T. and Reed, R. (2002) An extensive network of coupling among gene expression machines. *Nature* 416, 499–506
- Coscujuela Tarrero, L. *et al.* (2024) Nanodynamo quantifies subcellular RNA dynamics revealing extensive coupling between steps of the RNA life cycle. *Nat. Commun.* 15, 7725
- Lambert, S.A. *et al.* (2018) The human transcription factors. *Cell* 172, 650–665
- Chen, Y. *et al.* (2024) Chromatin accessibility: biological functions, molecular mechanisms and therapeutic application. *Signal Transduct. Target. Ther.* 9, 340
- Stadhouders, R. *et al.* (2019) Transcription factors and 3D genome conformation in cell-fate decisions. *Nature* 569, 345–354
- Core, L. and Adelman, K. (2019) Promoter-proximal pausing of RNA polymerase II: a nexus of gene regulation. *Genes Dev.* 33, 960–982

7. Muniz, L. *et al.* (2021) RNA polymerase II speed: a key player in controlling and adapting transcriptome composition. *EMBO J.* 40, e105740
8. Martinez-Rucobo, F.W. *et al.* (2015) Molecular basis of transcription-coupled pre-mRNA capping. *Mol. Cell* 58, 1079–1089
9. Shenasa, H. and Bentley, D.L. (2023) Pre-mRNA splicing and its cotranscriptional connections. *Trends Genet.* 39, 672–685
10. Geisberg, J.V. *et al.* (2022) Nucleotide-level linkage of transcriptional elongation and polyadenylation. *Elife* 11, e83153
11. Rambout, X. *et al.* (2018) Beyond transcription: roles of transcription factors in pre-mRNA splicing. *Chem. Rev.* 118, 4339–4364
12. Boumpas, P. *et al.* (2023) Integrating transcription and splicing into cell fate: transcription factors on the block. *Wiley Interdiscip. Rev.: RNA* 14, e1752
13. Pérez-Ortín, J.E. *et al.* (2019) Homeostasis in the central dogma of molecular biology: the importance of mRNA instability. *RNA Biol.* 16, 1659–1666
14. Dowdle, M.E. and Lykke-Andersen, J. (2025) Cytoplasmic mRNA decay and quality control machineries in eukaryotes. *Nat. Rev. Genet.* 26, 463–478
15. Yamada, T. and Akimitsu, N. (2019) Contributions of regulated transcription and mRNA decay to the dynamics of gene expression. *Wiley Interdiscip. Rev.: RNA* 10, e1508
16. Battich, N. *et al.* (2020) Sequencing metabolically labeled transcripts in single cells reveals mRNA turnover strategies. *Science* 367, 1151–1156
17. Yang, G. *et al.* (2024) Degradation and translation of maternal mRNA for embryogenesis. *Trends Genet.* 40, 238–249
18. Serdar, L.D. *et al.* (2025) mRNA stability fine-tunes gene expression in the developing cortex to control neurogenesis. *PLoS Biol.* 23, e3003031
19. Jaquet, V. *et al.* (2022) Determinants of the temperature adaptation of mRNA degradation. *Nucleic Acids Res.* 50, 1092–1110
20. García-Martínez, J. *et al.* (2025) Global changes in synthesis rates and mRNA stabilities during adaptive responses to cell wall stress in yeast. *Sci. Rep.* 15, 25260
21. Liu, H. *et al.* (2023) SLAM-Drop-seq reveals mRNA kinetic rates throughout the cell cycle. *Mol. Syst. Biol.* 19, 1–23
22. Koh, D. *et al.* (2025) Reduced UPF1 levels in senescence impair nonsense-mediated mRNA decay. *Commun. Biol.* 8, 83
23. Wolin, S.L. and Maquat, L.E. (2019) Cellular RNA surveillance in health and disease. *Science* 366, 822–827
24. Rambout, X. and Maquat, L.E. (2024) Nuclear mRNA decay: regulatory networks that control gene expression. *Nat. Rev. Genet.* 25, 679–697
25. Monaghan, L. *et al.* (2023) Translation-coupled mRNA quality control mechanisms. *EMBO J.* 42, e114378
26. Kurosaki, T. *et al.* (2019) Quality and quantity control of gene expression by nonsense-mediated mRNA decay. *Nat. Rev. Mol. Cell Biol.* 20, 406–420
27. Klauer, A.A. and van Hoof, A. (2012) Degradation of mRNAs that lack a stop codon: a decade of nonstop progress. *Wiley Interdiscip. Rev.: RNA* 3, 649–660
28. Doma, M.K. and Parker, R. (2006) Endonucleolytic cleavage of eukaryotic mRNAs with stalls in translation elongation. *Nature* 440, 561–564
29. Hia, F. *et al.* (2019) Codon bias confers stability to human mRNAs. *EMBO Rep.* 20, e48220
30. Passmore, L.A. and Collier, J. (2022) Roles of mRNA poly (A) tails in regulation of eukaryotic gene expression. *Nat. Rev. Mol. Cell Biol.* 23, 93–106
31. Ermolenko, D.N. and Mathews, D.H. (2021) Making ends meet: new functions of mRNA secondary structure. *Wiley Interdiscip. Rev.: RNA* 12, e1611
32. Eisen, T.J. *et al.* (2020) The dynamics of cytoplasmic mRNA metabolism. *Mol. Cell* 77, 786–799.e10
33. Chen, C.-Y.A. and Shyu, A.-B. (2011) Mechanisms of deadenylation-dependent decay. *Wiley Interdiscip. Rev.: RNA* 2, 167–183
34. Zhao, Q. *et al.* (2023) Structure and function of molecular machines involved in deadenylation-dependent 5'-3' mRNA degradation. *Front. Genet.* 14, 1233842
35. Schäfer, I.B. *et al.* (2019) Molecular basis for poly(A) RNP architecture and recognition by the Pan2-Pan3 deadenylase. *Cell* 177, 1619–1631.e21
36. Caulier, G. *et al.* (2025) The CCR4–NOT complex: a multifaceted sensor of molecular signals instructing eukaryotic mRNA translation and stability. *Nucleic Acids Res.* 53, gkaf1401
37. Raisch, T. *et al.* (2019) Reconstitution of recombinant human CCR4–NOT reveals molecular insights into regulated deadenylation. *Nat. Commun.* 10, 3173
38. Webster, M.W. *et al.* (2018) mRNA deadenylation is coupled to translation rates by the differential activities of Ccr4–Not nucleases. *Mol. Cell* 70, 1089–1100.e8
39. Yi, H. *et al.* (2018) PABP cooperates with the CCR4–NOT complex to promote mRNA deadenylation and block precocious decay. *Mol. Cell* 70, 1081–1088.e5
40. Mugridge, J.S. *et al.* (2018) Structural and molecular mechanisms for the control of eukaryotic 5'-3' mRNA decay. *Nat. Struct. Mol. Biol.* 25, 1077–1085
41. Keidel, A. *et al.* (2025) RNA-degrading exosome complexes: molecular mechanisms and structural insights. *Annu. Rev. Cell Dev. Biol.* 41, 505–528
42. Wiener, D. *et al.* (2021) Decoupling of degradation from deadenylation reshapes poly(A) tail length in yeast meiosis. *Nat. Struct. Mol. Biol.* 28, 1038–1049
43. Audebert, L. *et al.* (2024) RNA degradation triggered by decapping is largely independent of initial deadenylation. *EMBO J.* 43, 6496–6524
44. Wurm, J.P. and Sprangers, R. (2019) Dcp2: an mRNA decapping enzyme that adopts many different shapes and forms. *Curr. Opin. Struct. Biol.* 59, 115–123
45. He, F. and Jacobson, A. (2023) Eukaryotic mRNA decapping factors: molecular mechanisms and activity. *FEBS J.* 290, 5057–5085
46. Chowdhury, A. *et al.* (2007) The decapping activator Lsm1p-7p-Pat1p complex has the intrinsic ability to distinguish between oligoadenylated and polyadenylated RNAs. *RNA* 13, 998–1016
47. Brothers, W.R. *et al.* (2023) The EDC4–XRN1 interaction controls P-body dynamics to link mRNA decapping with decay. *EMBO J.* 42, e113933
48. Ozgur, S. *et al.* (2010) Human Pat1b connects deadenylation with mRNA decapping and controls the assembly of processing bodies. *Mol. Cell Biol.* 30, 4308–4323
49. Hu, W. *et al.* (2009) Co-translational mRNA decay in *Saccharomyces cerevisiae*. *Nature* 461, 225–229
50. Geisberg, J.V. *et al.* (2014) Global analysis of mRNA isoform half-lives reveals stabilizing and destabilizing elements in yeast. *Cell* 156, 812–824
51. Medina-Muñoz, S.G. *et al.* (2021) Crosstalk between codon optimality and cis-regulatory elements dictates mRNA stability. *Genome Biol.* 22, 14
52. Agarwal, V. and Kelley, D.R. (2022) The genetic and biochemical determinants of mRNA degradation rates in mammals. *Genome Biol.* 23, 245
53. Meyer, K.D. *et al.* (2012) Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons. *Cell* 149, 1635–1646
54. Mayr, C. (2017) Regulation by 3'-untranslated regions. *Annu. Rev. Genet.* 51, 171–194
55. Yang, X. *et al.* (2017) 5-Methylcytosine promotes mRNA export—NSUN2 as the methyltransferase and ALYREF as an m⁵C reader. *Cell Res.* 27, 606–625
56. He, S. *et al.* (2023) The nexus between RNA-binding proteins and their effectors. *Nat. Rev. Genet.* 24, 276–294
57. Gong, C. and Maquat, L.E. (2011) lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3' UTRs via Alu elements. *Nature* 470, 284–288
58. Becker, W.R. *et al.* (2019) Demonstration of protein cooperativity mediated by RNA structure using the human protein PUM2. *RNA* 25, 702–712

59. Modic, M. *et al.* (2024) Poised PABP–RNA hubs implement signal-dependent mRNA decay in development. *Nat. Struct. Mol. Biol.* 31, 1439–1447
60. Fallmann, J. *et al.* (2016) AREsite2: an enhanced database for the comprehensive investigation of AU/GU/U-rich elements. *Nucleic Acids Res.* 44, D90–D95
61. Barreau, C. *et al.* (2005) AU-rich elements and associated factors: are there unifying principles? *Nucleic Acids Res.* 33, 7138–7150
62. Sidali, A. *et al.* (2021) AU-rich element RNA binding proteins: at the crossroads of post-transcriptional regulation and genome integrity. *Int. J. Mol. Sci.* 23, 96
63. Lykke-Andersen, J. and Wagner, E. (2005) Recruitment and activation of mRNA decay enzymes by two ARE-mediated decay activation domains in the proteins TTP and BRF-1. *Genes Dev.* 19, 351–361
64. Jing, Q. *et al.* (2005) Involvement of microRNA in AU-rich element-mediated mRNA instability. *Cell* 120, 623–634
65. Pekovic, F. *et al.* (2025) Multivalent interactions with CCR4–NOT and PABPC1 determine mRNA repression efficiency by tristetraprolin. *Nat. Commun.* 16, 7528
66. García-Mauriño, S.M. *et al.* (2017) RNA binding protein regulation and cross-talk in the control of AU-rich mRNA fate. *Front. Mol. Biosci.* 4, 71
67. Mukherjee, N. *et al.* (2011) Integrative regulatory mapping indicates that the RNA-binding protein HuR couples pre-mRNA processing and mRNA stability. *Mol. Cell* 43, 327–339
68. Lu, Y.-C. *et al.* (2014) ELAVL1 modulates transcriptome-wide miRNA binding in murine macrophages. *Cell Rep.* 9, 2330–2343
69. Chen, Y. *et al.* (2019) Circular RNA circAGO2 drives cancer progression through facilitating HuR-repressed functions of AGO2–miRNA complexes. *Cell Death Differ.* 26, 1346–1364
70. Gebert, L.F.R. and MacRae, I.J. (2019) Regulation of microRNA function in animals. *Nat. Rev. Mol. Cell Biol.* 20, 21–37
71. Fischer, J.W. *et al.* (2020) Structure-mediated RNA decay by UPF1 and G3BP1. *Mol. Cell* 78, 70–84.e6
72. Kim, Y.K. and Maquat, L.E. (2019) UPF1 and center in RNA decay: UPF1 in nonsense-mediated mRNA decay and beyond. *RNA* 25, 407–422
73. Park, H. and Lim, C. (2026) Standing on the shoulders of giant ribosomes: UPF1-dependent surveillance of translation dynamics to proteostasis. *J. Mol. Biol.* <https://doi.org/10.1016/j.jmb.2026.169752>
74. Park, E. and Maquat, L.E. (2013) Staufen-mediated mRNA decay. *Wiley Interdiscip. Rev.: RNA* 4, 423–435
75. Gowravaram, M. *et al.* (2019) Insights into the assembly and architecture of a Staufen-mediated mRNA decay (SMD)-competent mRNP. *Nat. Commun.* 10, 5054
76. Boehm, V. *et al.* (2025) Rapid UPF1 depletion illuminates the temporal dynamics of the NMD-regulated human transcriptome. *Mol. Cell* 85, 3524–3546.e12
77. Kretz, M. *et al.* (2013) Control of somatic tissue differentiation by the long non-coding RNA TINCR. *Nature* 493, 231–235
78. Xu, T.-P. *et al.* (2015) SP1-induced upregulation of the long noncoding RNA TINCR regulates cell proliferation and apoptosis by affecting KLF2 mRNA stability in gastric cancer. *Oncogene* 34, 5648–5661
79. Delaunay, S. *et al.* (2024) RNA modifications in physiology and disease: towards clinical applications. *Nat. Rev. Genet.* 25, 104–122
80. Jiang, X. *et al.* (2021) The role of m⁶A modification in the biological functions and diseases. *Signal Transduct. Target. Ther.* 6, 74
81. Zaccara, S. *et al.* (2019) Reading, writing and erasing mRNA methylation. *Nat. Rev. Mol. Cell Biol.* 20, 608–624
82. Du, H. *et al.* (2016) YTHDF2 destabilizes m⁶A-containing RNA through direct recruitment of the CCR4–NOT deadenylase complex. *Nat. Commun.* 7, 12626
83. Kretschmer, J. *et al.* (2018) The m⁶A reader protein YTHDC2 interacts with the small ribosomal subunit and the 5′–3′ exoribonuclease XRN1. *RNA* 24, 1339–1350
84. Park, O.H. *et al.* (2019) Endoribonucleolytic cleavage of m⁶A-containing RNAs by RNase P/MRP complex. *Mol. Cell* 74, 494–507.e8
85. Zaccara, S. and Jaffrey, S.R. (2020) A unified model for the function of YTHDF proteins in regulating m⁶A-modified mRNA. *Cell* 181, 1582–1595.e18
86. Huang, H. *et al.* (2018) Recognition of RNA m⁶A-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. *Nat. Cell Biol.* 20, 285–295
87. Boo, S.H. and Kim, Y.K. (2020) The emerging role of RNA modifications in the regulation of mRNA stability. *Exp. Mol. Med.* 52, 400–408
88. Enssle, J. *et al.* (1993) Determination of mRNA fate by different RNA polymerase II promoters. *Proc. Natl. Acad. Sci. U. S. A.* 90, 10091–10095
89. Bregman, A. *et al.* (2011) Promoter elements regulate cytoplasmic mRNA decay. *Cell* 147, 1473–1483
90. Trcek, T. *et al.* (2011) Single-molecule mRNA decay measurements reveal promoter-regulated mRNA stability in yeast. *Cell* 147, 1484–1497
91. Dori-Bachash, M. *et al.* (2012) Widespread promoter-mediated coordination of transcription and mRNA degradation. *Genome Biol.* 13, R114
92. García-Martínez, J. *et al.* (2023) Enhanced gene regulation by cooperation between mRNA decay and gene transcription. *Biochim. Biophys. Acta Gene Regul. Mech.* 1866, 194910
93. Pérez-Ortín, J.E. *et al.* (2026) RNA imprinting by zinc-finger proteins. *Trends Biochem. Sci.* 51, 761–773
94. Lotan, R. *et al.* (2005) The RNA polymerase II subunit Rpb4p mediates decay of a specific class of mRNAs. *Genes Dev.* 19, 3004–3016
95. Lotan, R. *et al.* (2007) The Rpb7p subunit of yeast RNA polymerase II plays roles in the two major cytoplasmic mRNA decay mechanisms. *J. Cell Biol.* 178, 1133–1143
96. Harel-Sharvit, L. *et al.* (2010) RNA polymerase II subunits link transcription and mRNA decay to translation. *Cell* 143, 552–563
97. Collart, M.A. (2016) The Ccr4–Not complex is a key regulator of eukaryotic gene expression. *Wiley Interdiscip. Rev.: RNA* 7, 438–454
98. Babbarwal, V. *et al.* (2014) The Rpb4/7 module of RNA polymerase II is required for carbon catabolite repressor protein 4-negative on TATA (Ccr4-not) complex to promote elongation. *J. Biol. Chem.* 289, 33125–33130
99. Pérez-Ortín, J.E. and Chávez, S. (2022) Nucleocytoplasmic shuttling of RNA-binding factors: mRNA buffering and beyond. *Biochim. Biophys. Acta Gene Regul. Mech.* 1865, 194849
100. Cartwright, P. and Helin, K. (2000) Nucleocytoplasmic shuttling of transcription factors. *Cell. Mol. Life Sci.* 57, 1193–1206
101. Oksuz, O. *et al.* (2023) Transcription factors interact with RNA to regulate genes. *Mol. Cell* 83, 2449–2463.e13
102. Gerstberger, S. *et al.* (2014) A census of human RNA-binding proteins. *Nat. Rev. Genet.* 15, 829–845
103. Xiao, R. *et al.* (2019) Pervasive chromatin-RNA binding protein interactions enable RNA-based regulation of transcription. *Cell* 178, 107–121.e18
104. Dehingia, B. *et al.* (2025) RNA-binding proteins mediate the maturation of chromatin topology during differentiation. *Nat. Cell Biol.* 27, 1510–1525
105. Nabeel-Shah, S. *et al.* (2024) C2H2-zinc-finger transcription factors bind RNA and function in diverse post-transcriptional regulatory processes. *Mol. Cell* 84, 3810–3825.e10
106. Holehouse, A.S. and Kragelund, B.B. (2024) The molecular basis for cellular function of intrinsically disordered protein regions. *Nat. Rev. Mol. Cell Biol.* 25, 187–211
107. Kelbert, M. *et al.* (2024) The zinc-finger transcription factor Stp1 imprints specific classes of mRNAs and links their synthesis to cytoplasmic decay. *Elife* 12, RP90766
108. Gupta, I. *et al.* (2016) Translational capacity of a cell is determined during transcription elongation via the Ccr4–Not complex. *Cell Rep.* 15, 1782–1794

109. Richardson, L. *et al.* (2023) Context-dependent TGF β family signalling in cell fate regulation. *Nat. Rev. Mol. Cell Biol.* 24, 876–894
110. Bertero, A. *et al.* (2018) The SMAD2/3 interactome reveals that TGF β controls m⁶A mRNA methylation in pluripotency. *Nature* 555, 256–259
111. Aguilo, F. *et al.* (2015) Coordination of m⁶A mRNA methylation and gene transcription by ZFP217 regulates pluripotency and reprogramming. *Cell Stem Cell* 17, 689–704
112. Zhang, C. *et al.* (2016) Hypoxia-inducible factors regulate pluripotency factor expression by ZNF217- and ALKBH5-mediated modulation of RNA methylation in breast cancer cells. *Oncotarget* 7, 64527–64542
113. Liu, Q. *et al.* (2019) ZFP217 regulates adipogenesis by controlling mitotic clonal expansion in a METTL3-m⁶A dependent manner. *RNA Biol.* 16, 1785–1793
114. Song, T. *et al.* (2019) Zfp217 mediates m⁶A mRNA methylation to orchestrate transcriptional and post-transcriptional regulation to promote adipogenic differentiation. *Nucleic Acids Res.* 47, 6130–6144
115. Mordovkina, D. *et al.* (2020) Y-box binding proteins in mRNP assembly, translation, and stability control. *Biomolecules* 10, 591
116. Chen, X. *et al.* (2019) 5-Methylcytosine promotes pathogenesis of bladder cancer through stabilizing mRNAs. *Nat. Cell Biol.* 21, 978–990
117. Yang, Y. *et al.* (2019) RNA 5-methylcytosine facilitates the maternal-to-zygotic transition by preventing maternal mRNA decay. *Mol. Cell* 75, 1188–1202.e11
118. Zou, F. *et al.* (2020) *Drosophila* YBX1 homolog YPS promotes ovarian germ line stem cell development by preferentially recognizing 5-methylcytosine RNAs. *Proc. Natl. Acad. Sci. U. S. A.* 117, 3603–3609
119. Weidensdorfer, D. *et al.* (2009) Control of c-myc mRNA stability by IGF2BP1-associated cytoplasmic RNPs. *RNA* 15, 104–115
120. Feng, M. *et al.* (2021) YBX1 is required for maintaining myeloid leukemia cell survival by regulating *BCL2* stability in an m⁶A-dependent manner. *Blood* 138, 71–85
121. Sánchez, B.J. *et al.* (2023) The formation of HuR/YB1 complex is required for the stabilization of target mRNA to promote myogenesis. *Nucleic Acids Res.* 51, 1375–1392
122. Chen, C.-Y. *et al.* (2000) Nucleolin and YB-1 are required for JNK-mediated interleukin-2 mRNA stabilization during T-cell activation. *Genes Dev.* 14, 1236–1248
123. Li, K. *et al.* (2025) Spatiotemporal protein interactome profiling through condensation-enhanced photocrosslinking. *Nat. Chem.* 17, 111–123
124. Lockett, J. *et al.* (2024) The glucocorticoid receptor: isoforms, functions, and contribution to glucocorticoid sensitivity. *Endocr. Rev.* 45, 593–624
125. Parsonnet, N.V. *et al.* (2019) The glucocorticoid receptor DNA-binding domain recognizes RNA hairpin structures with high affinity. *Nucleic Acids Res.* 47, 8180–8192
126. Dhawan, L. *et al.* (2007) A novel role for the glucocorticoid receptor in the regulation of monocyte chemoattractant protein-1 mRNA stability. *J. Biol. Chem.* 282, 10146–10152
127. Cho, H. *et al.* (2015) Glucocorticoid receptor interacts with PNRC2 in a ligand-dependent manner to recruit UPF1 for rapid mRNA degradation. *Proc. Natl. Acad. Sci. U. S. A.* 112, E1540–E1549
128. Boo, S.H. *et al.* (2024) Transcriptome-wide analysis for glucocorticoid receptor-mediated mRNA decay reveals various classes of target transcripts. *Mol. Cell* 47, 100130
129. Park, O.H. *et al.* (2016) Identification and molecular characterization of cellular factors required for glucocorticoid receptor-mediated mRNA decay. *Genes Dev.* 30, 2093–2105
130. Dhawan, L. *et al.* (2012) Y-box binding protein 1 and RNase UK114 mediate monocyte chemoattractant protein 1 mRNA stability in vascular smooth muscle cells. *Mol. Cell. Biol.* 32, 3768–3775
131. Zhu, H. *et al.* (2021) Glucocorticoid counteracts cellular mechanoresponses by LINC01569-dependent glucocorticoid receptor-mediated mRNA decay. *Sci. Adv.* 7, eabd9923
132. Nassa, G. *et al.* (2019) The RNA-mediated estrogen receptor α interactome of hormone-dependent human breast cancer cell nuclei. *Sci. Data* 6, 173
133. Xu, Y. *et al.* (2021) ER α is an RNA-binding protein sustaining tumor cell survival and drug resistance. *Cell* 184, 5215–5229.e17
134. Wang, X. *et al.* (2025) Cytoplasmic PXR regulates glucose metabolism by binding mRNAs and modulating their stability. *Nat. Struct. Mol. Biol.* 32, 2144–2157
135. Moon, B.-S. *et al.* (2018) Kruppel-like factor 4-dependent Stau1-mediated mRNA decay regulates cortical neurogenesis. *Nat. Commun.* 9, 401
136. Rambout, X. *et al.* (2016) The transcription factor ERG recruits CCR4–NOT to control mRNA decay and mitotic progression. *Nat. Struct. Mol. Biol.* 23, 663–672
137. Galvan, B. *et al.* (2015) Subversion of mRNA degradation pathways by EWSR1::FLI1 represents a therapeutic vulnerability in Ewing sarcoma. *Nat. Commun.* 16, 6537
138. Grünewald, T.G.P. *et al.* (2018) Ewing sarcoma. *Nat. Rev. Dis. Primers* 4, 5
139. Nechanitzky, R. *et al.* (2013) Transcription factor EBF1 is essential for the maintenance of B cell identity and prevention of alternative fates in committed cells. *Nat. Immunol.* 14, 867–875
140. Yang, C.-Y. *et al.* (2016) Interaction of CCR4–NOT with EBF1 regulates gene-specific transcription and mRNA stability in B lymphopoiesis. *Genes Dev.* 30, 2310–2324
141. Nyati, K.K. and Kishimoto, T. (2021) Recent advances in the role of Arid5a in immune diseases and cancer. *Front. Immunol.* 12, 827611
142. Masuda, K. *et al.* (2013) Arid5a controls IL-6 mRNA stability, which contributes to elevation of IL-6 level in vivo. *Proc. Natl. Acad. Sci. U. S. A.* 110, 9409–9414
143. Masuda, K. *et al.* (2016) Arid5a regulates naive CD4⁺ T cell fate through selective stabilization of Stat3 mRNA. *J. Exp. Med.* 213, 605–619
144. Amatya, N. *et al.* (2018) IL-17 integrates multiple self-reinforcing, feed-forward mechanisms through the RNA binding protein Arid5a. *Sci. Signal.* 11, eaat4617
145. Zaman, M.M.-U. *et al.* (2016) Arid5a exacerbates IFN- γ -mediated septic shock by stabilizing T-bet mRNA. *Proc. Natl. Acad. Sci. U. S. A.* 113, 11543–11548
146. Hanieh, H. *et al.* (2018) Arid5a stabilizes *OX40* mRNA in murine CD4⁺ T cells by recognizing a stem-loop structure in its 3'UTR. *Eur. J. Immunol.* 48, 593–604
147. Higa, M. *et al.* (2018) Regulation of inflammatory responses by dynamic subcellular localization of RNA-binding protein Arid5a. *Proc. Natl. Acad. Sci. U. S. A.* 115, E1214–E1220
148. Wu, S.-L. *et al.* (2015) Genome-wide analysis of YB-1-RNA interactions reveals a novel role of YB-1 in miRNA processing in glioblastoma multiforme. *Nucleic Acids Res.* 43, 8516–8528
149. Coles, L.S. *et al.* (2004) 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.* 271, 648–660
150. Capowski, E.E. *et al.* (2001) Y box-binding factor promotes eosinophil survival by stabilizing granulocyte-macrophage colony-stimulating factor mRNA. *J. Immunol.* 167, 5970–5976
151. Nie, M. *et al.* (2012) Stress- and Rho-activated ZO-1-associated nucleic acid binding protein binding to p21 mRNA mediates stabilization, translation, and cell survival. *Proc. Natl. Acad. Sci. U. S. A.* 109, 10897–10902
152. Cooke, A. *et al.* (2019) The RNA-binding protein YBX3 controls amino acid levels by regulating SLC mRNA abundance. *Cell Rep.* 27, 3097–3106.e5
153. Awad, S. *et al.* (2024) The YBX3 RNA-binding protein posttranscriptionally controls SLC1A5 mRNA in proliferating and differentiating skeletal muscle cells. *J. Biol. Chem.* 300, 105602

154. Pei, G. *et al.* (2025) Transcription regulation by biomolecular condensates. *Nat. Rev. Mol. Cell Biol.* 26, 213–236
155. Lee, T.I. and Young, R.A. (2013) Transcriptional regulation and its misregulation in disease. *Cell* 152, 1237–1251
156. Pérez-González, A. *et al.* (2023) Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat. Can.* 4, 1063–1082
157. Perron, G. *et al.* (2022) Pan-cancer analysis of mRNA stability for decoding tumour post-transcriptional programs. *Commun. Biol.* 5, 851
158. Adamo, P. and Ladomery, M.R. (2016) The oncogene ERG: a key factor in prostate cancer. *Oncogene* 35, 403–414
159. He, Z. *et al.* (2023) KLF4 transcription factor in tumorigenesis. *Cell Death Discov.* 9, 118