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# Posttranscriptional Gene Regulation by Long Noncoding RNA

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## Abstract

Eukaryotic cells transcribe a vast number of noncoding RNA species. Among them, long noncoding RNAs (lncRNAs) have been widely implicated in the regulation of gene transcription. However, examples of posttranscriptional gene regulation by lncRNAs are emerging. Through extended base-pairing, lncRNAs can stabilize or promote the translation of target mRNAs, while partial base-pairing facilitates mRNA decay or inhibits target mRNA translation. In the absence of complementarity, lncRNAs can suppress precursor mRNA splicing and translation by acting as decoys of RNA-binding proteins or microRNAs and can compete for microRNA-mediated inhibition leading to increased expression of the mRNA. Through these regulatory mechanisms, lncRNAs can elicit differentiation, proliferation, and cytoprotective programs, underscoring the rising recognition of lncRNA roles in human disease. In this review, we summarize the mechanisms of posttranscriptional gene regulation by lncRNAs identified until now.

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## Introduction

The majority of RNAs transcribed in mammalian cells do not contain protein-coding sequences.[1–3] Although many transcripts in this group are eventually processed into small mature RNAs (e.g., microRNAs, Piwi-interacting RNAs, tRNA-derived stress-induced fragment RNAs, and small nucleolar RNAs), a subset of them produce long noncoding RNAs (lncRNAs), with lengths of over 200 nt. LncRNAs are transcribed by RNA polymerase II, even though many lncRNA genes contain histone modification signatures distinct from those of protein-coding genes (H3K4me3 and H3K36me).[4,5] After transcription, most lncRNAs are processed similar to protein-coding RNAs, including 5′-end capping, 3′-end polyadenylation, splicing of introns, and intracellular transport. Many lncRNAs have small open reading frames, but they are not predicted to codify for proteins.[6–8] However, recent RNA-seq analysis identified many lncRNAs associated with ribosomes, suggesting that they could have protein-coding potential and may play additional cytoplasmic roles in mRNA metabolism.[9]

### LncRNAs as transcriptional regulators

Functionally, lncRNAs are best known for their roles as regulators of transcription. Over 30 years ago, Paul and Duerksen reported the surprising discovery that chromatin is purified with twice as much as RNA as DNA, suggesting that RNA may regulate chromatin structure and gene transcription.[10] Subsequent studies have shown that some lncRNAs are associated with chromatin modification enzymes and mediate gene activation or silencing.[3] For instance, during X chromosome dosage compensation in mammals, the lncRNA *XIST* is expressed from one X chromosome in female cells and inactivates the other X chromosome by recruiting PRC2 (*P*olycomb *r*epressive *c*omplex *2*).[11] In plants, the seasonal timing of flowering (vernalization) is mediated by *COLDAIR*, a cold-inducible intronic lncRNA that silences *FLC*, a gene that

regulates flowering.[12] In mammalian cells, the lncRNA *HOTAIR* associates with PRC2 and modulates H3K27me3 distribution in genomic targets.[13,14] In addition, two p53-regulated lncRNAs, *lincRNA-p21* and *PANDA*, repress target gene transcription by interacting with DNA-binding proteins heterogeneous nuclear ribonucleoprotein K and nuclear transcription factor Y alpha, respectively.[15,16] Together with other examples, the role of lncRNAs as regulators of gene transcription is well established. However, their involvement in other modes of gene regulation remains relatively unknown.

## LncRNAs as posttranscriptional regulators

Recently, a small number of lncRNAs have been reported to regulate gene expression posttranscriptionally in a variety of ways (Fig. 1). For example, the lncRNA *MALAT1* (*m*etastasis-*a*ssociated *l*ong *a*denocarcinoma *t*ranscript *1*) was implicated in

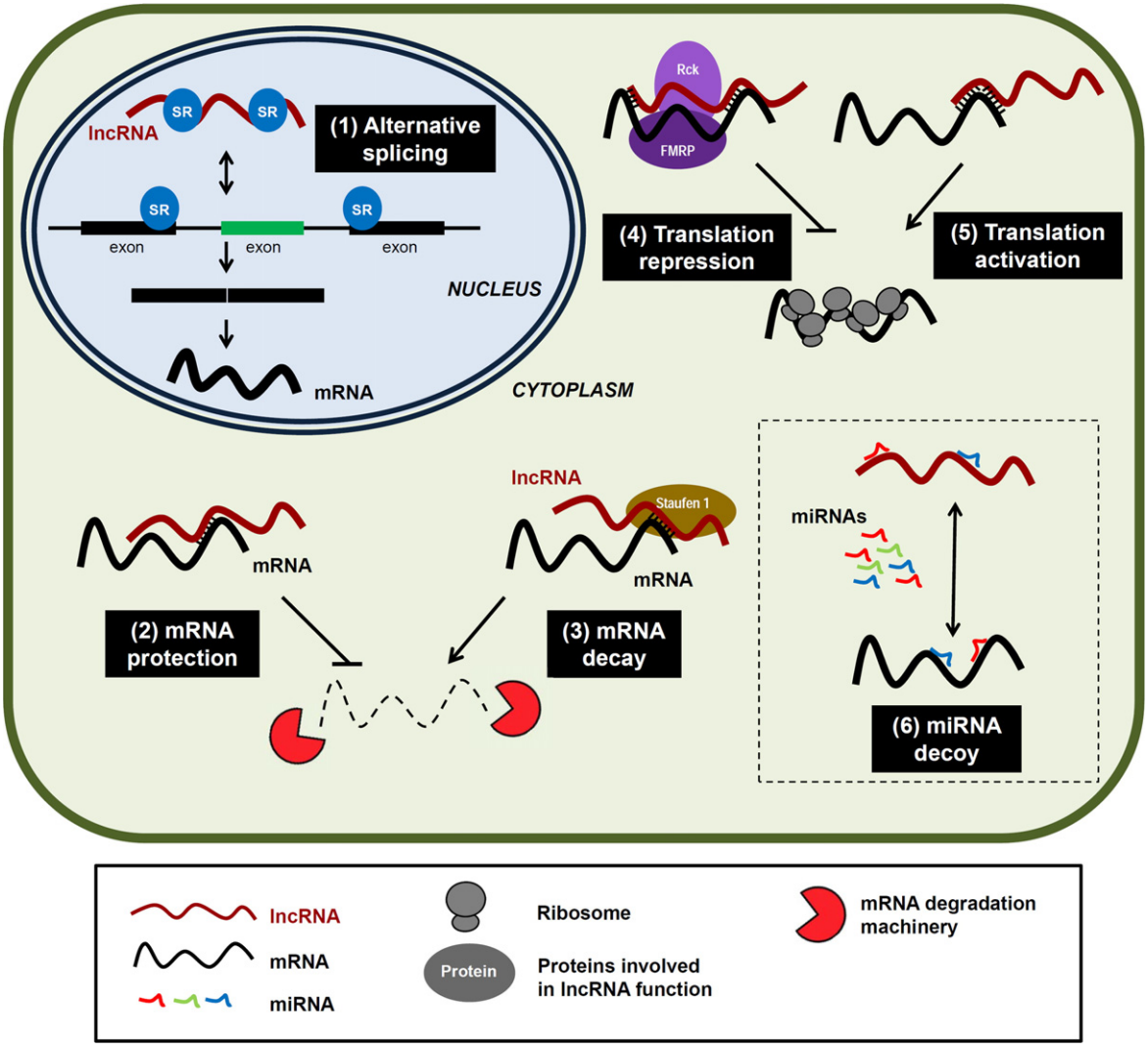


**Fig. 1.** Levels of posttranscriptional gene regulation by lncRNAs. The major posttranscriptional processes influenced by lncRNAs are indicated in black boxes. (1) Splicing of pre-mRNAs, which is modulated by lncRNAs that compete for binding for splicing regulatory proteins (e.g., SR, Fox). (2) Protection from mRNA decay, as exemplified by lncRNA *BACE1-AS*, which forms a hybrid and hence prevents the decay of *BACE1* mRNA. (3) Acceleration of mRNA decay, as reported for 1/2-sbsRNAs, which function jointly with Staufen 1 to promote the decay of Alu-containing mRNAs. (4) Repression of mRNA translation, as demonstrated for *lincRNA-p21* via interaction with partially complementary mRNAs and recruitment of translation repressors Rck and Fmrp. (5) Activation of mRNA translation, as illustrated by the interaction of *AS Uchl1* via a SINEB2 sequence and a segment fully complementary with the 5′ end of *Uchl1* mRNA; this association helps to recruit ribosomes to *Uchl1* mRNA and enhances its translation. (6) Functional association with microRNAs, as shown for *linc-MD1*, which "sponges" microRNAs, for *H19*, which hosts microRNAs, and for *BACE1-AS*, which promotes *BACE1* mRNA translation by competing with a microRNA. See the text for further details.