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Review

Interplay between viruses and host mRNA degradation ☆

Krishna Narayanan [a,*], Shinji Makino [b,1]

[a] Department of Microbiology and Immunology, The University of Texas Medical Branch at Galveston, Galveston, TX 77555-1019, USA
[b] Department of Microbiology and Immunology, Center for Biodefense and Emerging Infectious Diseases, UTMB Center for Tropical Diseases, and Sealy Center for Vaccine Development, The University of Texas Medical Branch at Galveston, Galveston, TX 77555-1019, USA

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ABSTRACT

Messenger RNA degradation is a fundamental cellular process that plays a critical role in regulating gene expression by controlling both the quality and the abundance of mRNAs in cells. Naturally, viruses must successfully interface with the robust cellular RNA degradation machinery to achieve an optimal balance between viral and cellular gene expression and establish a productive infection in the host. In the past several years, studies have discovered many elegant strategies that viruses have evolved to circumvent the cellular RNA degradation machinery, ranging from disarming the RNA decay pathways and co-opting the factors governing cellular mRNA stability to promoting host mRNA degradation that facilitates selective viral gene expression and alters the dynamics of host–pathogen interaction. This review summarizes the current knowledge of the multifaceted interaction between viruses and cellular mRNA degradation machinery to provide an insight into the regulatory mechanisms that influence gene expression in viral infections. This article is part of a Special Issue entitled: RNA Decay mechanisms.

1. Introduction

Gene expression in eukaryotic cells is the result of a series of complex and highly regulated events that include transcription, translation, decay of mRNAs and protein degradation. Among these fundamental cellular processes, mRNA turnover by the cellular RNA decay machinery plays a major role in regulating gene expression by altering the stability of mRNAs in response to developmental, physiological and environmental signals [1–4]. The surveillance arm of the cellular RNA decay machinery also controls the quality of gene expression by constantly monitoring the newly synthesized RNA transcripts for aberrant structural and sequence features and targets them for destruction [5–8]. Thus, the cellular RNA decay machinery, consisting of a multitude of enzymes, auxiliary factors and pathways, controls the fate of newly synthesized RNA transcripts and mRNAs undergoing translation in a cell [9–12]. In addition to the conventional RNA decay pathways, eukaryotic cells also have specialized RNA decay pathways that are induced in response to external stress signals like virus infection [13]. It is reasonable to expect that nascent viral RNA transcripts carrying features that are recognized as "aberrant or non-self" by host mRNA surveillance pathways would also be shunted to the cellular RNA decay machinery for degradation. Therefore, viruses must not only contend with the intrinsically antiviral host immune response pathways but also evolve strategies to elude, counter or sometimes even utilize the inherently hostile cellular mRNA degradation machinery to facilitate viral gene expression and establish a successful infection. The goal of this review is to highlight this complex interplay between viruses and cellular mRNA degradation pathways by illustrating the diverse array of mechanisms that viruses utilize to gain an advantage in this evolutionary arms race with their hosts.

2. Cellular mRNA degradation pathways

The different pathways of mRNA decay in eukaryotic cells involve the coordinated action of exoribonucleases and endoribonucleases that target an mRNA substrate for destruction depending on the presence of cis-acting instability elements, trans-acting mRNA destabilizing factors and cellular environment [9,11] (Fig. 1). A majority of eukaryotic mRNAs carry a 5′ 7-methylguanosine cap and a 3′ poly(A) tail that serve as primary determinants of mRNA stability by protecting the ends from the action of exoribonucleases, besides influencing different aspects of mRNA metabolism including splicing and nuclear export [3,14–16]. Furthermore, binding of the cytoplasmic proteins eIF4E and the poly(A)-binding protein (PABP) to the 5′ cap and the 3′ poly(A) tail, respectively, ensures efficient translation initiation [17,18]. The fate of an mRNA molecule after translation is controlled by processes that target these mRNA stability determinants at the ends of the molecule. The major pathway of cytoplasmic

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* Corresponding author. Tel.: +1 409 772 8172; fax: +1 409 772 5065.
E-mail addresses: krnaraya@utmb.edu (K. Narayanan), shmakino@utmb.edu (S. Makino).
[1] Tel.: +1 409 772 2323; fax: +1 409 772 5065.

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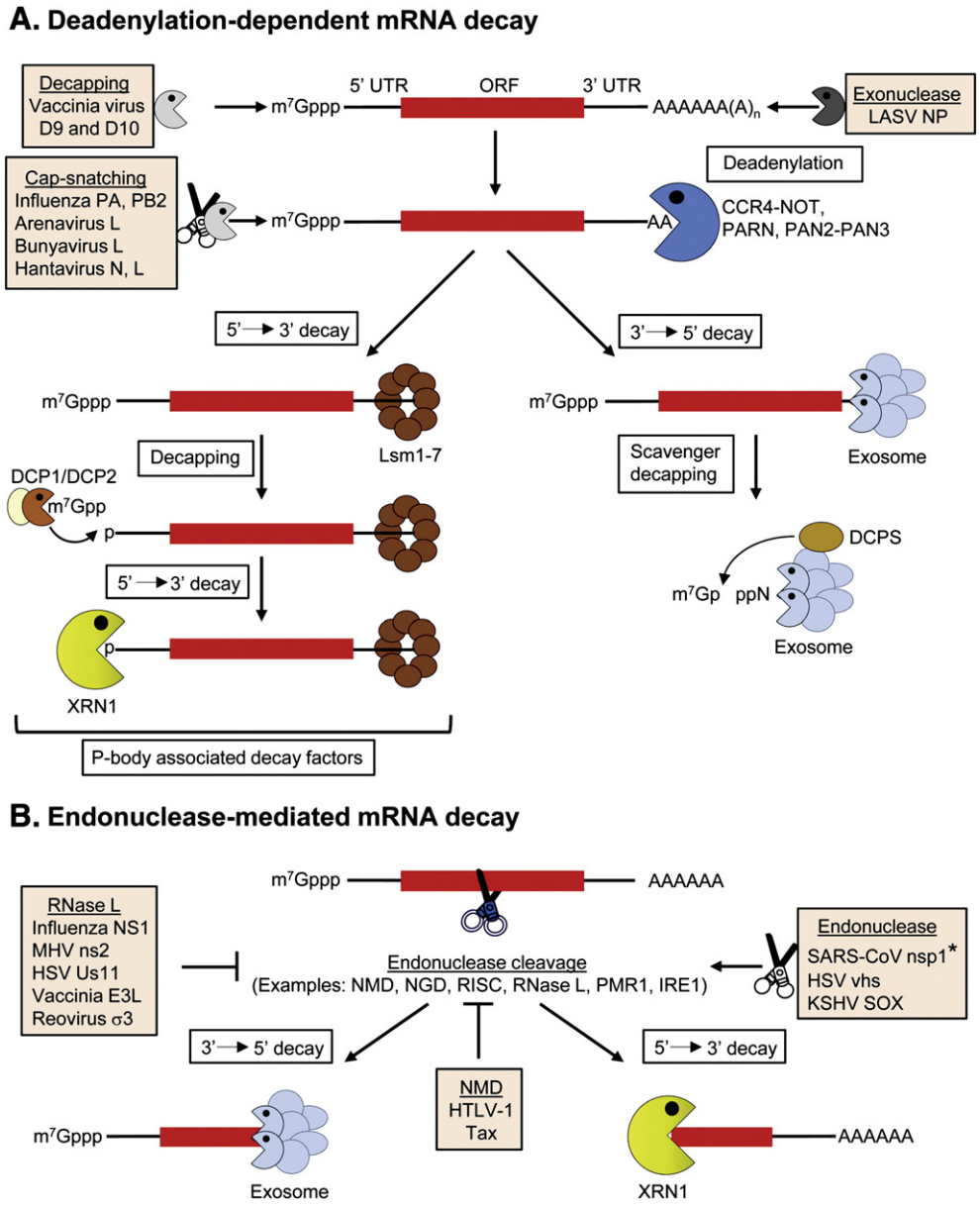

Fig. 1. Major pathways of cellular mRNA decay. A) A majority of cellular mRNAs are degraded by the deadenylation-dependent decay pathway. The cellular deadenylase complexes, CCR4-NOT, PARN or PAN2-PAN3 removes the poly(A) tail and subsequently, the body of the deadenylated mRNA is degraded by 5′-3′ or 3′-5′decay mechanisms. In the 5′-3′ decay pathway, the Lsm1-7 protein complex binds to the 3′-end of the deadenylated mRNA and stimulates decapping by the DCP1-DCP2 enzyme complex that generates a monophosphorylated 5′-end. Following decapping, the mRNA body is degraded by the action of the 5′-3′ exoribonuclease, XRN1. Most of the proteins involved in the 5′-3′ decay pathway are localized in P bodies. The 3′-5′ decay of the deadenylated mRNA is catalyzed by the 3′-5′ exoribonucleolytic activity of the exosome followed by the removal of the cap structure by the scavenger decapping enzyme, DCPS. B) The endonuclease-mediated decay pathway triggers the degradation of some mRNAs, including those recognized by cellular mRNA surveillance and stress response pathways like NMD, NGD, RNase L and IRE1. The decay is initiated by an endonuclease cleavage event followed by the digestion of the resulting unprotected fragments by exosome and XRN1. The figure is adapted from Fig. 1 in Ref. [9]. Selected examples of viral proteins that interfere with the cellular mRNA decay machinery are provided. See text for details. * denotes that the SARS-CoV nsp1-induced endonuclease activity could be host-encoded.

mRNA decay in eukaryotic cells is initiated by the removal of one of these barriers to exoribonucleases through a process known as deadenylation that results in the shortening of the poly(A) tail [19]. Deadenylation is the first and often the rate-limiting step of mRNA decay that is performed by one or more of the cellular deadenylase enzyme complexes, CCR4-NOT, PAN2-PAN3 and PARN [20,21].

Following deadenylation, the body of mRNA is degraded by two exonuclease-mediated decay pathways acting either at the 3′ or 5′ end. The 3′-5′ decay is carried out by the cytoplasmic exosome, which is a highly conserved multi-protein complex of 3′-5′ exoribonucleases, RRP44 and exosome component 10 (EXOSC10, otherwise known as RRP6 in yeast and PM/SCL-100 in humans) [22,23]. In mammalian cells, DIS3L, the cytoplasmic form of the processive exonuclease RRP44, is involved in 3′-5′ mRNA degradation [23]. The exosome activity is regulated by cofactors that include the SKI complex [22]. Subsequently, the action of the scavenger decapping enzyme DCPS on the products of exosome-mediated mRNA decay removes the cap structure [24,25].

Alternatively, the decay of the deadenylated transcript proceeds in a 5′-3′ direction through the removal of the 5′ cap structure by the cellular decapping enzyme DCP2 (or NUDT16) [26]. Decapping is a highly regulated process involving several cofactors that function as decapping enhancers, including Lsm1-7 protein complex that binds

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