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Editorial

RNA decay mechanisms: Specificity through diversity

Nature has invented the polymerization of RNA from a DNA template twice: In the first case, multi-subunit RNA polymerases drive transcription in both prokaryotes and the nuclei of eukaryotes. In the second case, single-subunit polymerases drive transcription in mitochondria, chloroplasts and some viruses. A third class of polymerases homo-oligomerizes adenosine and uridine in an untemplated fashion. While three structural designs account for all RNA polymerization in living organisms, it may come as a surprise that the decomposition of RNA polymers, RNA degradation for short, is carried out by more than 30 families of ribonucleases. We estimate the total number of ribonucleases to be 24 in *Escherichia coli*, 25 in *Bacillus subtilis*, at least 34 in *Saccharomyces cerevisiae*, and more than 60 in *Homo sapiens* (Table 1). These numbers reflect the diversity of functions ribonucleases must fulfill: as factors essential for the precise maturation – or processing – of RNA molecules from longer precursors, as components of intricate quality control systems that dispose of defective RNA, as guardians against the invasion of viral genomes and the propagation of transposable elements, as effectors of signaling pathways that control gene expression at the posttranscriptional level, and – we tend to forget – as enzymes that help us to digest our daily bread. The purpose of this special issue on "RNA decay mechanisms" is to provide a panoramic view of enzymes and machines that degrade RNA, to reveal similarities and differences between the bacterial and eukaryotic systems, and to illuminate the fascinating biology that sets the stage for ribonuclease action (Fig. 1). This task is achieved by 24 review articles that collectively summarize recent advances in our understanding of ribonuclease function at all levels. With the attempt to bring together as many ideas as possible, most reviews were jointly written by authors from different labs.

The issue opens with a comprehensive overview by Arraiano and colleagues on the major protein domain families capable of degrading RNA, emphasizing structural aspects important for each of the protein folds. An entire review by Dominski and colleagues is dedicated to the β-CASP family of ribonucleases, highly conserved metallo-enzymes involved in mRNA maturation and degradation in all three kingdoms of life. Cook and colleagues review toxin–antitoxin systems, powerful endoribonucleases capable of executing stress responses and suicidal programs in bacteria. The activity of some ribonucleases is coordinated in large, multi-subunit RNA decay machines, which in bacteria are called "degradosomes". Bandyra and colleagues provide insight into the composition and function of the representative *E. coli* degradosome and describe how this membrane-anchored machine contributes to precursor RNA processing, general RNA turnover and regulation of gene expression. In eukaryotes, the exosome represents a structurally related RNA destruction machine, covered in a review by Chlebowski and colleagues. Reviews by Wahle and Winkler as well as Godwin and colleagues summarize our current knowledge of deadenylases, a diverse group of ribonucleases that remove poly(A) tails and thereby initiate the degradation of numerous eukaryotic mRNAs. As if the attack from the 3′ end was not enough, eukaryotic mRNAs are also vulnerable to enzymes that remove the 5′ cap and degrade RNA from 5′ to 3′. Arribas-Layton and colleagues as well as Nagarajan and colleagues cover this assault strategy by discussing structures, mechanisms and functions of mRNA decapping enzymes and XRN 5′-3′ exoribonucleases.

Aberrantly processed, defective RNA molecules can damage cells — the detection and removal of such aberrant RNAs are accomplished by a variety of intricate surveillance mechanisms. Porrua and Libri review different RNA quality control mechanisms that operate in the nucleus. Schweingruber and colleagues update us on the mechanistic models of nonsense-mediated mRNA decay, whereas Karam and colleagues review the implications of this pathway for physiology and disease. Inada concludes the section on RNA quality control by a description of two related systems that are activated when ribosomes stall during elongation or run all the way into the poly(A) tail.

The level at which any RNA is expressed is determined to the same extent by its rate of transcription and its rate of degradation. In recent years, numerous signaling pathways that control the half-lives of specific mRNAs have been discovered, underscoring the role of RNA degradation in the regulation of gene expression. Haimovich and colleagues review unexpected findings suggesting that RNA synthesis and degradation are mechanistically coupled. Scott and Norbury summarize our current knowledge about 3′ uridylation, a recently discovered RNA modification we are only beginning to understand. Similar to transcription factors, an array of RNA-binding proteins serve as adaptors that recognize specific sets of mRNAs and control their decay rates by the recruitment of RNA degrading enzymes. Signal transduction pathways further modulate the activity of such adaptors and thereby regulate the expression of specific mRNAs. Prototypic examples of such adaptors are covered by four reviews in this issue: Brooks and Blackshear report on the highly active mRNA destabilizing zinc finger protein TTP, White and colleagues review AUF1-mediated mRNA degradation, Briata and colleagues provide insight into the role of KSRP in miRNA processing and mRNA turnover, and Valasova-St. Lois and colleagues reflect on mRNA decay mediated by the family of CELF proteins. The last review in this section by Uehata and Akira introduces an intriguing regulatory mechanism by which an endoribonuclease, Regnase-1, binds its target mRNAs directly.

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Table 1
Ribonuclease and ribonuclease families.

E. coli	*B. subtilis*	*S. cerevisiae*	*H. sapiens*
DEDD (3′ Exo)			
RNase D/*rnd*		Rrp6	RRP6
RNase T/*rnt*		Rex2	REXO1
Oligo-RNase/*orn*		Rex3	REXO1L1
		Rex4	REXO2
		Rex1/Rnh70	REXO4
		Pop2	CAF1a/CNOT7
		Pan2	CAF1b/CNOT8
			CAF1z
			PAN2
			PARN
			3′hExo/ERI1
			ERI2
			ERI3
			ISG20
			ISG20L1/AEN
			ISG20L2
			NEF-sp/LOC81691
RNase II (3′ Exo)			
RNase II = B/*rnb*	RNase R/*rnr*	Rrp44/Dis3	DIS3
RNase R/*rnr*		Dss1	DIS3L
		Ssd1	DIS3L2
PDX (3′ Exo, phosphorolytic)			
RNase PH/*rph*	RNase PH/*rph*	(Rrp41)[1]	PNPase/PNPT1
PNPase/*pnp*	PNPase/*pnpA*	(Rrp42)[1]	(Rrp41/EXOSC4)[1]
		(Rrp43)[1]	(Rrp42/EXOSC7)[1]
		(Rrp45)[1]	(Rrp43/EXOSC8)[1]
		(Rrp46)[1]	(Rrp45/EXOSC9)[1]
		(Mtr3)[1]	(Rrp46/EXOSC5)[1]
			(Mtr3/EXOSC6)[1]
EEP (3′ Exo, Endo)			
		Ccr4	CCR4a/CNOT6
		Ngl1	CCR4b/CNOT6L
		Ngl2	Nocturnin/CCRN4L
		Ngl3	PDE12
			(ANGEL1)[2]
			(Ccr4d/ANGEL2)[2]
DHH (5′ Exo, maybe 3′ Exo)			
	NrnA/*nrnA*		
	NrnB/*nrnB*		
	YngD/*yngD*		
Nudix Hydrolase (5′ Exo)			
RppH/*ygdP*	*mutT*	Dcp2	DCP2
			NUDT16
HIT Pyrophosphatase (5′ Exo)			
		Dcs1	DCPS
		Dcs2	
XRN (5′ Exo)			
		Xrn1	XRN1
		Rat1	XRN2
β-lactamase/(5′ Exo, Endo)			
RNase Z = BN/*rbn*	RNase Z/*rnz*	RNase Z/Trz1	RNase Z1/ELAC1
	RNase J1/*rnjA*	Cpsf73/Ysh1	RNase Z2/ELAC2
	RNase J2/*rnjB*	(Cpsf100/Ydh1)[1]	CPSF73
			INTS9
			CPSF3L/INTS11
			(CPSF100)[1]
RNase P (Endo)			
RNase P[3]/*rnpB*	RNase P[3]/*rnpB*	RNase P[3]/RPR1	RNase P[3]/RPPH1
		RNase MRP[3]/RPM1	RNase MRP[3]/RMRP
			(RNase P RNA-like)[2]
			(RNase MRN RNA-like)[2]
RNase III (Endo, dsRNA)			
RNase III/*rnc*	RNase III/*rnc*	Rnt1	DROSHA
	Mini III/*yazC*		DICER1
	MrnC/*mrnC*		

Table 1 (*continued*)

E. coli	*B. subtilis*	*S. cerevisiae*	*H. sapiens*
RNase H (Endo, RNA:DNA, dsRNA)			
RNase HI/*rnhA*	RNase H/*rnhA*	RNase H1/Rnh1	RNase H1/RNASEH1
RNase HII/*rnhB*	RNase HII/*rnhB*	RNase H2/Rnh201	RNase H2A/RNASEH2A
(YghN/*yhgN*)[2]	RNase HIII/*rnhC*		AGO2
RNase T2 (Endo)			
RNase I/*rna*		Rny1	RNase T2/RNASET2
PIN (Endo)			
	YacP/*yacP*	Dis3 = Rrp44	DIS3
	YacL/*yacL*	Nob1	SMG6
			Regnase/ZC3H12A
PemK (Endo)			
MazF/*mazF*	EndoA/*ndoA*		
ChpB/*ChpB*			
Plasmid-stabil (Endo)			
RelE/*relE*			
YoeB/*yoeB*			
YafQ/*yafQ*			
RNase LS (Endo)			
RNase LS/*rnlA*			
YhaV (Endo)			
YhaV/*yhaV*			
Ferredoxin-like (Endo)			
Cas2/*ygbF*			
RNase E/G (DNase I, Endo)			
RNase E/*rne*			
RNase G/*rng*			
HD (Endo, 3′ Exo)			
	RNase Y/*rny*		
	YhaM/*yhaM*		
Toprim (Endo)			
	RNase M5/*rnmV*		
	YusF/*yusF*		
(DNA-)Endonuclease I (Endo)			
	Bsn/*bsn*		
Reg B (Endo)			
(Reg B)[4]			
Spliceosome (Endo)			
		U2/U5/U6 snRNP[5]	U2/U5/U6 snRNP[5]
Calcineurin-like Phosphoesterase (Endo)			
		Dbr1	DBR1
tRNA intron Endonuclease (Endo)			
		Sen2	TSEN2
		Sen34	TSEN34
RNase Ire1-like (Endo)			
		Ire1	Ire1/ERN1
			RNase L/RNASEL
DNA/RNA non-specific Endonuclease (Endo)			
		Nuc1	Endonuclease G/ENDOG
PLD (Endo)			
			Zucchini/PLD6
Apurinic–Apyrimidinic (DNA-)Endonuclease (Endo)			
			APE1/APEX1
RNase A (Endo)			
			RNASE1
			RNASE2
			RNASE3
			RNASE4
			RNASE5 = Angiogenin/ANG
			RNASE6
			RNASE7
			RNASE8
			(RNASE9, 10, 12, 13)[1]

[1] Inactive.
[2] Activity uncertain.
[3] In most organisms, the catalytic activity of RNase P and RNase MRP is contained in the RNA component, yet human mitochondrial RNase P is a protein-only enzyme.
[4] Expressed by bacteriophage T4.
[5] Catalytic site of the spliceosome is formed by U2 and U6 snRNA.

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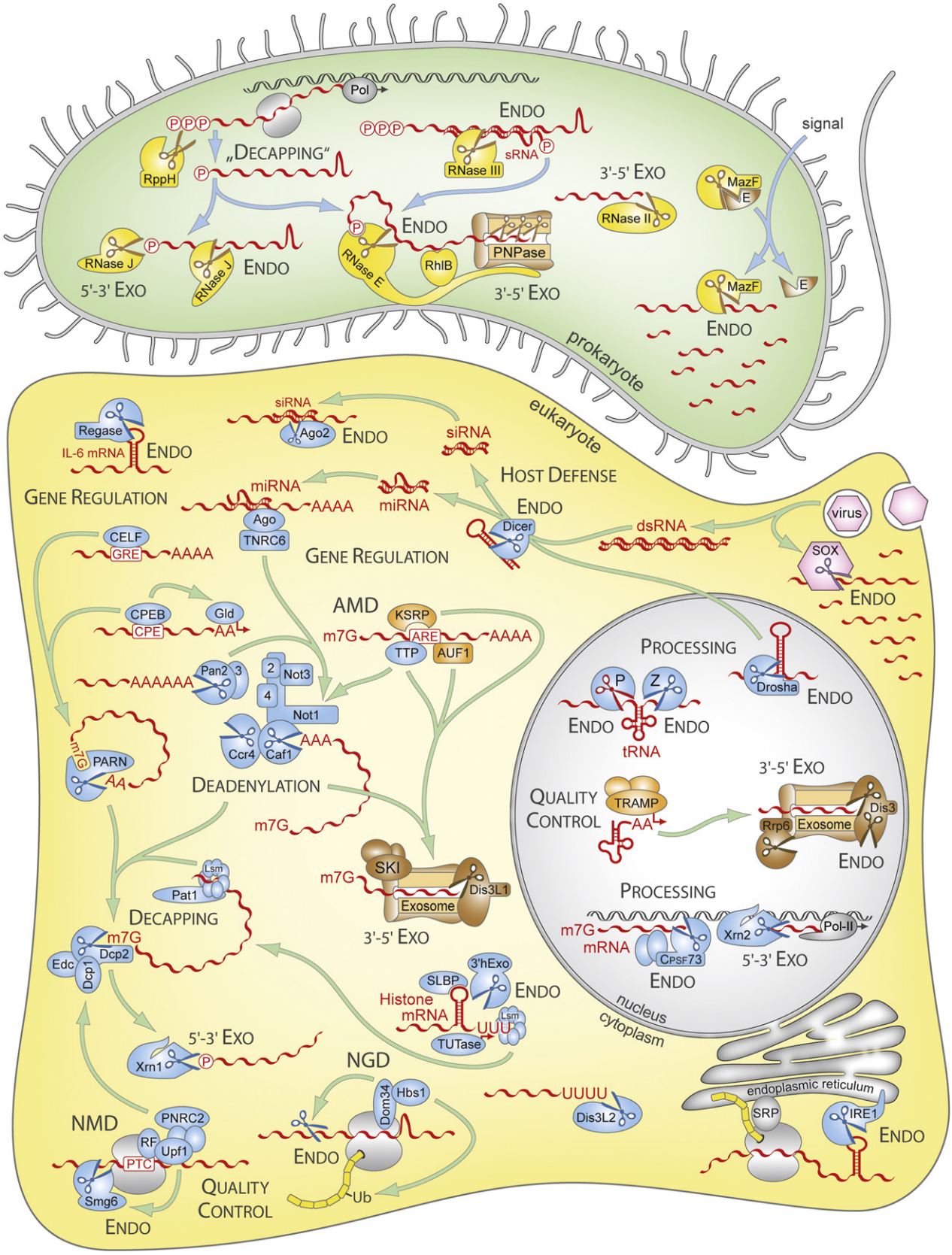

Fig. 1. RNA-degrading enzymes in prokaryotes and eukaryotes. A large number of ribonucleases are essential for the processing of primary transcripts to mature RNAs, for RNA quality control, for host defense and for the regulation of gene expression. Ribonucleases belong to more than 30 distinct protein families, only a small number of which could be depicted in the scheme. These enzymes operate as endoribonucleases (Endo), 3′-5′ exoribonucleases (Exo) or 5′-3′ exoribonucleases. Cleavage by endoribonucleases generates substrates for 3′-5′ and 5′-3′ exonucleolytic decay, resulting in a tight cooperation between different RNA degrading systems. In eukaryotes, deadenylation and decapping represent key steps in mRNA turnover. AMD stands for ARE-mediated mRNA decay, NMD for nonsense-mediated mRNA decay, and NGD for no-go mRNA decay. Please note the generalizing character of the scheme. For example, not all enzymes depicted here in one cell exist in every prokaryote or eukaryote. For more detailed information on individual enzymes and ribonuclease families, please refer to Table 1 and reviews in this issue.

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The final section is devoted to a more comprehensive view on biological systems that depend on RNA degradation. In germ cells and early embryos, the absence of transcription requires maternal mRNAs to be stored, translated and degraded in a precisely orchestrated fashion essential for the first steps in embryonic development. This topic is covered in a review by Barckmann and Simonelig. Weil and Hollien summarize recent and unexpected findings that link organelle function to the localization and degradation of mRNAs. For successful propagation, viruses have evolved elegant strategies not only to escape the cellular RNA degradation machinery, but also to specifically promote host mRNA decay, as described by Narayanan and Makino. Finally, Lalaouna and colleagues review potent systems in prokaryotes that make use of non-coding regulatory RNAs to target specific mRNAs for decay. A simple lesson this impressive range of reviews teaches us is that the diversity of ribonucleases and their regulators serves the purpose of achieving maximum specificity in degrading the right RNA at the right time in the right place, while avoiding damage to all other RNAs.

As guest editors of this special issue on RNA turnover mechanisms, we sought to cover the breadth of the many different RNA decay pathways that are currently known. Attentive readers will notice several white spots on our global RNA turnover map, most notably RNA interference pathways by which small RNAs induce degradation of complementary mRNAs in eukaryotes. While this map is certainly incomplete in many ways, we believe that readers of this issue – from students to senior investigators, RNA aficionados or not – will find a wealth of novel information, ideas and thoughts on what turns out to be a fascinating panoply of RNA degrading mechanisms.

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