Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Ribonucleases are counterweights in the balance of gene expression and are also involved in the maturation of functional RNA. Recent structural data reveal how ribonucleases recognize and cleave targets, in most cases with the catalytic assistance of metal cofactors. Many of these enzymes are ‘processive’, in that they make multiple scissions following the binding of substrates; crystallographic data can account for this solution behaviour. These data not only explain how ribonucleases turn over transcripts, but also provide hints about how they often play dual roles in quality control checks on structured RNA.

Addresses
Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge CB2 1GA, UK

Corresponding author: Luisi, Ben F (bfl20@mole.bio.cam.ac.uk)

Introduction
Only a few decades ago, when the genetic code was still in its infancy of abstraction, Crick, Brenner, Jacob and Monod reasoned that the information encoded by DNA must be converted into protein through an intermediary that is short-lived and consequently does not accumulate in the cell. This message was subsequently shown to be composed of RNA and its short life is a well-known curse of its infancy of abstraction, Crick, Brenner, Jacob and Monod reasoned that the information encoded by DNA must be converted into protein through an intermediary that is short-lived and consequently does not accumulate in the cell. The instability is caused principally by the activity of ribonucleases, which are abundant in cells and seem to lie eagerly in wait of vulnerable substrates. Seemingly nuisances, these enzymes in fact play important roles in the regulation of gene expression, for example, in the course of development or in response to environmental change [1]. In prokaryotes, nucleases affect the differential processing and rate of degradation of polycistronic transcripts, and thus may contribute to the coordinated stoichiometric synthesis of the subunits of multicomponent complexes [2].

The apparent wanton destruction of RNA by ribonucleases poses several questions: how do cells maintain folded RNA structures, such as rRNA and ribosomes, in the presence of all these keen ribonucleases? Conversely, how are unstructured or damaged RNAs identified and turned over? Lastly, many different types of structured RNAs are synthesized as precursors that must be trimmed to form the mature species. Are there dedicated, highly specific nucleases that do this controlled trimming? Perhaps the answer to all these questions stems from the observation that the turnover of mRNA and the processing of structural RNA share common steps; for instance, in Escherichia coli, the processing of rRNA and the degradation of mRNA both start with endonucleolytic cleavage followed by exonucleolytic attack on the fragments [3**]. Many of the ribonucleases that turn over transcripts play dual roles in the degradation of stable RNA and the processing or fidelity checking and stress-activated decay of structured RNA. As proposed by Deutscher [5**], the structure of the RNA itself may be the signal that steers it to a course of maturation or to a fate of destruction; we shall explore how these implicit signals are recognized. As is often the case, eukaryotes are more complicated and might have dedicated complex machinery for the different tasks of degradation and quality control [1]. Here, the choice of processing versus turnover may be affected by the time lag of processing, in analogy to kinetic proofreading of translational fidelity [4**].

We summarize some recent structural and functional data that provide insight into these processes, as represented by key bacterial ribonucleases and a few from archaea and eukaryotes. For convenience and perspective, we group these ribonucleases into the context of enzymes from E. coli, an organism for which we are rapidly approaching comprehensive coverage (Table 1). Not all of our questions about ribonucleases are answered by these structures, but some good hints are provided. The role of RNA structural determinants is a unifying theme, but the related catalytic chemistries also provide another connection between these new structures.

Structure and function of RNase E
In E. coli, the endoribonuclease RNase E plays a key role in initiating transcript turnover [5]. RNase E is an essential enzyme that affects the balance and composition of the mRNA population [6,7]. RNase E targets specific transcripts for destruction, in conjunction with the destruction of small regulatory RNAs [8]. In addition to its role in destroying transcripts, RNase E also plays a creative role in generating certain RNA species by maturing larger precursors. These include rRNA (9S
RNA), tRNA, tmRNA, which is required to rescue stalled ribosomes, and RNase P, a conserved ribozyme involved in tRNA processing [9–13].

The crystal structure of the RNase E catalytic domain has been solved in complex with RNA substrate at 2.85 Å (Figure 1a) [14**]. The ribonuclease is a composite of...
recurrent folds, although these were not detected by sequence similarity. The catalytic domain of RNase E contains structural subdomains, such as DNase I and RNase H (Figure 1a), and an S1 subdomain, which occurs in many different RNA-binding proteins. In RNase E, the S1 subdomain clamps down on the RNA substrate and appears to be flexibly tethered to the body of the nuclease (see the summary in Figure 2). The catalytic site is situated in the DNase I subdomain, where a single metal-binding site is found (Figure 1b); however, it is possible that there is a second metal-binding site in the transition state. (The use of two-metal clusters as catalytic
centres is a recurrent theme in other ribonucleases; see Table 1.) Cleavage is by nucleophilic attack on the phosphate backbone within a single-stranded A/U-rich region, generating fragments with a free 3'-OH (on the 5' side of cleavage) and a 5'-monophosphate (on the 3' side). The RNase E structure suggests that recognition of the 5' end of the substrate induces a conformational switch that results in the phosphate backbone being oriented for attack by an OH group activated by a coordinated magnesium ion.

In *E. coli* and probably many other related Gram-negative bacteria, RNase E is part of a multienzyme assembly known as the RNA degradosome [15,16]. The other components of the degradosome are the glycolytic enzyme enolase, an ATP-dependent RNA helicase (RhlB) and the phosphorolytic exoribonuclease polynucleotide phosphorylase (PNPase). The physical association of these proteins within the degradosome coordinates their enzymatic activities. PNPase is a successive phosphorolytic exonuclease that may work together with RNase E to ensure the cooperative destruction of substrates once the first cleavage is made; it is also involved in checking the fidelity of rRNA precursors as a quality control mechanism [17]. RhlB is required to unwind structured RNA substrates so that they become suitable substrates for the nucleases of the degradosome. The role of enolase is unclear, but the available evidence indicates that its recruitment into the degradosome assembly is required to control levels of transcripts for the glucose transporter [18,19]. An enolase recognition motif occurs in RNase E homologues from other Gram-negative bacteria, including pathogens such as *Salmonella*, and it seems likely that, in these organisms, the enolase interacts with RNase E [20].

**RNase II and RNase R**

The exoribonuclease RNase II is representative of an extensive enzyme family found in all three domains of life, whose members play roles in the maturation, turn-

---

*Schematic summary of the modes of RNA processing of some of the endoribonucleases (RNase E) and exoribonucleases discussed in the text and in Table 1. Common protein domains are indicated and scissors represent the positions of the active sites. For the exosome and PNPase schematic, only one active site is represented for clarity. RNase D and RNase III share no common structural features with the other ribonucleases. The two-colour scheme for the RNA substrates of RNase R, the exosome and PNPase highlights how the duplex regions, indicated in green, become melted as the single-stranded regions, shown in red, are cleaved.*
over and quality control of certain species of structured RNA [3**]. RNase II cuts single-stranded (ss)RNA processively in a 3’ to 5’ direction, using a hydrolytic mechanism, and releases nucleotide monophosphates as it gallops along (summarized in Figure 2). Crystal structures of the apo form of E. coli RNase II and of an inactive mutant in complex with ssRNA have been reported [21**,22**] (Figure 3a). This revealed another multidomain molecular montage, composed of two cold-shock domains (CSDs) at the N-terminal end, followed by a catalytic domain and, finally, an S1 domain. The X-ray data reveal that the single-stranded substrate lies deep in a channel at the bottom of which is the catalytic site [21**] (Figure 3a). One magnesium ion is present in the active site, coordinated by aspartates. The inactivating mutation in RNase II lies at a putative metal-coordinating residue, D209N, and Frazão et al. [21**] propose that two metals may be involved in the activation of a water molecule for hydrolysis of the terminal phosphodiester, analogous to the active sites of polymerases and perhaps some ribozymes [23]. This hypothesis is corroborated by the mutagenesis studies of Zuo et al.[22**]. The organization of the active site of RNase II has striking parallels with the active site of the endoribonuclease RNase H; thus, even though the folds differ, the enzymes are likely to share similar catalytic chemistries.

RNase R is a homologue of RNase II, but with an intriguing and distinctive property: it appears to have a built-in ability to unwind the secondary structure of RNA substrates, even if they contain many strong G•C base pairs. In a striking parallel with certain types of RNA helicases, RNase R can sense the polarity of the phosphodiester backbone of the substrate. Thus, the ribonuclease greatly prefers substrates with single-stranded regions at the 3’ end. The ribonuclease can processively degrade structured substrates, provided they have a 3’ single-stranded overhang that is seven or more nucleotides in length [24*]. Cleavage occurs at the single-stranded 3’ overhang and proceeds processively in the 5’ direction, ploughing straight through the secondary structure (Figure 2). Whereas DEAD-box helicases use the free energy of ATP binding and hydrolysis to disrupt secondary structure, RNase R transduces the favourable free energy of RNA backbone hydrolysis into mechanical work that translates the single-stranded substrate further into the catalytic pocket, much like a ratchet. The linkage between RNA cleavage and unwinding of secondary structure is most likely indirect, and may involve changes in the energy of RNA binding to the catalytic pocket and to the S1 subdomain. One hypothesis is that the energy-dependent ratcheting mechanism pulls the duplex RNA against the apex of the tunnel, into which it cannot fit, thus causing it to unwind. It is not presently clear why RNase R manages to perform this operation, whereas homologous RNase II does not. Nevertheless, RNase R seems to have evolved a very clever mechanism to convert the energy of hydrolysis into work of unwinding, and thus seems to be a model of energy conservation. In eukaryotes, the RNase R homologue is a component of the exosome assembly, which we will discuss below.

**RNase H and RNase III**

Both RNase H and RNase III are representative of components of the RNA interference (RNAi) machinery, which is described elsewhere in this issue [25]. We mention them here briefly to emphasize the role of metals in catalysis, one common theme of the ribonucleases presented here (Table 1). RNase H enzymes cleave duplex RNA or RNA–DNA hybrids, and are representative of a large family whose members include transposases and the Argonaute ribonuclease, which is involved in RNA silencing. RNase III cleaves double-stranded (ds)RNA and the E. coli enzyme is a model system for the entire family, which includes eukaryotic enzymes such as Dicer (involved in the RNAi mechanism). The protein uses induced fit to recognize RNA substrates [26] (Figure 2). As seen in the other ribonucleases, divalent metals are again the key components of the catalytic site.

The structure of RNase H from mouse leukaemia virus has been solved at high resolution [27*] and corroborates the presence of a magnesium-binding site in the catalytic site, consistent with the two-magnesium mechanism proposed earlier by Yang et al. [28] for E. coli RNase H. A recent crystallographic analysis reveals the stepwise participation of the two magnesium metals in the RNase H mechanism, with the first participating in nucleophilic activation of water and the second metal stabilizing the transition state [29,30]. Reflecting the distinct roles of the two metals, they are coordinated in non-equivalent ways. By contrast, metal coordination is symmetrical in the RNase-H-like transposases; this is required because the metals have equivalent roles in the successive steps of nucleophilic activation of water during strand cleavage and 3’-OH activation during strand transfer [31].

**RNase Z and the metallo-β-lactamase fold**

RNase Z is a conserved endonuclease that cleaves tRNA precursors at the 3’ end in preparation for the addition of a CCA aminoacylation motif. The fold belongs to the β-lactamase structural family and the active site contains two coordinated zinc ions that participate in the hydrolysis of the RNA backbone. Structures are available for the apo and tRNA-bound forms from Bacillus subtilis (Figure 3b), revealing that substrate binding causes conformational moulding of both macromolecules to organize the catalytic site [32*,33*]. This induced fit appears to result in recognition of the shape and contour of the tRNA, as well as direct recognition of two conserved guanine bases.

*B. subtilis* has two other endoribonucleases that are proposed to have a similar metallo-β-lactamase fold: RNase J1
RNA recognition by RNase II and RNase Z. (a) Structure of the RNase II active site variant D209N from *E. coli* in complex with RNA (PDB code 2ix1). The individual domains are labelled and the 13-mer ssRNA, which was bound to the 'as isolated' variant, is shown as pink spheres. The magnesium ion found in the active site is represented as a green sphere. (b) Structure of RNase Z from *B. subtilis* bound to tRNA Thr (PDB code 2fk6). The monomer of the asymmetric unit is shown in red (for the Zn β-lactamase subdomain), yellow (strands) and green (coils). The functional dimer created by a symmetry-related molecule is shown in blue. The 52-nucleotide tRNA Thr is shown in stick representation, with the zinc ions involved in catalysis indicated as spheres.
and RNase J2 [34]. These two enzymes appear to be RNase E homologues in function, but emphatically not in sequence or fold.

The exosome

In eukaryotes and archaea, the multienzyme exosome plays many key roles in RNA processing and turnover, RNAi and quality control surveillance. The central component of the exosome is a phosphorolytic ribonuclease that is structurally homologous to the bacterial PNPase of the degradosome. The subunits of the exosome and the subdomains of PNPase closely resemble the ancient fold found in the phosphorolytic exoribonuclease RNase PH [35]. Crystal structures of the core of the exosomes from the archaea Sulfolobus solfataricus and Archaeoglobus fulgidus have recently become available, revealing a hexameric ring comprising two types of RNase-PH-like subunits, known as Rrp41 and Rrp42 (rRNA-processing proteins 41 and 42; see Figure 4a) [36,37,38]. Three of the exosome subunits are likely to have catalytic activity for phosphorolysis, whereas the other three might not. Instead, these non-catalytic subunits might provide a surface for the recruitment of the other exosome components. In the phosphorolytic reaction, the last \( 3' \) phosphodiester bond of the substrate is attacked by phosphate, to leave a \( 3' \)-OH and nucleotide diphosphates.

In addition to the hexameric core, the archaecal exosome contains the subunits known as Rrp4, which have the S1 fold (also present in RNase E and RNase II) and the KH fold, another ancient and ubiquitous RNA-binding motif. The RNase PH, S1 and KH domains are organized into a quaternary structure that is remarkably similar to bacterial PNPase (Figure 4b). Although not yet elucidated, it is likely that this structure is also conserved in the eukaryotic exosome. The active site lies within the central channel of the hexameric ring and is 50–60 Å from the exterior surface that engages the Rrp4 subunit, suggesting that a product of 10–20 nucleotides is the limit of digestion; thus, auxiliary components might be needed to complete the processing of undigested residual fragments (Figure 2).

The auxiliary components of the eukaryotic exosome include ATP-dependent helicases and hydrolytic ribonucleases, such as homologues of RNase R (described earlier) and the metal-dependent exoribonuclease RNase D (described below) (Figure 2). In eukaryotes, exosomes are found in the cytoplasm and nucleus, where they have different auxiliary components and specialized function. The cytoplasmic exosome is involved in the turnover of both normal and defective transcripts [4**]. The nuclear exosome is involved in processing precursors of structured RNA, such as 5.8S rRNA, and in quality control surveillance of many different types of RNA [4**]. The structure of the nuclear auxiliary factor Rrp6p has been solved [39], confirming that this enzyme is related to the RNase D family of exonucleases; this family includes the proofreading subdomain of DNA polymerase I [40] and the poly(A)-specific ribonuclease [41]. In these enzymes, characterized by conserved acidic residues, two divalent metal ions activate a water molecule for hydrolysis of the terminal phosphodiester. The interaction of a C-terminal domain of Rrp6p with the exosome core might modulate its function [39]. In eukaryotes, additional hydrolytic exoribonucleases function to hydrolyze substrates in

Figure 4

Ribbon or surface representation of (a) the archaecal core exosome from A. fulgidus (PDB code 2ba0) and (b) PNPase from Streptomyces antibioticus (PDB code 1e3p) viewed along the threefold rotation axis. In the exosome, a ring of alternating Rrp41 and Rrp42 subunits (green and blue) forms a hexameric core structure, with three Rrp4 subunits (orange) binding to the top face. The core domains of the exosome share the same RNase PH fold as the bacterial PNPase. The S1 and KH domains, common to both the exosome and PNPase structures, are indicated. The S1 domains of the Rrp4 subunits are ideally situated to guide the \( 3' \) end of ssRNA into the pore (10 Å diameter) for processing. In the PNPase structure, the S1 domains are not well defined, suggesting high mobility in the absence of bound RNA.
the 5' to 3' direction (Rat1 and Xrn1 and their homologues) [1].

**EndoU: a new endoribonuclease structural class**

In vertebrates, small nucleolar RNAs (snoRNAs) function in ribosome processing in the nucleolus; some have a role in the modification of bases or cutting of rRNA precursors [42]. Some snoRNAs are processed by endonucleolytic cleavage, through the action of enzymes such as the manganese-dependent endoribonuclease XendoU from the amphibian *Xenopus laevis* [43]. Sequence alignment reveals similar proteins in other eukaryotes (including human, *Drosophila melanogaster*, *Caenorhabditis elegans* and *Arabidopsis thaliana*), nidoviruses and, remarkably, the cyanobacterium *Nostoc punctiforme* [44]. This might indicate the versatile use of this fold in RNA processing.

A homologous enzyme, known as NendoU, is a component of the genomic replication apparatus of the SARS virus and other members of the coronavirus family [45]. These enzymes, which we refer to as belonging to the EndoU family, are specific for uracil and the product has a 2'-3' cyclic phosphate; this is usually an indication that the ribose sugar 2'-OH is oriented and activated to act as a nucleophile. Crystal structures have become available for the NendoU enzymes from SARS virus [46] and mouse hepatitis virus [47], and for XendoU from *X. laevis* [44].

These data reveal a common, unique fold that distinguishes the EndoU family from any other ribonuclease family identified thus far (Figure 5). Remarkably, the position of the key catalytic residues in the active sites of XendoU and NendoU mimics the position of corresponding residues in the ribonuclease RNase A (two histidines, which serve as general acid/general base, and a lysine) (Figure 5). This congruence is achieved with different folds and serves as a striking example of convergent evolution. The re-invention of a catalytic site usually indicates an important function, but the precise role of the viral protein is currently not well understood.

**Conclusions**

The use of metals to activate a nucleophile is a common theme for both endonucleases and exonucleases of the hydrolytic class. These hydrolytic reactions are highly exergonic; by contrast, phosphorolysis, in which inorganic phosphate attacks the backbone to drive bond cleavage, corresponds to a much smaller free energy change. It seems reasonable to expect that selective pressure would affect the balance of one reaction over the other. In the course of the evolution of eukaryotes, the associated genomic expansion and the tremendous amount of non-coding RNA necessitates significant investment of resources and energy. Perhaps the exosome represents an energy-efficient means of coping with the recycling of
oligonucleotides, compared with the costs associated with hydrolytic decay. Some hydrolytic enzymes, such as RNase R, can use the free energy of hydrolysis to ‘drive through’ secondary structure, so that this does not require the assistance of an energy-consuming RNA helicase. Most RNAs are spared this expensive mode of destruction unless they are specified by a single-stranded 3' tail of minimal length or an exposed 5' monophosphate together with a single-stranded region. As the structure rather than the sequence itself is recognized, the fold must be under considerable evolutionary scrutiny and might be optimised to fine-tune the levels of populations of transcripts, so that the enzymes they encode have an extra layer of regulatory connections. Therefore, one speculation is that the targeting of selected transcript classes for turnover by ribonucleases might also permit the coordinated regulation of different genes and thus might deepen connections between metabolic processes [16]. This hypothesis awaits testing.

Acknowledgements
The authors are supported by the Wellcome Trust. We thank Gadi Schuster, Kyoshi Nagai, Chris Smith, Murray Deutscher, Beatrice Vallone, Maria Armeénia Carrondo, Richard J Jackson and AJ Carpousis for helpful discussions. We also thank Maria Armeénia Carrondo and Colin McVey for kindly providing the figure of RNase II.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Parker R, Song H: The enzymes and control of eukaryotic mRNA turnover. Nat Struct Mol Biol 2004, 11:121-127.

2. Maden U, Hennig S, Heckler M, Hornuth G: Transcriptional organization and posttranscriptional regulation of the Bacillus subtilis branched-chain amino acid biosynthesis genes. J Bacteriol 2004, 186:2240-2252.

3. Deutscher MP: Degradation of RNA in bacteria: comparison of mRNA and stable RNA. Nucleic Acids Res 2006, 34:659-668. This well-written review presents a clear and cogent summary of ribonuclease function, and proposes a dual role for ribonucleases in processing RNA and in turnover. The key determinants are in the RNA itself.

4. Houseley J, LaCava J, Tollervey D: RNA-quality control by the exosome. Nat Rev Mol Cell Biol 2006, 7:529-539. A comprehensive review of the role of the exosome and its auxiliary components in RNA turnover and quality control checks in eukaryotes.

5. Condon C, Putzer H: The phylogenetic distribution of bacterial ribonucleases. Nucleic Acids Res 2002, 30:5339-5346.

6. Bernstein JA, Lin P-H, Cohen SN, Lin-Chao S: Global analysis of Escherichia coli RNA degradasme function using DNA microarrays. Proc Natl Acad Sci USA 2004, 101:2758-2763.

7. Lee K, Bernstein JA, Cohen SN: RNase G complementation of me null mutation identifies functional interrelationships with RNase E in Escherichia coli. Mol Microbiol 2002, 43:1445-1456.

8. Massé E, Escoria FE, Gottesman S: Coupled degradation of a small regulatory RNA and its mRNA targets in Escherichia coli. Genes Dev 2003, 17:2374-2383.

9. Lundberg U, Altman S: Processing of the precursor to the catalytic RNA subunit of RNase P from Escherichia coli. RNA 1995, 1:327-334.

10. Ow MC, Kushner SR: Initiation of tRNA maturation by RNase E is essential for cell viability in Escherichia coli. Genes Dev 2002, 16:1102-1115.

11. Li Z, Pandit S, Deutscher MP: RNase G (ColA protein) and RNase E are both required for the 5' maturation of 16S ribosomal RNA. EMBO J 1999, 18:2878-2885.

12. Lin-Chao S, Wei C-L, Lin Y-T: RNase E is required for the maturation of ssrA RNA and normal ssrA RNA peptide-tagging activity. Proc Natl Acad Sci USA 1999, 96:12406-12411.

13. Kim K-S, Lee Y: Regulation of 6S RNA biogenesis by switching utilization of both sigma factors and endoribonucleases. Nucleic Acids Res 2004, 32:6057-6068.

14. Callaghan AJ, Marcaida MJ, Stead JA, McDowall KJ, Scott WG, Luisi BF: Structure of Escherichia coli RNase E catalytic domain and its implications for RNA turnover and processing. Nature 2005, 437:1187-1191.

The first crystal structure of a member of the RNase E/RNase G family is described.

15. Carpousis AJ: The Escherichia coli RNA degradasome: structure, function and relationship to other ribonucleolytic multienzyme complexes. Biochim Biophys Acta 2002, 150-155.

16. Marcaida MJ, DePristo MA, Chandran V, Carpousis AJ, Luisi BF: The RNA degradasome: life in the fast lane of adaptive molecular evolution. Trends Biochem Sci 2006, 31:359-365.

17. Cheng ZF, Deutscher MP: Quality control of ribosomal RNA mediated by polynucleotide phosphorylase and RNase R. Proc Natl Acad Sci USA 2003, 100:6386-6393.

18. Morita T, Kawamoto H, Mizota T, Inada T, Alba H: Enolase in the RNA degradasome plays a crucial role in the rapid decay of glucose transporter mRNA in response to phoshoergic stress in Escherichia coli. Mol Microbiol 2004, 54:1063-1075.

19. Morita T, Maki K, Alba H RNase E-based ribonucleoprotein complexes: mechanical basis of mRNA destabilization mediated by bacterial noncoding RNAs. Genes Dev 2005, 19:2176-2186.

20. Chandran V, Luisi BF: Recognition of enolase in the Escherichia coli RNA degradasome. J Mol Biol 2006, 358:8-15.

21. Frazão C, McVey CE, Amblar M, Barbas A, Vonrhein C, Arraiano CM, Carrondo MA: Unravelling the dynamics of RNA degradation by ribonuclease II and its RNA-bound complex. Nature 2006, 443:110-114. The first reported crystal structure of a member of the RNase II/RNase R family.

22. Zuo Y, Vincent HA, Zhang J, Wang Y, Deutscher MP, Malhotra A: Structural basis for processivity and single-strand specificity of RNase II. Mol Cell 2006, 24:149-156.

The crystal structure of E. coli RNase II is presented, together with a proposal for the processing and catalytic mechanism.

23. Steitz TA, Steitz JA: A general two-metal-ion mechanism for catalytic RNA. Proc Natl Acad Sci USA 1993, 90:6498-6502.

24. Vincent HA, Deutscher MP: Substrate recognition and catalysis by the exoribonuclease RNase R. J Biol Chem 2006, 281:149-156. This analysis of enzyme cutting rates and affinity for RNA substrates established the key determinants of recognition.

25. MacRae IJ, Doudna JA: Ribonuclease revisited: structural insights into ribonuclease III family enzymes. Curr Opin Struct Biol 2007, 17: in press.

26. Gan J, Tropea JE, Austin BP, Court DL, Waugh DS, Ji X: Structural insight into the mechanism of double-stranded RNA processing by ribonuclease III. Cell 2006, 124:355-366.

27. Lim D, Gregorio GG, Bingman C, Martinez-Hackett E, Hendrickson WA, Goff SP: Crystal structure of the moloney murine leukemia virus RNase H domain. J Virol 2006, 80:8379-8389.

The structure of a eukaryotic viral RNase H, which cleaves RNA–DNA hybrids, is described.
28. Yang W, Hendrickson WA, Crouch RJ, Satow Y: Structure of ribonuclease H phased at 2 Å resolution by MAD analysis of the selenomethionyl protein. Science 1990, 249:1398-1405.

29. Nowotny M, Yang W: Stepwise analyses of metal ions in RNase H catalysis from substrate destabilization to product release. EMBO J 2006, 25:1924-1933.

30. Nowotny M, Gaidamakov SA, Crouch RJ, Yang W: Crystal structures of RNase H bound to an RNA/DNA hybrid: substrate specificity and metal-dependent catalysis. Cell 2005, 121:1005-1016.

31. Yang W, Lee JY, Nowotny M: Making and breaking nucleic acids: two-Mg2+-ion catalysis and substrate specificity. Mol Cell 2006, 22:5-13.

32. Li de la Sierra-Gallay I, Mathy N, Pellegrini O, Condon C: Structure of the ubiquitous 3’ processing enzyme RNase Z bound to transfer RNA. Nat Struct Mol Biol 2006, 13:376-377.

33. This continuation of their earlier structural studies [33] reveals structural moulding of RNA substrate and enzyme upon engagement.

34. Li de la Sierra-Gallay, Pellegrini O, Condon C: Structural basis for substrate binding, cleavage and lability in the tRNA maturation RNase Z. Nature 2005, 433:567-561.

35. The first structure of a member of the RNase Z family is presented, together with a speculative model for substrate-induced structural change.

36. Even S, Pellegrini O, Zig L, Labas V, Vinh J, Bréchremmier-Baey, Putzer H: Ribonucleases J1 and J2: two novel endoribonuclease families. Nucleic Acids Res 2005, 33:2141-2152.

37. A proposal for the fold of the family of B. subtilis RNase J1 and J2, which are functional homologues of RNase E.

38. Symmons MF, Williams MG, Luisi BF, Jones GH, Carposijs AJ: Running rings around RNA: a superfAMILY of phosphate-dependent RNases. Trends Biochem Sci 2002, 27:11-18.

39. Lorentzen E, Conti E: Structural basis of 3’ end RNA recognition and exoribonuclease cleavage by an exosome RNase PH core. Mol Cell 2005, 20:473-481.

40. This continuation of the studies described in [37] shows how RNA substrate is engaged by the exosome.

41. Lorentzen E, Walter P, Fribourg S, Evgueniieva-Hackenberg E, Klug O, Conti E: The archaeal exosome core is a hexameric ring structure with three catalytic subunits. Nat Struct Mol Biol 2005, 12:575-581.

42. The first structure of an archaeobacterial exosome demonstrates the arrangement of RNase-PH-like subunits in a ring that resembles the PNPase architecture. It reveals that exonuclease activity resides in only three of the identical subunits.

43. Büttnern K, Wenig K, Hopfner K-P: Structural framework for the mechanism of archaeal exosomes in RNA processing. Mol Cell 2005, 20:461-471.

44. The authors present the structure of the complete archaeal exosome core.

45. Midgaard SF, Assenholdt J, Jonsrup AT, Van LB, Jensen TH, Brodersen DE: Structure of the nuclear exosome component Rrp6p reveals an interplay between the active site and the HRDC domain. Proc Natl Acad Sci USA 2006, 103:11898-11903.

46. The crystal structure of a component of the nuclear exosome from yeast (Saccharomyces cerevisiae) confirms its structural relationship with the bacterial RNase D exonuclease and corroborates its mode of metal binding.

47. Zuo Y, Wang Y, Malhotra A: Crystal structure of Escherichia coli RNase D, an exoribonuclease involved in structured RNA processing. Structure 2005, 13:973-984.

48. The structure of E. coli RNase D reveals a structural relationship with the exonuclease domain of DNA polymerase I.

49. Wuu M, Reuter M, Lilie H, Liu Y, Wahle E, Song H: Structural insight into poly(A) binding and catalytic mechanism of human PARN. EMBO J 2005, 24:4082-4093.

50. Filipowicz W, Pogacic V: Biogenesis of small nuclear ribonucleoproteins. Curr Opin Cell Biol 2002, 14:319-327.

51. Lanee P, Altieri F, Fiori ME, Scalon A, Bozzoni I, Caffarelli E: Purification, cloning, and characterization of XendoU, a novel endoribonuclease involved in processing of intron-encoded small nuclear RNAs in Xenopus laevis. J. Biol Chem 2003, 278:13026-13032.

52. Renzi F, Caffarelli E, Lanee P, Bozzoni I, Brunori M, Vallone B: The structure of the endoribonuclease XendoU: from small nucleolar RNA processing to severe acute respiratory syndrome coronavirus replication. Proc Natl Acad Sci USA 2006, 103:12365-12370.

53. This paper presents the structure and postulated mechanism of XendoU from the amphibian X. laevis, representing the vertebrate homologue of a new structural class of manganese-dependent endoribonuclease (see also [46]).

54. Ivanov KA, Hertzig T, Rozanov M, Bayer S, Thiell V, Gorbulevsky AE, Ziebuhr J: Major genetic marker of nodiviruses encodes a replicative endoribonuclease. Proc Natl Acad Sci USA 2004, 101:12694-12699.

55. Even S, Pellegrini O, Zig L, Labas V, Vinh J, Bréchremmier-Baey, Putzer H: Ribonucleases J1 and J2: two novel endoribonuclease families. Nucleic Acids Res 2005, 33:2141-2152.

56. A proposal for the fold of the family of B. subtilis RNase J1 and J2, which are functional homologues of RNase E.

57. Symmons MF, Williams MG, Luisi BF, Jones GH, Carposijs AJ: Running rings around RNA: a superfAMILY of phosphate-dependent RNases. Trends Biochem Sci 2002, 27:11-18.

58. Lorentzen E, Conti E: Structural basis of 3’ end RNA recognition and exoribonuclease cleavage by an exosome RNase PH core. Mol Cell 2005, 20:473-481.

59. This continuation of the studies described in [37] shows how RNA substrate is engaged by the exosome.

60. Lorentzen E, Walter P, Fribourg S, Evgueniieva-Hackenberg E, Klug O, Conti E: The archaeal exosome core is a hexameric ring structure with three catalytic subunits. Nat Struct Mol Biol 2005, 12:575-581.

61. The first structure of an archaeobacterial exosome demonstrates the arrangement of RNase-PH-like subunits in a ring that resembles the PNPase architecture. It reveals that exonuclease activity resides in only three of the identical subunits.

62. Büttnern K, Wenig K, Hopfner K-P: Structural framework for the mechanism of archaeal exosomes in RNA processing. Mol Cell 2005, 20:461-471.

63. The authors present the structure of the complete archaeal exosome core.

64. Midgaard SF, Assenholdt J, Jonsrup AT, Van LB, Jensen TH, Brodersen DE: Structure of the nuclear exosome component Rrp6p reveals an interplay between the active site and the HRDC domain. Proc Natl Acad Sci USA 2006, 103:11898-11903.

65. The crystal structure of a component of the nuclear exosome from yeast (Saccharomyces cerevisiae) confirms its structural relationship with the bacterial RNase D exonuclease and corroborates its mode of metal binding.

66. Zuo Y, Wang Y, Malhotra A: Crystal structure of Escherichia coli RNase D, an exoribonuclease involved in structured RNA processing. Structure 2005, 13:973-984.

67. The structure of E. coli RNase D reveals a structural relationship with the exonuclease domain of DNA polymerase I.

68. Wuu M, Reuter M, Lilie H, Liu Y, Wahle E, Song H: Structural insight into poly(A) binding and catalytic mechanism of human PARN. EMBO J 2005, 24:4082-4093.