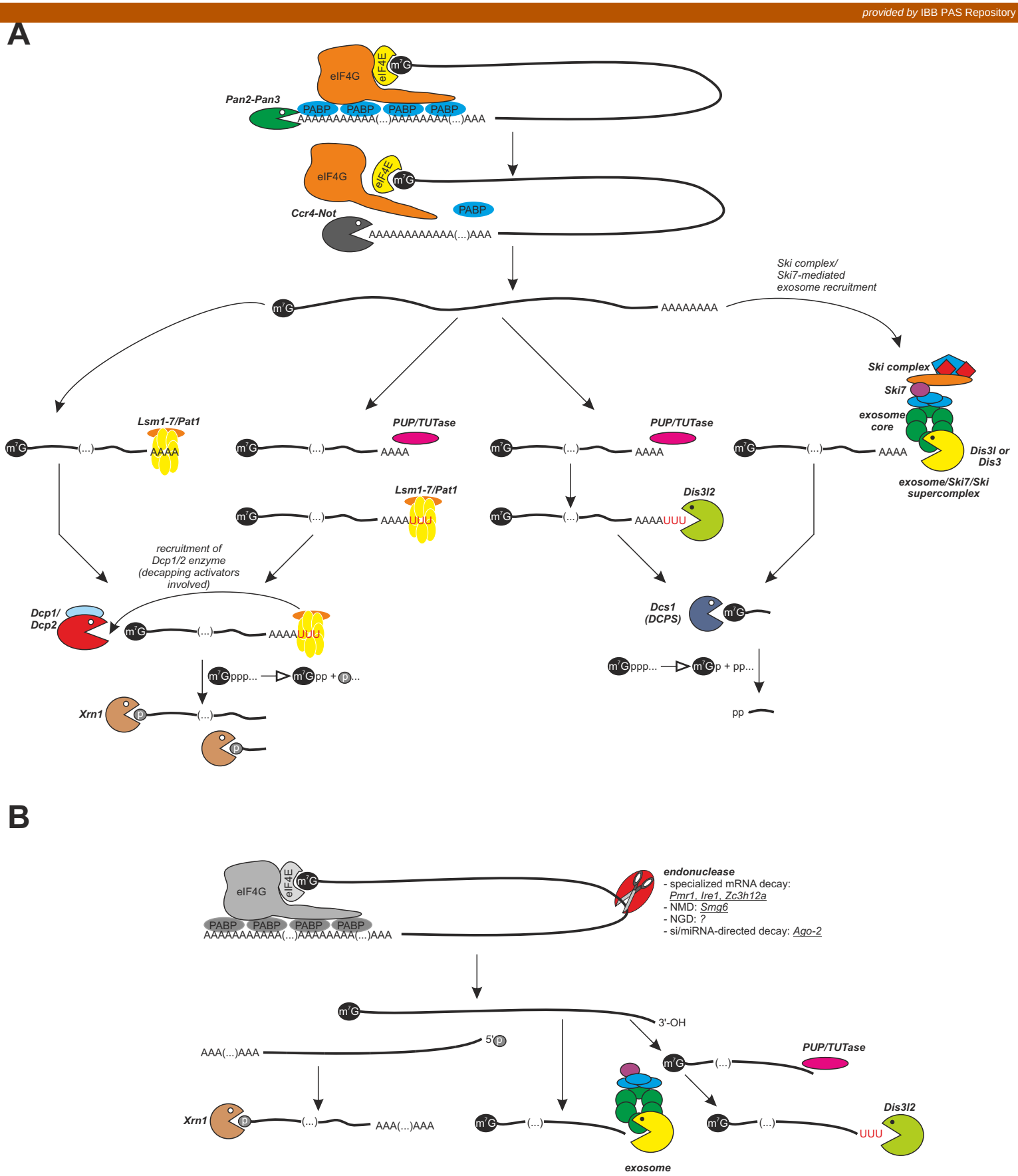

Fig. 1. An overview of cytoplasmic poly(A)+ mRNA decay pathways. A – degradation mechanisms initiated by disruption of the closed circle mRNA structure and deprotection of mRNA termini. The roles of deadenylation, 3'-terminal uridylation, Ski complex/Ski7 protein and decapping in the stimulation of 3'-5' exonucleases (Dis3/Dis3l associated with the exosome core or Dis3l2) and 5'-3' exonuclease (Xrn1) are described in sections 1.1-1.6. B – mRNA degradation in specialized and quality control pathways can be also initiated by endonucleolytic cleavage within the transcript body. This leads to the exposure of unprotected 3' and 5' termini on the proximal and distal products, respectively, which become accessible to the exosome and Dis3l2 or Xrn1, respectively.

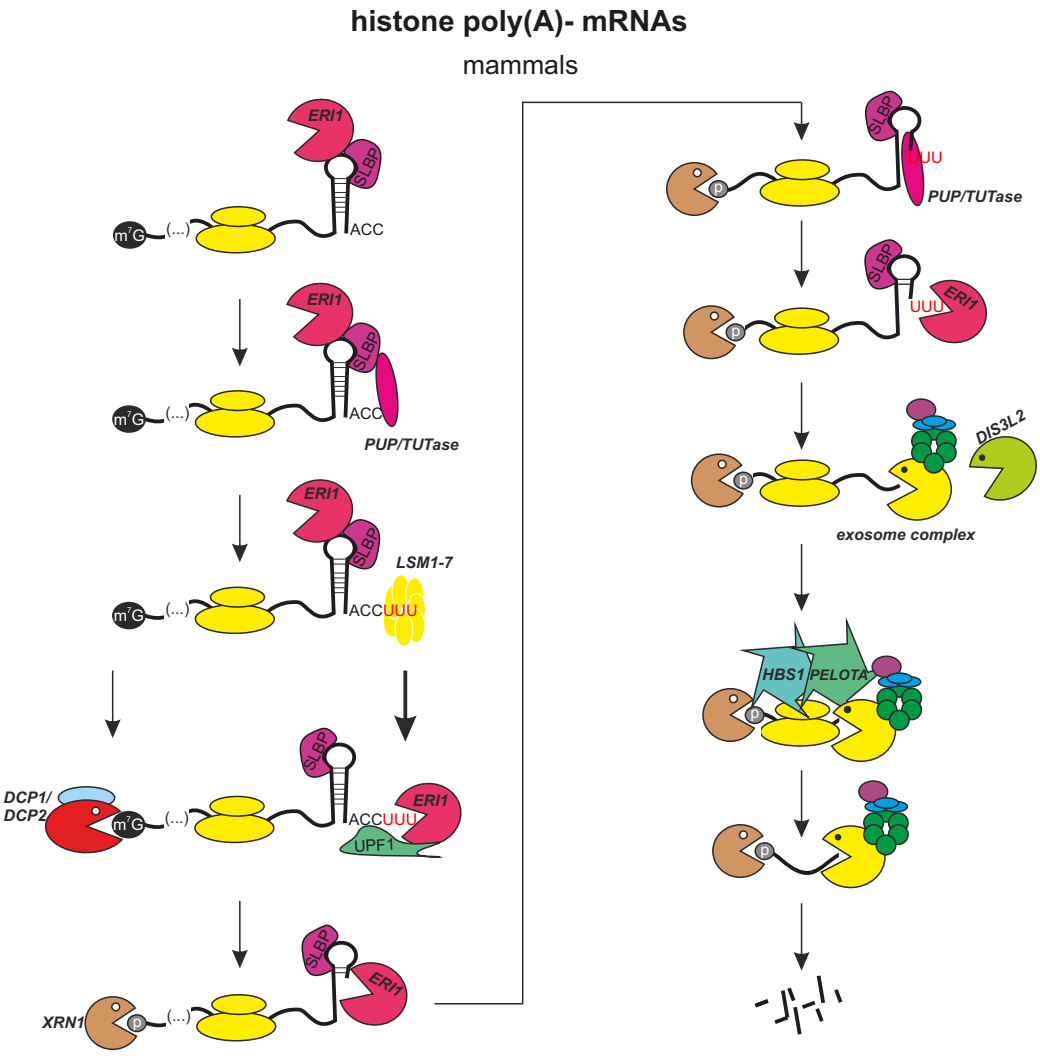

Fig. 2. Schematic presentation of poly(A)- histone-coding mRNA decay pathway in mammalian cells. See section 1.7 for details on ERI1 3'-5' exonuclease action and the role of repetitive uridylation in the removal of stem-loop (SL) structure, recruitment of decapping factors mediated by LSM1-7 complex and the involvement of exosome, DIS3L2 and HBS1/PELOTA heterodimer in the degradation process.

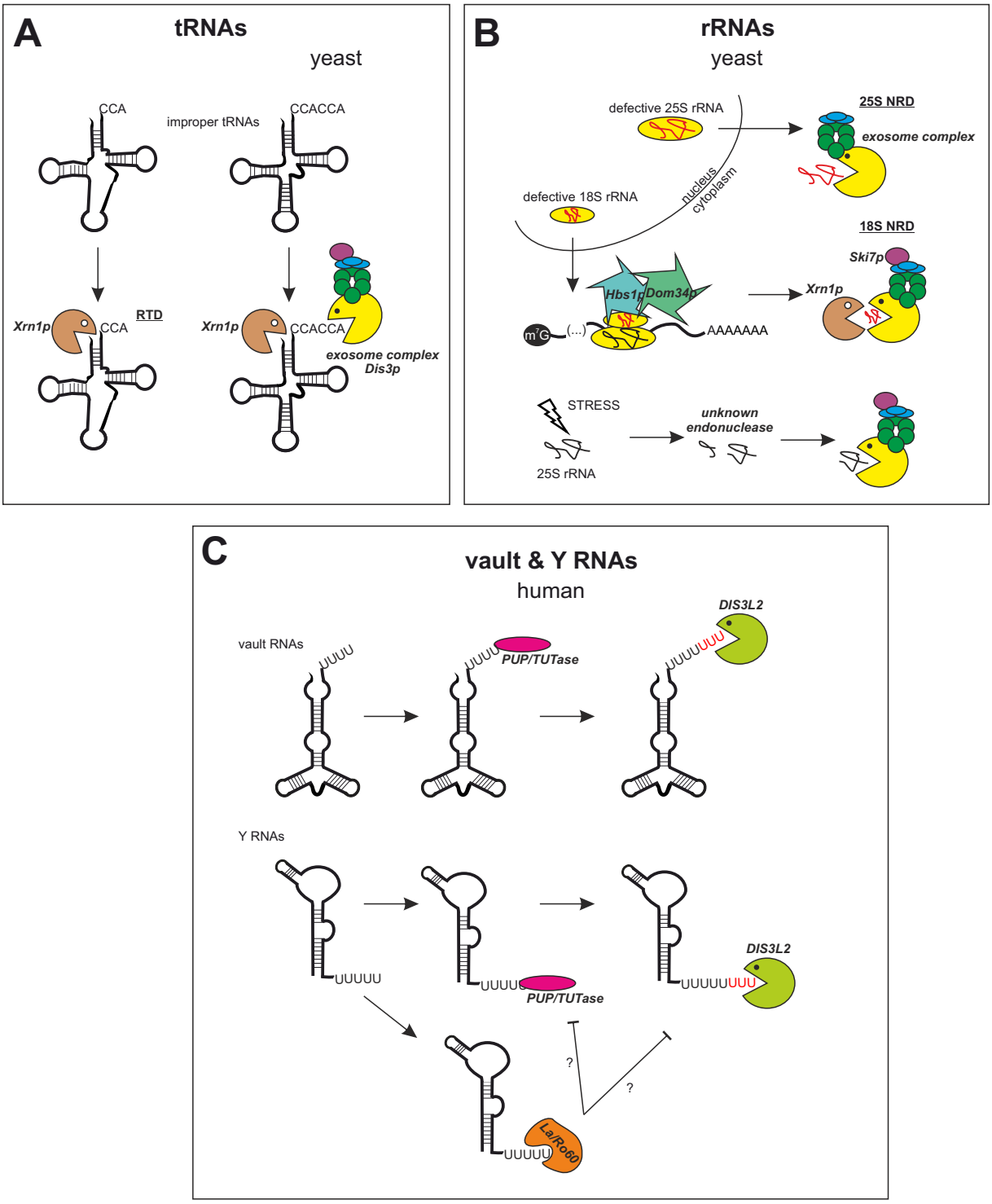

Fig. 3. Cytoplasmic pathways of tRNA (A), rRNA (B), vault RNA and Y RNA (C) degradation. See sections 2.1, 2.2, and 2.3 for details, respectively. A – aberrant yeast tRNAs can undergo RTD (rapid tRNA decay), or be removed followed addition of CCACCA sequence by tRNA terminal nucleotidyltransferase. B – defective rRNAs (18S and 25S) are degraded in yeast via respective, distinct, NRD (non-functional rRNA decay) mechanisms; in addition, stress-induced endonucleolysis can also initiate rRNA decay. C – vault and Y RNAs are short, structured, human transcripts, degraded most likely by uridylation-stimulated DIS3L2 exonucleolytic activity; La and Ro60 proteins possibly exert inhibitory effect on the decay process.

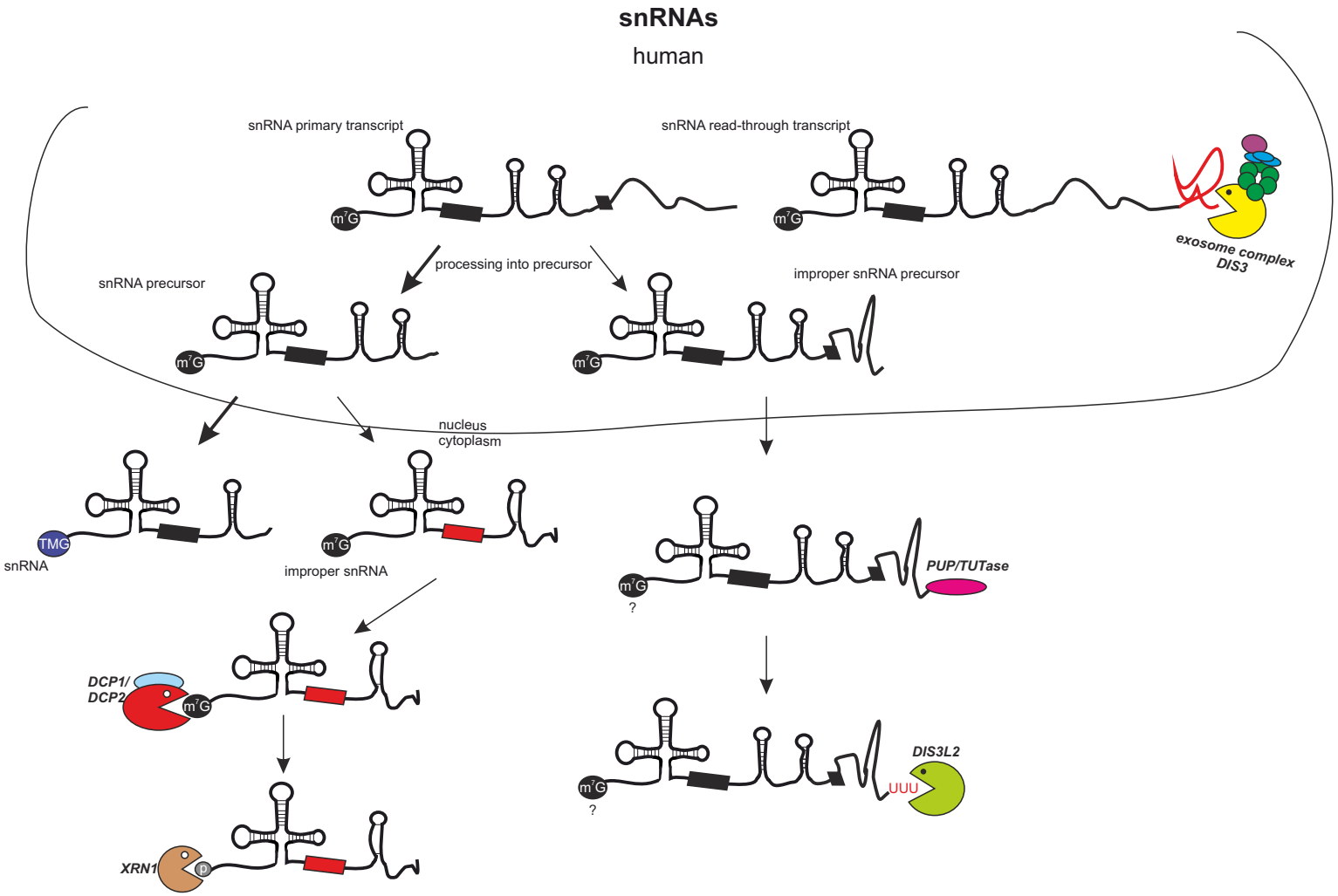

Fig. 4. Quality control of human snRNA biogenesis. See section 2.4 for a more detailed description. snRNA read-through transcripts can be degraded by the exosome/DIS3 already in the nucleus. snRNAs defective in snRNP formation are degraded in the cytoplasm by decapping/XRN1 5'-3' pathway. 3'-extended snRNA precursors may escape from the nucleus to the cytoplasm, where they are removed by DIS3L2, following uridylation. m7G – monomethylated cap; TMG – hypermethylated cap.

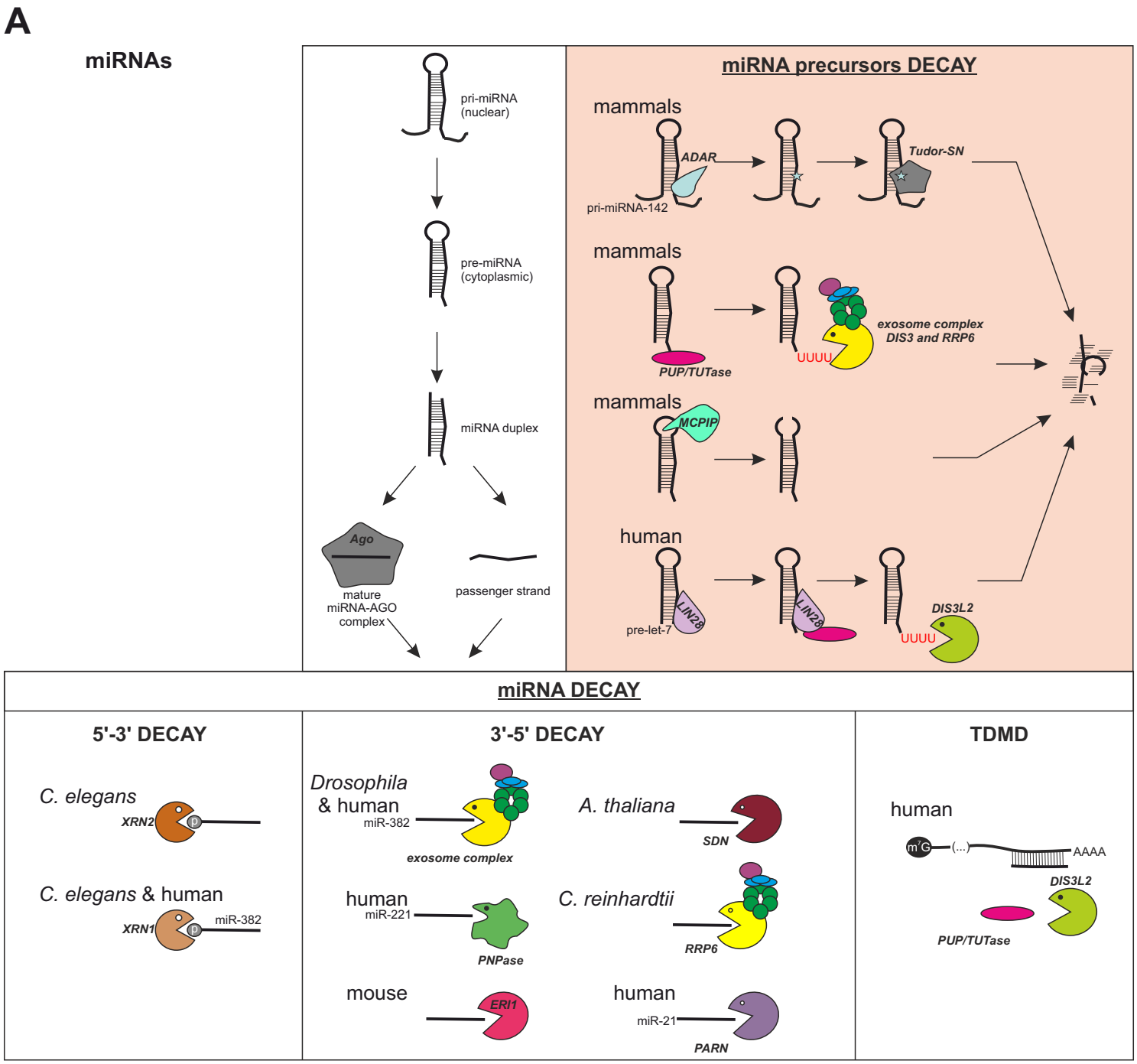
A
miRNAs
pri-miRNA (nuclear)
pre-miRNA (cytoplasmic)
miRNA duplex
Ago
mature miRNA-AGO complex
passenger strand
miRNA precursors DECAY
mammals
ADAR
pri-miRNA-142
Tudor-SN
mammals
PUP/TUTase
UUUU
exosome complex DIS3 and RRP6
mammals
MCPIP
human
pre-let-7
LIN28
LIN28
DIS3L2
UUUU
miRNA DECAY
5'-3' DECAY
C. elegans
XRN2
C. elegans & human
XRN1
miR-382
3'-5' DECAY
Drosophila & human
miR-382
exosome complex
A. thaliana
SDN
human
miR-221
PNPase
C. reinhardtii
RRP6
mouse
ERI1
human
miR-21
PARN
TDMD
human
m7G
(...)
AAAA
DIS3L2
PUP/TUTase
B
piRNAs
zebrafish
Piwi
mature piRNA-PIWI complex
Hen1
UUUU
C
endo-siRNAs
dsRNA
Drosophila
AGO
mature endo-siRNA-AGO complex
HEN1
UUUU
X. laevis
ADAR
Tudor-SN

Fig. 5. Decay pathways for pre-miRNAs and miRNAs (A), piRNAs (B) and endo-siRNAs (C). See sections 2.5, 2.6, and 2.7 for details, respectively. A – miRNA biogenesis is a multi-step pathway, beginning with the synthesis of pri-miRNAs, which are processed to pre-miRNAs in the nucleus. Pre-miRNAs are then exported to the cytoplasm and further processed to miRNA duplexes. Each of the miRNA biogenesis intermediates can undergo degradation in the cytoplasm, since pri-miRNAs are known to escape to the latter compartment. Such pri-miRNAs can be degraded by Tudor-SN, following modification by ADAR. In turn, pre-miRNAs are known to be degraded by exosome/DIS3/RRP6 in conjunction with uridylation, or undergo MCPIP endonucleolytic cleavage. Pre-miRNAs from let-7 family are oligouridylated by TUTases with the help of LIN28, and subsequently degraded by DIS3L2. Mature miRNAs can be degraded from both 5'-end (by enzymes from XRN family) and 3'-end (by various exonucleolytic activities, including exosome, RRP6, PARN, ERI1, PNPase, SDN), depending on the organism and miRNA species. In human cells, target-mediated miRNA degradation (TDMD) path, dependent on uridylation and DIS3L2 activity, was discovered. B – piRNAs are protected from degradation through association with Piwi proteins, as well as owing to Hen1-mediated 2'-O-methylation of the 3'-terminus; piRNAs lacking this modification undergo uridylation and degradation by an unknown exonuclease. C – endo-siRNAs degradation is controlled similarly to piRNAs; in addition, dsRNA being the source of endo-siRNAs can be modified by ADAR and thus targeted to degradation by Tudor-SN.

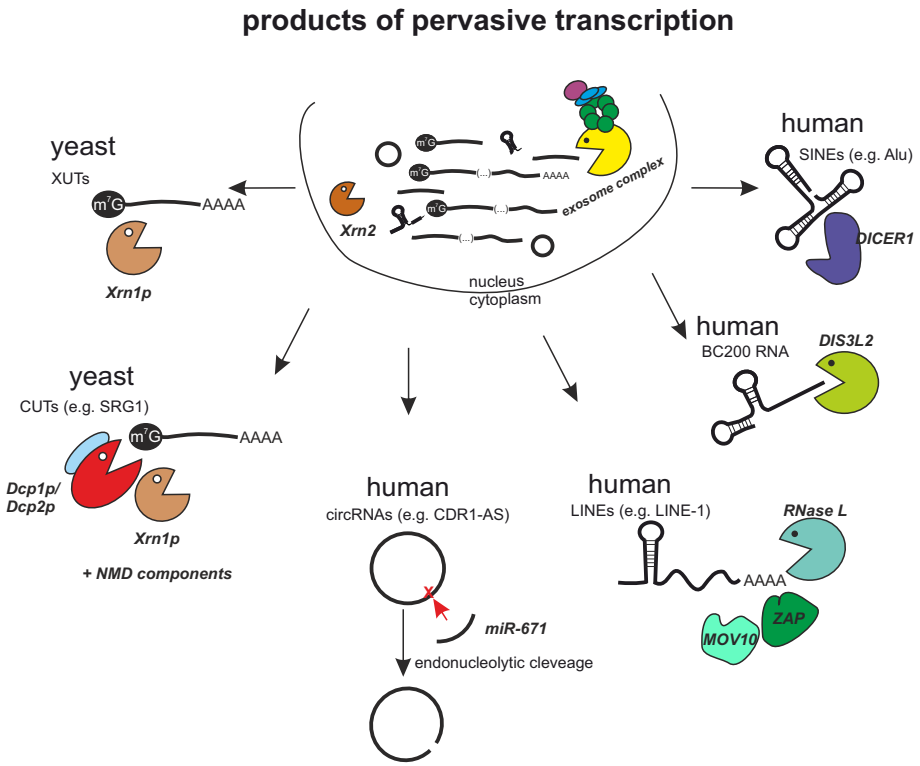

Fig. 6. Degradation of pervasive transcription products in eukaryotic cells. See section 2.8 for details. A large fraction of eukaryotic genomes is transcribed, giving rise to a variety of unstable ncRNA species, which are degraded by different mechanisms. While many of them undergo exosome- and/or Xrn2-mediated degradation already in the nucleus, some of them escape to the cytoplasm, where their decay takes place. For instance, degradation of XUTs and CUTs in yeast is dependent on Xrn1p, and decay of the latter may require also decapping enzyme and some NMD factors. CircRNAs (circular RNAs) in human cells do not have free ends, so their degradation is initiated by endonucleolytic cleavage, possibly assisted by miRNA. ncRNAs originating from repetitive DNA elements, such as LINEs or SINEs are degraded by distinct, not yet fully explored mechanisms, involving the action of RNase L, MOV10 helicase and ZAP protein (LINEs) or DICER1 (Alu family of SINEs). BC200 Alu-related element is in turn degraded with the help of DIS3L2.