REGULATION OF GENE EXPRESSION BY NONCODING RNAs

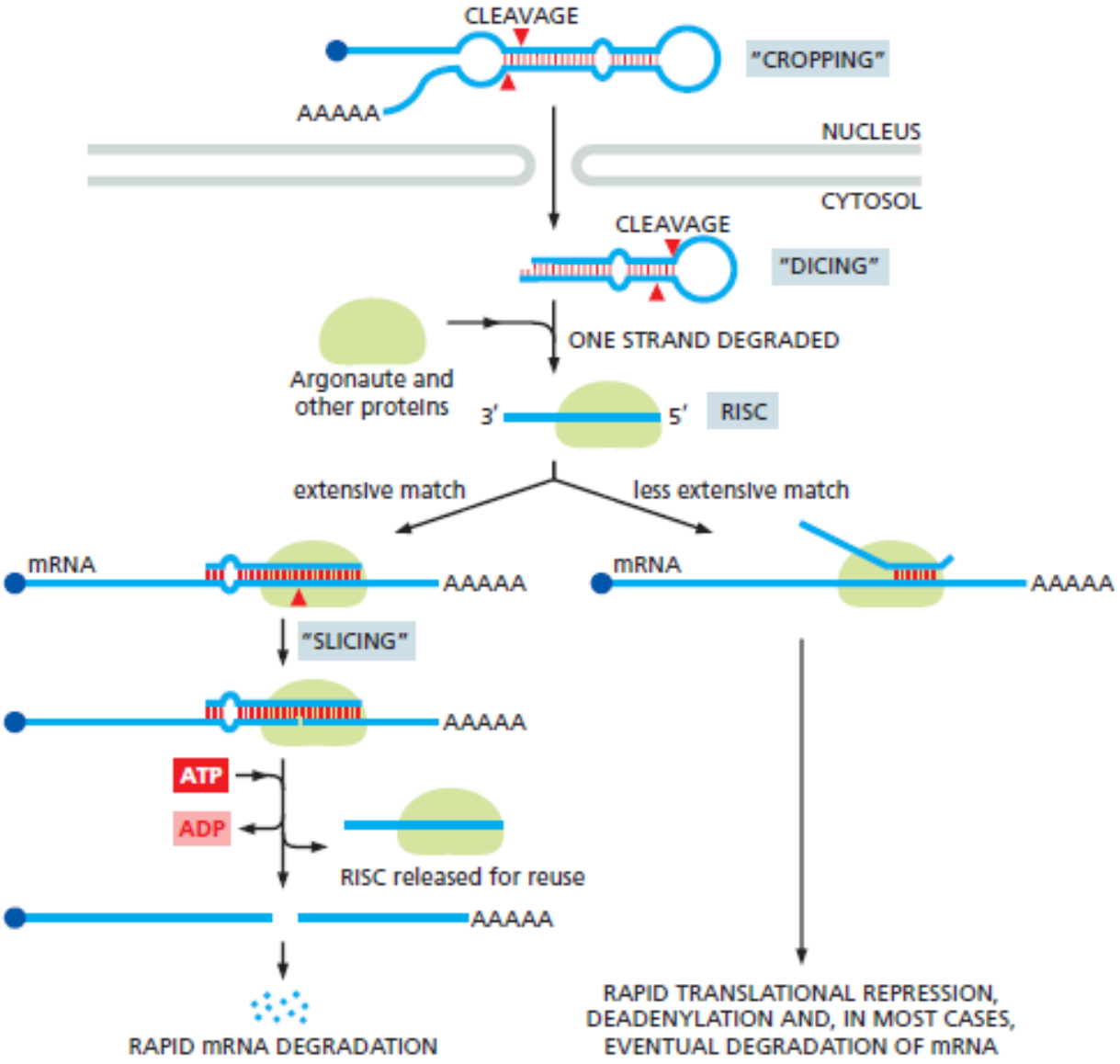
The noncoding RNAs include:

- The rRNA and tRNA molecules, which are responsible for reading the genetic code and synthesizing proteins.
- The RNA molecule in telomerase serves as a template for the replication of chromosome ends
- snRNAs direct RNA splicing.
- **Short RNAs that carry out RNA interference (RNAi)**. Here, short single-stranded RNAs (20–30 nucleotides) serve as guide RNAs that selectively bind—through complementary base-pairing—other RNAs in the cell. When the target is a mature mRNA, the small noncoding RNAs can inhibit its translation or catalyze its rapid destruction. If the target RNA molecule is in the process of being transcribed, the small noncoding RNA can bind to it and direct the formation of repressive chromatin on its attached DNA template to block further transcription

- Three classes of small noncoding RNAs work in this way— ***microRNAs (miRNAs)***, ***small interfering RNAs (siRNAs)***, and ***piwi-interacting RNAs (piRNAs)***. Although they differ in both the way the short pieces of single-stranded RNA are generated and in their ultimate functions, all three types of RNAs locate their targets through RNA–RNA base pairing, and they generally cause reductions in gene expression.

❖ miRNAs Regulate mRNA Translation and Stability

- More than 1000 different microRNAs (miRNAs) are produced from the human genome. Once made, miRNAs base-pair with specific mRNAs and fine-tune their translation and stability.
- The miRNA precursors are synthesized by **RNA polymerase II** and are **capped** and **polyadenylated**. They then **undergo a special type of processing**, after which the miRNA (typically 23 nucleotides in length) is **assembled with a set of proteins** to form an ***RNA-induced silencing complex, or RISC***. Once formed, the RISC seeks out its target mRNAs by searching for complementary nucleotide sequences



The precursor miRNA, through complementary base pairing between one part of its sequence and another, forms a double-strand structure. This RNA is “cropped” while still in the nucleus and then exported to the cytosol, where it is further cleaved (“diced”) by the **Dicer** enzyme to form the miRNA proper.

Argonaute, in conjunction with other components of RISC, initially associates with both strands of the miRNA and then cleaves and discards one of them. The other strand guides RISC to specific mRNAs through base-pairing.

- In animals, the extent of base-pairing is typically at least seven nucleotide pairs, and this pairing most often occurs in the 3′ UTR of the target mRNA. Once an mRNA has been bound by an miRNA, several outcomes are possible.
- **If the base-pairing is extensive** (which is unusual in humans but common in many plants), the mRNA is cleaved (*sliced*) by the Argonaute protein, effectively removing the mRNA's poly-A tail and exposing it to exonucleases.
- After cleavage of the mRNA, the RISC with its associated miRNA is released, and it can seek out additional mRNAs. Thus, a single miRNA can act catalytically to destroy many complementary mRNAs. These miRNAs can thus be thought of as guide sequences that repeatedly bring destructive nucleases into contact with specific mRNAs.

- If the base-pairing between the miRNA and the mRNA is less extensive (as observed for most human miRNAs), Argonaute does not slice the mRNA; rather, translation of the mRNA is repressed by the recruitment of deadenylase enzymes—which shorten the poly-A tail—and other proteins that directly block access of the mRNA to the proteins needed to translate it