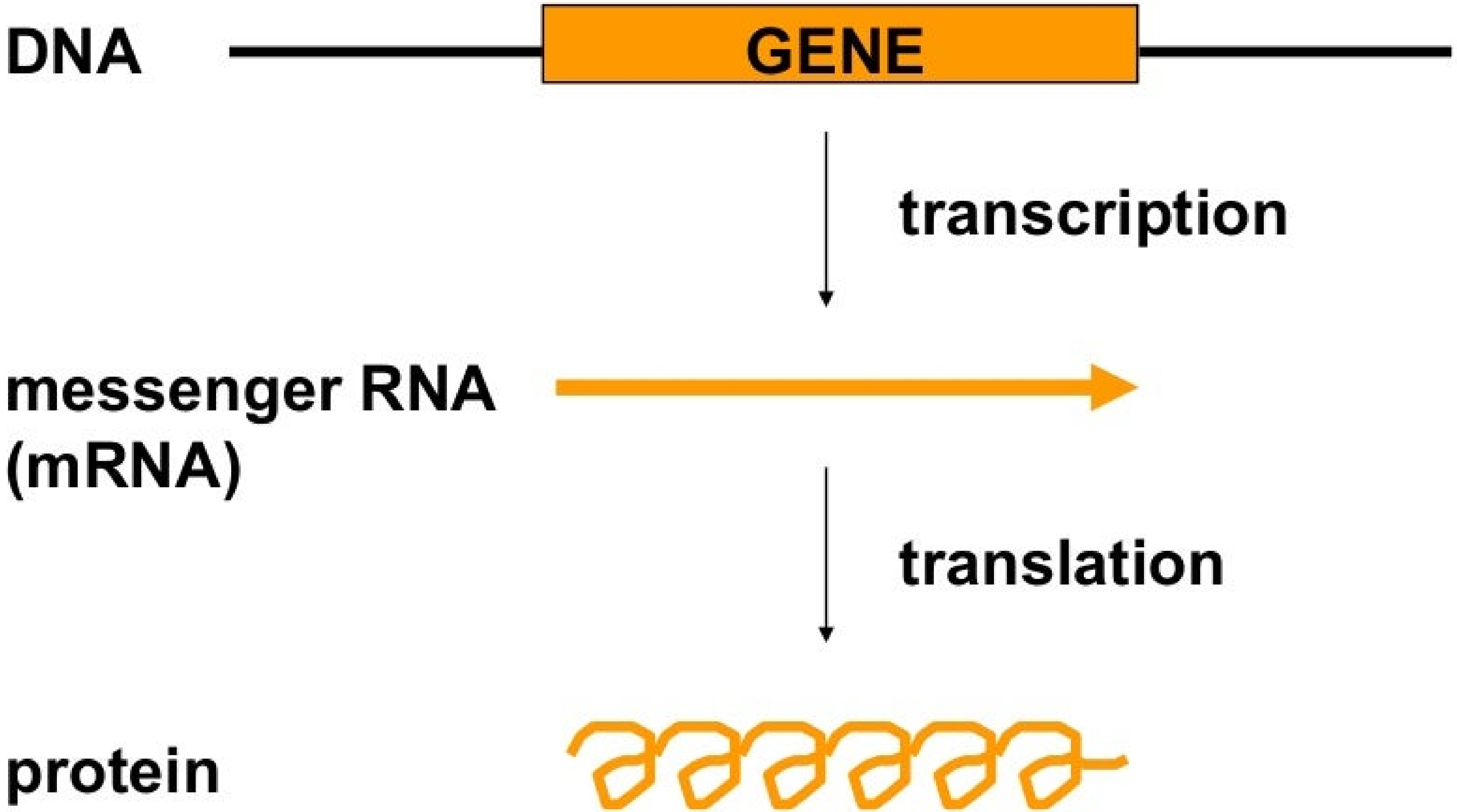
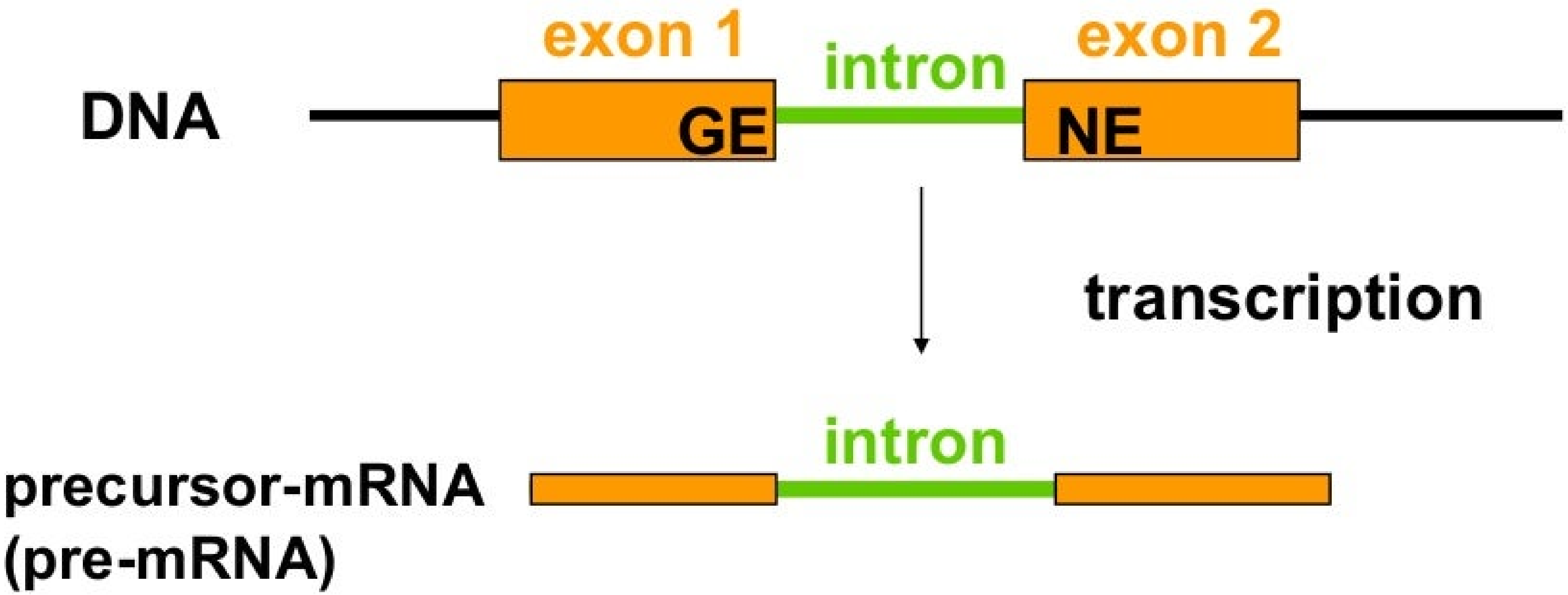
What is RNA splicing?

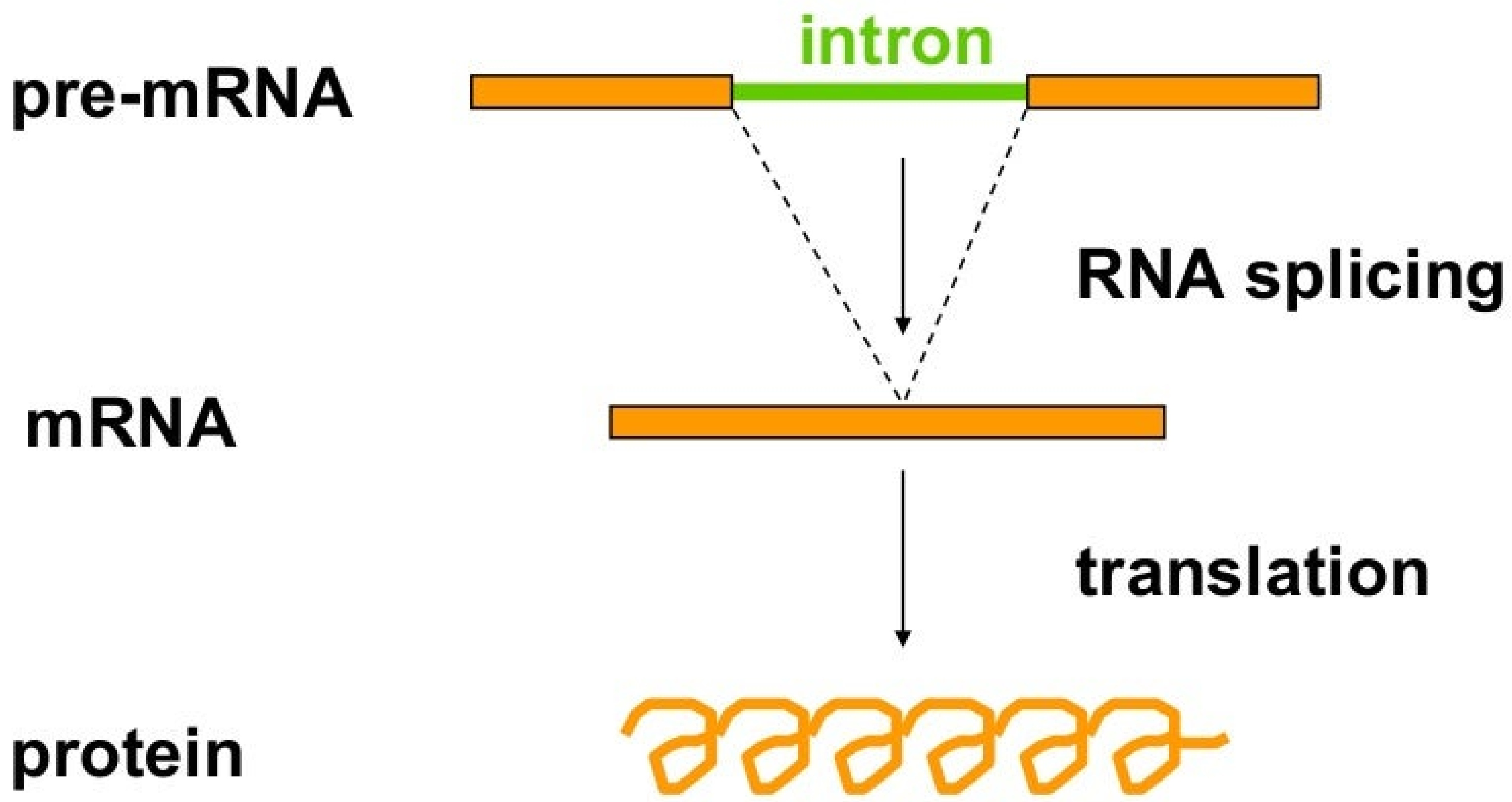
Genetic information is transferred from genes to the proteins they encode via a "messenger" RNA intermediate



Most genes have their protein-coding information interrupted by non-coding sequences called "introns". The coding sequences are then called "exons"



The intron is also present in the RNA copy of the gene and must be removed by a process called "RNA splicing"



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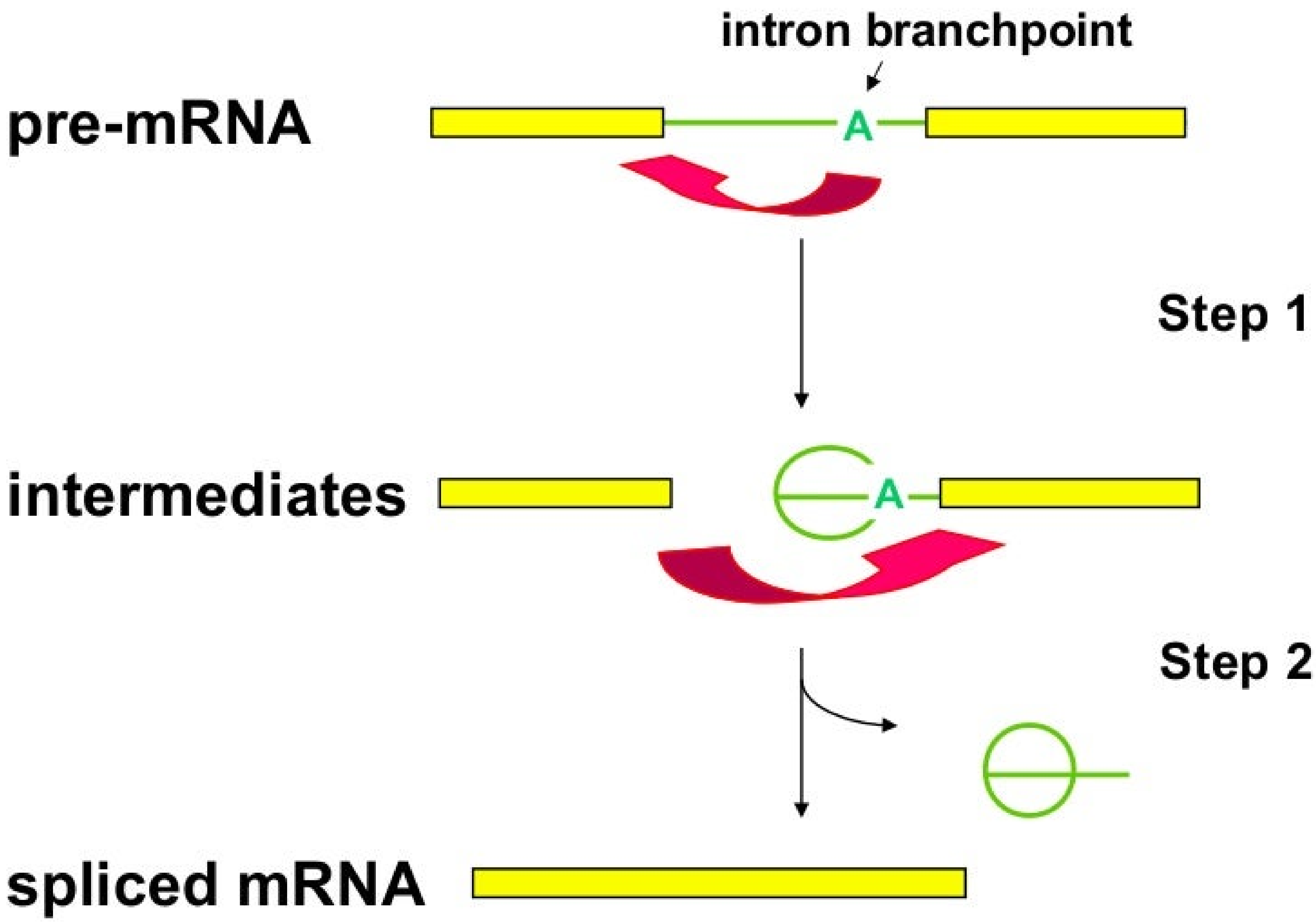
Splicing a pre-mRNA involves two reactions



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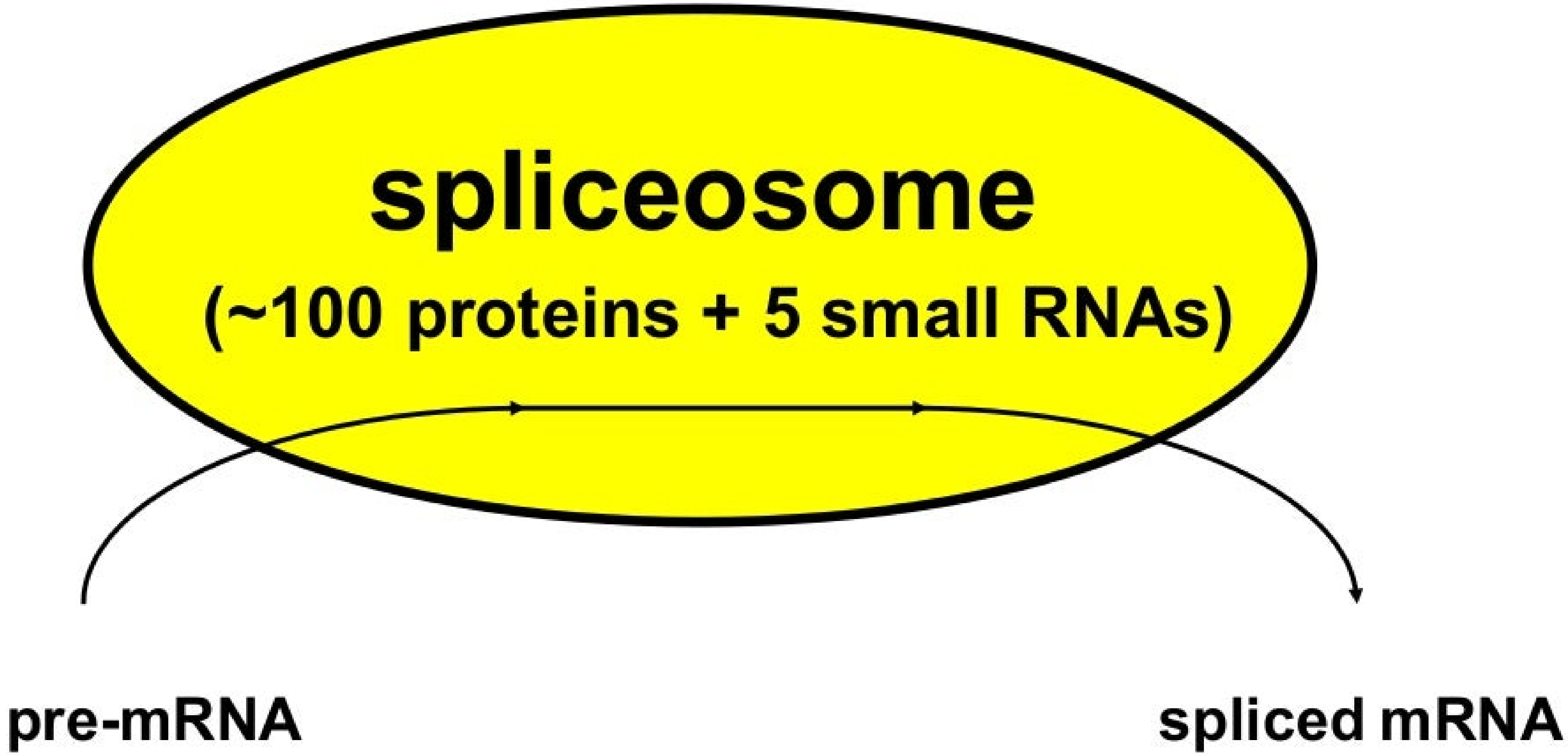
Splicing occurs in a "spliceosome" an RNA-protein complex (simplified)

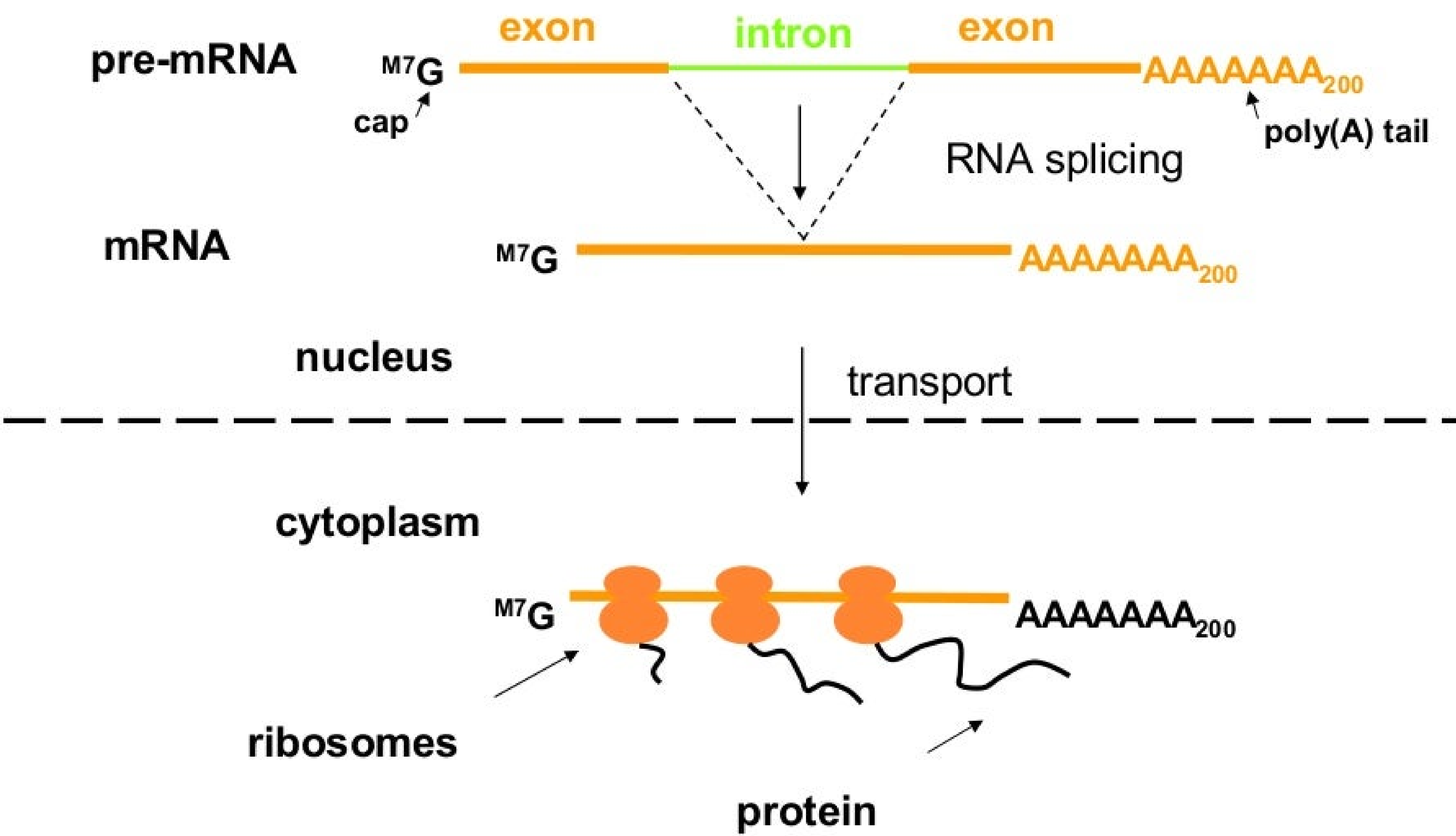


Splicing works similarly in different organisms, for example in yeast, flies, worms, plants and animals.

RNA is produced in the nucleus of the cell. The mRNA has to be transported to the cytoplasm to produce proteins

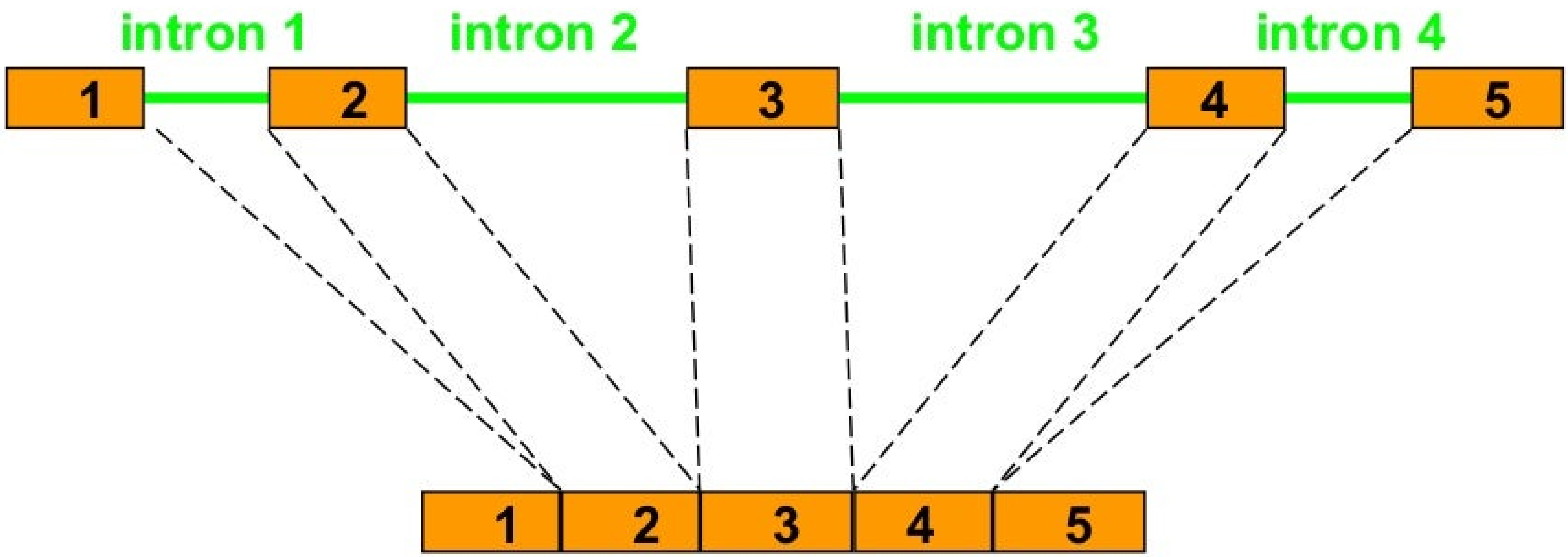
Ribosomes are RNA-protein machines that make proteins, translating the coding information in the mRNA

Pre-messenger RNA Processing



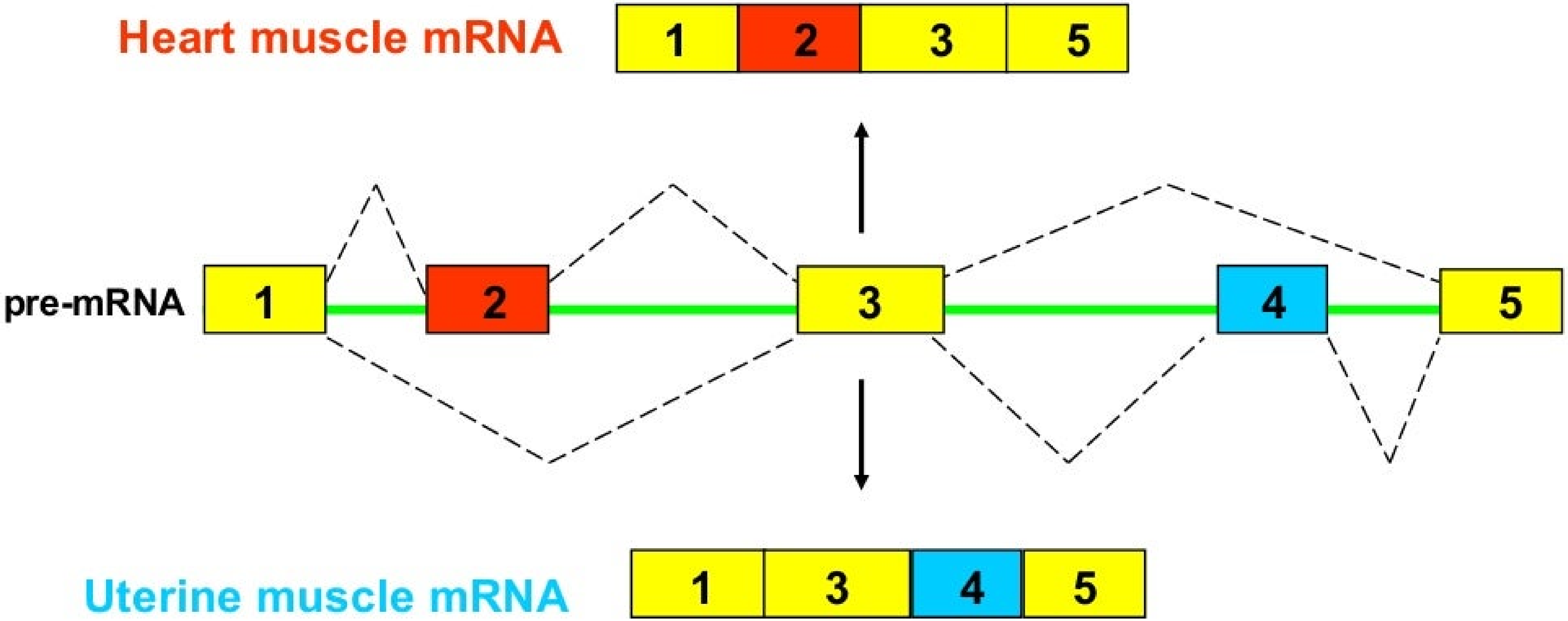
Alternative splicing

In humans, many genes contain multiple introns



Usually all introns must be removed before the mRNA can be translated to produce protein

However, multiple introns may be spliced differently in different circumstances, for example in different tissues.

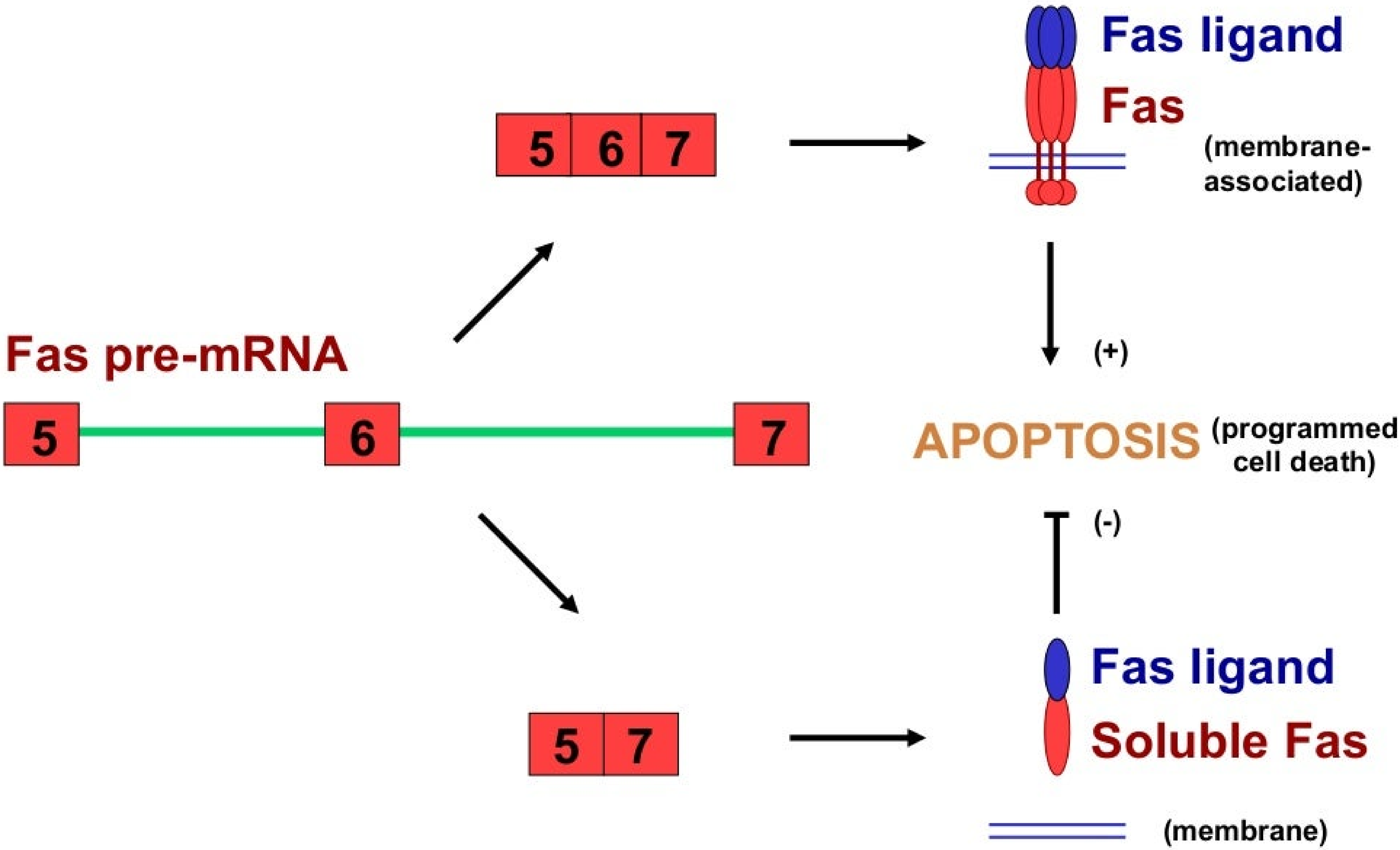


Thus one gene can encode more than one protein. The proteins are similar but not identical and may have distinct properties. This is important in complex organisms

Different signals in the pre-mRNA and different proteins cause spliceosomes to form in particular positions to give alternative splicing

We are studying how mRNAs and proteins interact in order to understand how these machines work in general and, in particular, how RNA splicing is regulated as it affects which proteins are produced in each cell and tissue in the body.

Alternative splicing can generate mRNAs encoding proteins with different, even opposite functions



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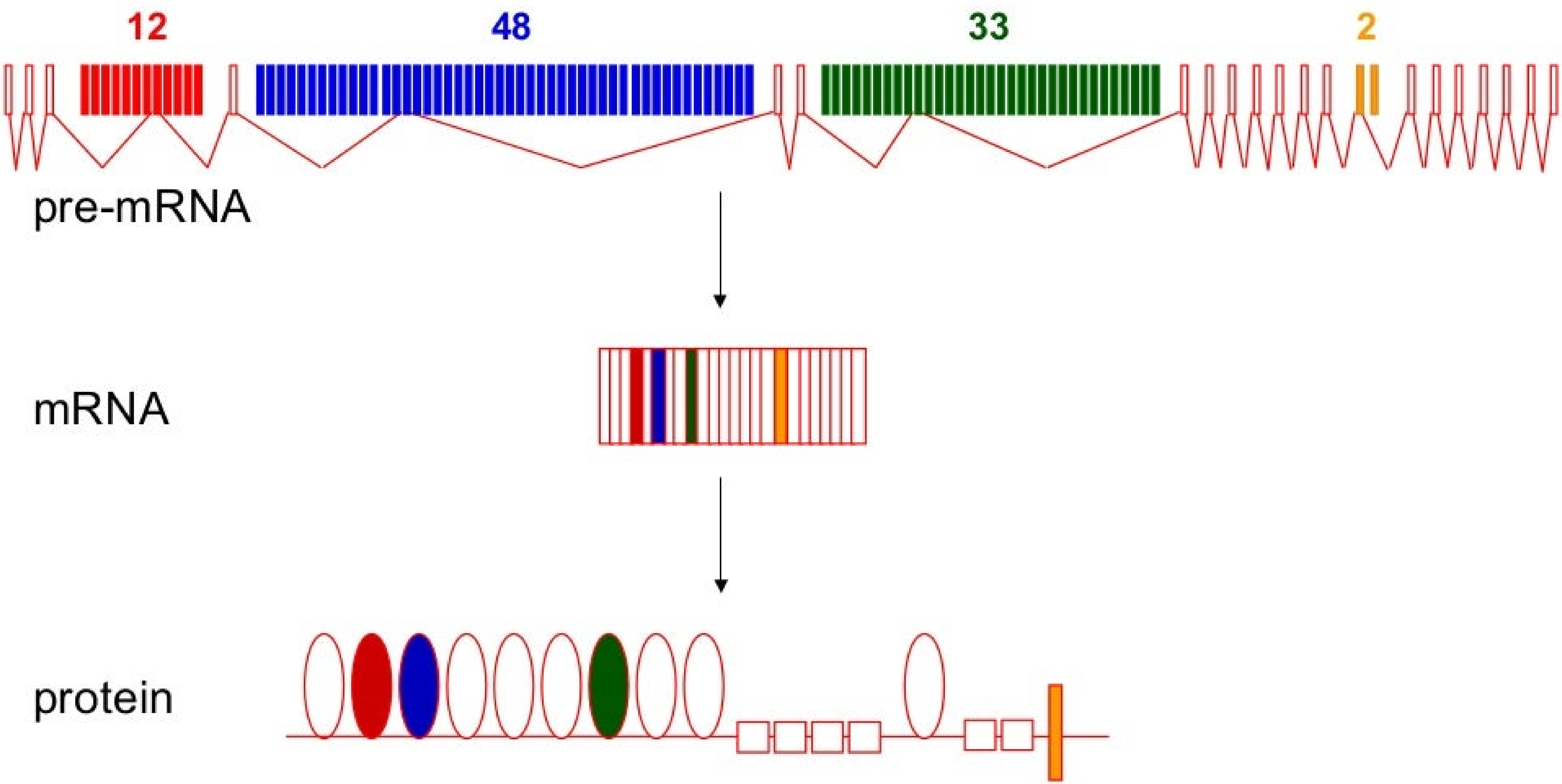
Alternative splicing can generate tens of thousands of mRNAs from a single primary transcript

Combinatorial selection of one exon at each of four variable regions generates more than 38,000 different mRNAs and proteins in the Drosophila cell adhesion molecule Dscam



The protein variants are important for wiring of the nervous system and for immune response

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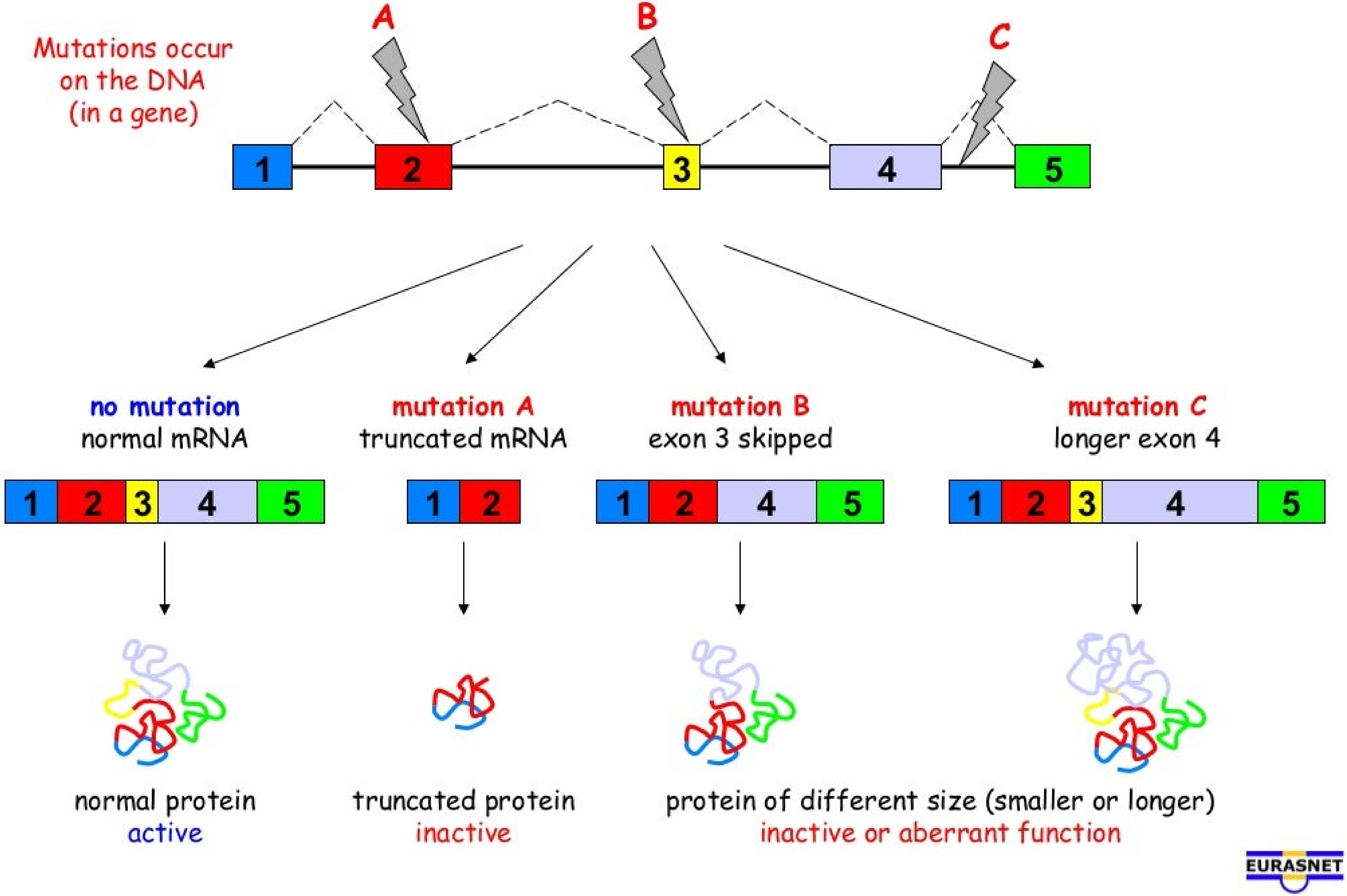
Examples of the potential consequences of mutations on splicing



Pathologies resulting from aberrant splicing can be grouped in two major categories

- Mutations affecting proteins that are involved in splicing
  Examples: Spinal Muscular Atrophy
  Retinitis Pigmentosa
  Myotonic Dystrophy

- Mutations affecting a specific messenger RNA and disturbing its normal splicing pattern
  Examples: ß-Thalassemia
  Duchenne Muscular Dystrophy
  Cystic Fibrosis
  Frasier Syndrome
  Frontotemporal Dementia and Parkinsonism

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Therefore, understanding the mechanism of RNA splicing in normal cells and how it is regulated in different tissues and at different stages of development of an organism is essential in order to develop strategies to correct aberrant splicing in human pathologies