SnapShot: Formation of mRNPs

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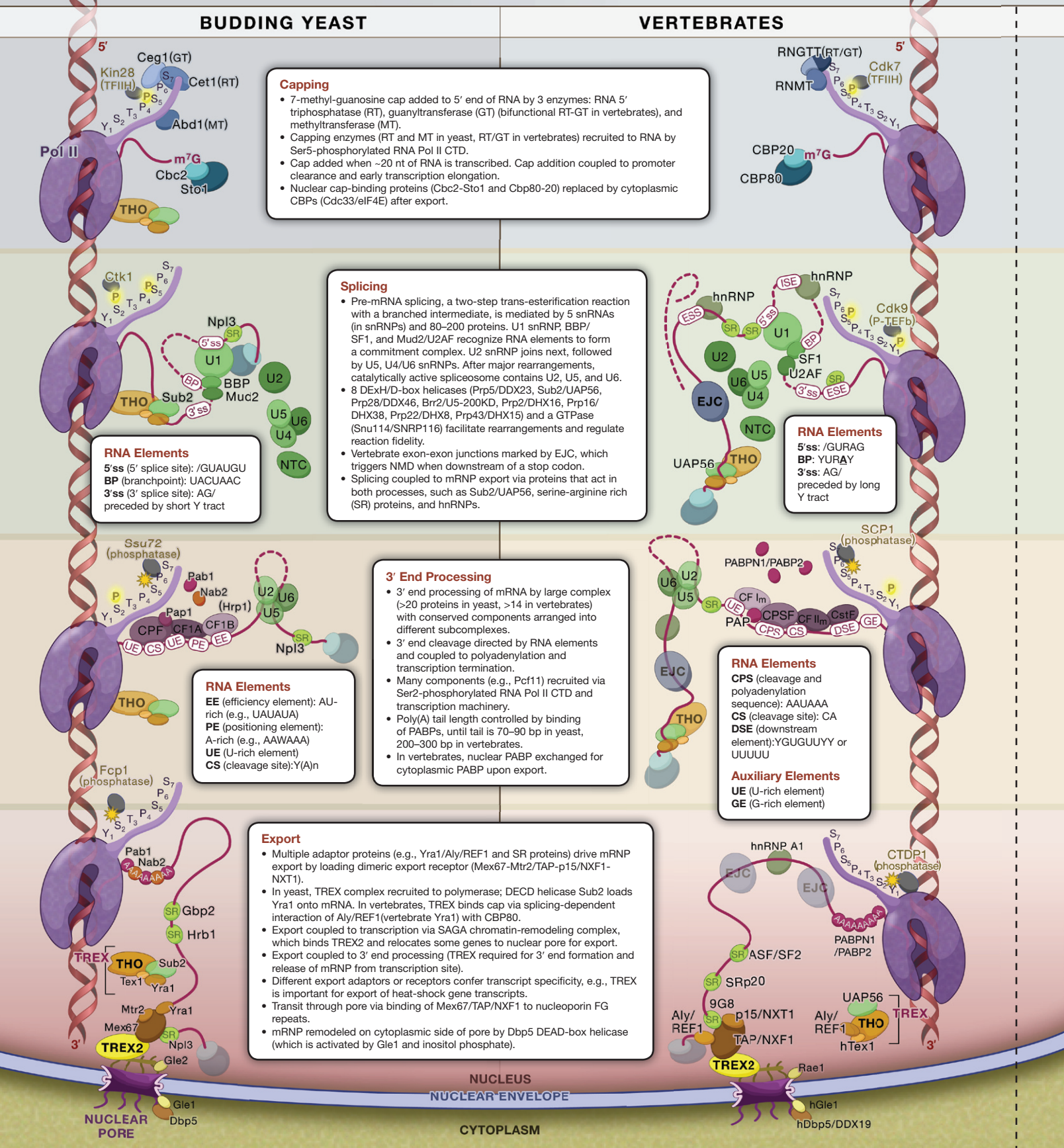
Cell



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The biosynthesis of a functional messenger RNA (mRNA) requires multiple covalent modifications of the nascent transcript, including 5′ capping, splicing, and generation of a polyadenylated 3′ end. These steps, collectively termed mRNA processing, generate an mRNA that must then be delivered to the nuclear pore, where it is exported to the cytoplasm for translation. This SnapShot provides a broad overview of the major pathways for these nuclear steps of gene expression in yeast and vertebrates. For ease of presentation, these steps are partitioned into four sets of reactions, but it is important to note that these processes are generally tightly coupled physically, temporally, and often functionally. For example, the addition of the m^7G cap to the 5′ end of the mRNA transcript occurs early but is required for most of the downstream steps in mRNA processing and export. Similarly, 3′ end processing promotes the export, stability, and translation of the mRNA. Importantly, although they can be uncoupled in vitro, most of the processing reactions occur cotranscriptionally in vivo. Consistent with this, the phosphorylation state of the heptad repeats (tyrosine-serine-threonine-proline-serine-proline-serine, YSTPSPS, repeated 26 times in budding yeast and 52 times in vertebrates) on the carboxy-terminal domain (CTD) of the largest subunit of RNA polymerase II plays an important role in recruiting and coordinating the activities of the various RNA-processing machineries. Although many regulatory factors and processes are conserved between yeast and vertebrates, it should be noted that vertebrates have longer, more numerous introns and more degenerate consensus sequences and can undergo alternative splicing, which is mediated in part by the binding of various SR proteins and hnRNPs to exonic and intronic enhancers and silencers (ESE, ESS, ISE, and ISS).

Because nascent mRNAs exist as complex ribonucleoprotein particles (RNPs) with a highly dynamic constellation of associated proteins, the precise composition of a biological substrate for a given mRNA-processing reaction is difficult to define. In any case, the complex interplay between the nascent RNA structure, the multiple RNA-binding proteins (with varied sequence preferences), and the large splicing and 3′ end processing machineries provides rich opportunities for regulation. It has been estimated that >90% of human genes are alternatively spliced and >50% have alternative 3′ ends, which generally arises from competition between weak and strong binding sites on the nascent RNA transcripts and competition between the splicing and poly(A) machineries. Although not shown here, these RNA-processing steps are under quality control. For example, improperly processed mRNPs can be selectively retained and degraded in the nucleus by the nuclear exosome. Thus, the emerging picture of mRNP formation is one of a dynamic, regulated, and coordinated series of processing steps that contribute significantly to the overall control of gene expression.

Abbreviations and Definitions

BBP, branchpoint binding protein; CF, cleavage factor; CPSF, cleavage and polyadenylation specificity factor; CStF, cleavage stimulation factor; CTD, carboxy-terminal domain (of the largest subunit of RNA polymerase II); DExD/H-box helicase, a member of a family of ATP-dependent, RNA-stimulated helicases characterized by a DExD/H motif, among others; EJC, exon junction complex; ESE, exonic splicing enhancer; ESS, exonic splicing silencer; hnRNP, heterogeneous ribonucleoprotein particle; ISE, intronic splicing enhancer; ISS, intronic splicing silencer; NMD, nonsense-mediated mRNA decay; NTC, prp nineteen-associated complex; PABP, poly(A) binding protein; Pol II, RNA polymerase II; R, purine nucleotide (G or A); snRNP, small nuclear ribonucleoprotein particle; SR, serine-arginine rich protein; TFIIH, RNA polymerase II transcription factor H; TREX, transcription and export complex; W, “weak binding” nucleotide (A or U); Y, pyrimidine nucleotide (C or U).

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