How is polyadenylation restricted to 3' untranslated regions?

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Abstract

Polyadenylation occurs at numerous sites within 3' untranslated regions (3' UTRs) but rarely within coding regions. How does Pol II travel through long coding regions without generating poly(A) sites, yet then permits promiscuous polyadenylation once it reaches the 3' UTR? The cleavage/polyadenylation (CpA) machinery preferentially associates with 3' UTRs, but it is unknown how its recruitment is restricted to 3' UTRs during Pol II elongation. Unlike coding regions, 3' UTRs have long AT-rich stretches of DNA that may be important for restricting polyadenylation to 3' UTRs. Recognition of the 3' UTR could occur at the DNA (AT-rich), RNA (AU-rich), or RNA:DNA hybrid rU:dA- and/or rA:dT-rich) level. Based on the nucleic acid critical for 3' UTR recognition, there are three classes of models, not mutually exclusive, for how the CpA machinery is selectively recruited to 3' UTRs, thereby restricting where polyadenylation occurs: 1) RNA-based models suggest that the CpA complex directly (or indirectly through one or more intermediary proteins) binds long AU-rich stretches that are exposed after Pol II passes through these regions. 2) DNA-based models suggest that the AT-rich sequence affects nucleosome depletion or the elongating Pol II machinery, resulting in dissociation of some elongation factors and subsequent recruitment of the CpA machinery. 3) RNA:DNA hybrid models suggest that preferential destabilization of the Pol II elongation complex at rU:dA- and/or rA:dT-rich duplexes bridging the nucleotide addition and RNA exit sites permits preferential association of the CpA machinery with 3' UTRs. Experiments to provide evidence for one or more of these models are suggested.

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