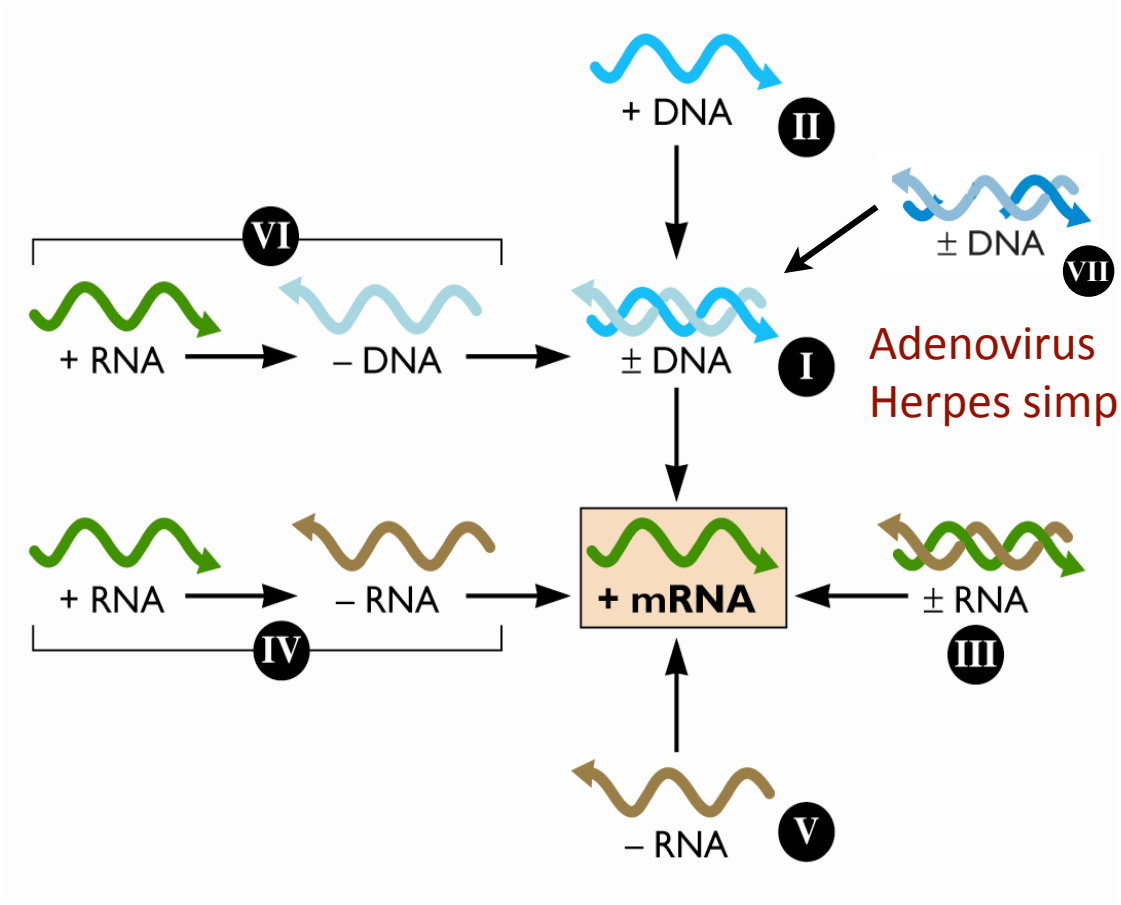
Transcription and RNA processing

Lecture 7
Biology W3310/4310
Virology
Spring 2016

It is possible that Nature invented DNA for the purpose of achieving regulation at the transcriptional rather than at the translational level
—ALAN CAMPBELL

Parvovirus



Hepatitis B virus

Retrovirus

Adenovirus

Herpes simplex virus

Poliovirus

Reovirus

Rotavirus

Influenza virus

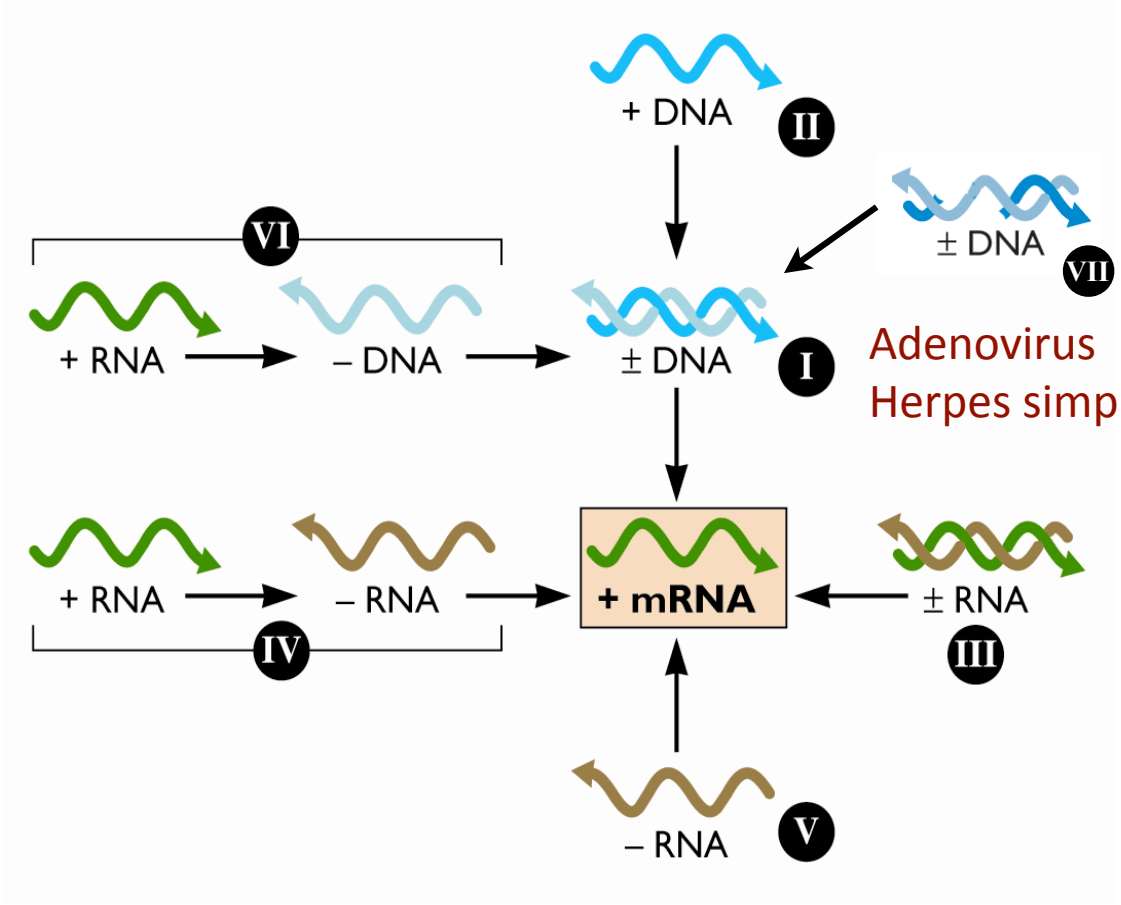
Ebola virus

Eukaryotic DNA-dependent RNA polymerases

Enzyme	Cellular RNA	Viral RNA
RNA pol I	Pre-rRNA	None known
RNA pol II	Pre-mRNA Pri-miRNA SnRNA	Pre-mRNA Pri-miRNA HDV genome RNA and mRNA
RNA pol III	Pre-tRNAs 5S rRNA U6 snRNA	Ad-2 VA RNAs EBV EBER RNAs MHV68 pri-miRNA

Transcription is the first biosynthetic reaction to occur in cells infected with dsDNA viruses

Parvovirus



Hepatitis B virus

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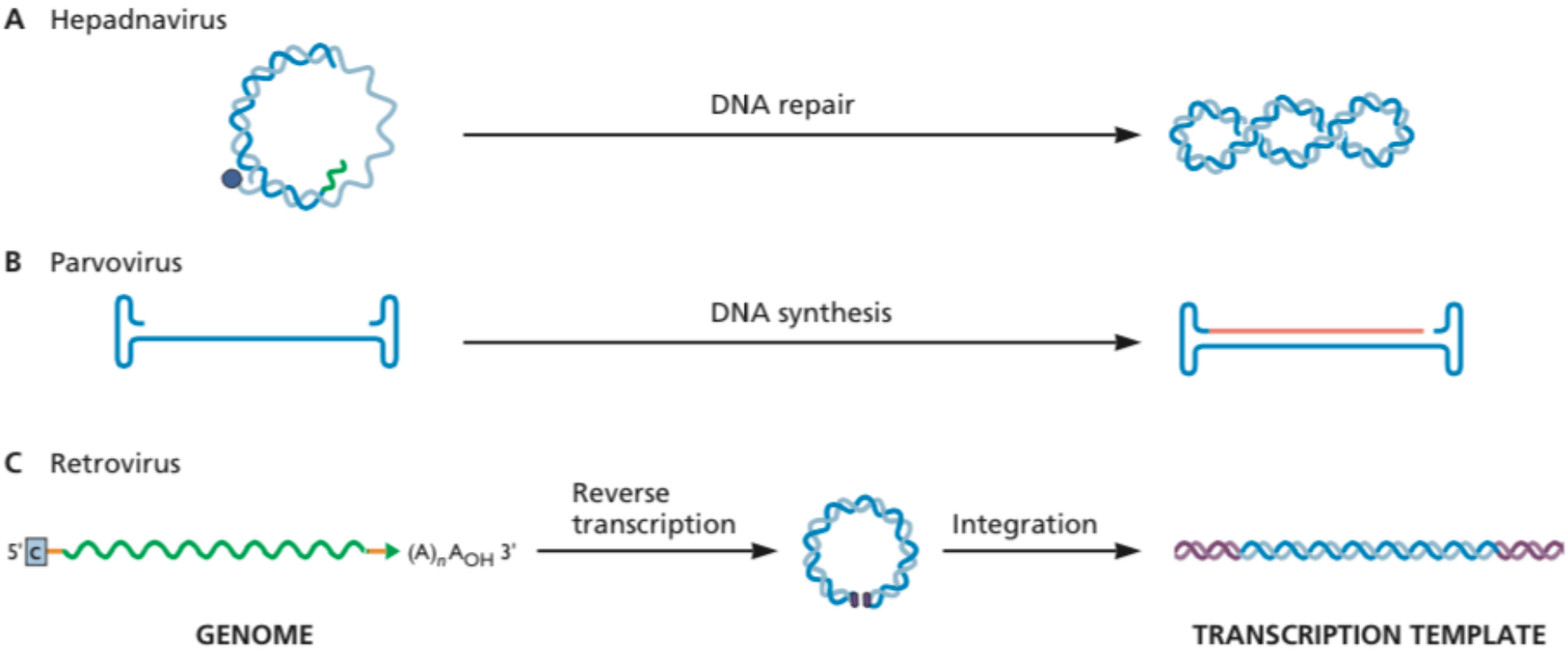
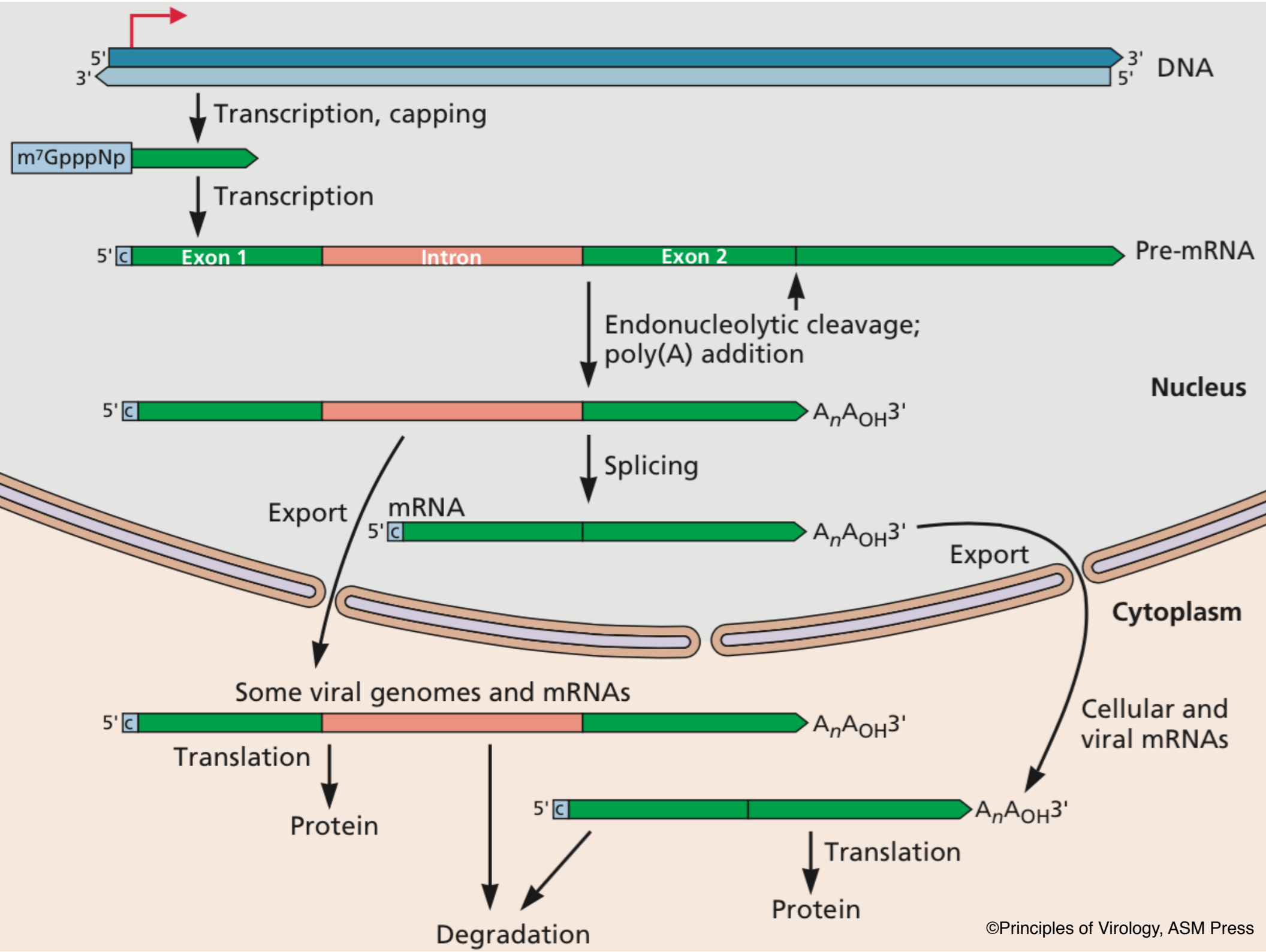
Conversion of viral genomes to templates for transcription




5'
3'
DNA
3'
5'
Transcription, capping
m7GpppNp
Transcription
5'
c
Exon 1
Intron
Exon 2
Pre-mRNA
Endonucleolytic cleavage;
poly(A) addition
Nucleus
5'
c
AnAOH3'
Splicing
Export
mRNA
5'
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AnAOH3'
Export
Cytoplasm
Some viral genomes and mRNAs
5'
c
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Translation
Protein
Degradation
Cellular and
viral mRNAs
5'
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AnAOH3'
Translation
Protein
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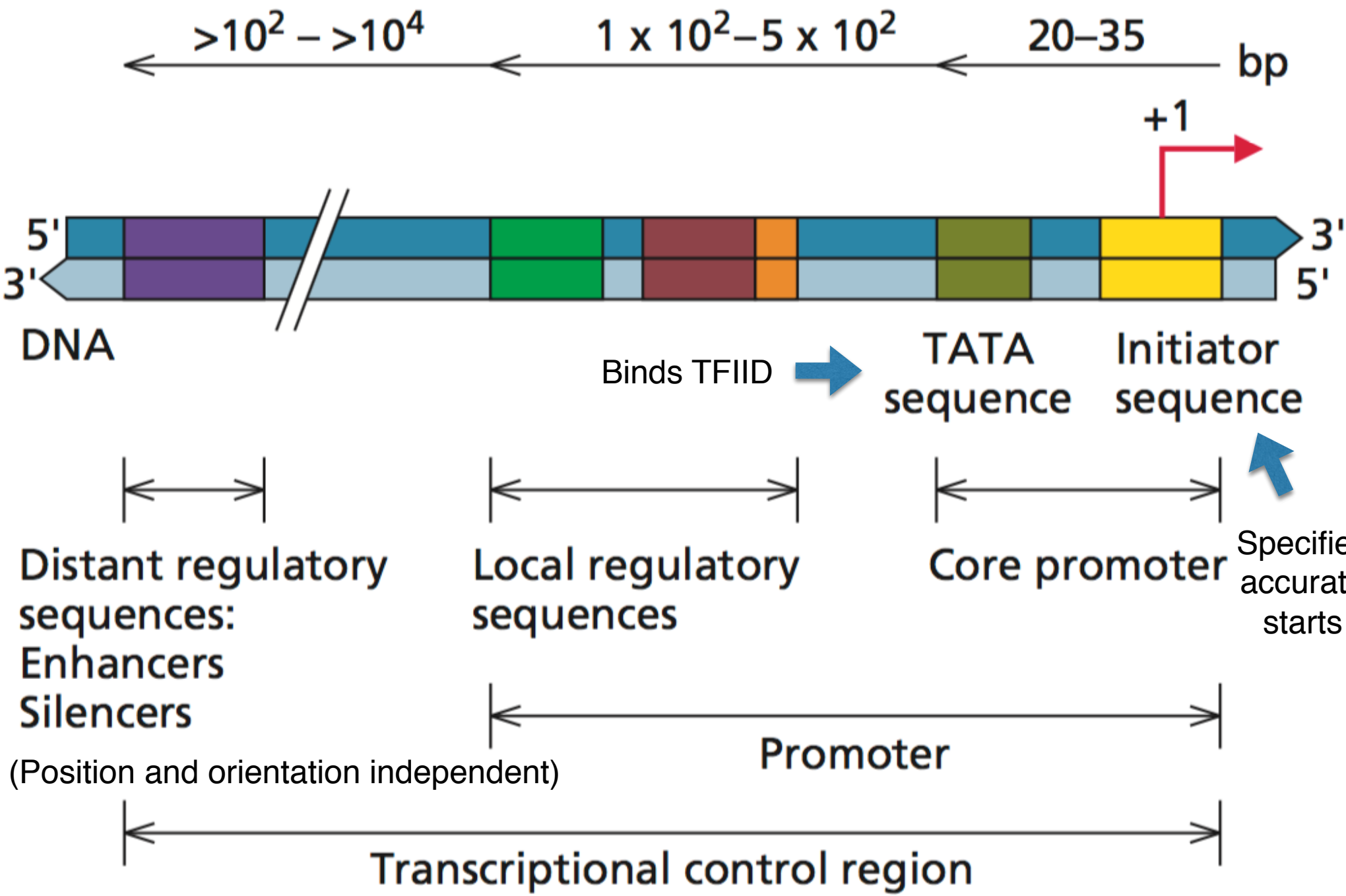
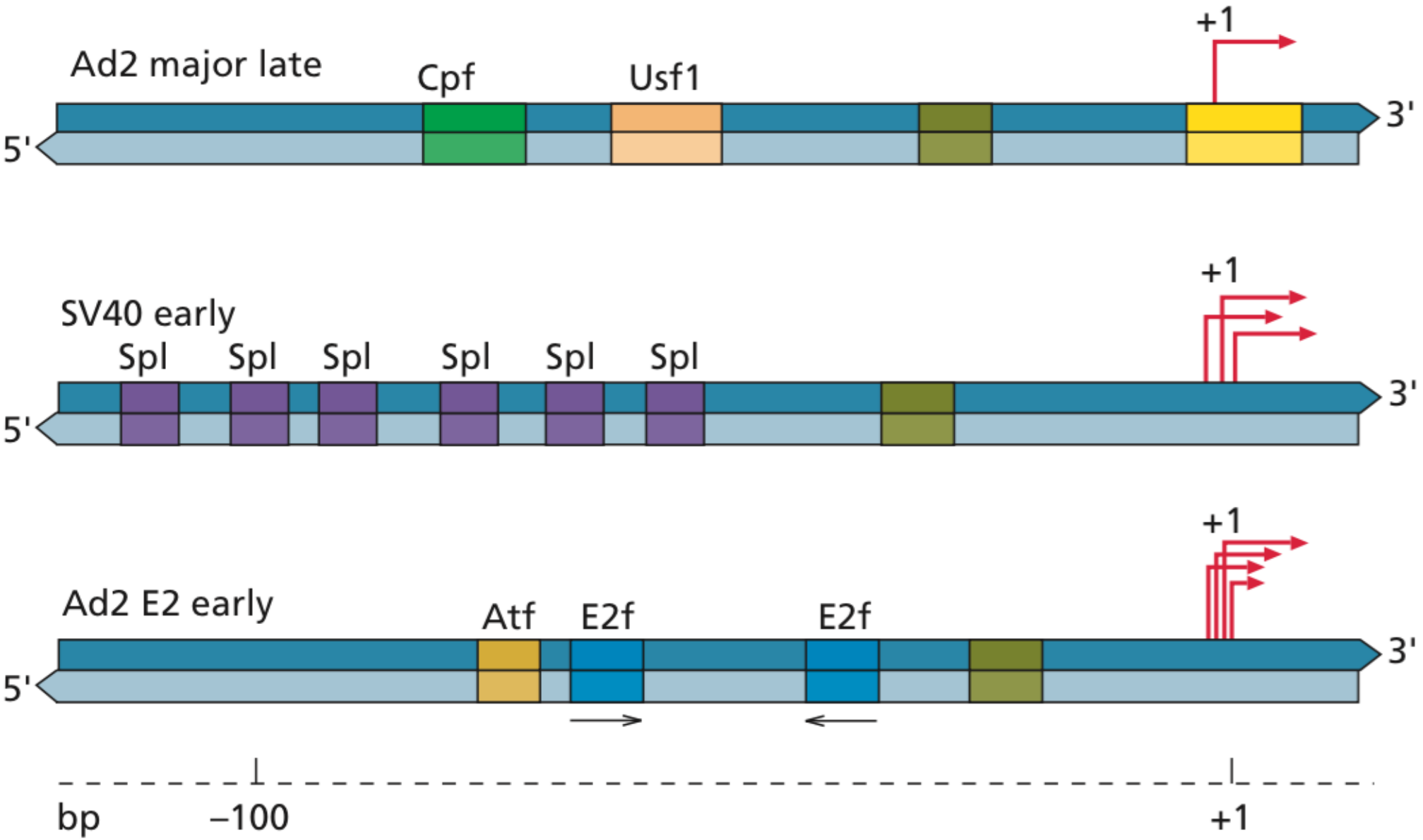
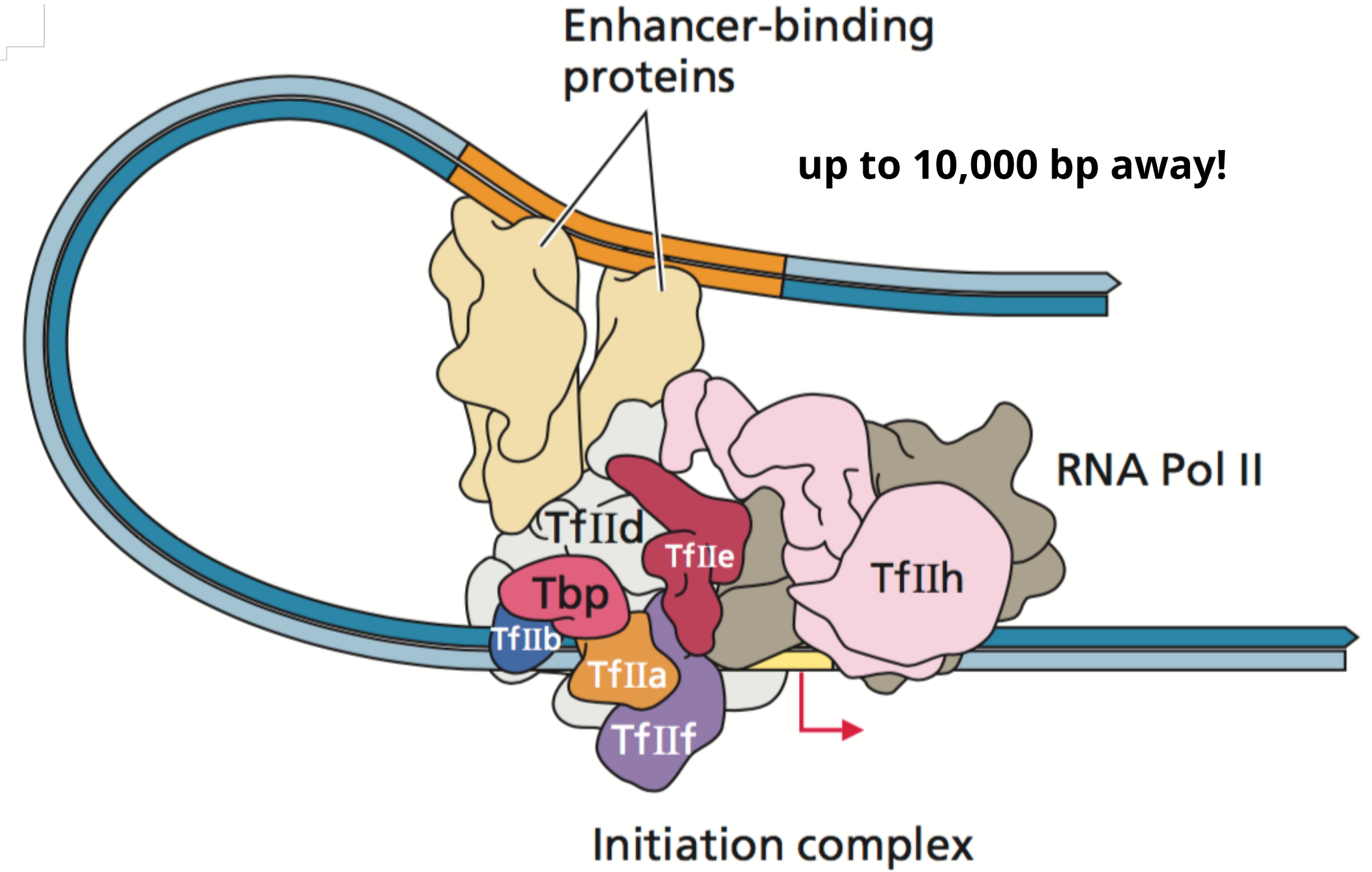


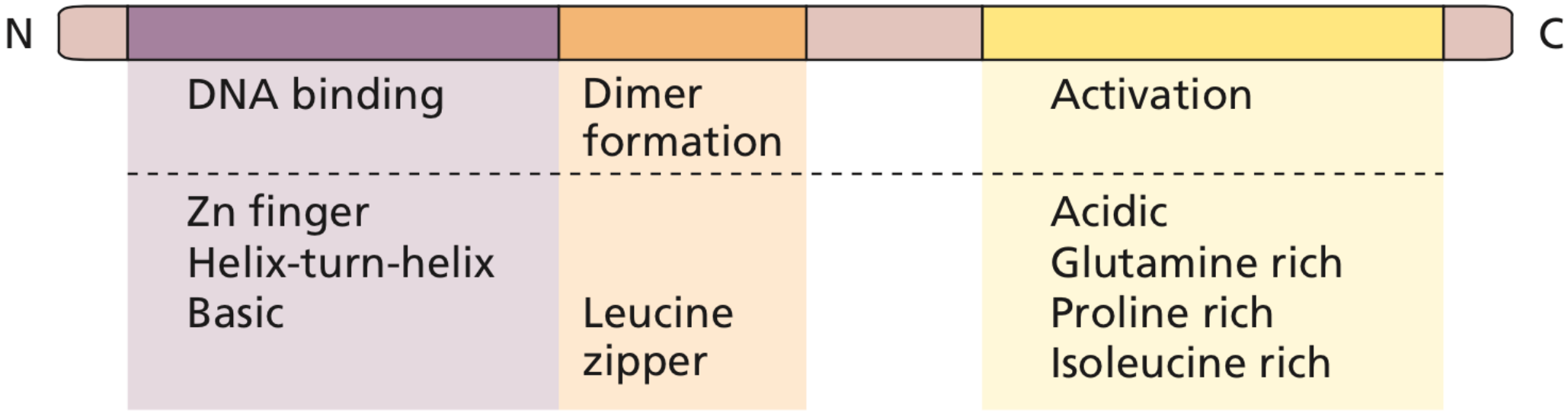
Regulatory sequences in transcriptional control regions





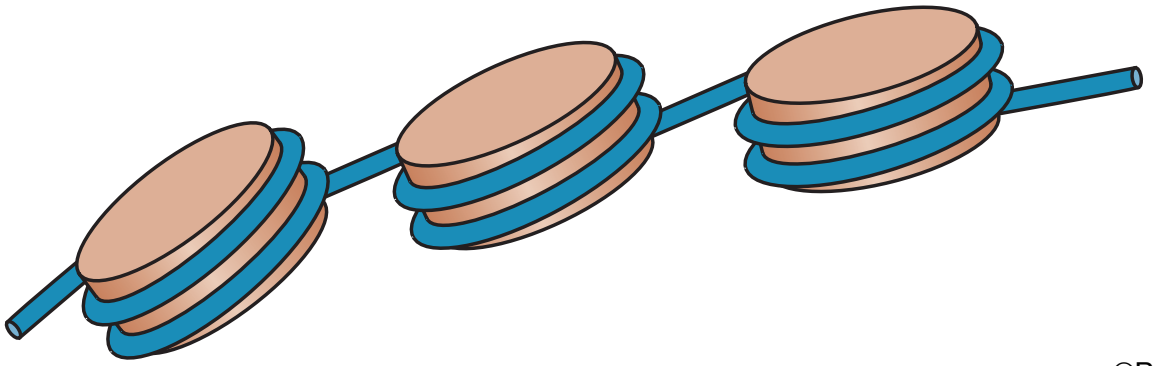
Enhances initiation!

Sequence-specific transcriptional activators

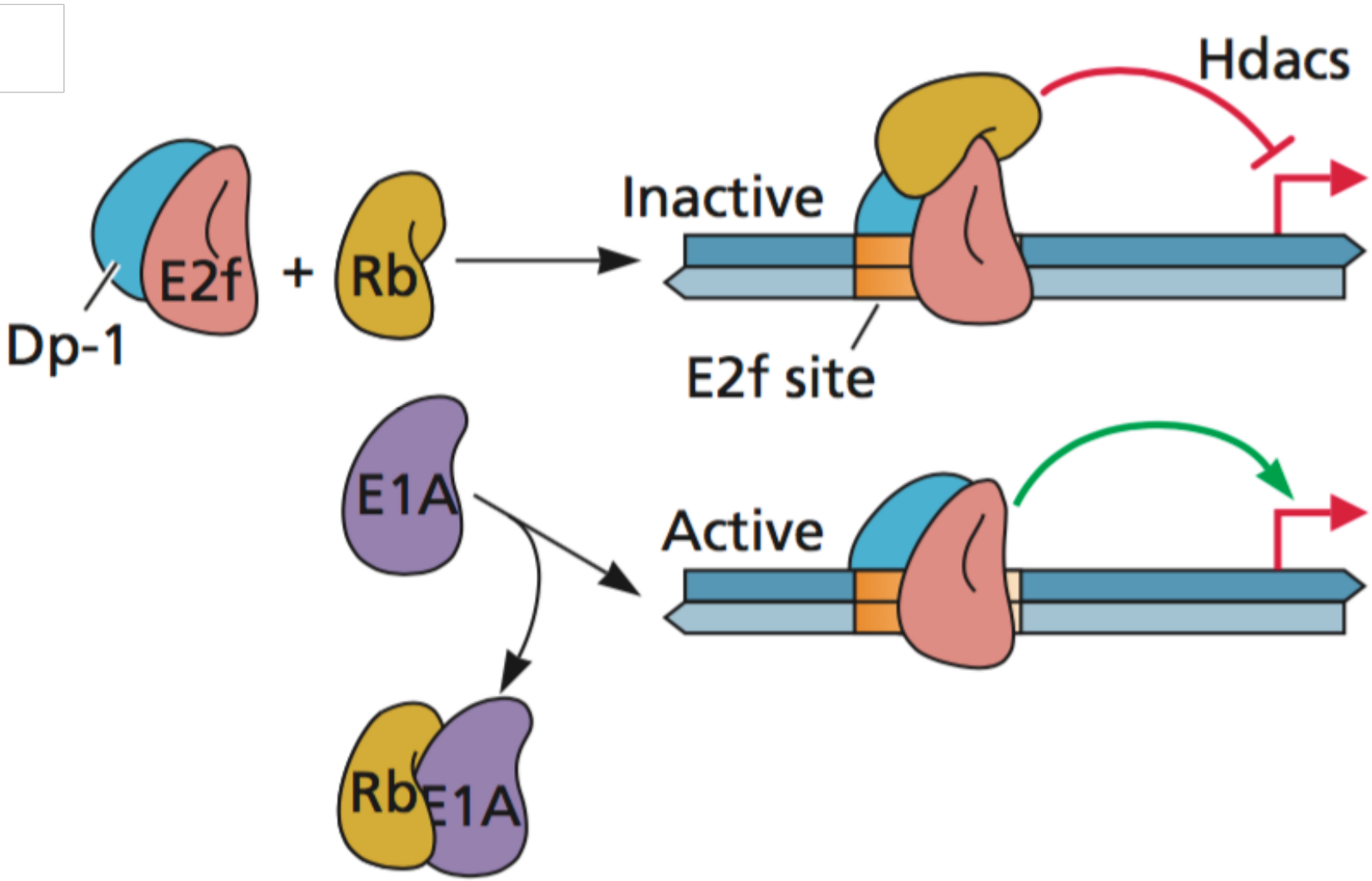


Proteins that regulate transcription

- Host and/or virus sequence-specific DNA binding proteins
- Viral co-activating molecules (do not bind DNA but can modulate transcription) also required
- Many co-activators modulate structure of nucleosomal templates



Stimulation of transcription by Ad E1A proteins



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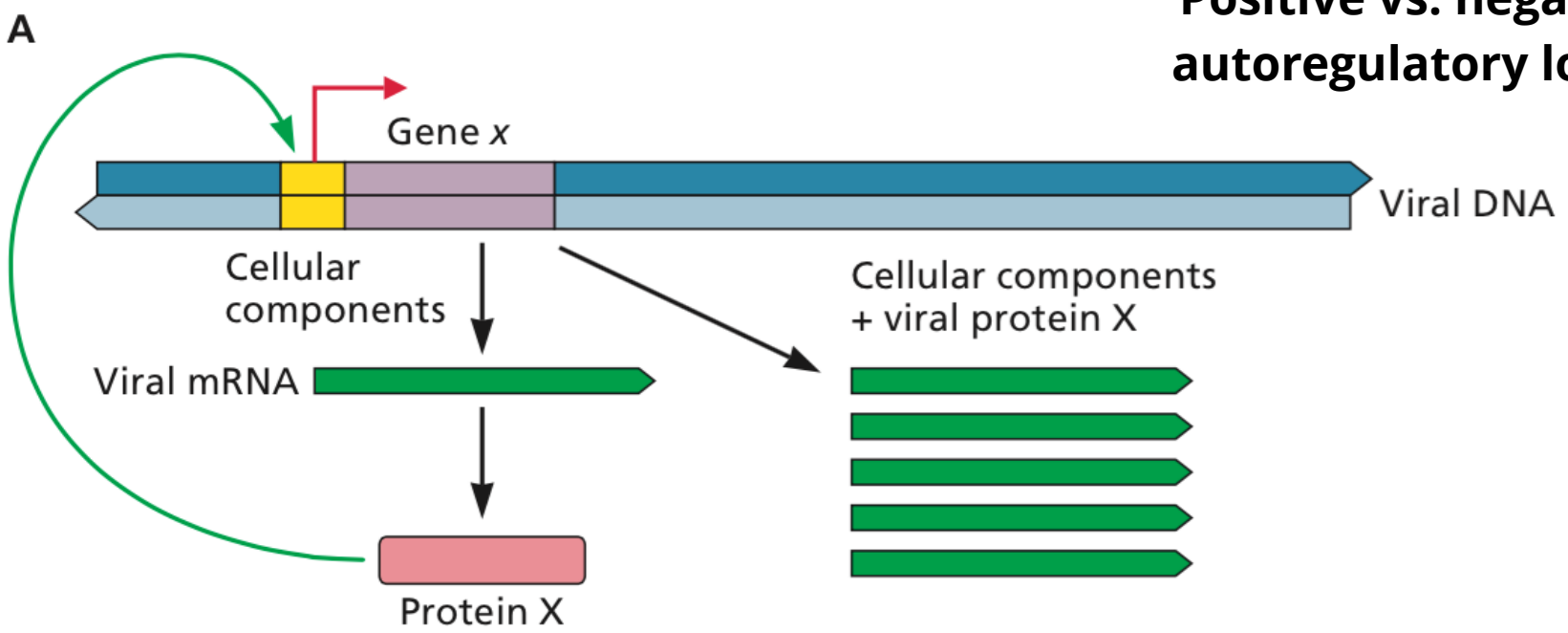
What is the first biosynthetic event that occurs in cells infected with DNA viruses?

1. Membrane fusion
2. Transcription
3. DNA replication
4. Protein synthesis
5. All of the above

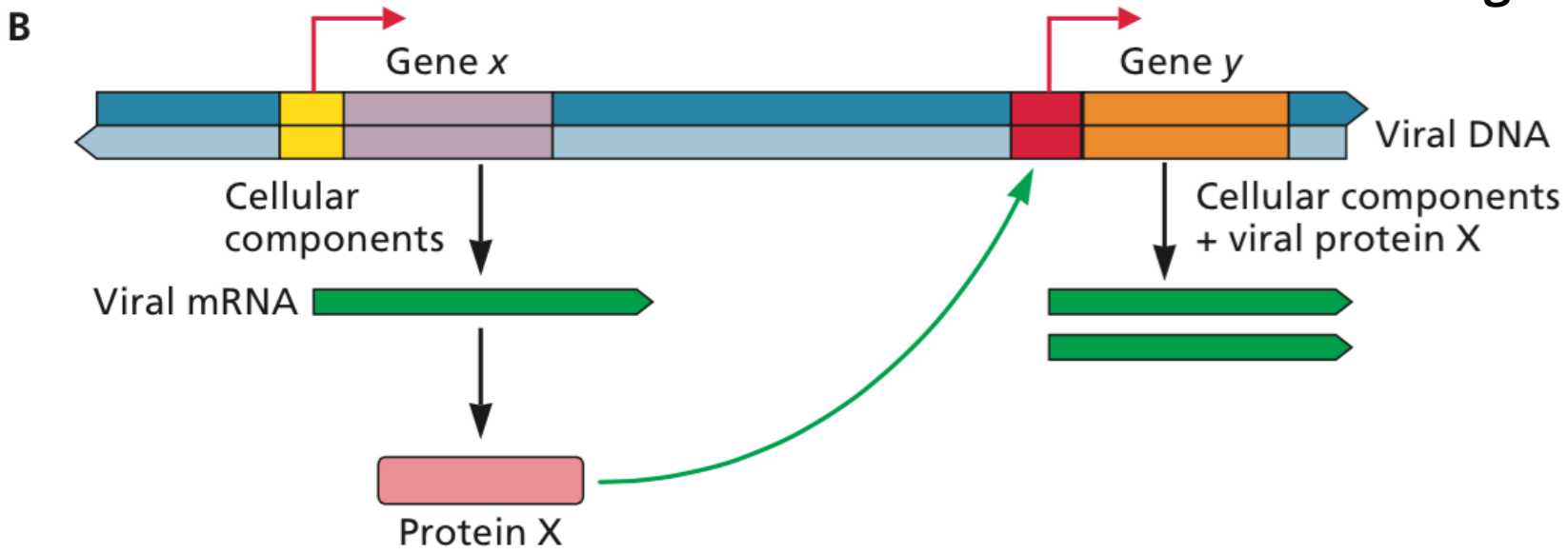
Strategies of transcription of viral DNA

Origin of transcriptional components	Virus
Host only	Simple retroviruses
Host plus one viral protein that regulates transcription	Complex retroviruses, parvoviruses, papillomaviruses, polyomaviruses
Host plus >1 viral protein that stimulate transcription	Adenoviruses, herpesviruses
Viral	Poxviruses

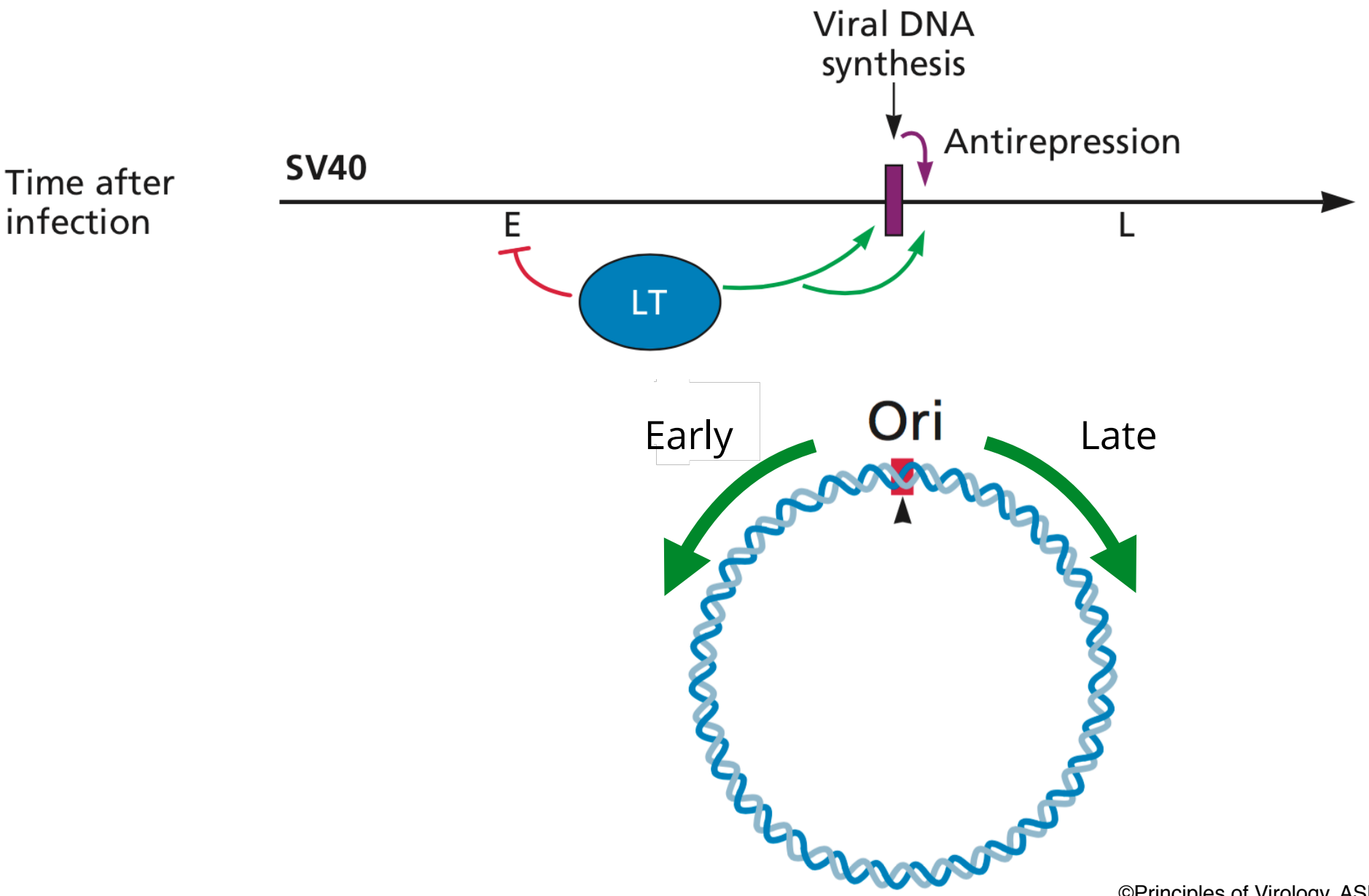
Positive vs. negative autoregulatory loops



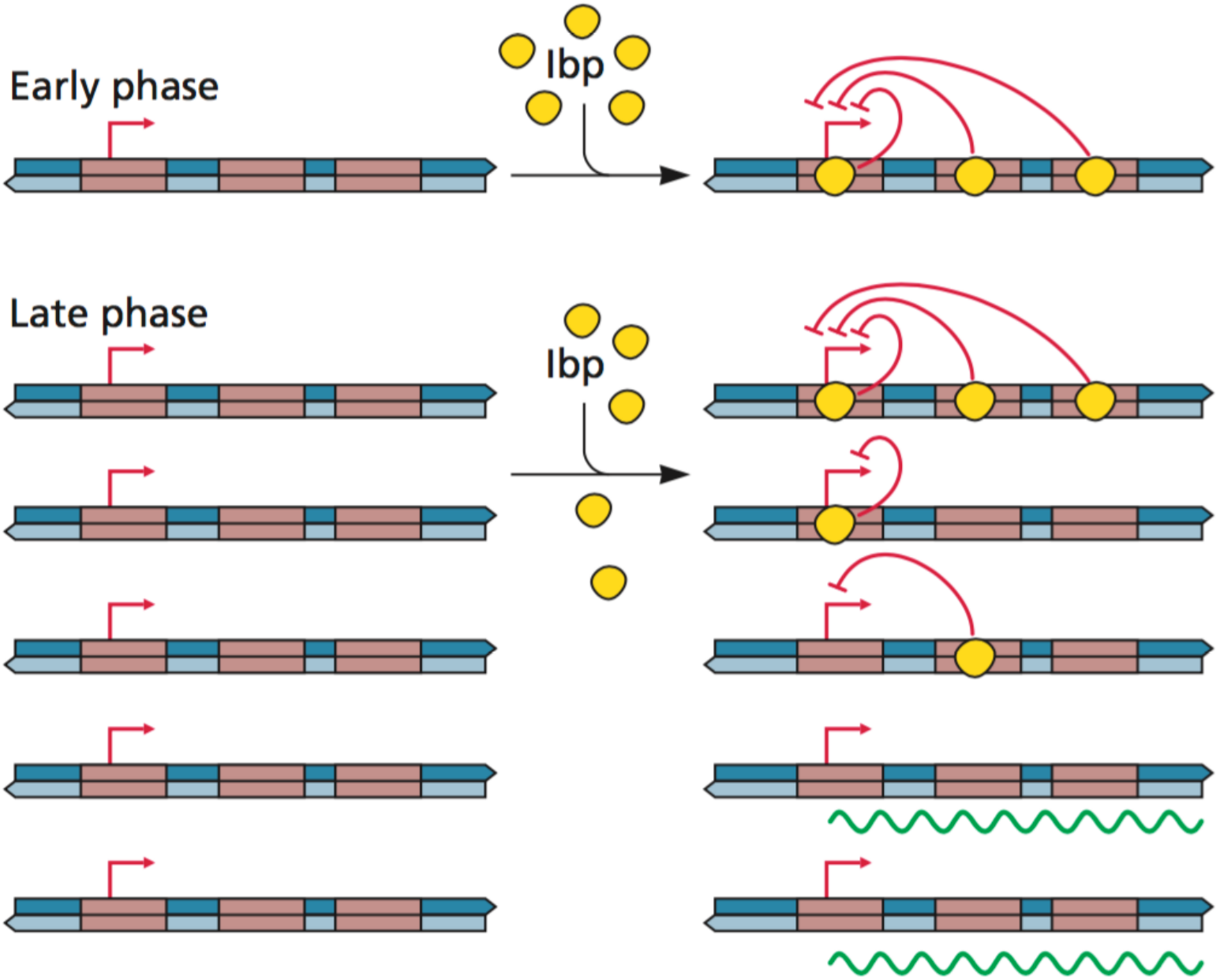
Cascade regulation

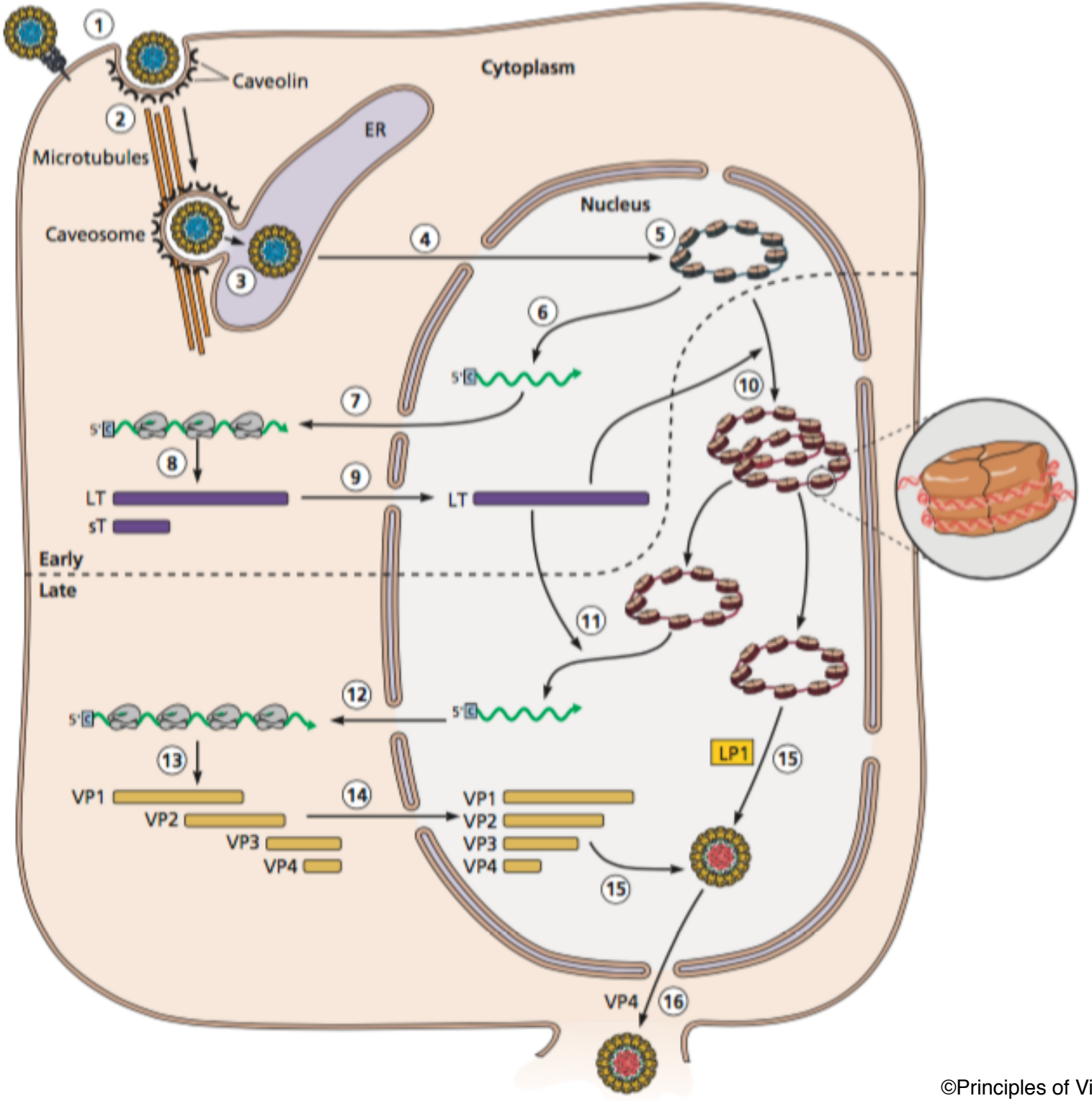


Viral transcriptional programs



Regulation of SV40 late promoter by cellular repressors

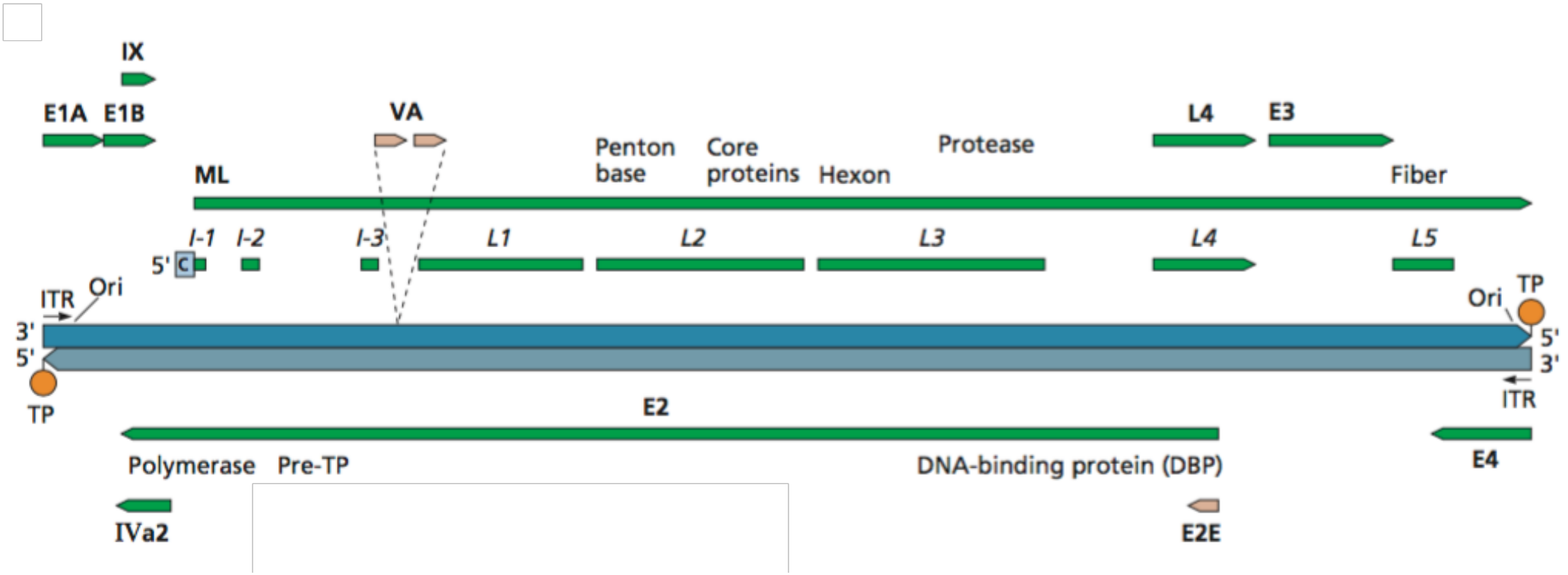


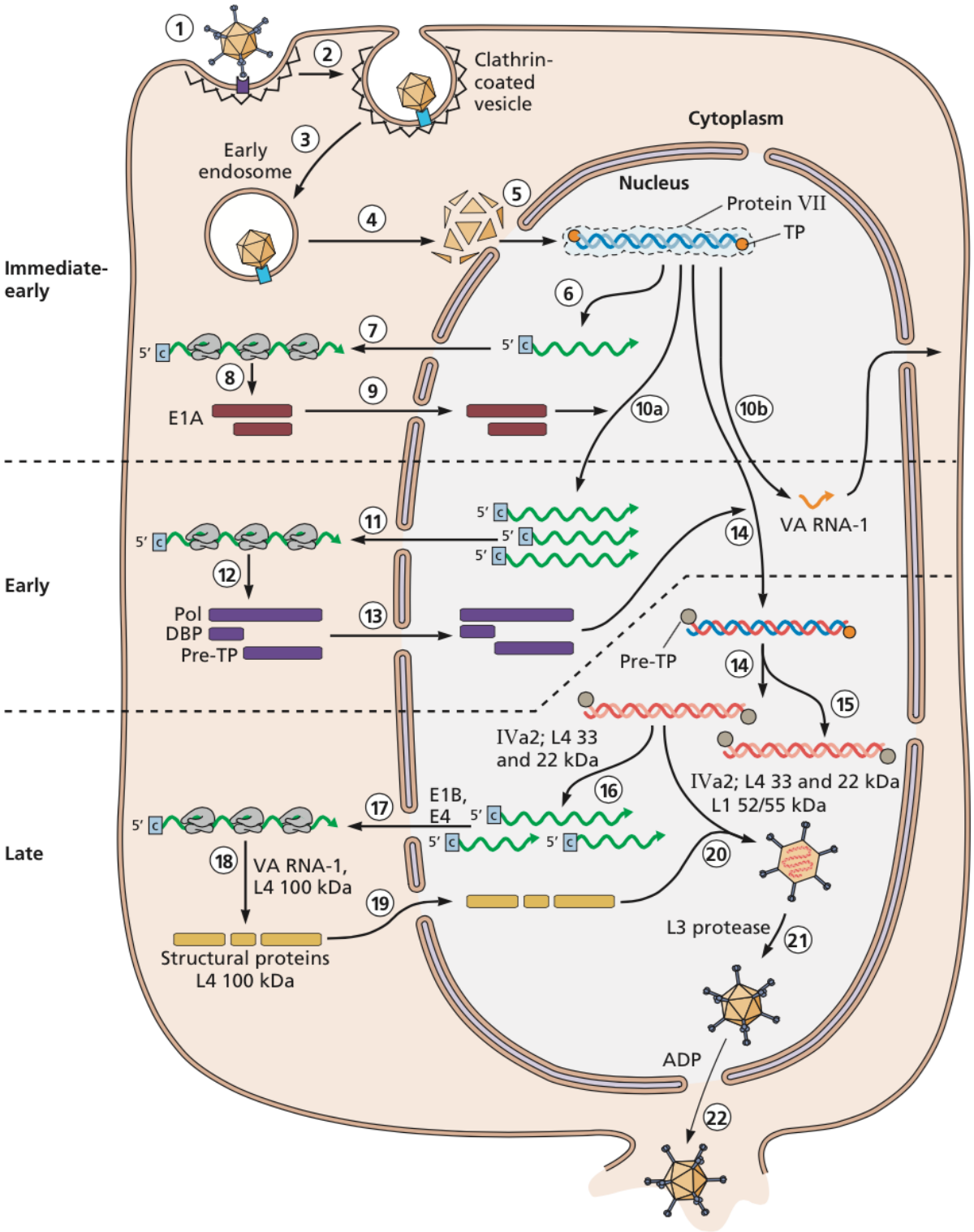


Adenovirus transcriptional regulation

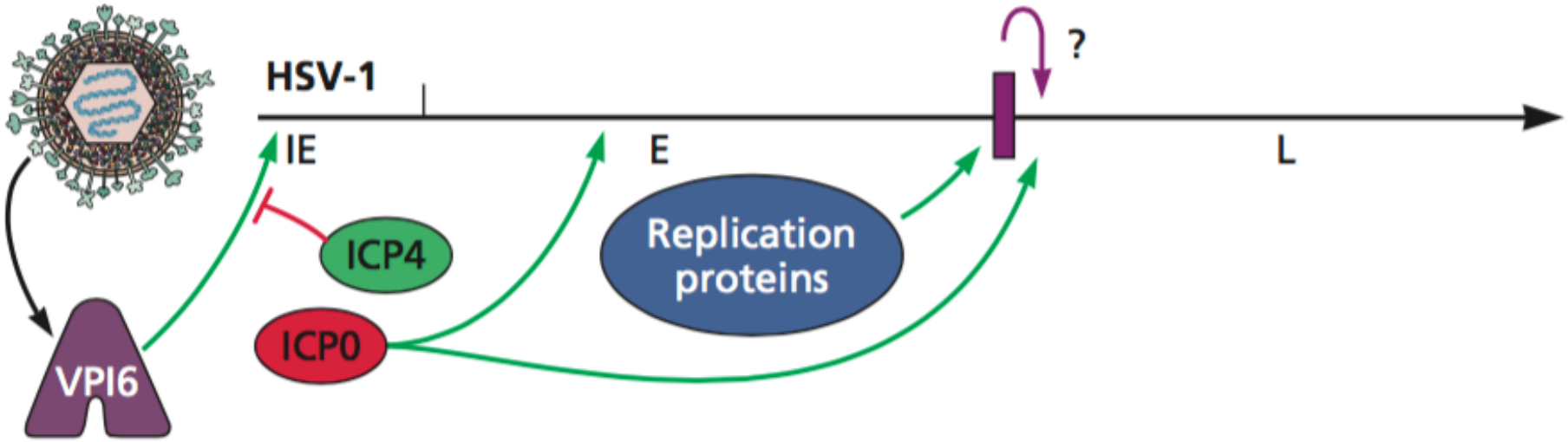
- Three viral proteins and DNA synthesis govern phase transitions
- E1A necessary for transcription of all E transcription units
- E2 required for DNA synthesis and entry into L phase, increases initiation from major late promoter
- IVa2 enhances L gene transcription

Adenovirus transcription units

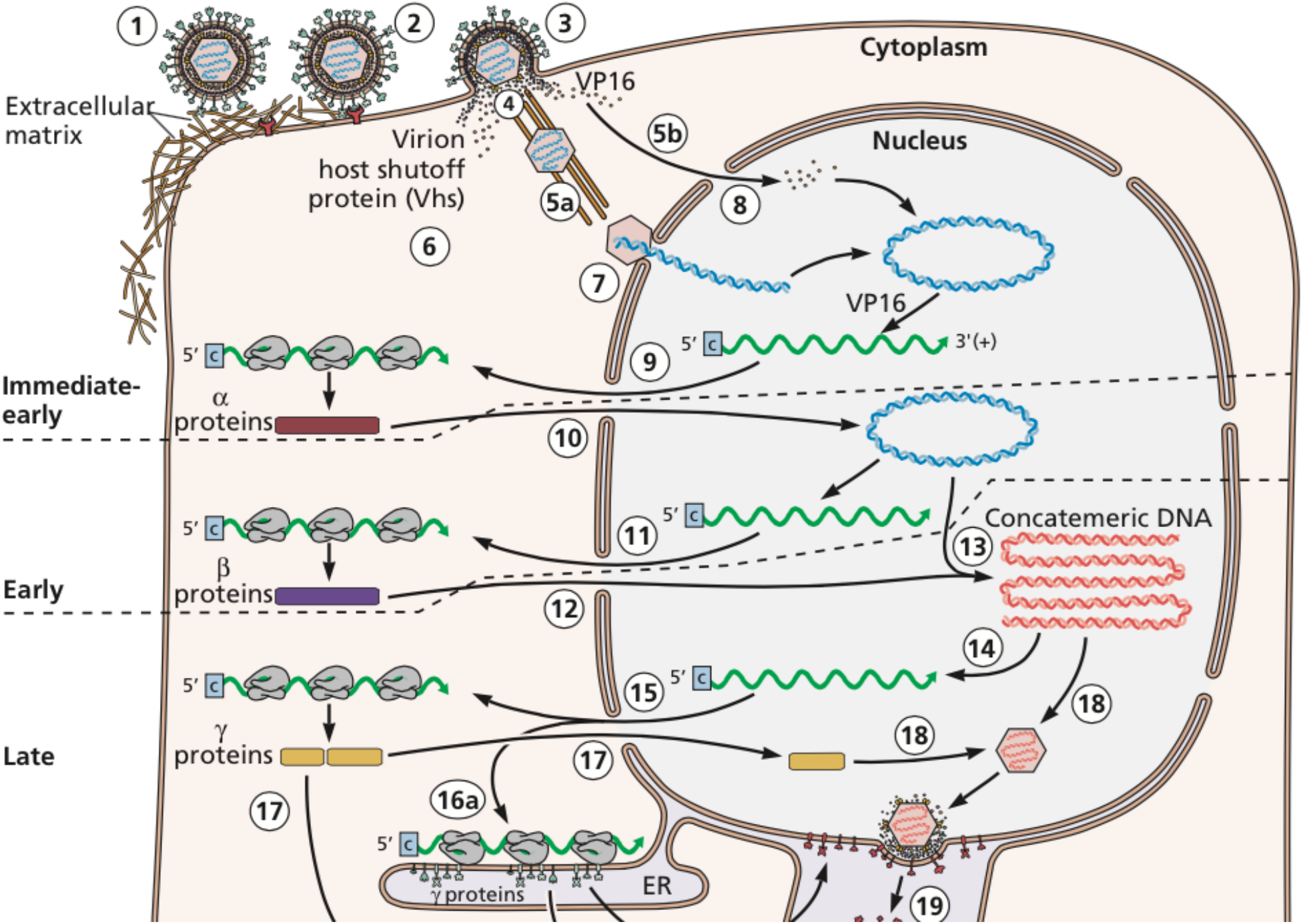




Herpesvirus transcriptional programs



- Initiated by VP16, a virion associated protein (differs from Py, Ad)
- Activates IE transcription
- IE proteins control transcription from all virus genes
- Expression of E genes and DNA synthesis
- Expression of DL and L genes, DNA dependency
- Ensures coordinated production of DNA genomes and structural proteins



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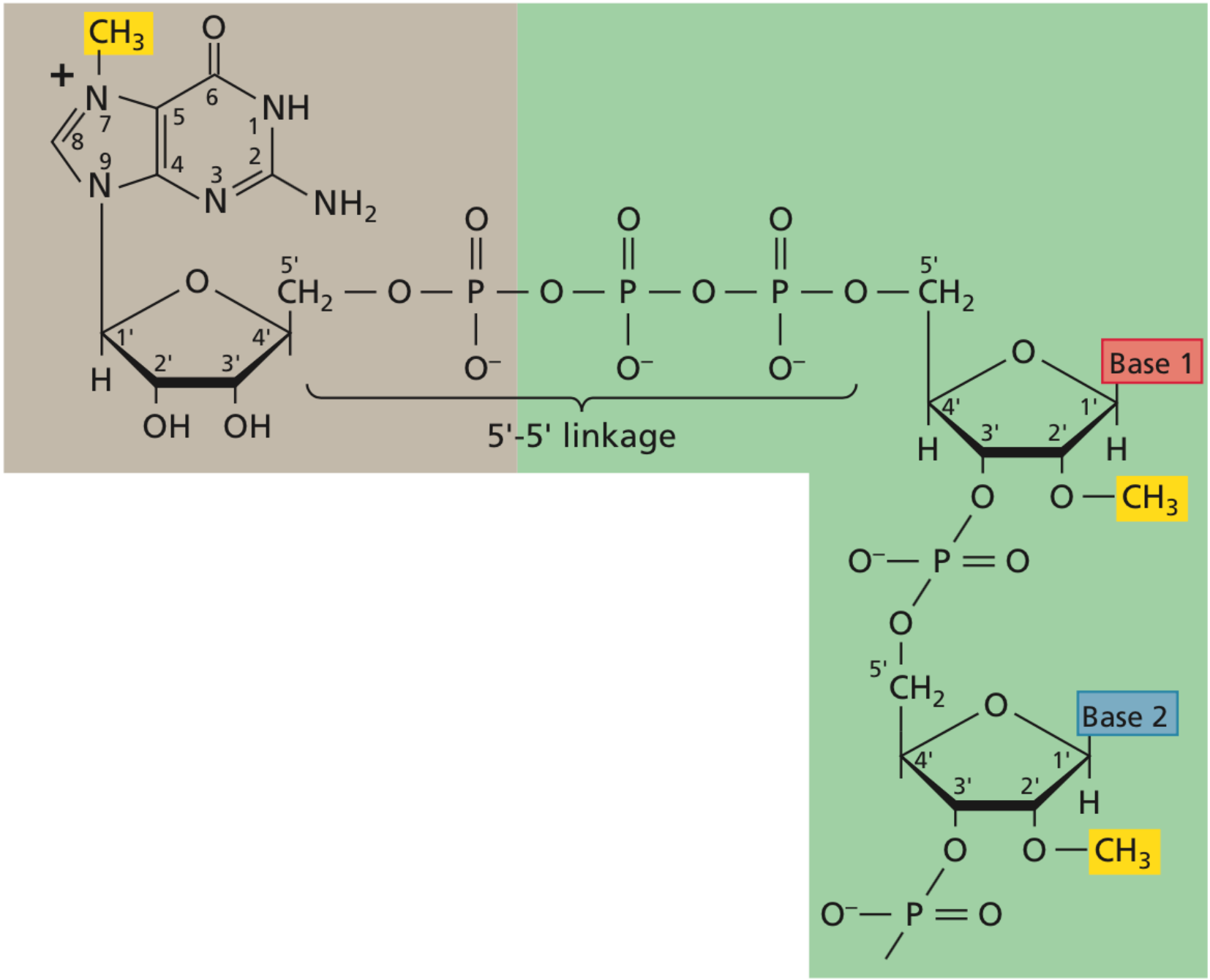
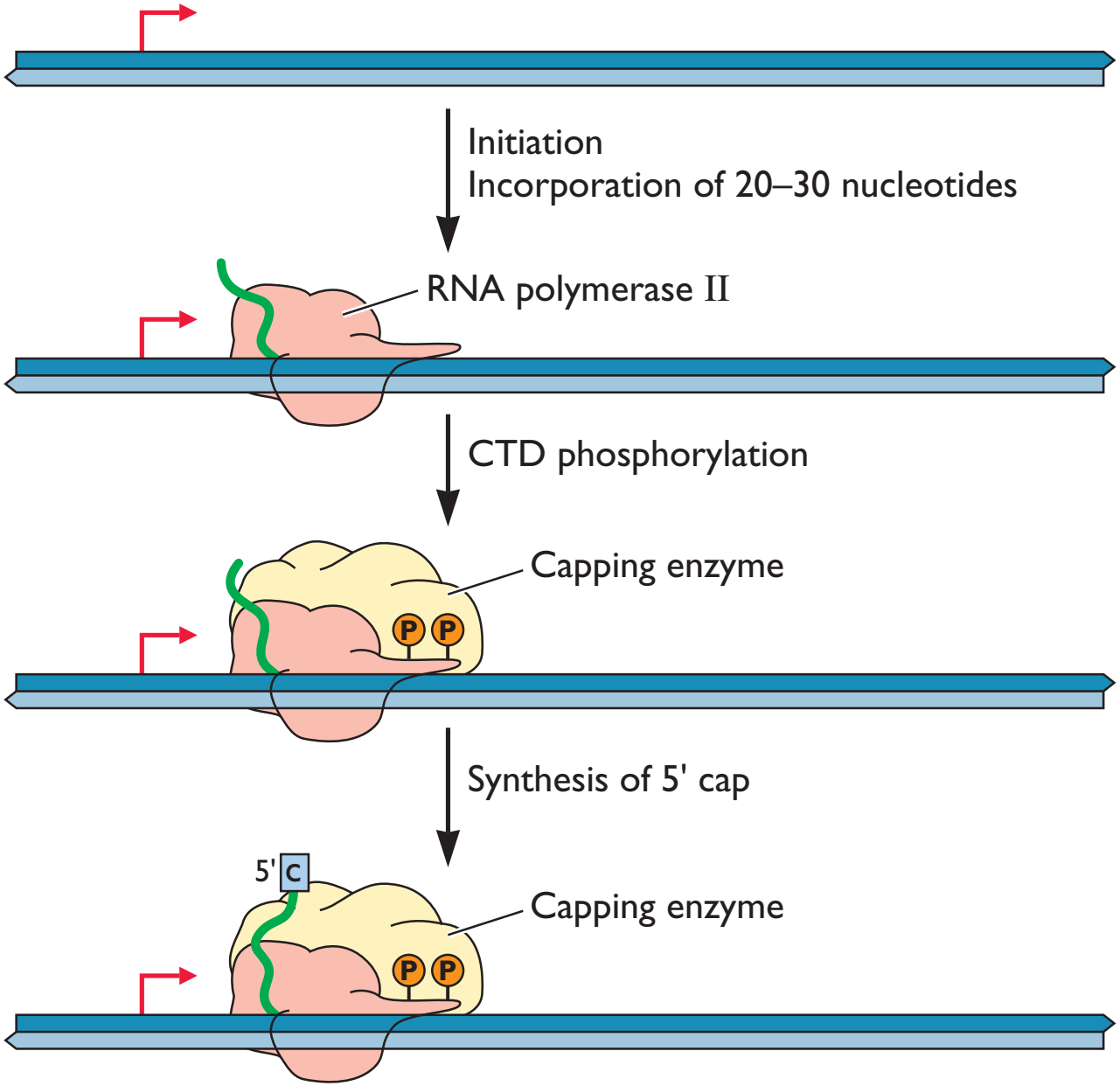
Adenovirus E1A protein stimulating the expression of adenovirus E2 protein which then stimulates the expression of adenovirus IVa2 & L4 protein is an example of:

1. A negative autoregulatory loop
2. Repression of gene expression
3. Cascade regulation
4. Dimerization

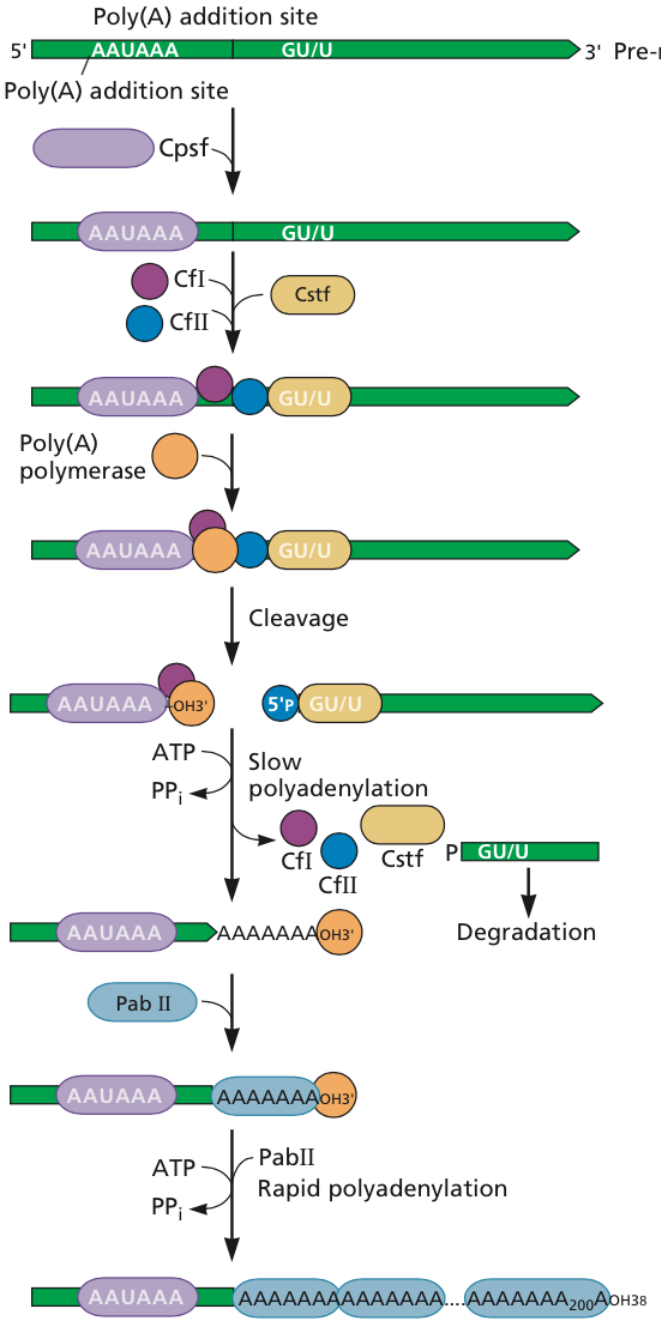
5’-cap structure



Co-transcriptional capping



Cleavage and polyadenylation



~200 A

Addition of poly(A) to viral mRNAs

Mechanism	Enzyme	Viruses
Post-transcriptional		
Cleavage of pre-mRNA followed by polyadenylation	Cellular	Adenovirus, HBV, HDV, herpesviruses, polyomavirus, retrovirus
During mRNA synthesis		
Reiterative copying at stretches of U in template RNA	Viral	Influenza virus, VSV
Copying of long U stretch in template RNA	Viral	Poliovirus, togavirus

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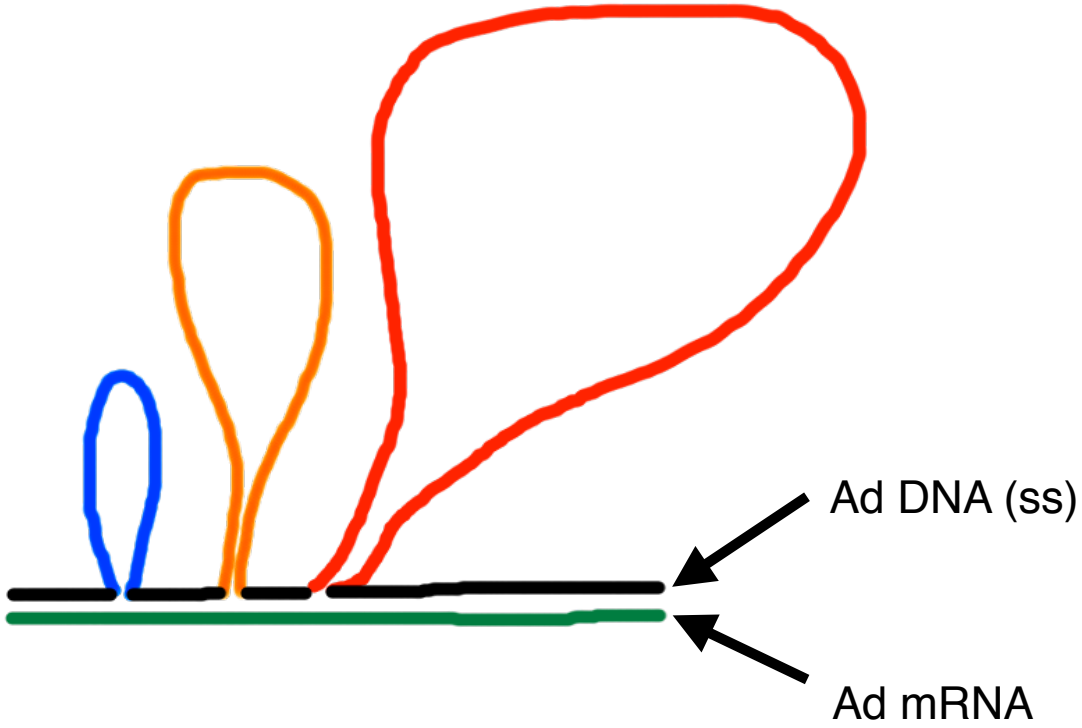
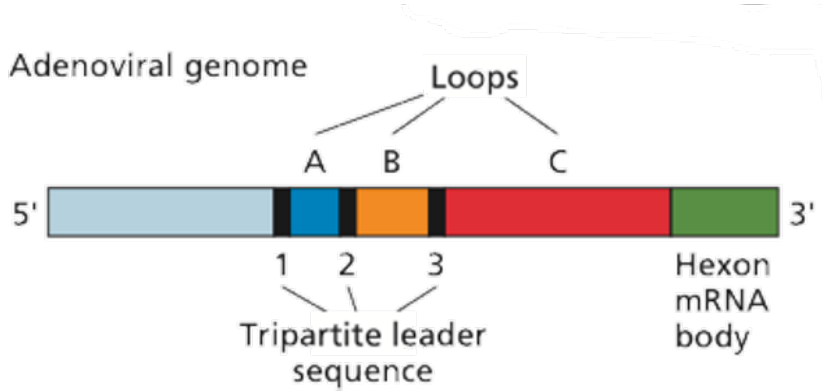
Which statement about polyadenylation of DNA virus mRNAs is correct?

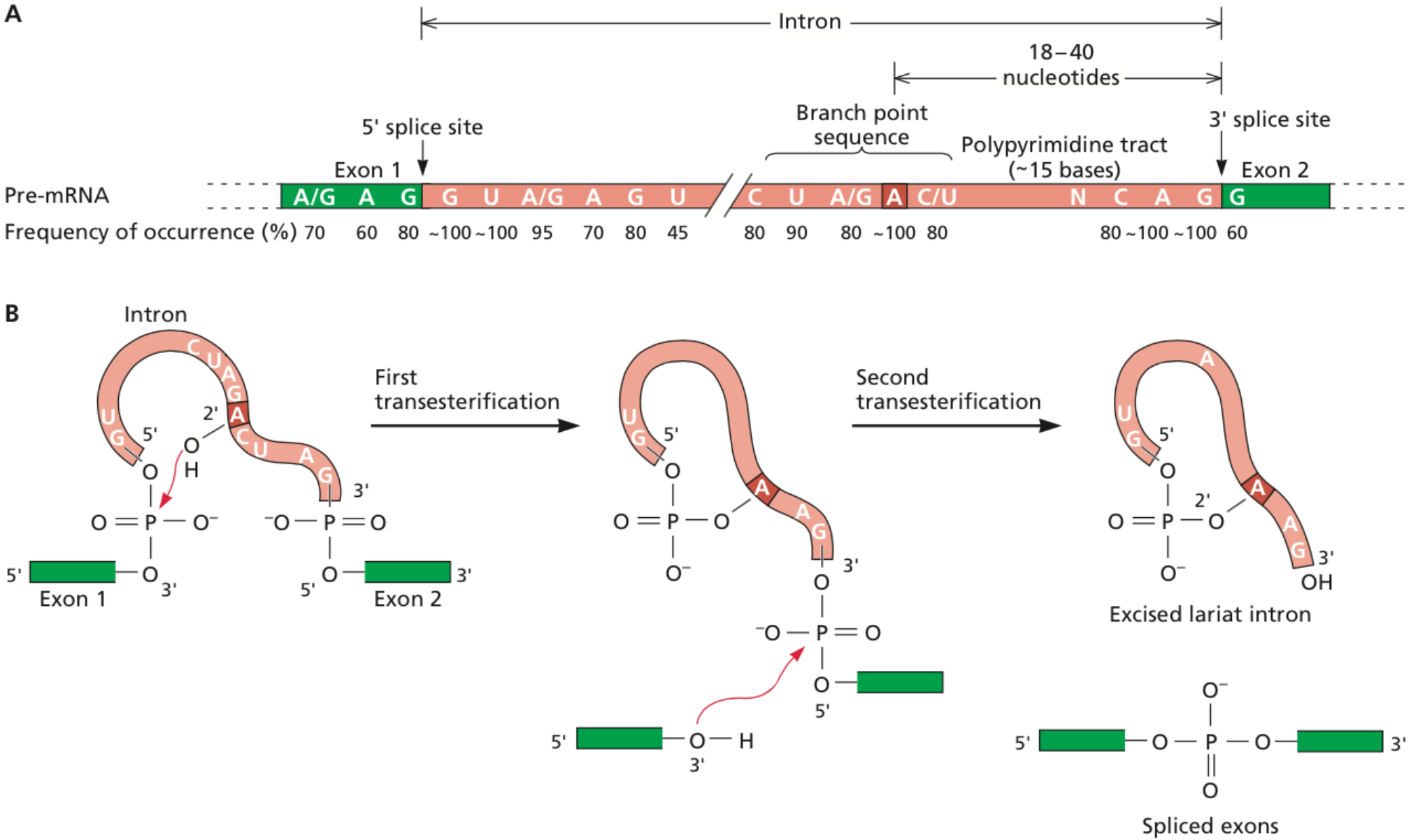
1. It always occurs in the cytoplasm
2. It occurs after cleavage of pre-mRNA
3. Poly(A) is added at the 5’-end of pre-mRNA
4. Is specified by a stretch of U residues in the template

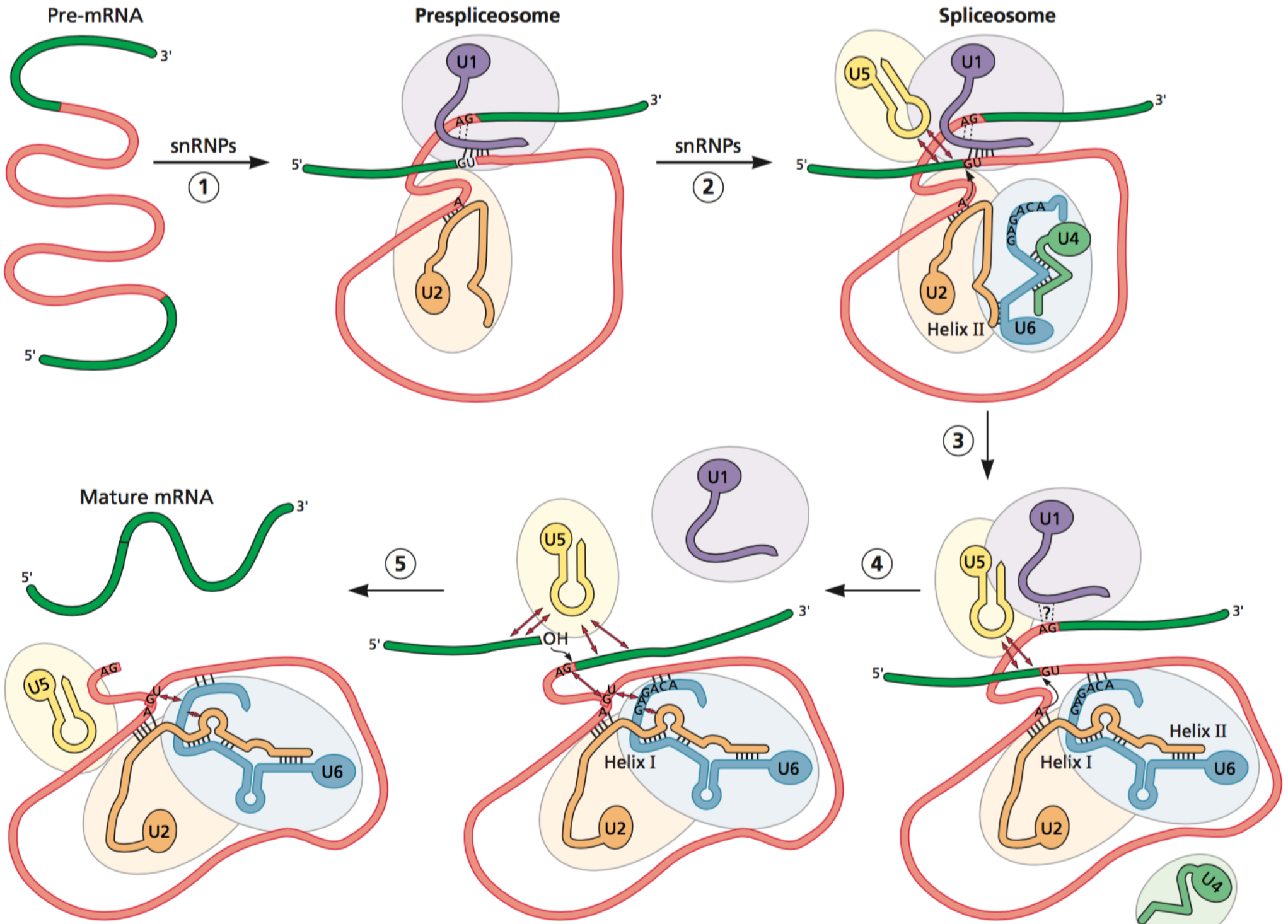
Discovery of mRNA splicing in Ad infected cells





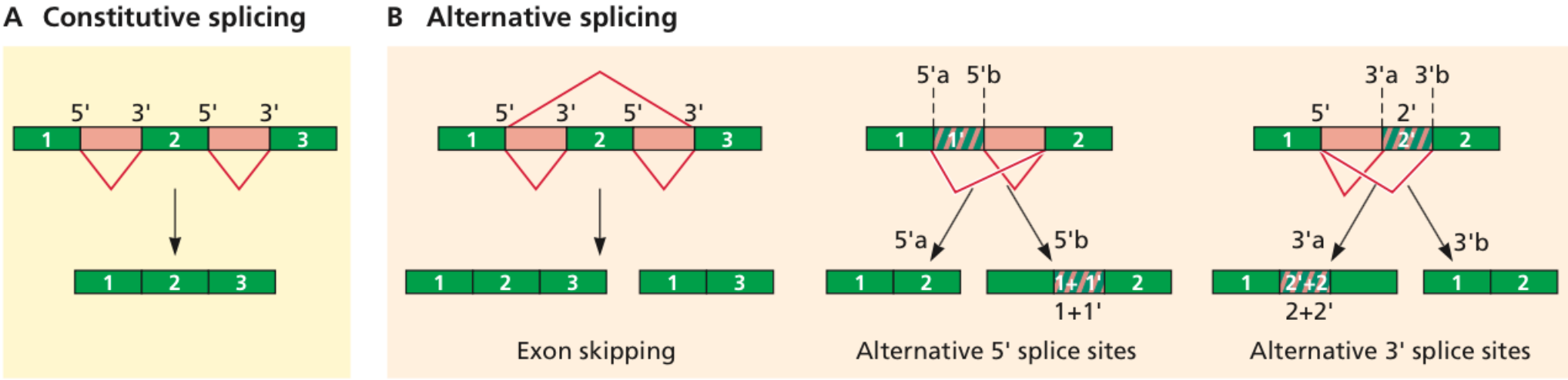
Splicing of pre-mRNA

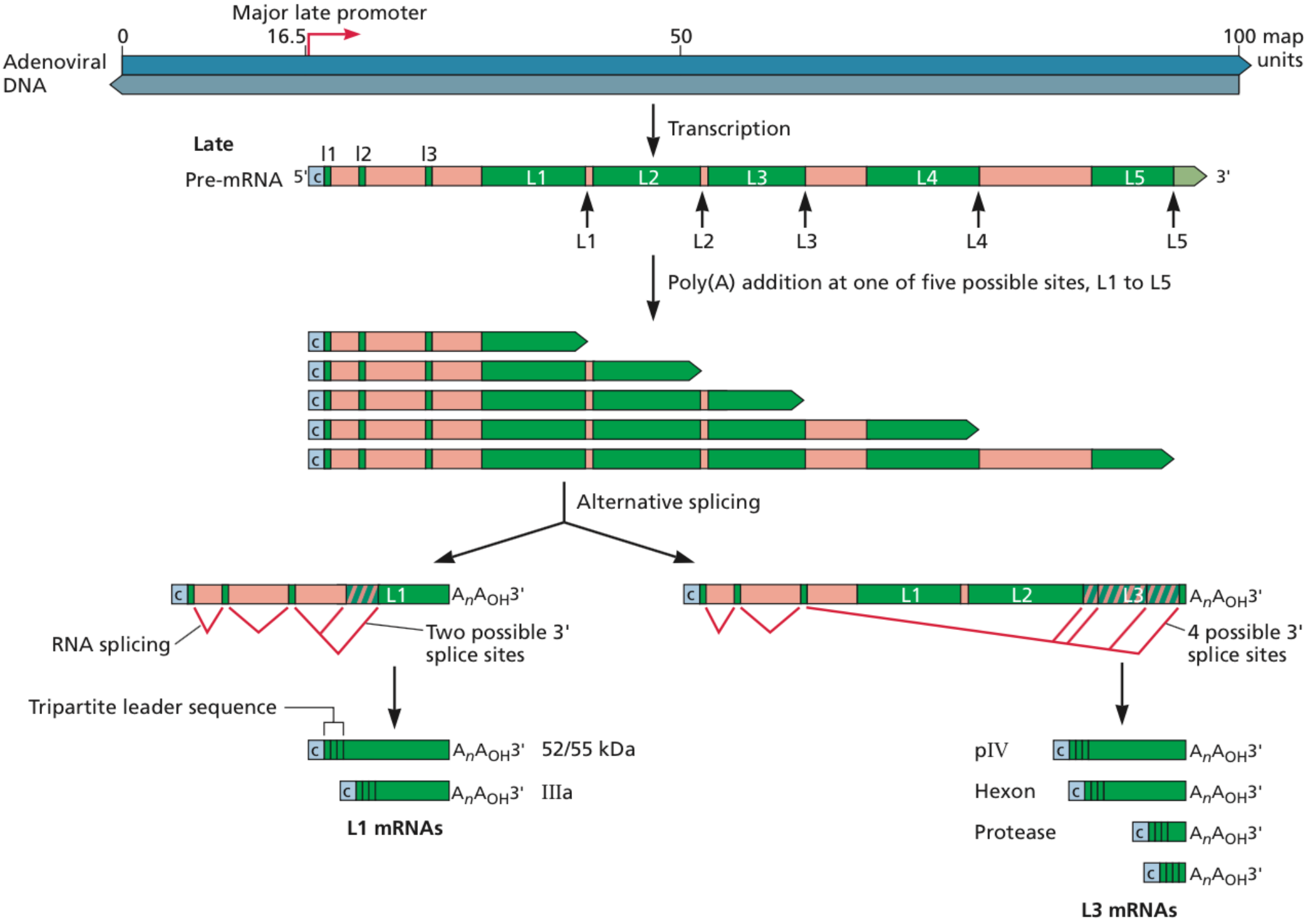




spliceosome = ribozyme

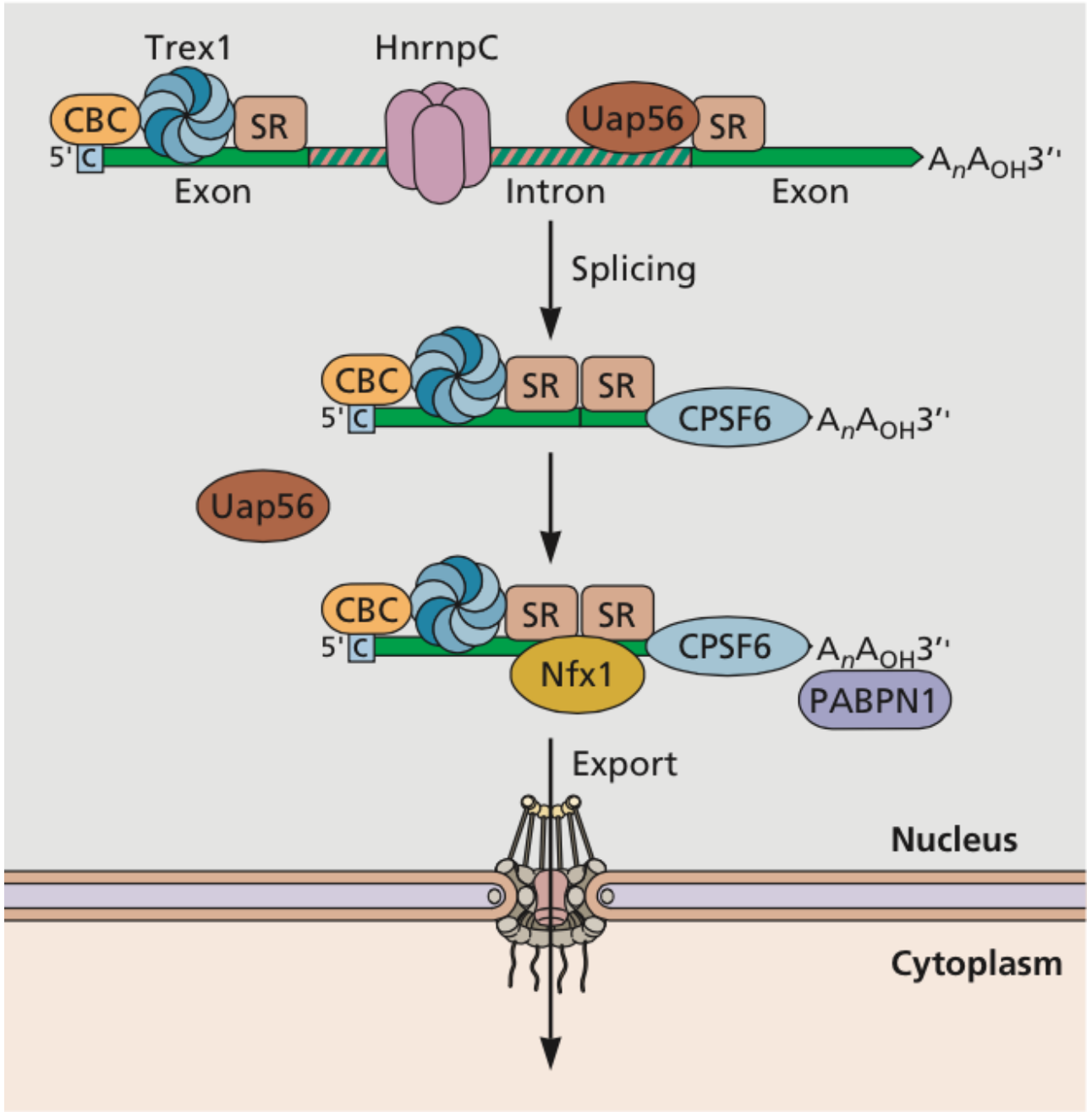
Constitutive and alternative splicing





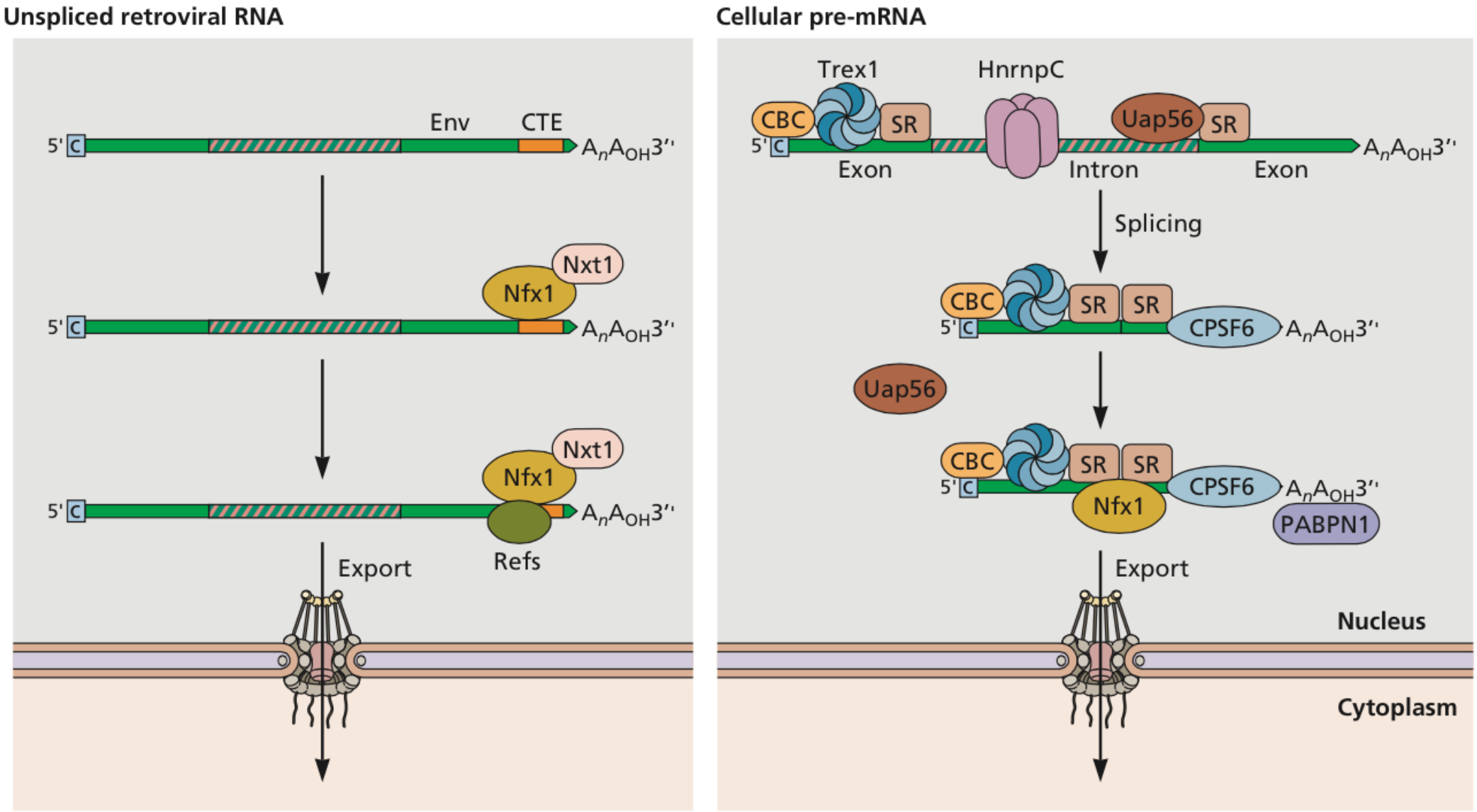
Viral proteins can regulate alternative splicing

Splicing marks mRNAs for nuclear export



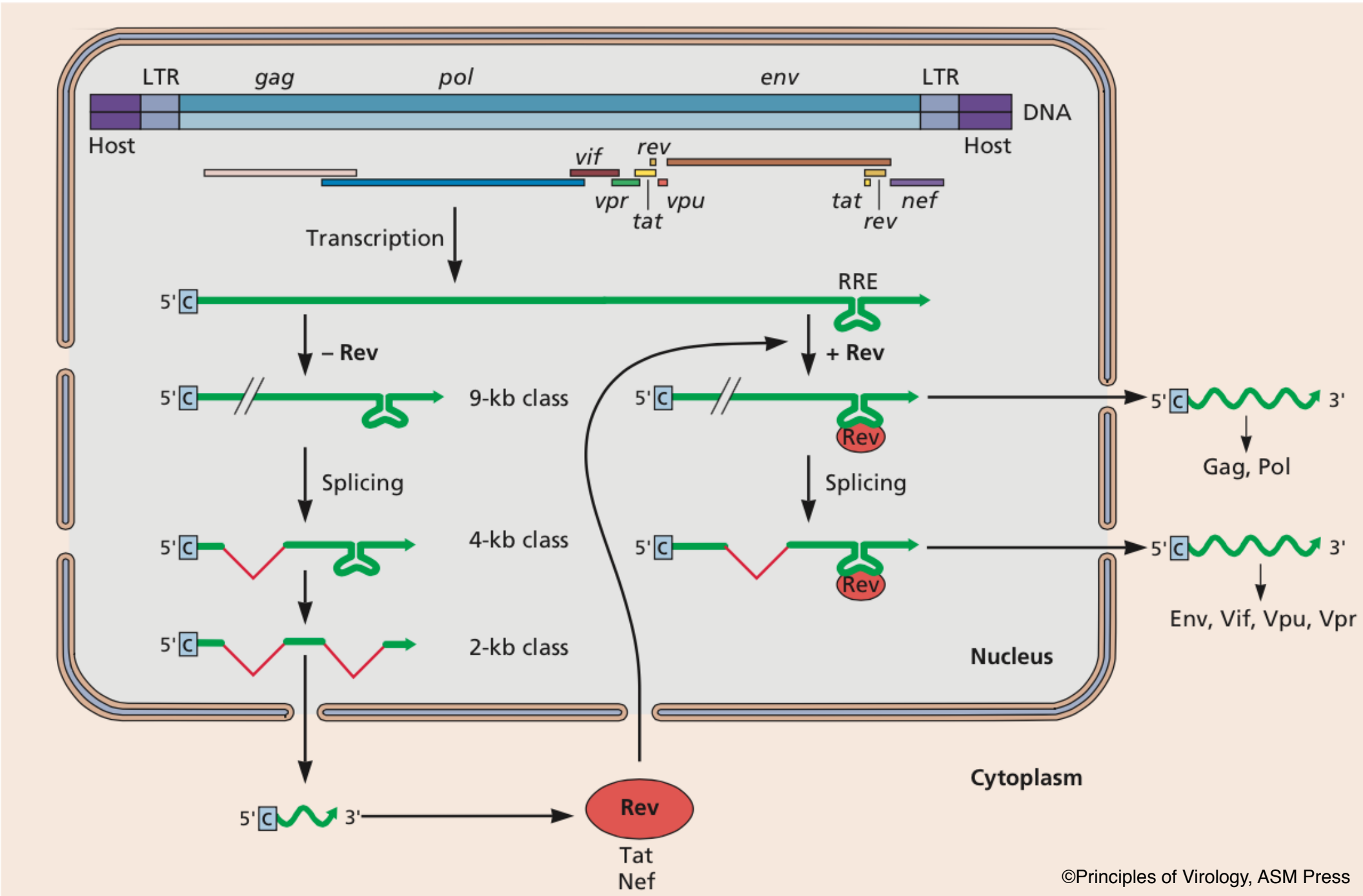
components of nuclear export pathway

Retroviral mRNA export without rev



CTE = Constitutive transport element

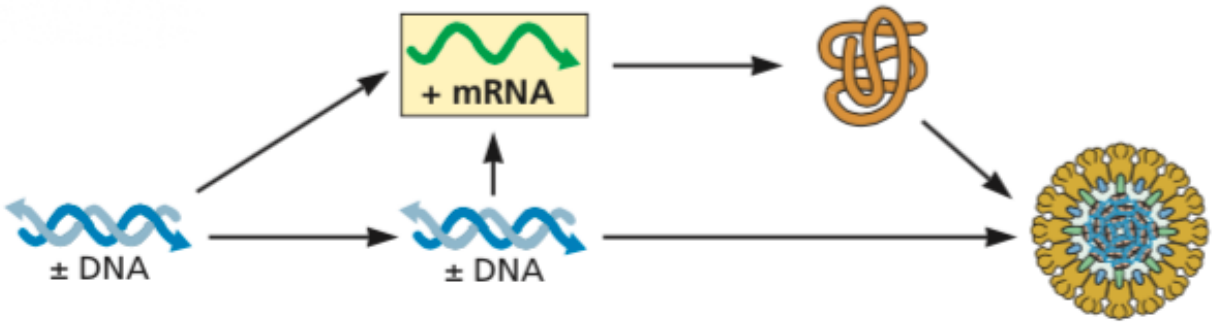
Rev protein regulates export of HIV mRNA



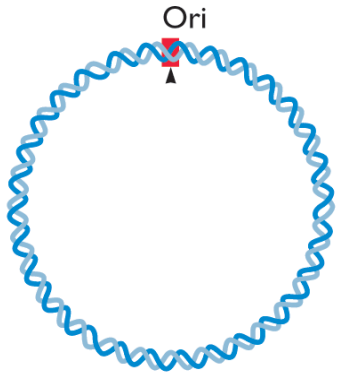
Splicing = Value added

- Alternative splicing creates new functional genes
- Coding information of a small DNA genome is expanded
- Regulation of gene expression

DNA genomes

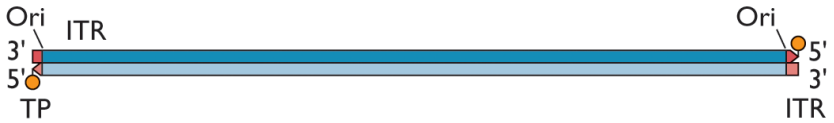


***Polyomaviridae* (5 kbp)**

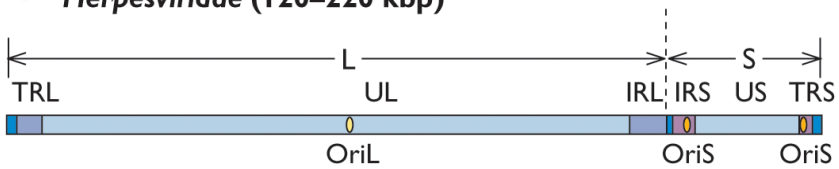


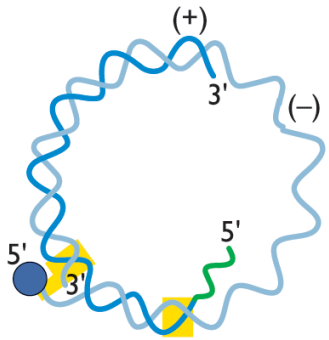
***Circoviridae* (1.7–2.2 kb)**

***Adenoviridae* (36–48 kbp)**



***Herpesviridae* (120–220 kbp)**





***Parvoviridae* (4–6 kb)**

***Poxviridae* (130–375 kbp)**

Why does transcription occur first for DNA viruses?

Viral DNA replication always requires synthesis of at least one viral protein, sometimes many - hence it is always delayed after infection