The Infected Cell

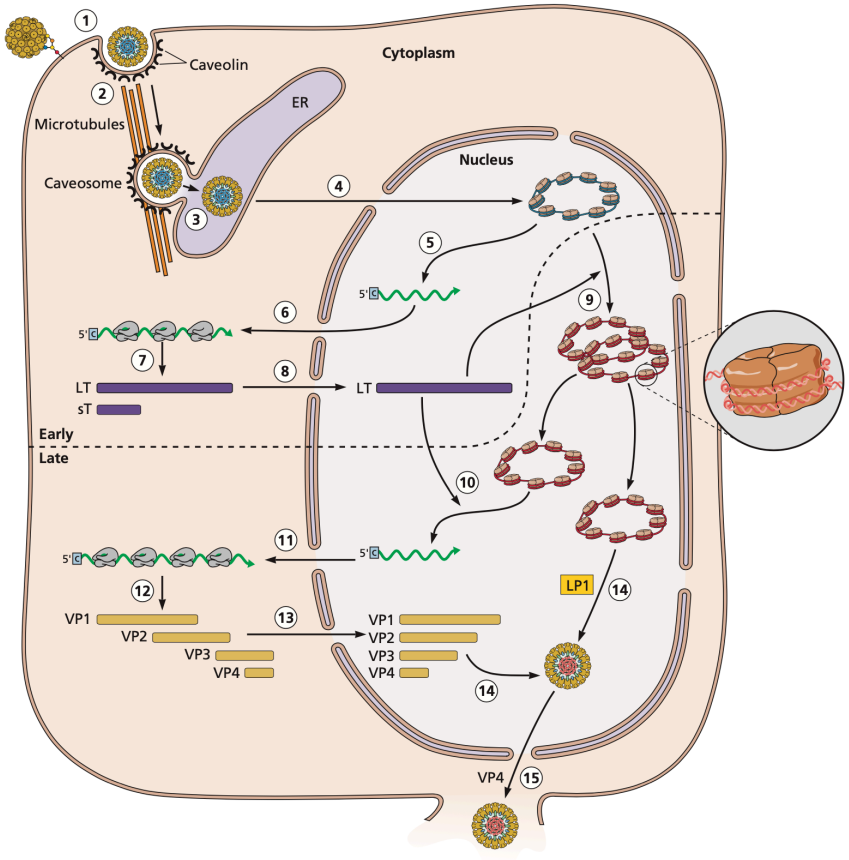
Session 11

Virology Live

Fall 2021

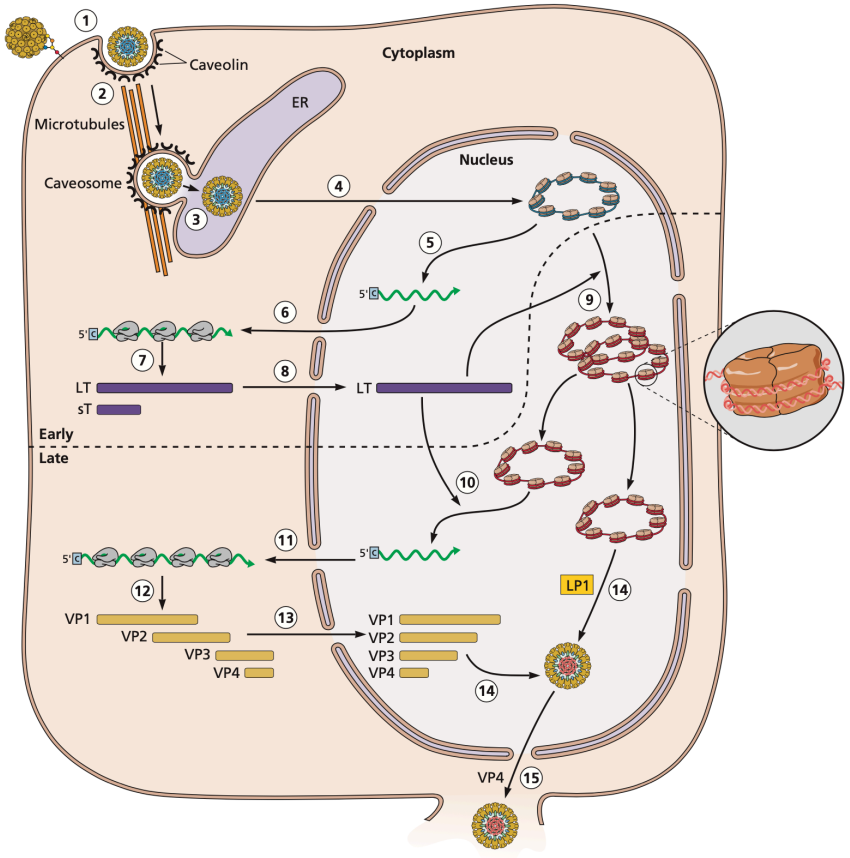
He hath eaten me out of house and home.
—William Shakespeare
King Henry IV, Part II

The Infected Cell



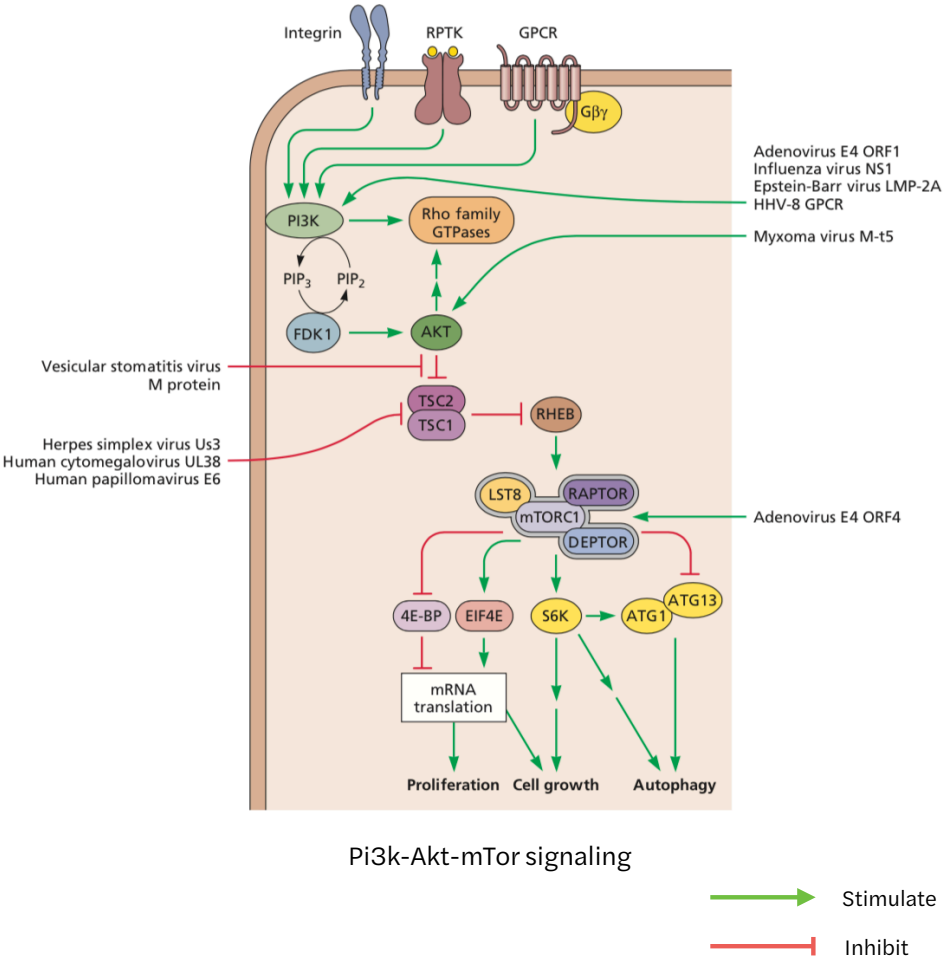
- So far we have focused on viral gene expression, genome replication, and assembly of virus particles
- These depend on host metabolic, biosynthetic, signaling and trafficking systems
- An integrated description of the impact of virus infection on the host cell

The Infected Cell



- Signal transduction
- Gene expression
- Metabolism
- Remodeling of cellular organelles

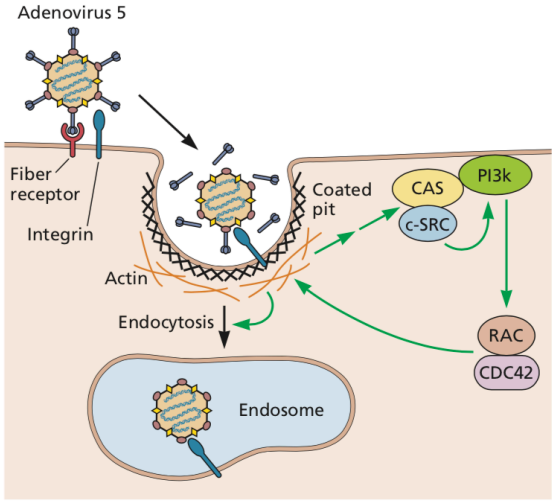
Signal transduction

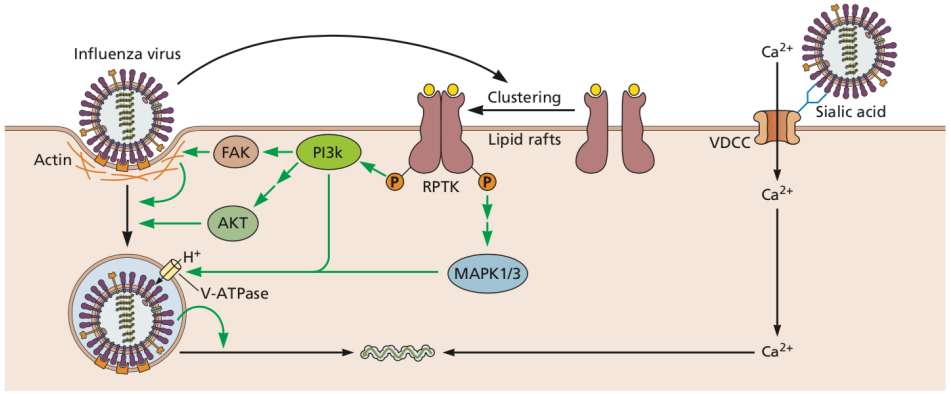


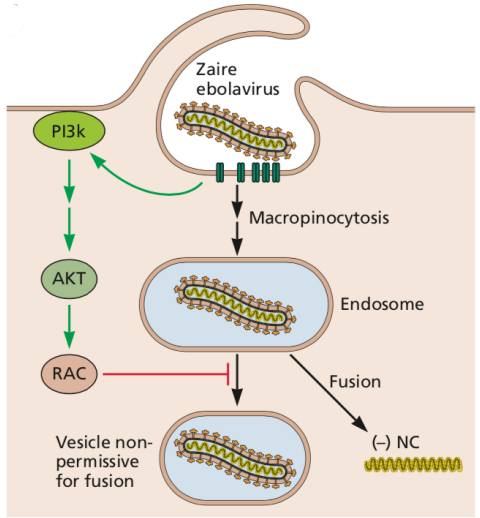
Pi3k-Akt-mTor signaling

- Cells must sense their environment and respond appropriately
- Signal transduction pathways govern every aspect of cell physiology and conduct
- Virus infections can change signaling to promote reproduction

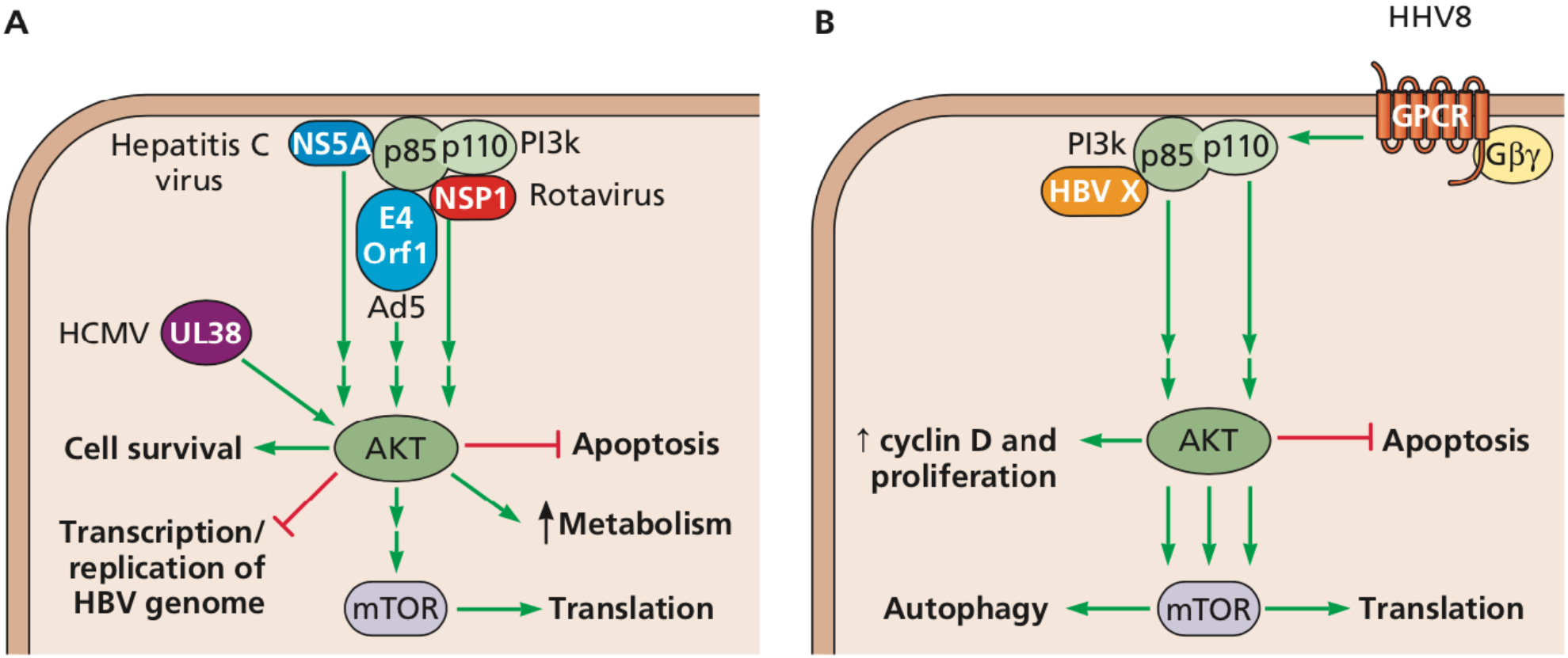
Signaling via Pi3k facilitates virus entry



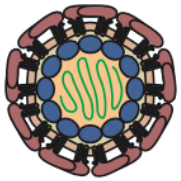


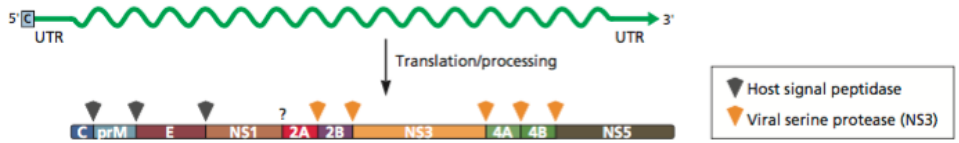


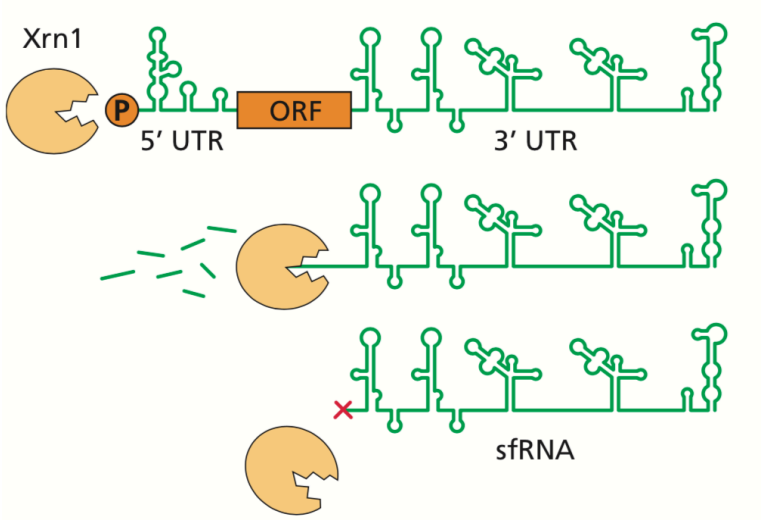
Common activation of Pi3k-mTor relay



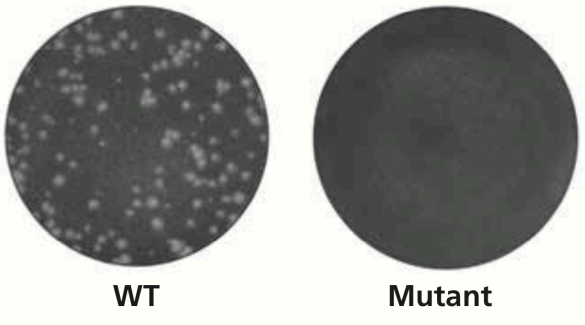
Viral RNA blocks Akt activation to induce apoptosis







sfRNA needed for formation of plaques and pathogenicity in mice

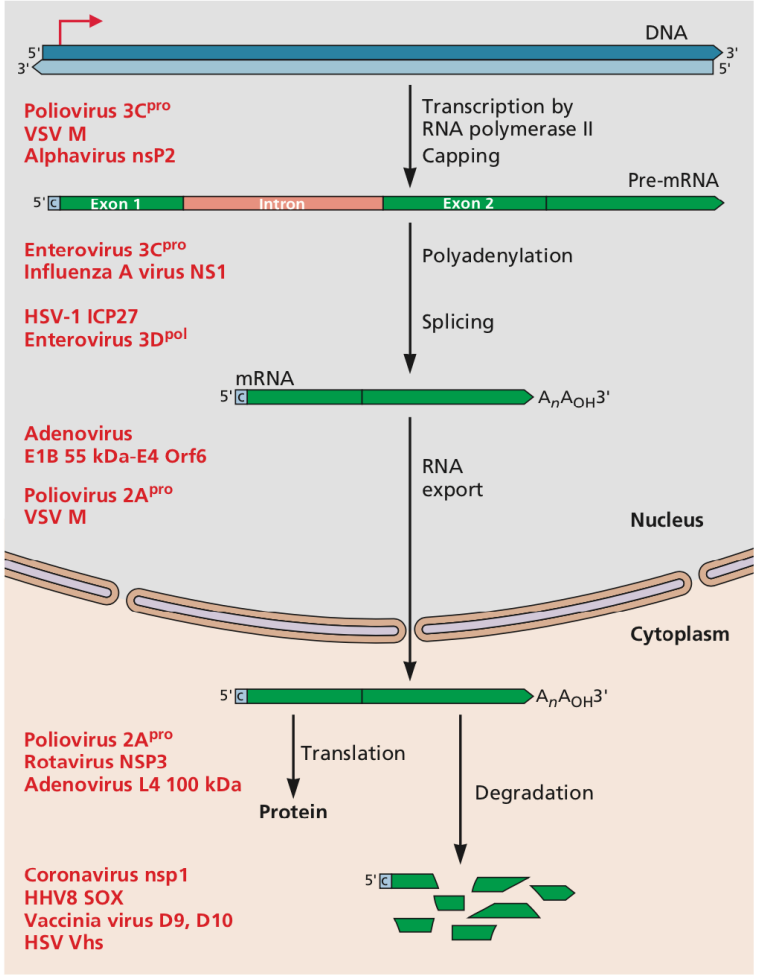


Deletion near 3'-end prevents production of sgRNA

sfRNA inactivates Akt, promotes apoptosis (concentration of anti-apoptotic protein Bcl-2 is reduced)

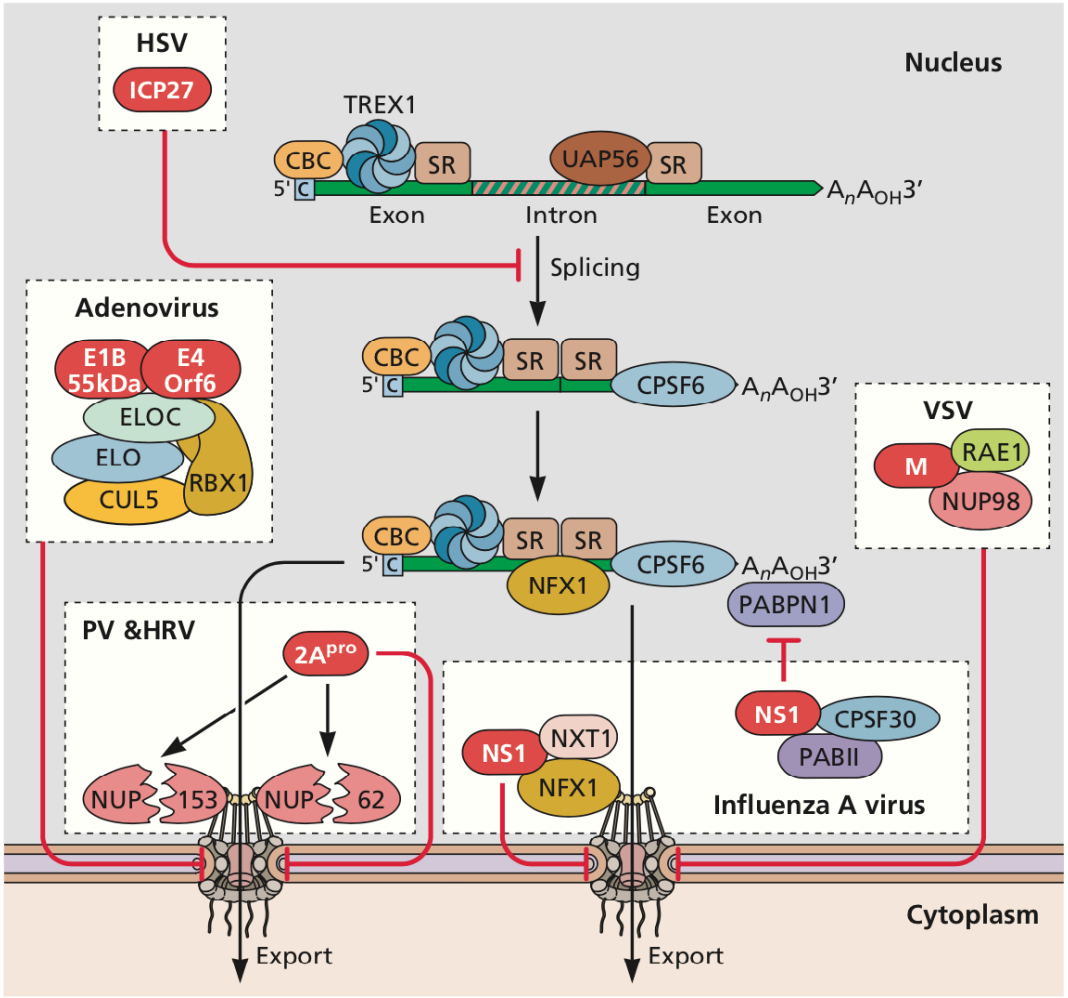
Inhibition of cellular gene expression

Poliovirus infection also inhibits pol I, pol III

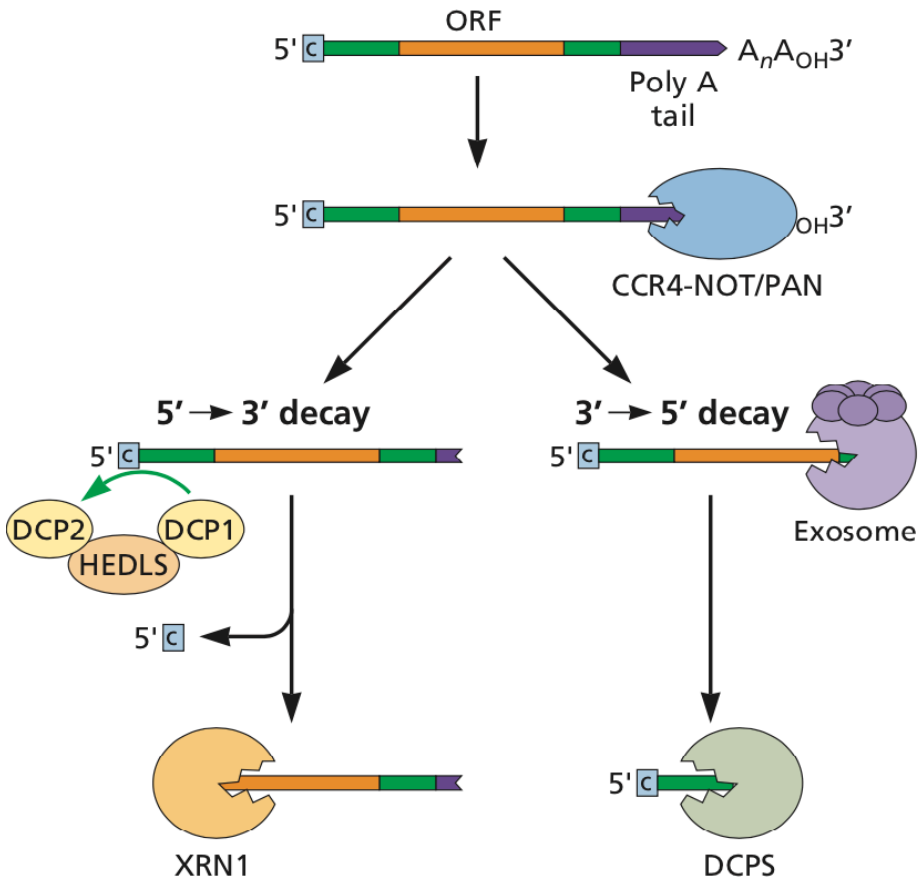


Reduce competition of cellular with viral mRNAs for translation machinery

Inhibition of cellular pre-mRNA processing by viral proteins

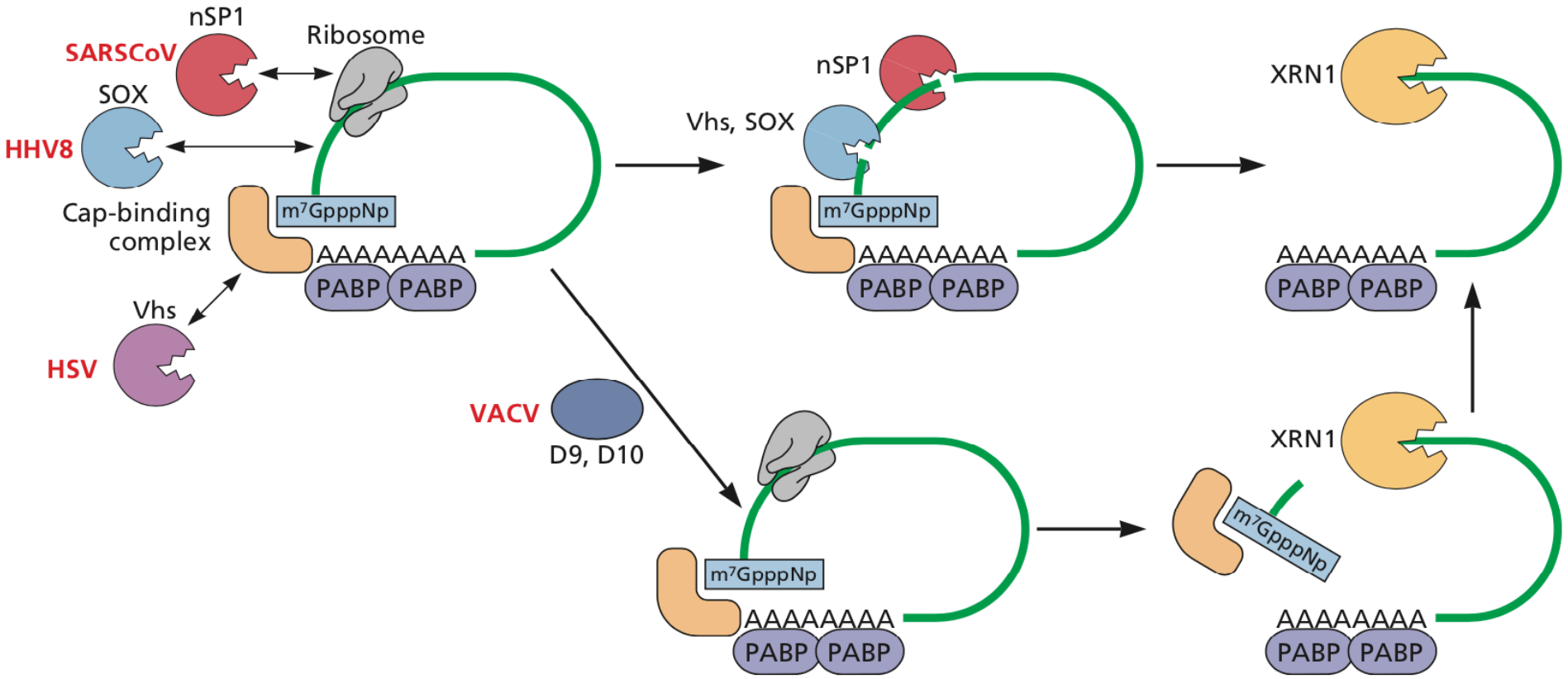


Regulation of mRNA turnover



- Cell mRNA degradation proteins removed or relocalized in virus infected cells
- Pan, Dcp1a, Xrn1 degraded in poliovirus infected cells

Viral proteins initiate mRNA degradation



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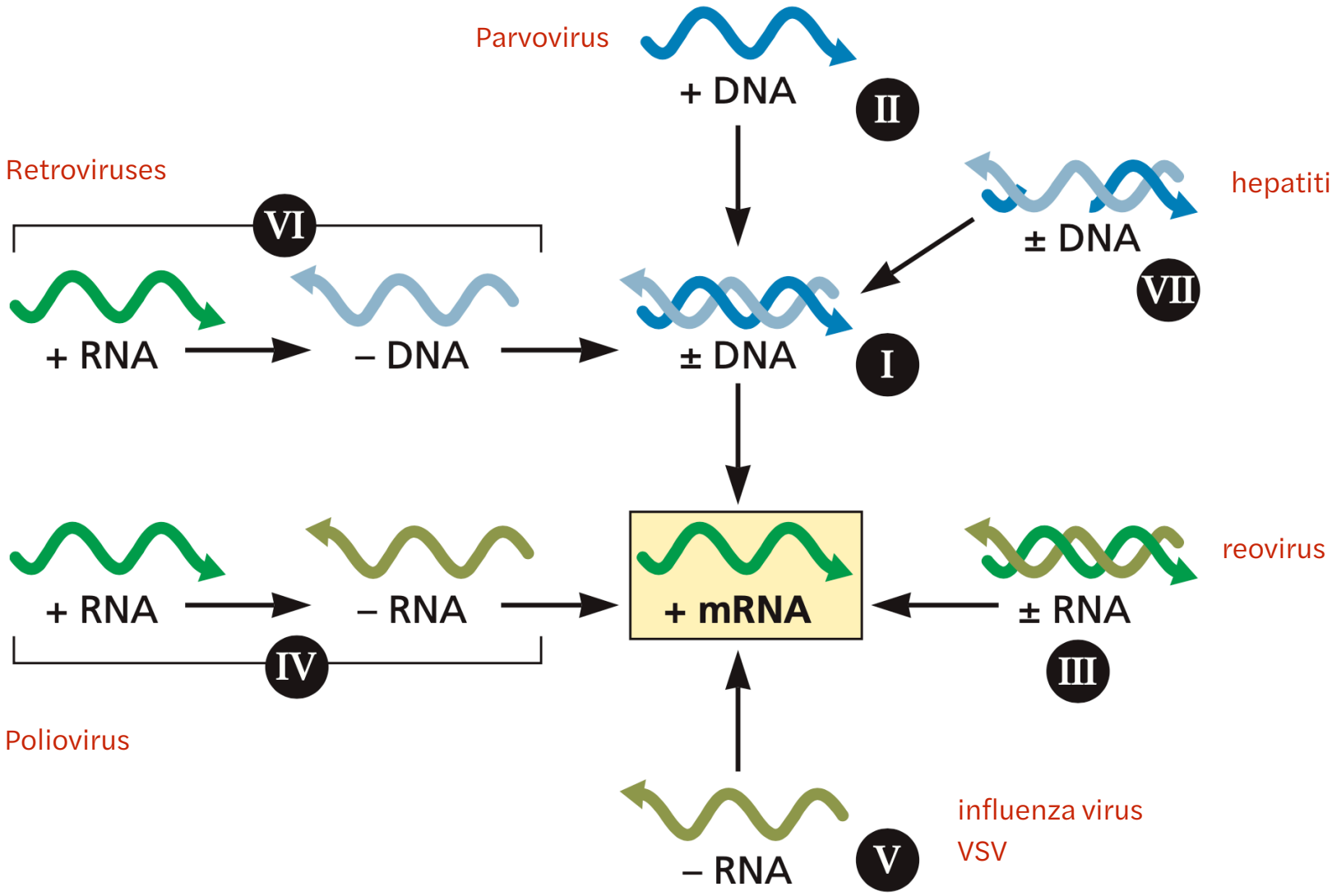
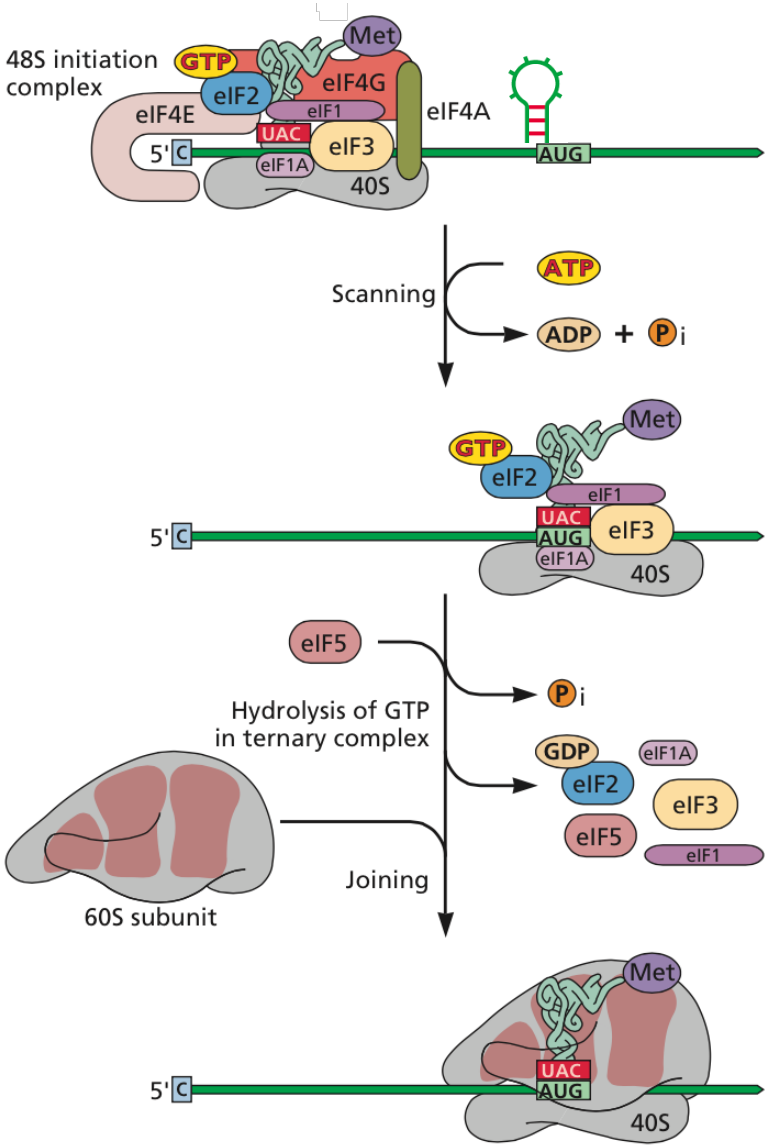
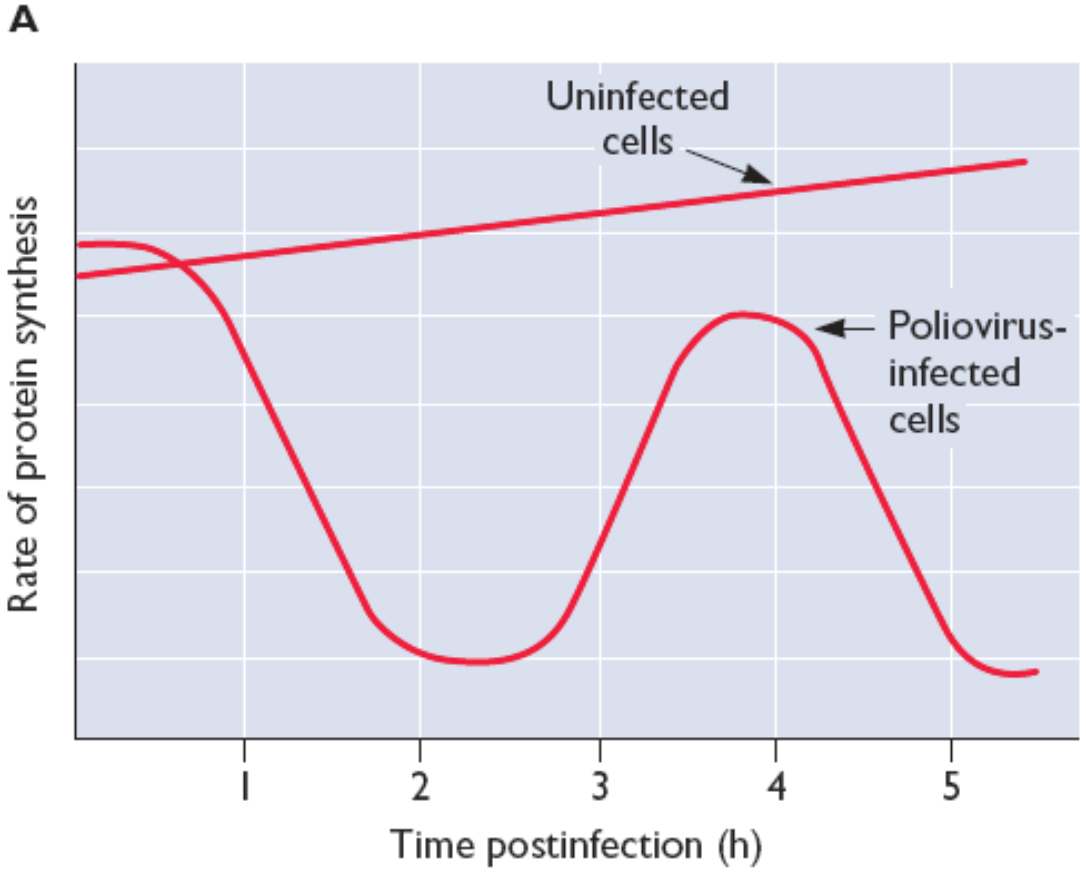
Which of the following is a consequence of viral proteins modifying signal transduction pathways to promote replication?

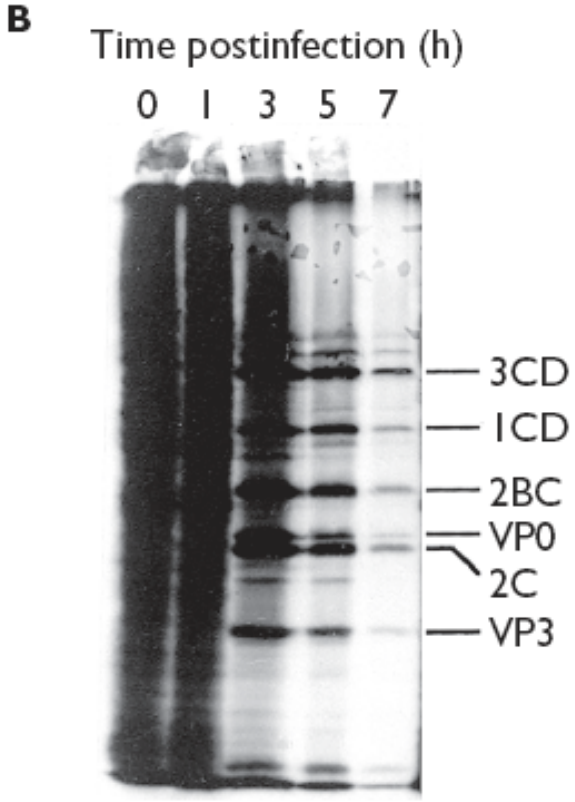
A. Poliovirus inhibition of transcription by RNA pol II
B. Herpes simplex virus protein blocking pre-mRNA splicing
C. Disruption of actin filaments to allow endocytosis
D. Initiation of mRNA degradation by viral proteins



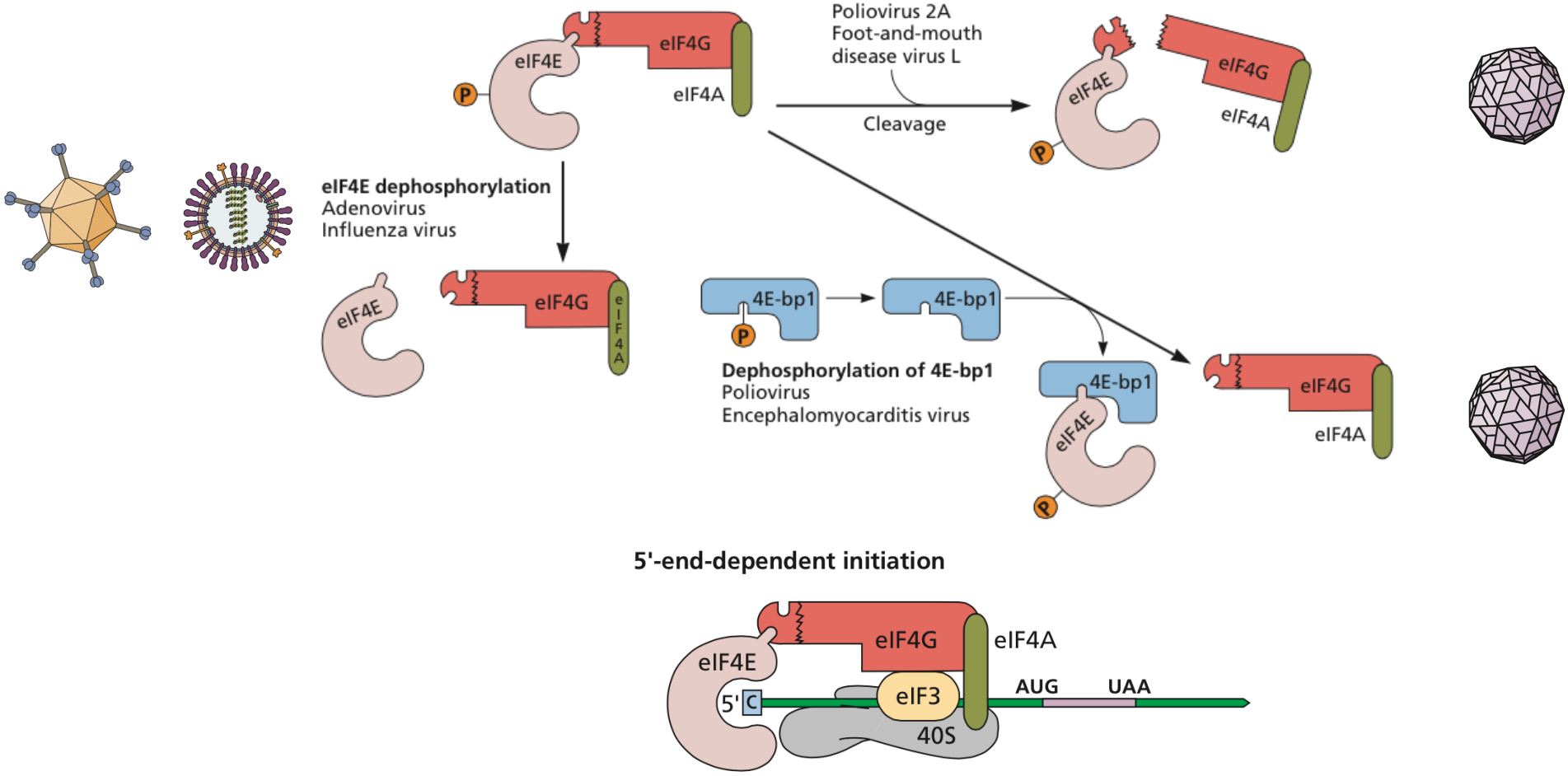


Viral inhibition of cell translation

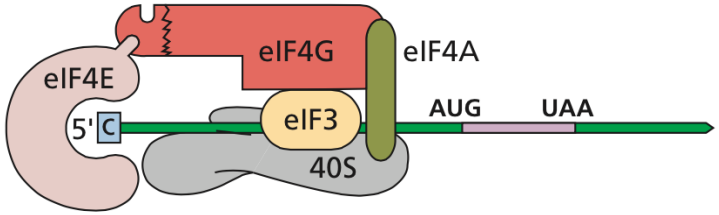




Modulation of cap recognition



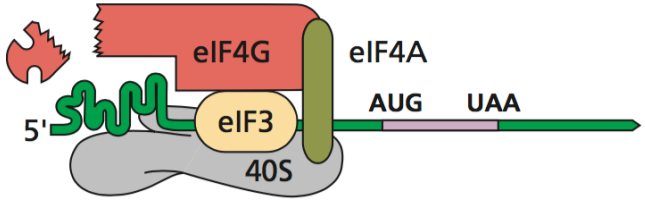
5'-end-dependent initiation



all eIFs

Internal initiation

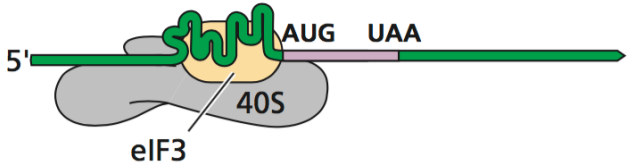
Type 1 or 2 IRES



all eIFs except eIF4E

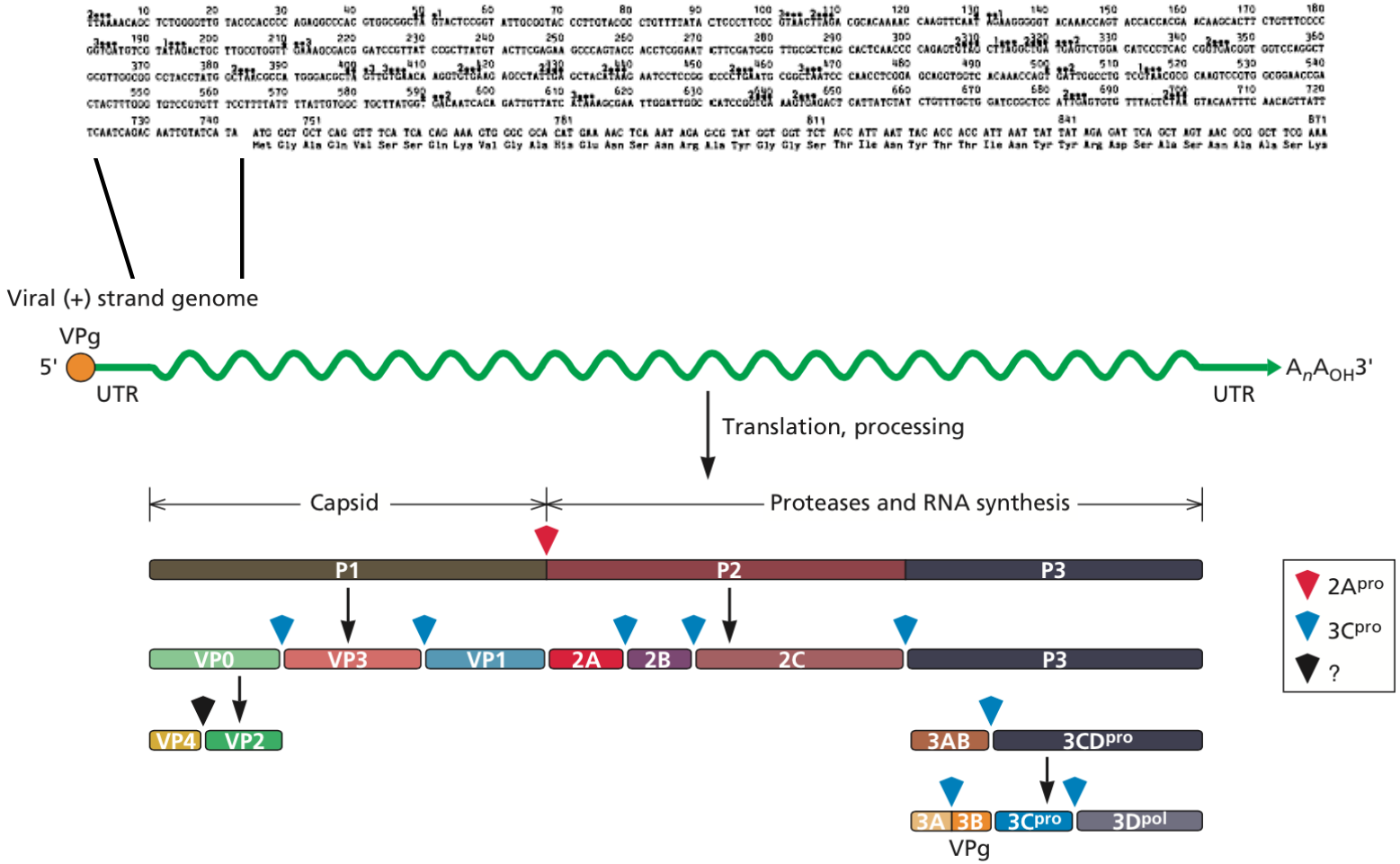
Internal initiation

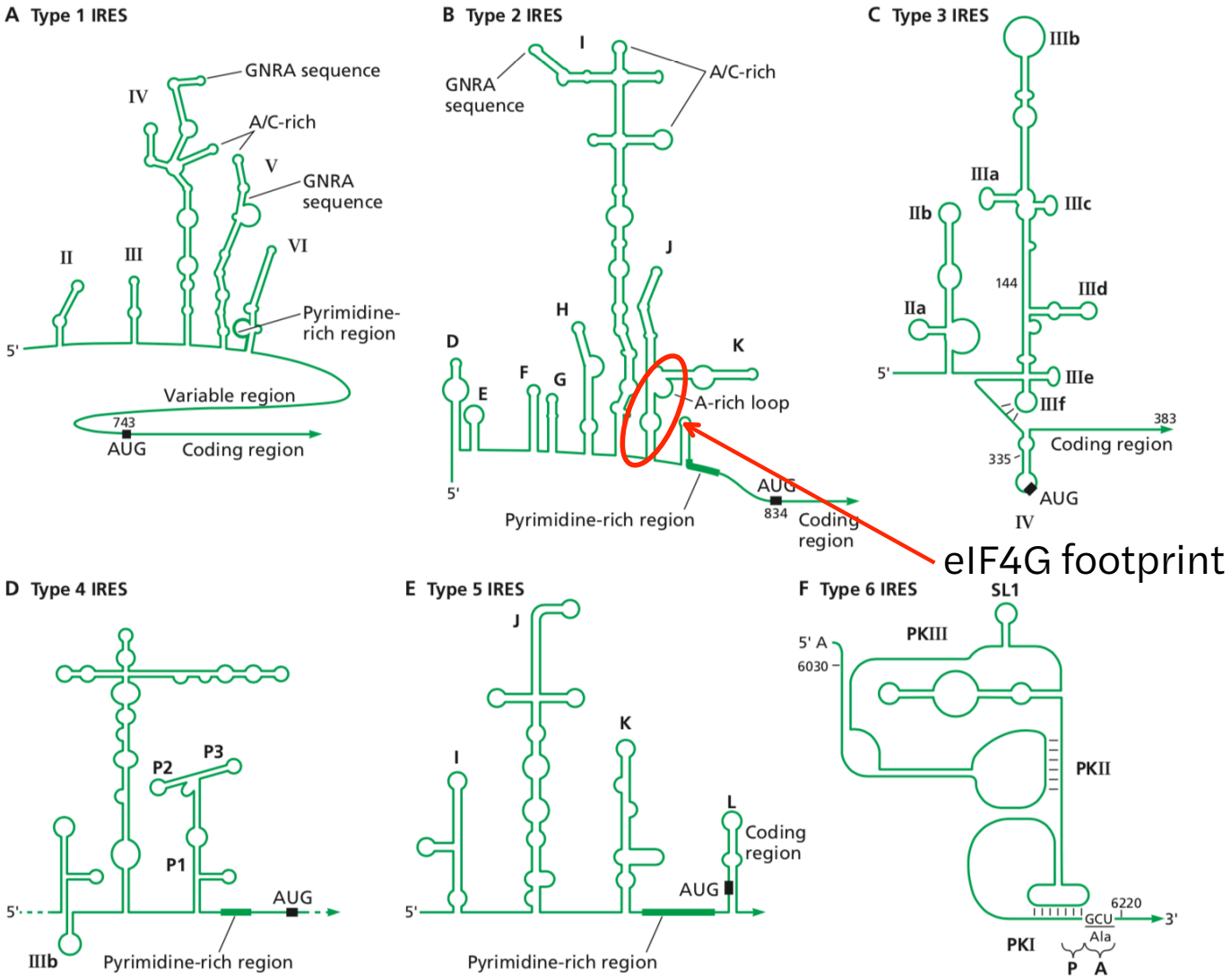
Hepatitis C virus IRES



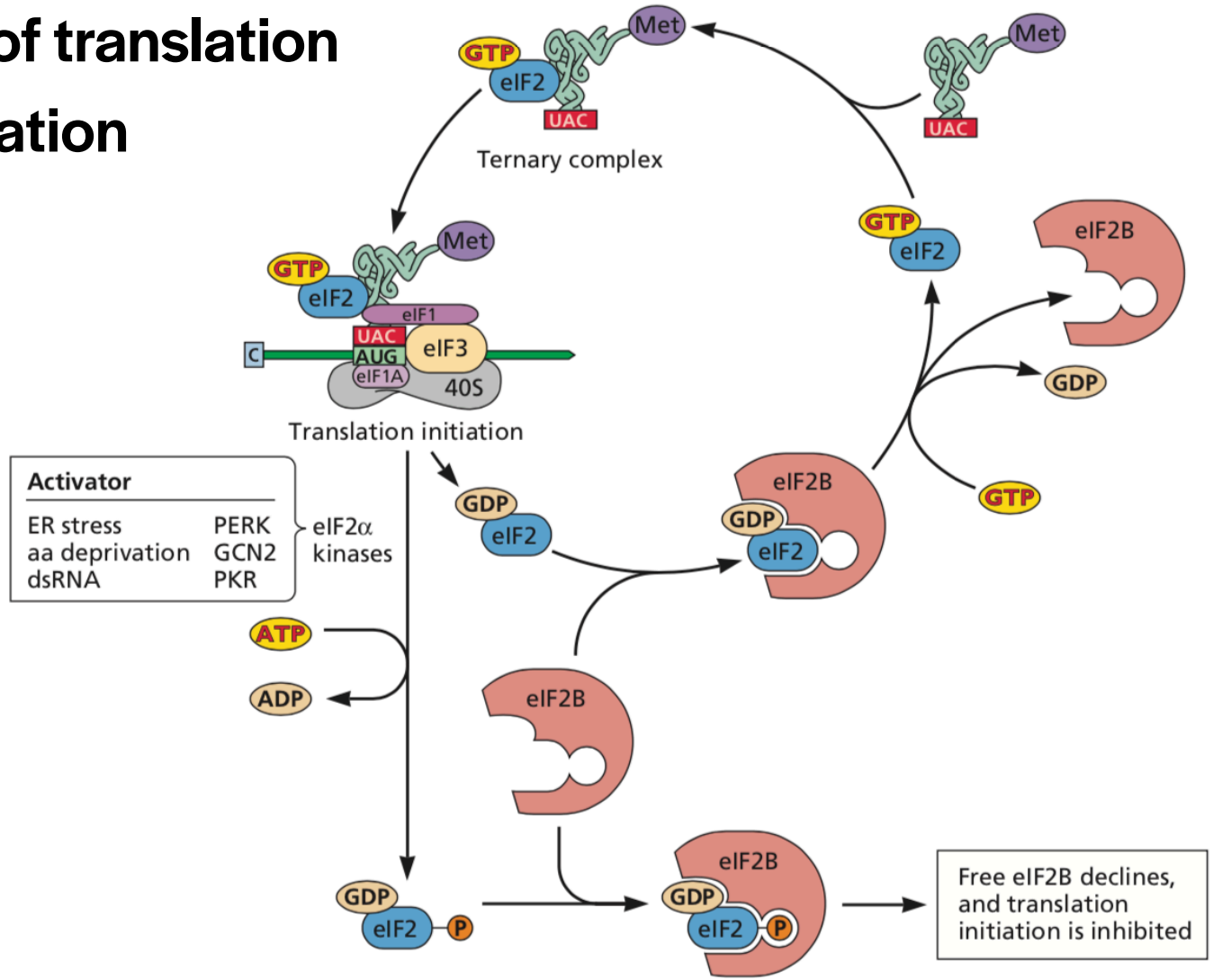
eIF2, eIF3

Internal initiation

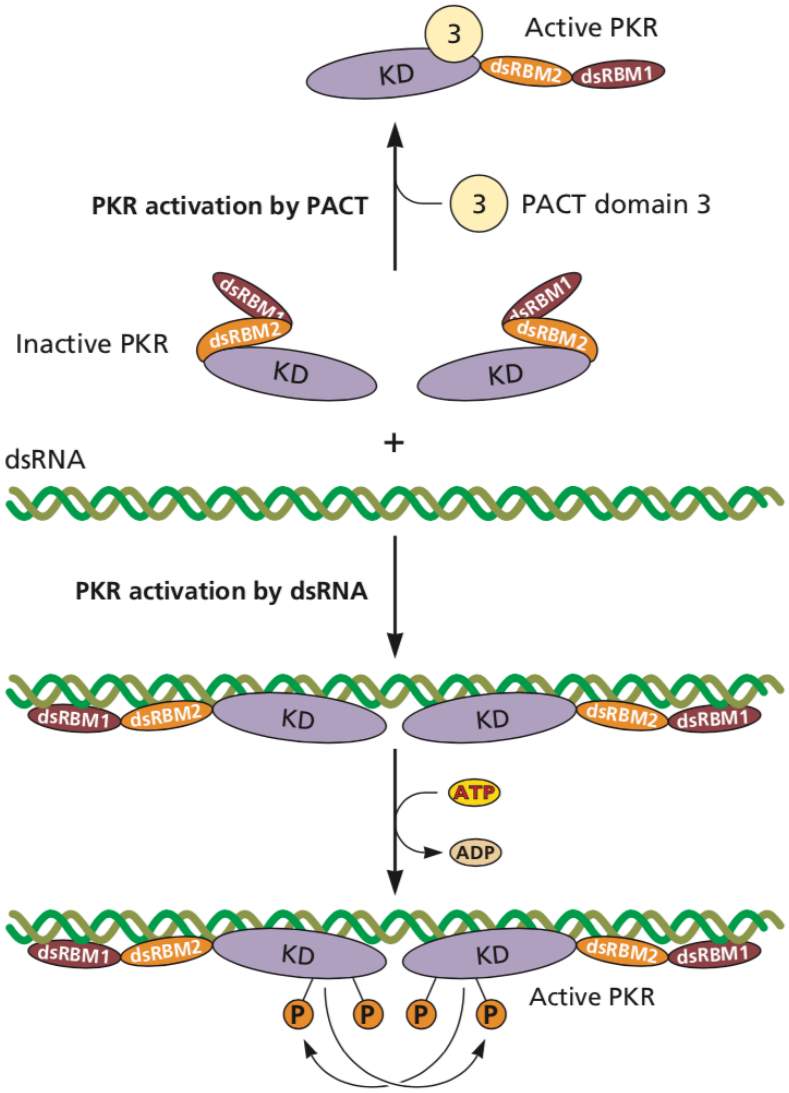




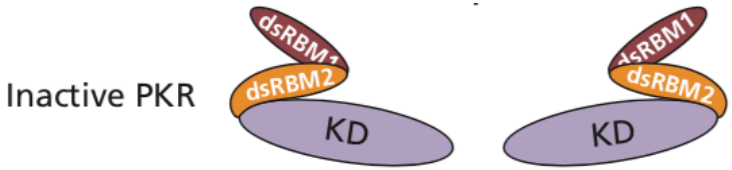
Regulation of translation initiation



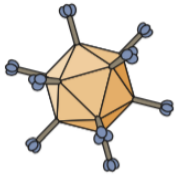
Activation of Pkr



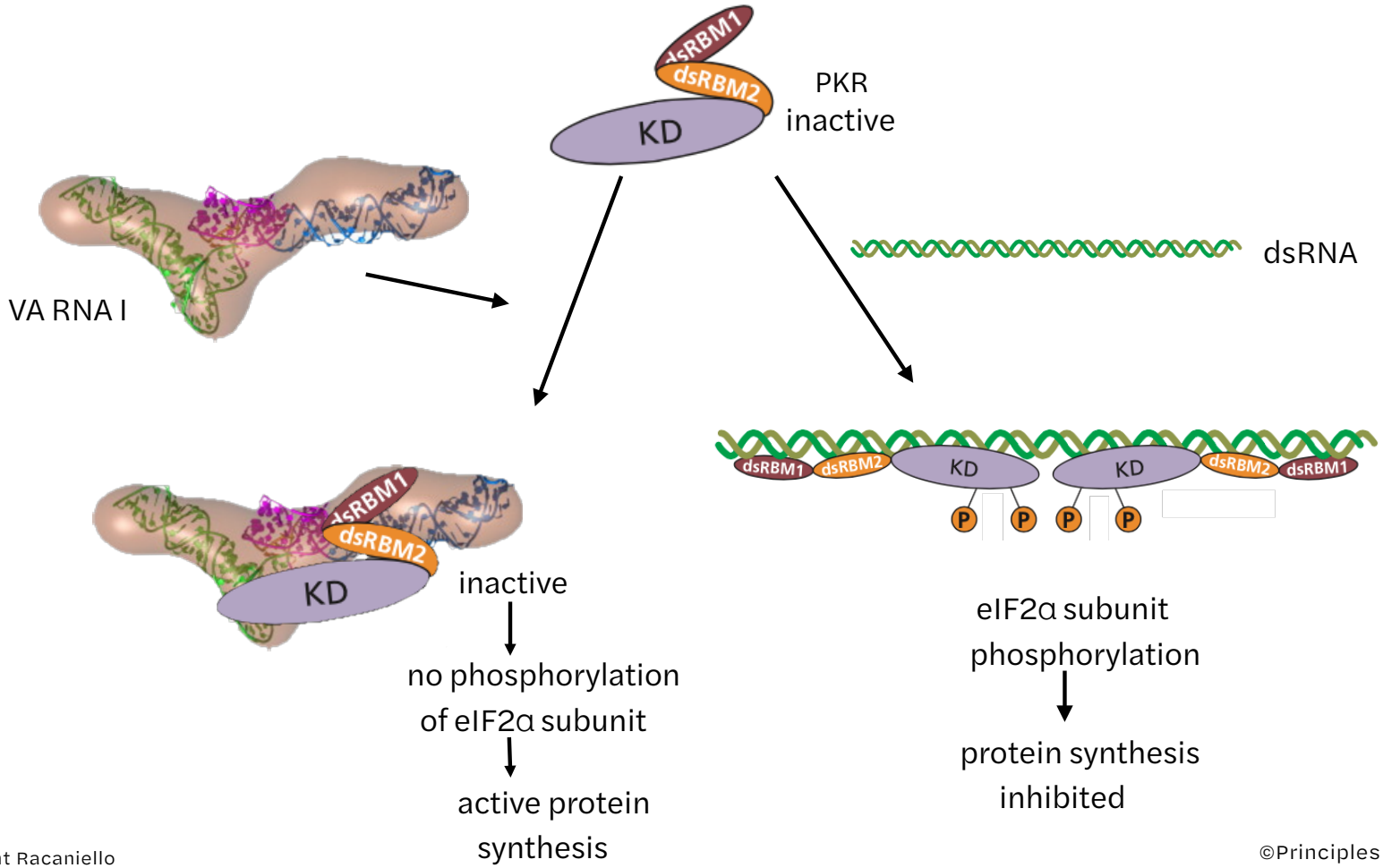
PKR and cellular antiviral response



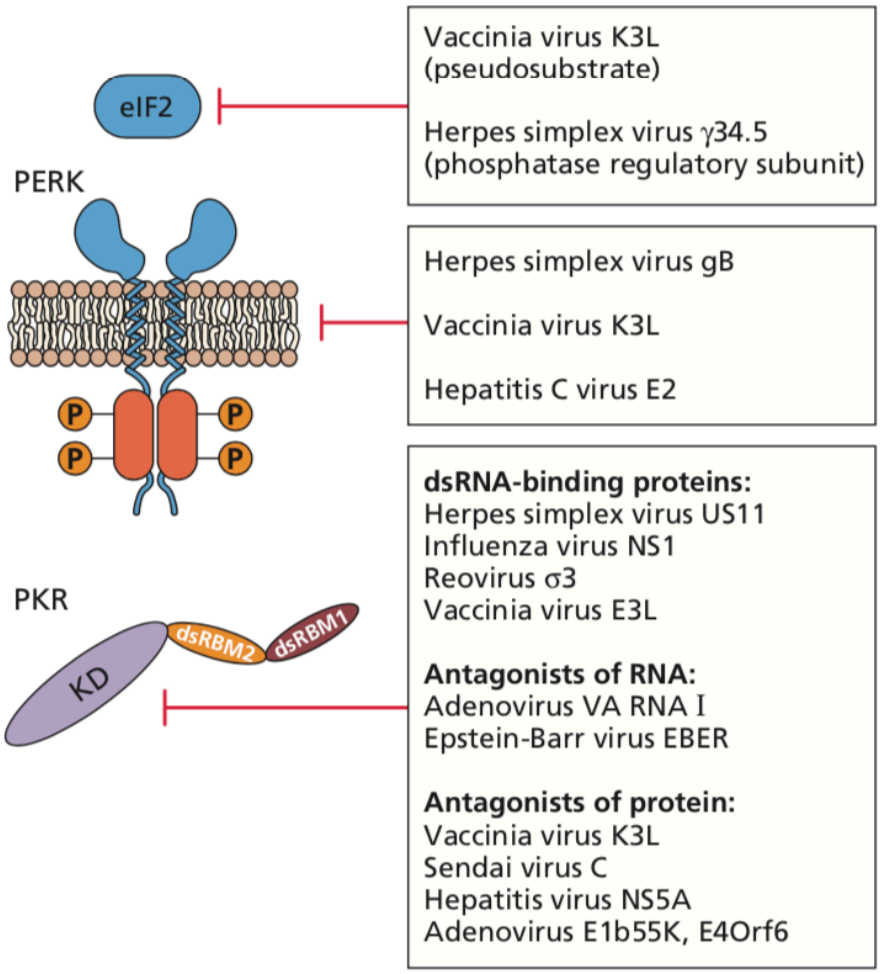
- PKR induced and activated by virus infection
- Leads to inhibition of host translation, apoptosis
- Different viral mechanisms have evolved to inactivate the PKR pathway



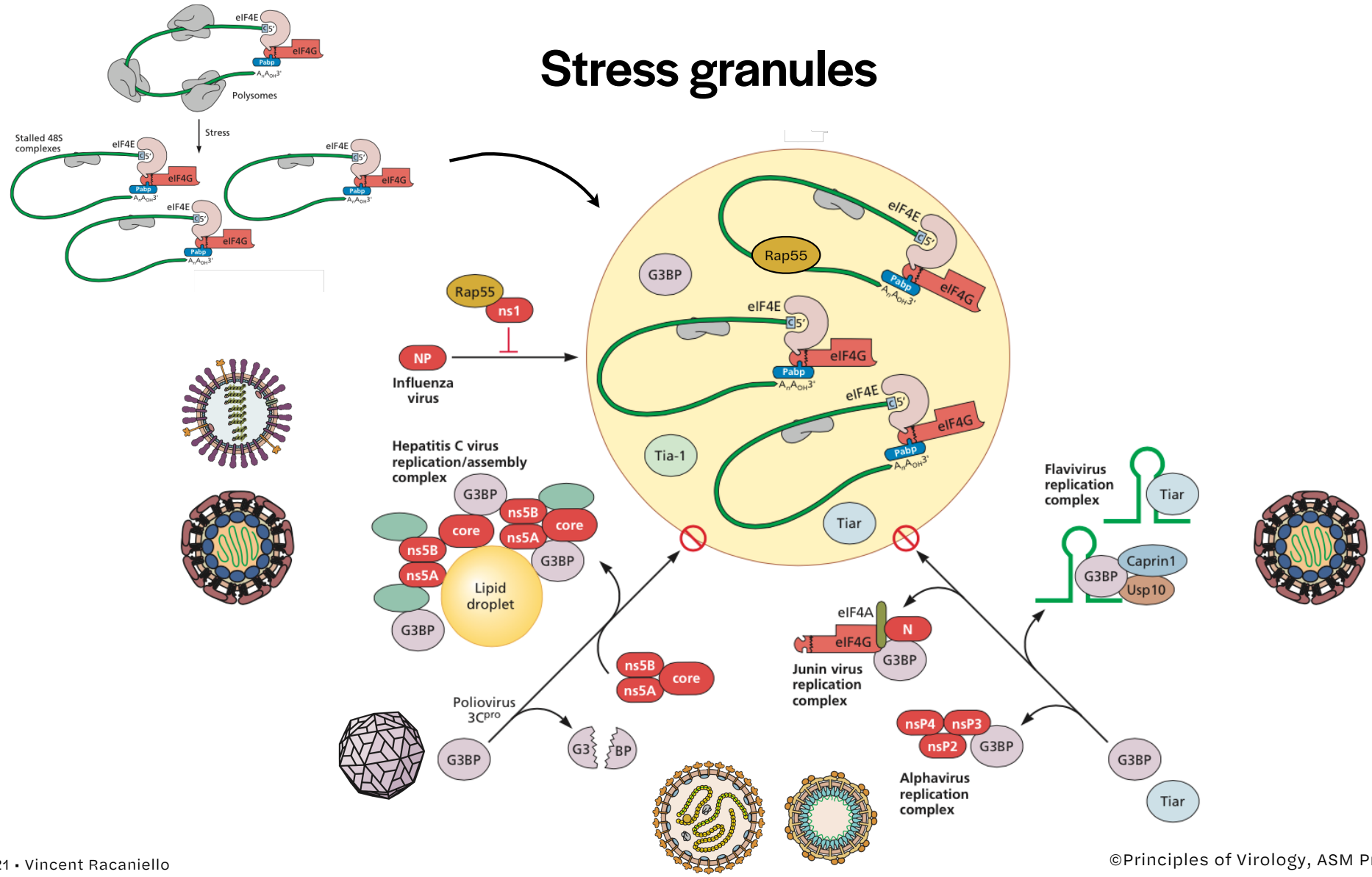
Adenovirus VA RNA I prevents activation of PKR



Viral proteins and RNAs that counter inactivation of eIF2



Stress granules



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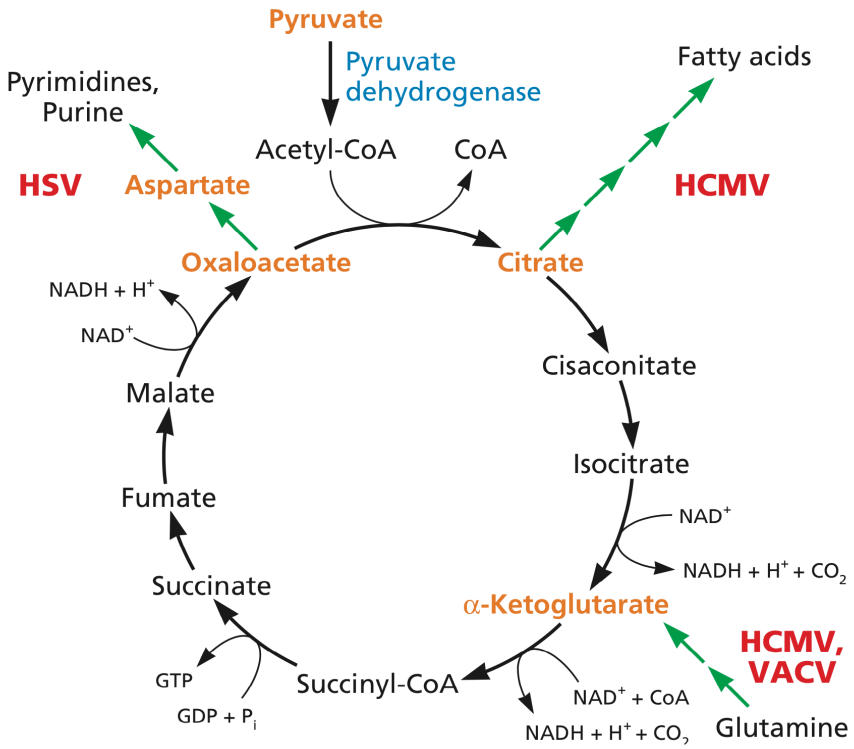
PKR is an interferon-induced enzyme that is activated by _____, leading to phosphorylation of _____ and inhibition of translation.

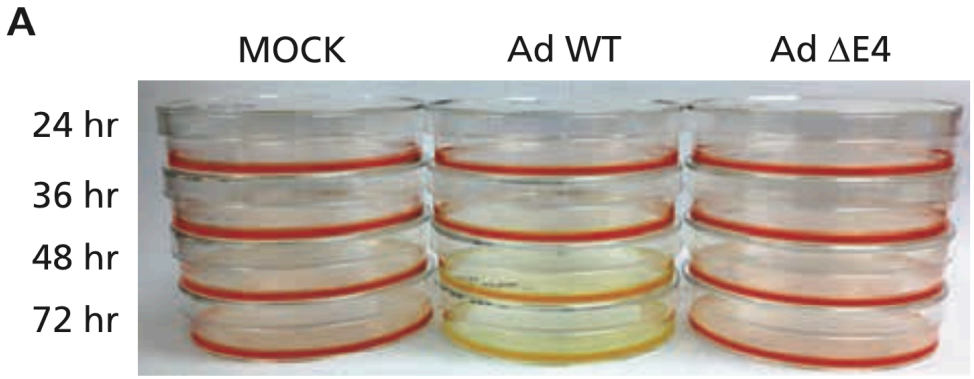
A. GDP, eIF2alpha
B. dsRNA, eIF2alpha
C. dsRNA, eIF2B
D. ssRNA, eIF2alpha
E. None of the above

Metabolism

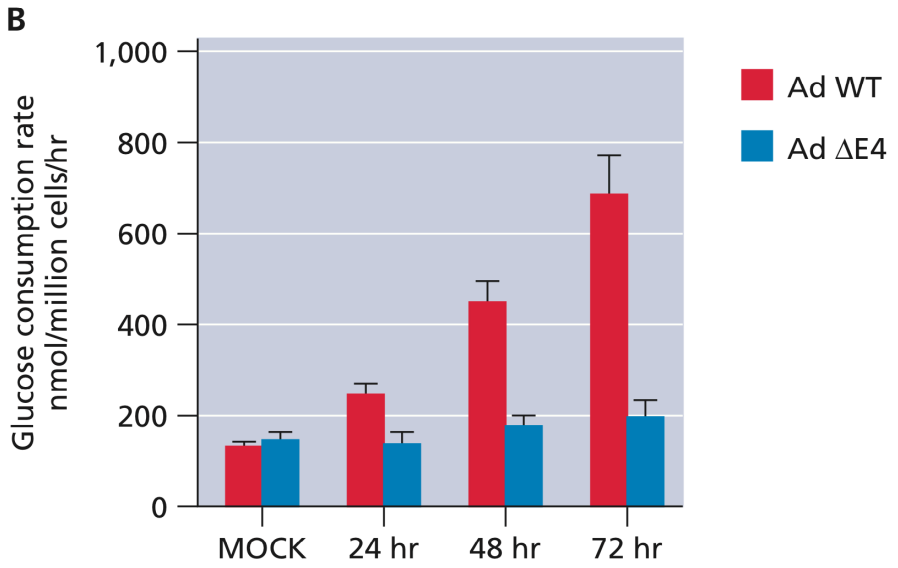


- Production of large quantities of virus particles places high demands on host cell biosynthetic systems
- Nucleotides, amino acids, fatty acids
- Energy is needed! 4 ATP to make a single peptide bond
- Virus infection impacts cell metabolism

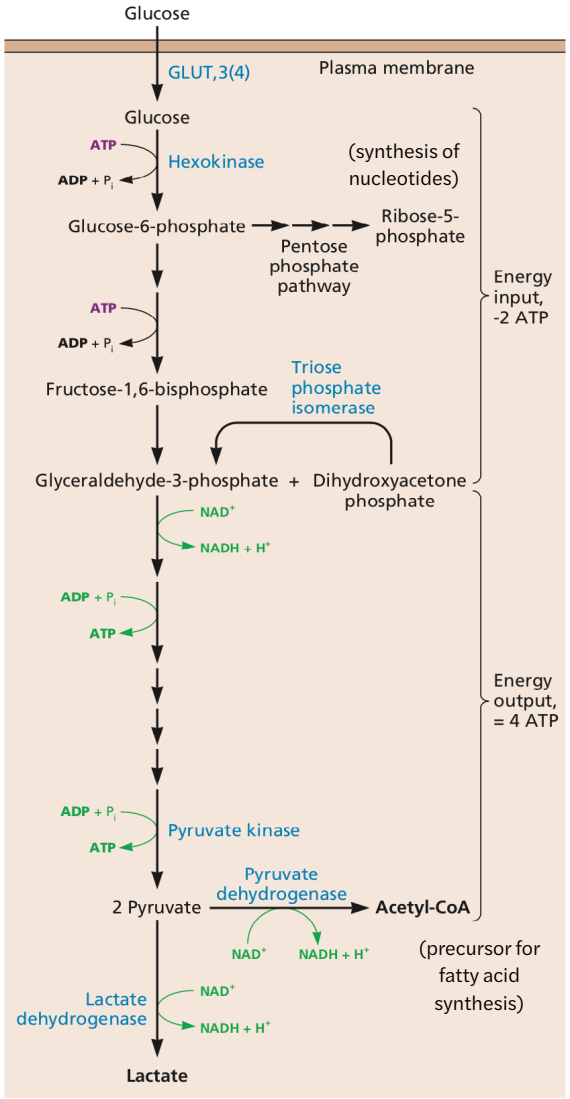
Increased glycolysis in virus infected cells



Low pH = production of lactic acid, product of glycolysis



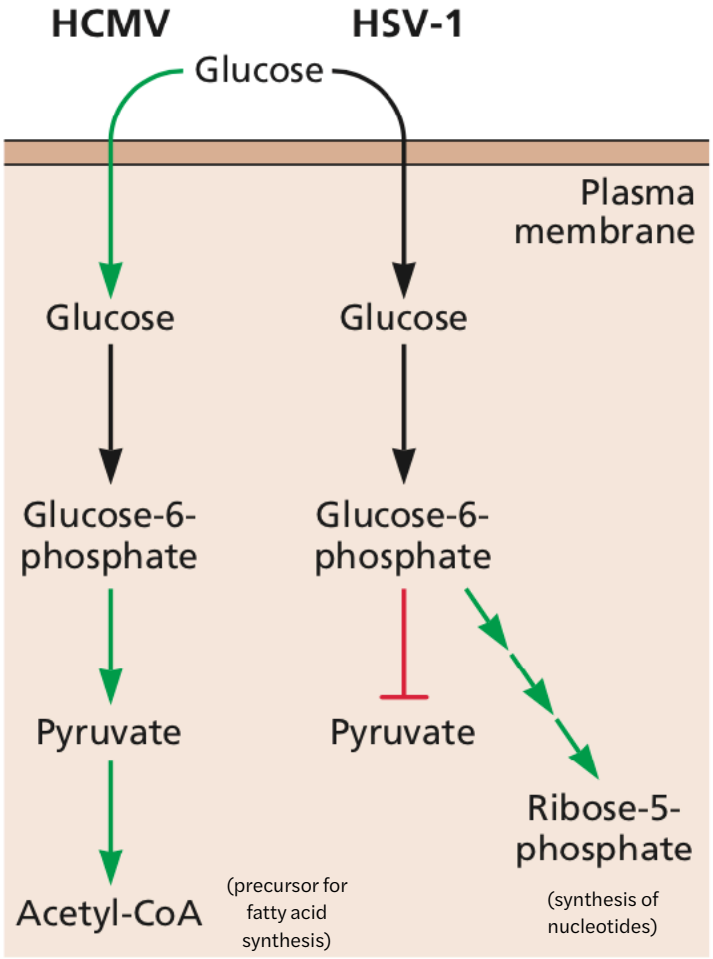
See Rhinoviruses have a sweet tooth
http://www.virology.ws/2018/08/23/rhinoviruses-have-a-sweet-tooth/



Glucose metabolism

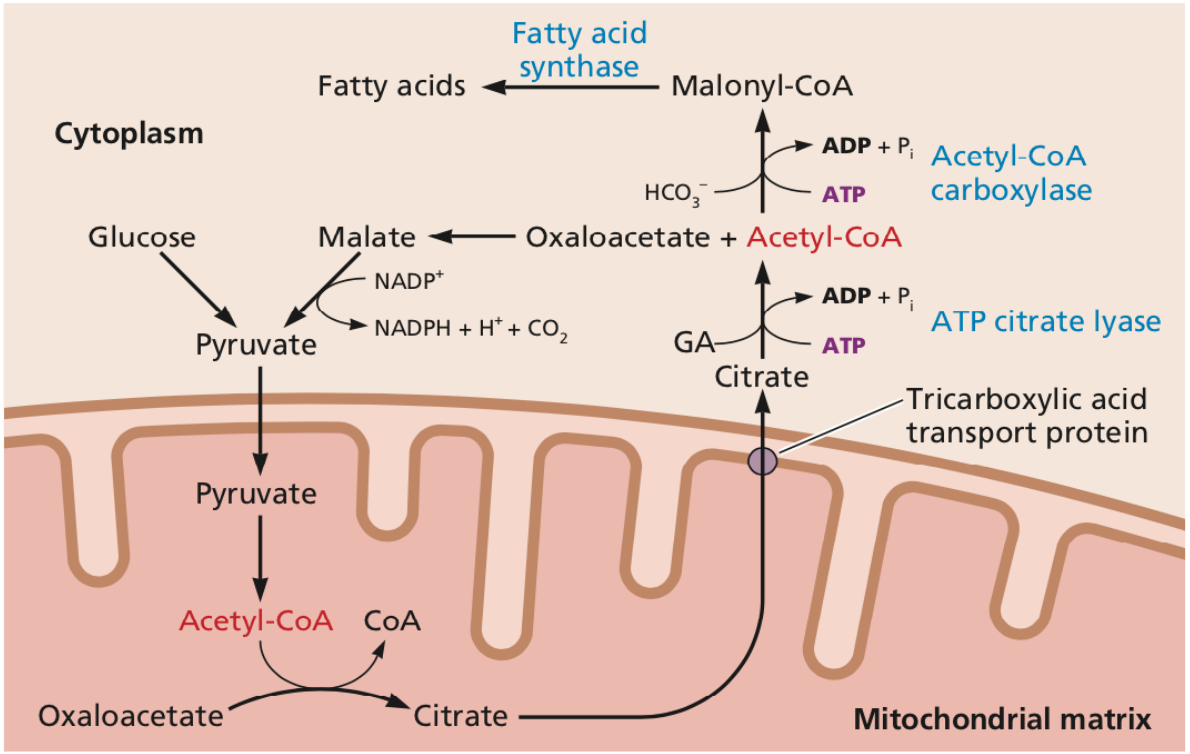
- Glucose is major breakdown product of dietary carbohydrate
- Converted to pyruvate, yields 2 ATP and 2 NADH
- Intermediates allow more ATP synthesis
- Perturbed in virus infected cells

Virus effects on glycolysis



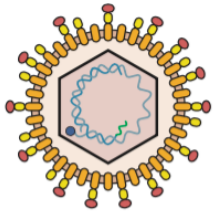
- Two herpesviruses have different effects on glycolysis
- Hypothesis: HSV has shorter reproduction cycle, need more nucleotide precursors to synthesize viral DNAs

Fatty acid synthesis

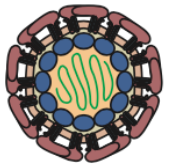


- Acetyl-CoA cannot cross mitochondrial membrane
- Most citrate in HCMV infected cells leave mitochondria for fatty acid synthesis
- Inhibition of malonyl-CoA or FAS reduces yield of HCMV particles
- Activity of another member of this shuttle is increased in cells infected with VSV

Virus-induced changes in glucose metabolism and human disease



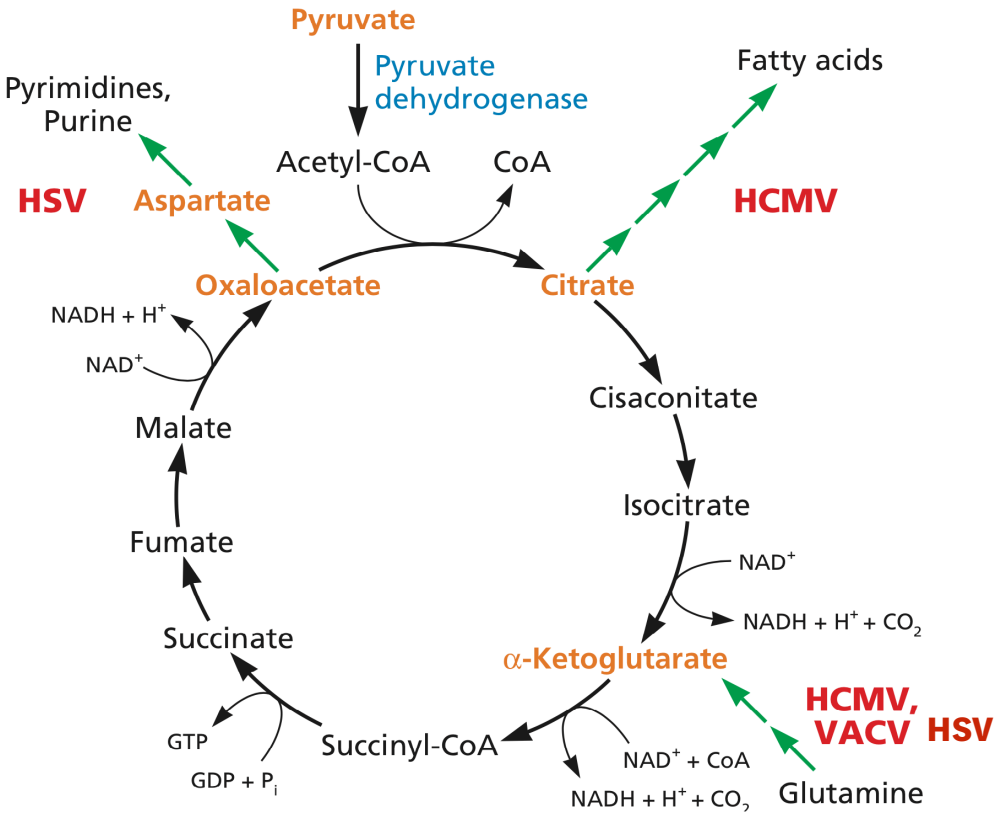
Two hepatotropic viruses



- Liver site of glycogen and *de novo* glucose synthesis
- HBV infection associated with development of type 2 diabetes*; infection stimulates levels of enzymes involved in glucose synthesis
- T2D also associated with HCV infection, which causes reduced glucose uptake and increased gluconeogenesis

*insulin deficiency/resistance

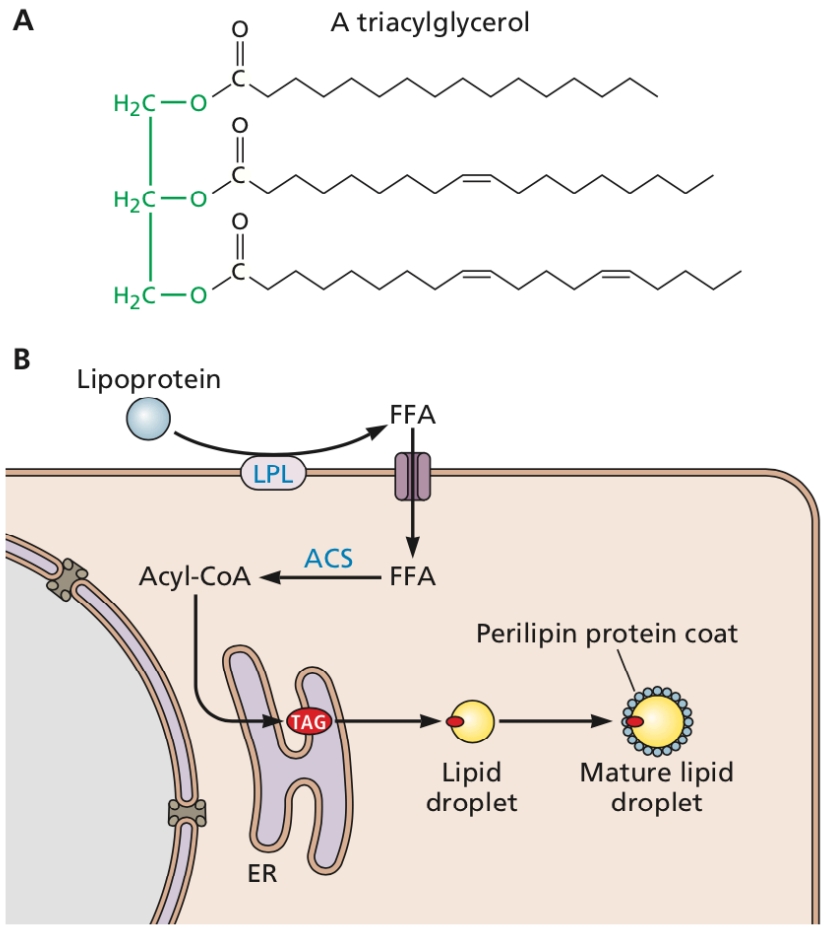
Citric acid (TCA) cycle



- Central hub of carbon metabolism
- Yields precursors for biosynthesis of many compounds
- Virus infections impact cycle

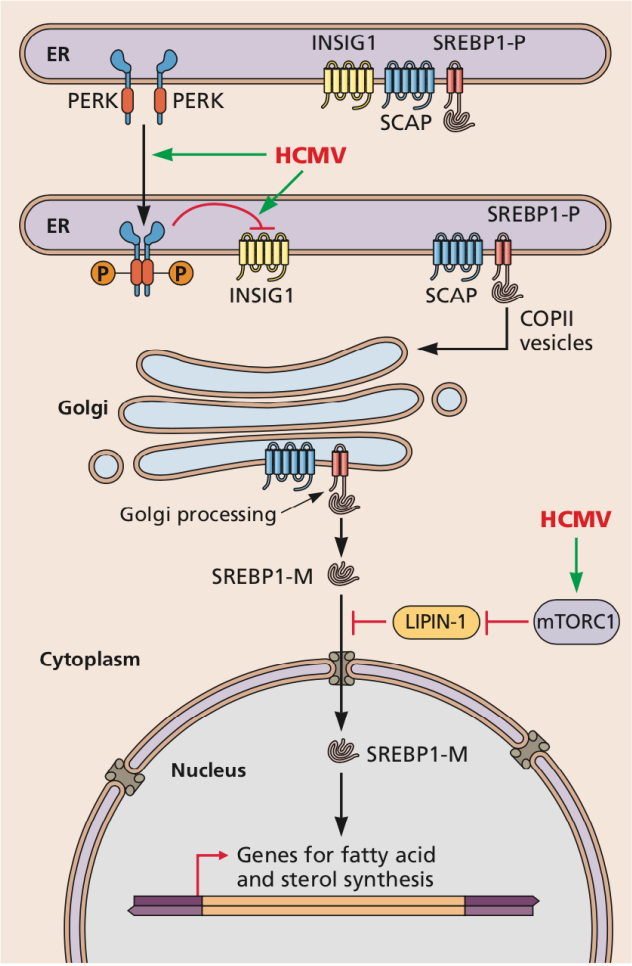
(prevents halting of TCA cycle)

Lipid metabolism



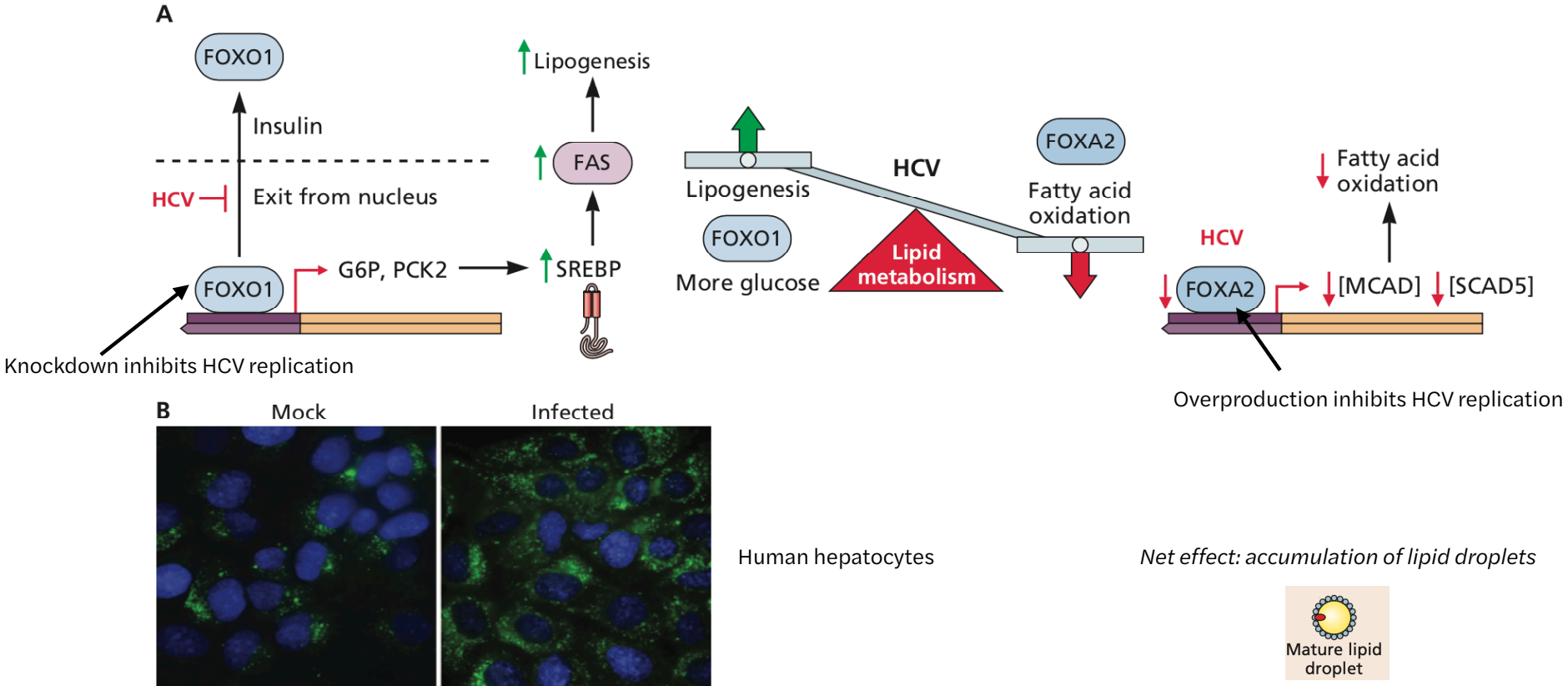
- Triacylglycerols are primary energy source (oxidation) and store in most organisms
- Membrane synthesis
- Lipid metabolism modulated in virus infected cells: oxidation, synthesis

HCMV infection induces synthesis of very long chain fatty acids for assembly



- HCMV infection increases carbon flux from glucose to acetyl-CoA
- Not only increased FA production but very long chain FA found in viral membrane - required for infectivity
- Increased availability of activators for transcription of genes for lipid synthesis

Increased synthesis and accumulation of fatty acids in HCV infected cells



Human hepatocytes

Net effect: accumulation of lipid droplets

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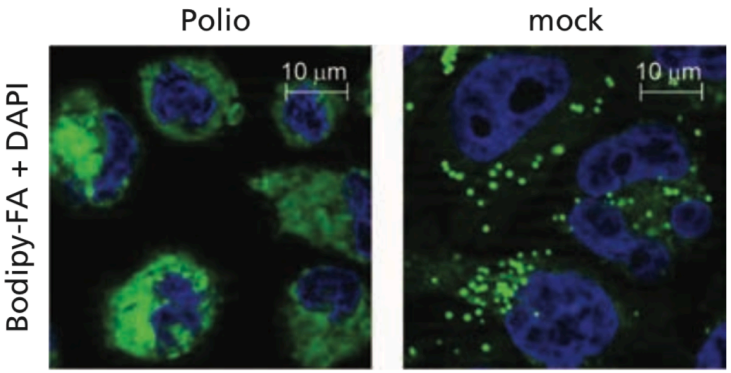
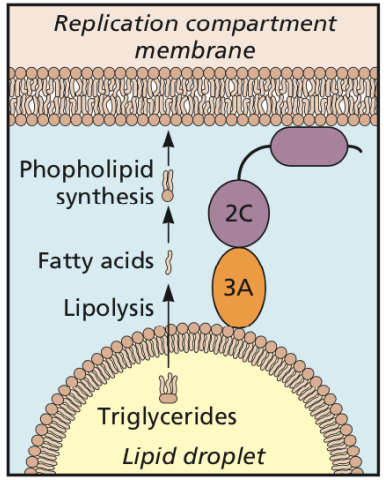
How might virus infection lead to increased levels of ATP?

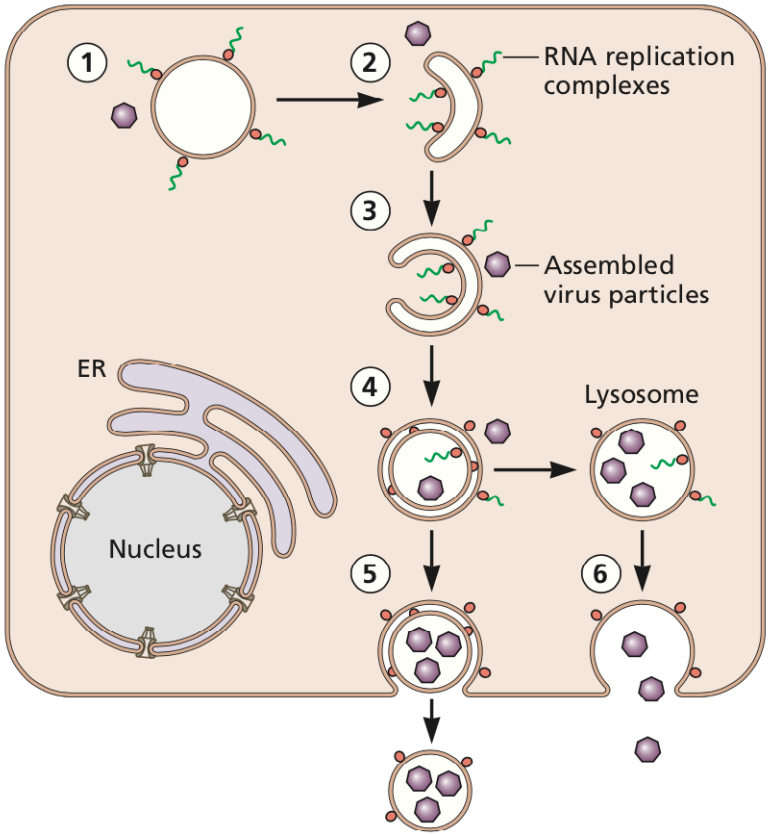
A. Stimulation of glucose uptake
B. Increased glycolysis
C. Increased oxidation of fatty acids
D. Increased utilization of glutamine
E. All of the above

Remodeling of cellular organelles:
Co-option of cytoplasmic membranes in PV infected cell

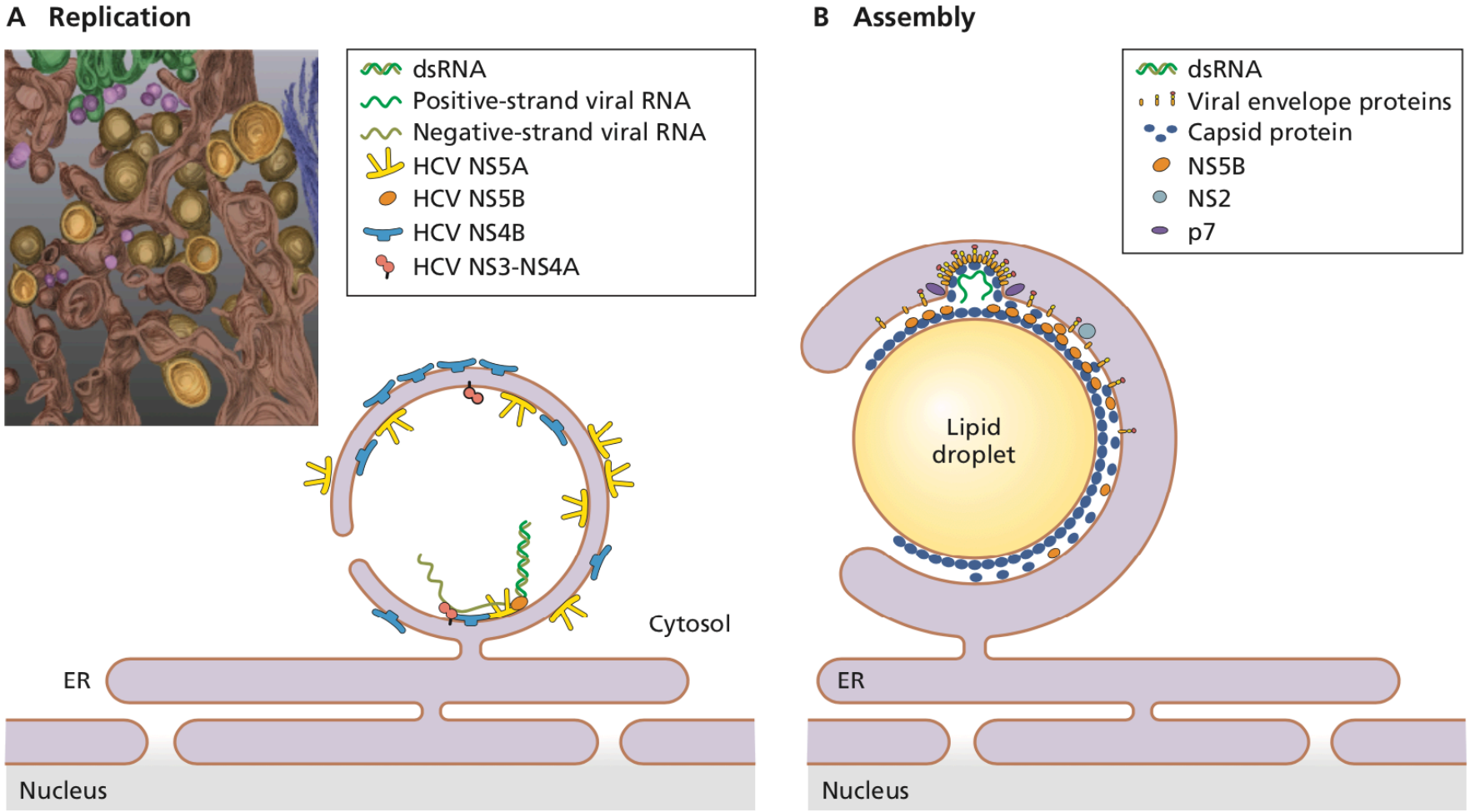


Increased import of fatty acids into poliovirus-infected cells



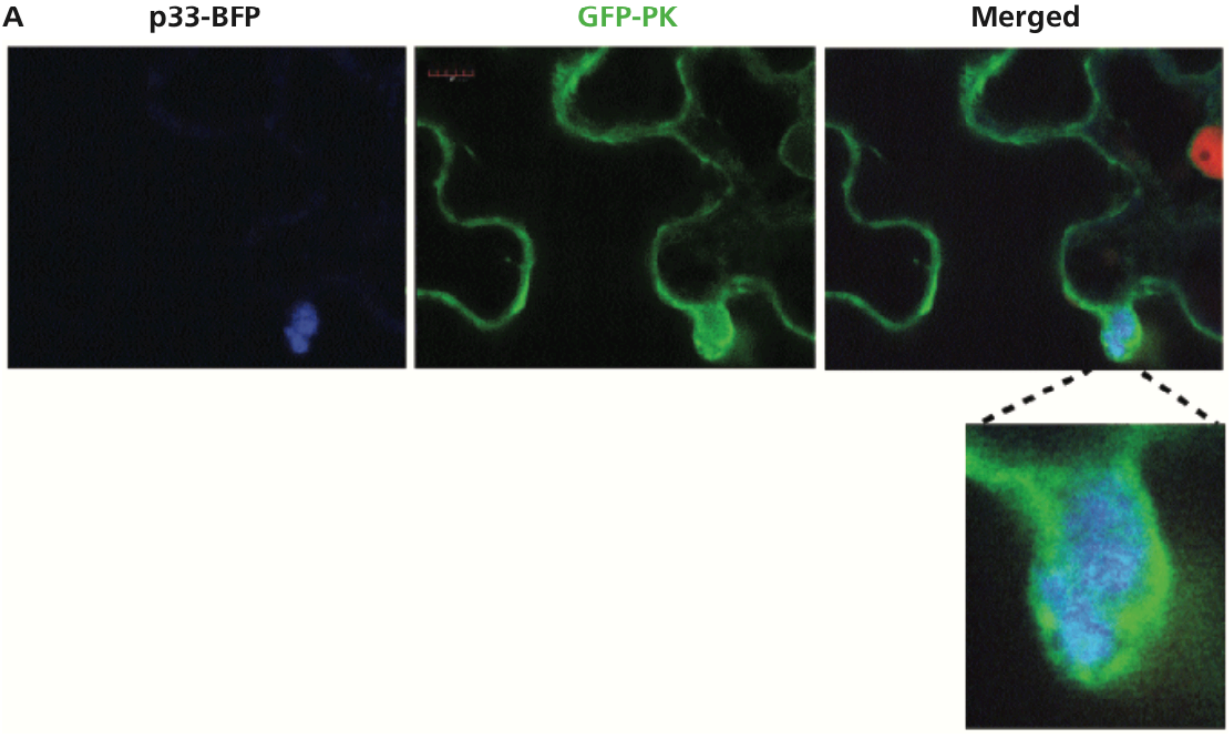


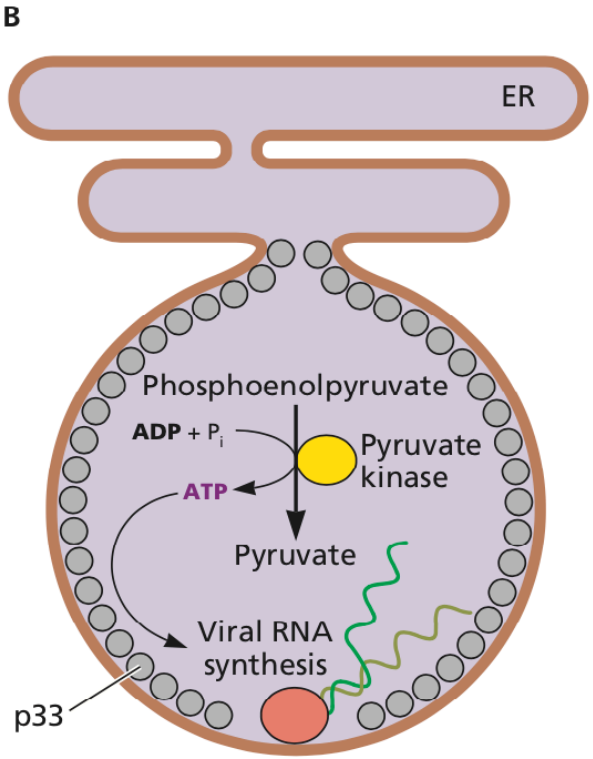
HCV replication and assembly compartments



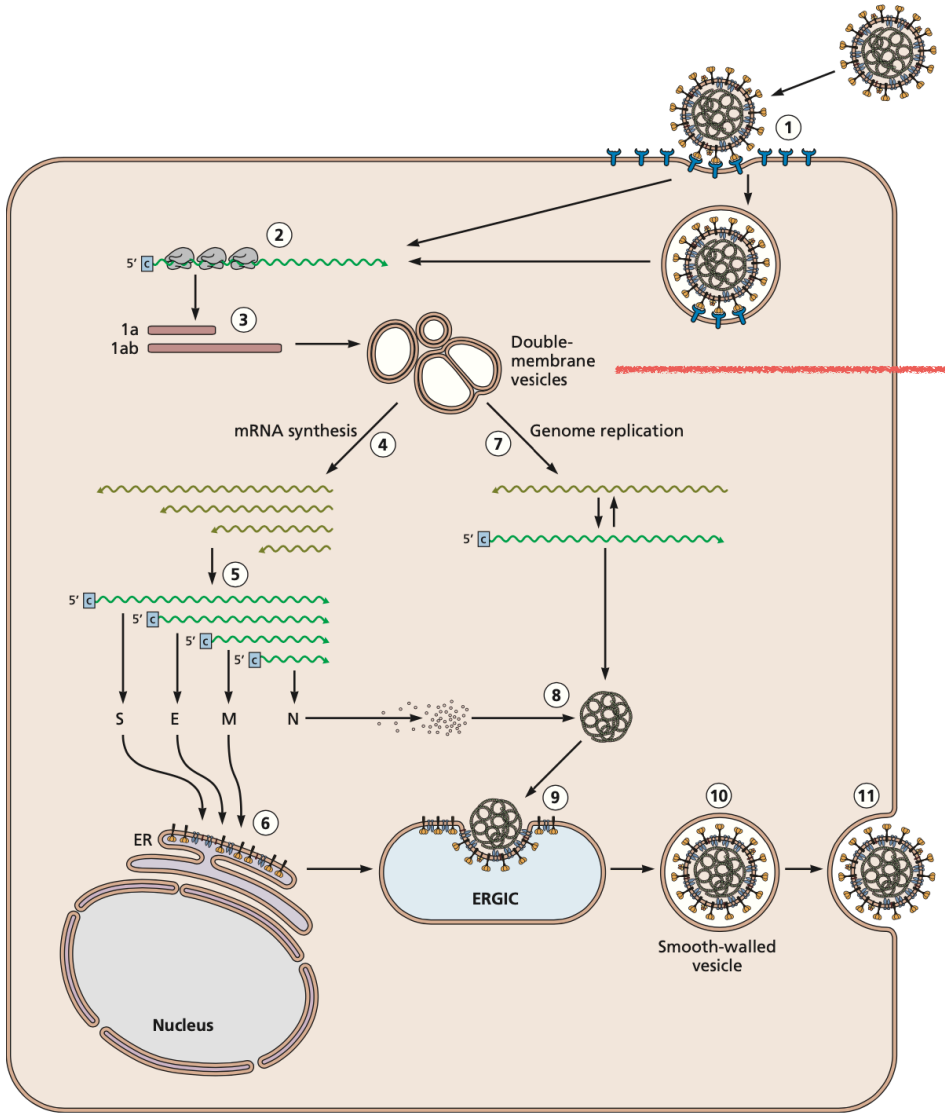
Glycolytic pyruvate kinase recruited into viral replication complex to generate ATP for RNA synthesis

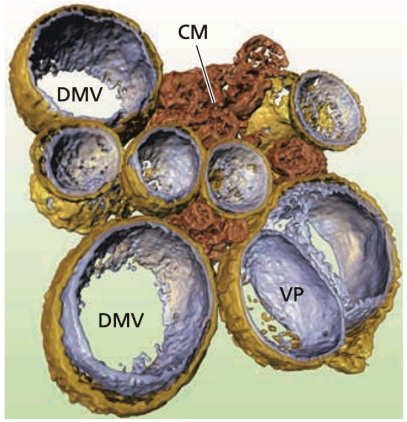
Tomato bushy stunt virus





PK supplies ATP for helicases





Next time: Infection basics