The Chinese University of Hong Kong

Joint Graduate Seminar Dec 2009

The Interplay of Human Papillomavirus Early Proteins

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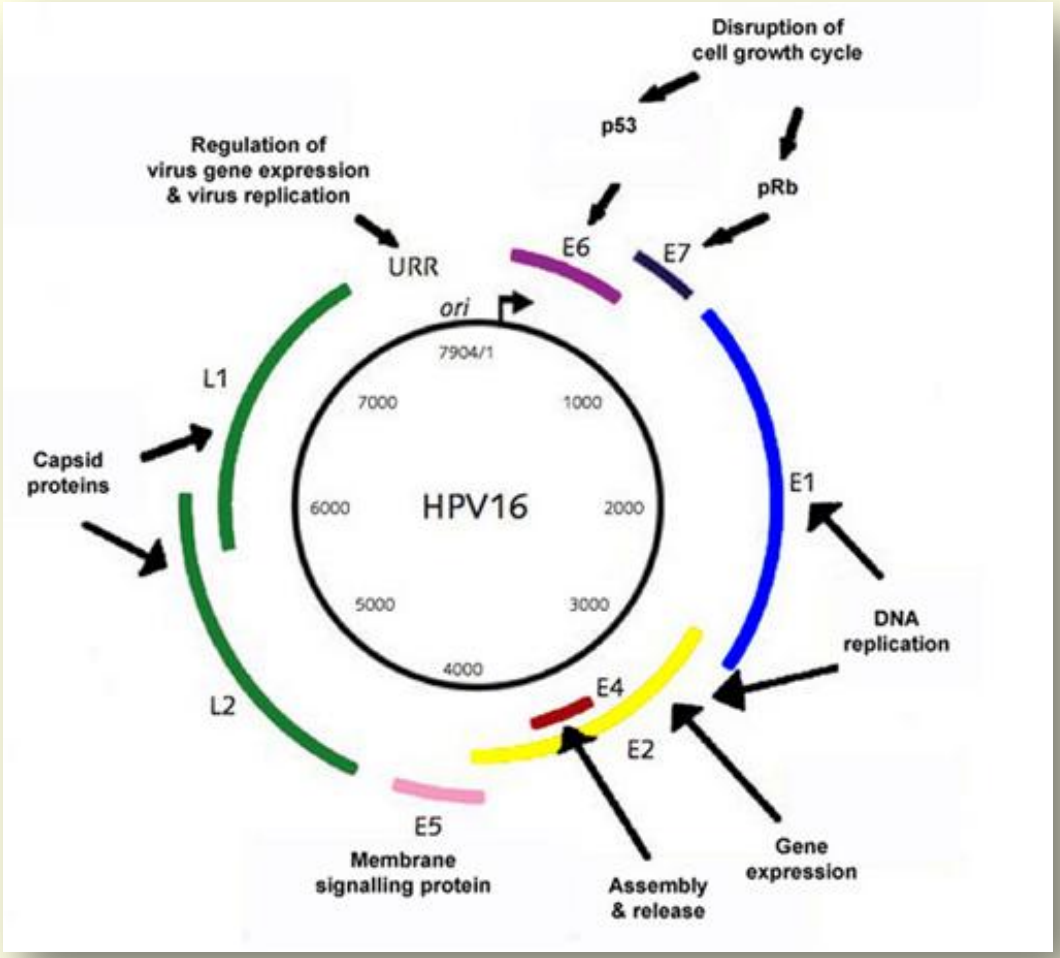
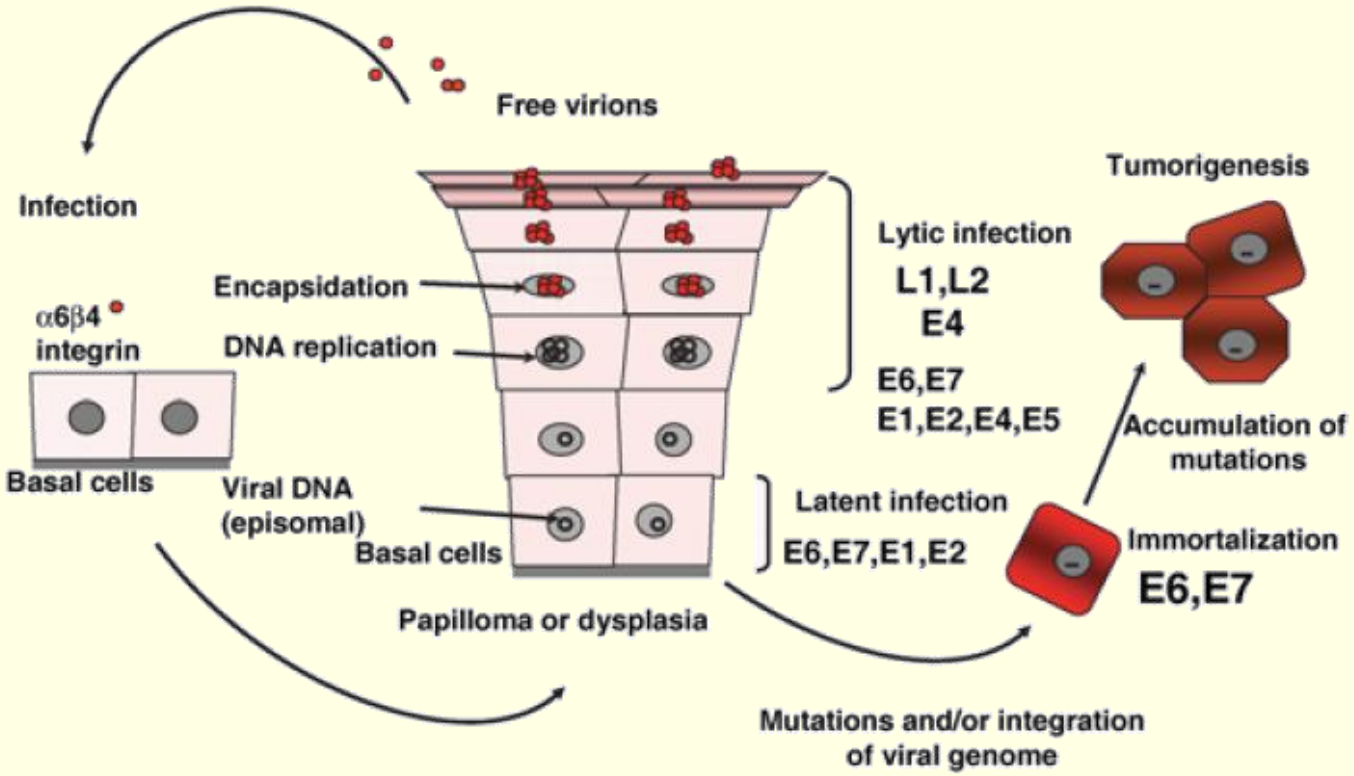
The HPV genome



Protein	Function
E1	Replication
E2	Transcription, replication
E4	Disruption of cytokeratin networks/cell growth arrest
E5	Transformation
E6	Transformation (binds to p53 amongst other proteins)
E7	Transformation (to pRb amongst other proteins)
L1	Major capsid protein
L2	Minor capsid protein

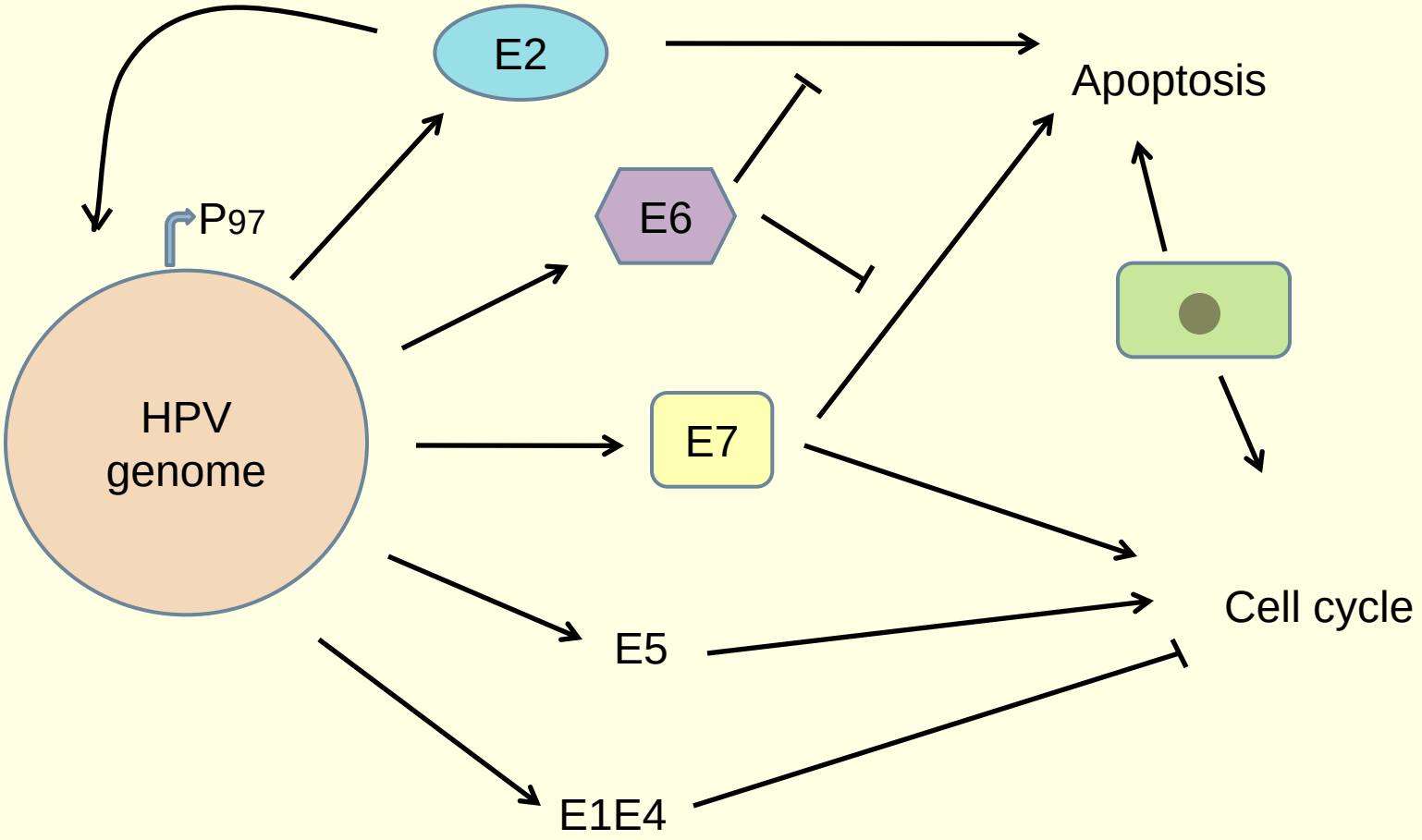
Hamid N.D et al Cell. Mol. Sci. 66 (2009) 1700-1717

The HPV life cycle



Narisawa-Saito M et al, Cancer Sci (2007) 98 1505-1511

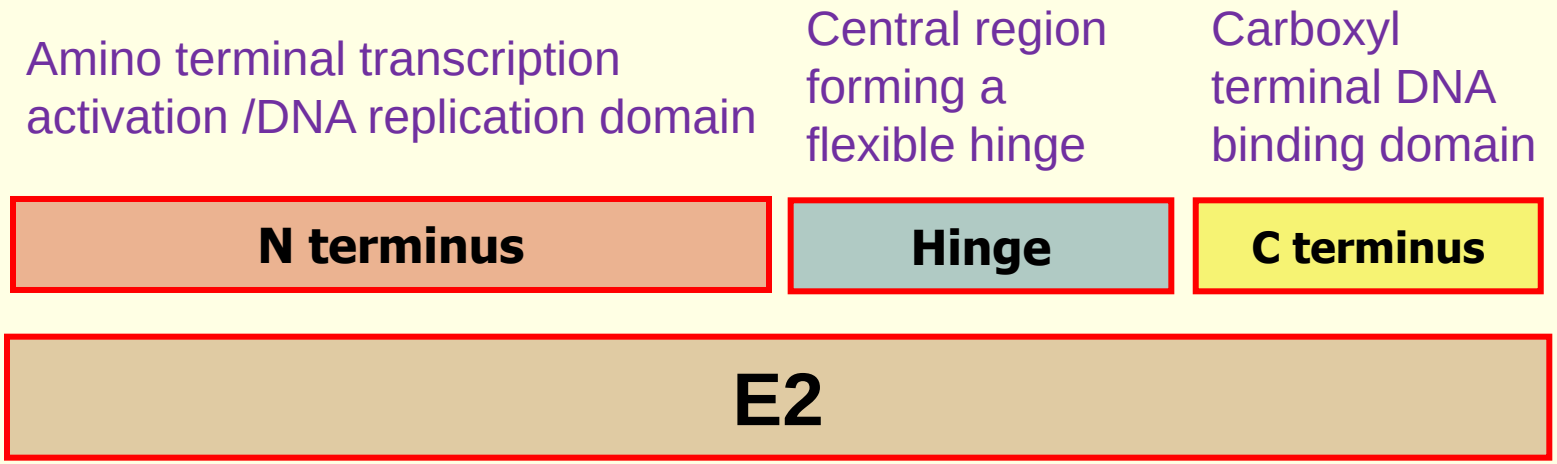
HPV early proteins



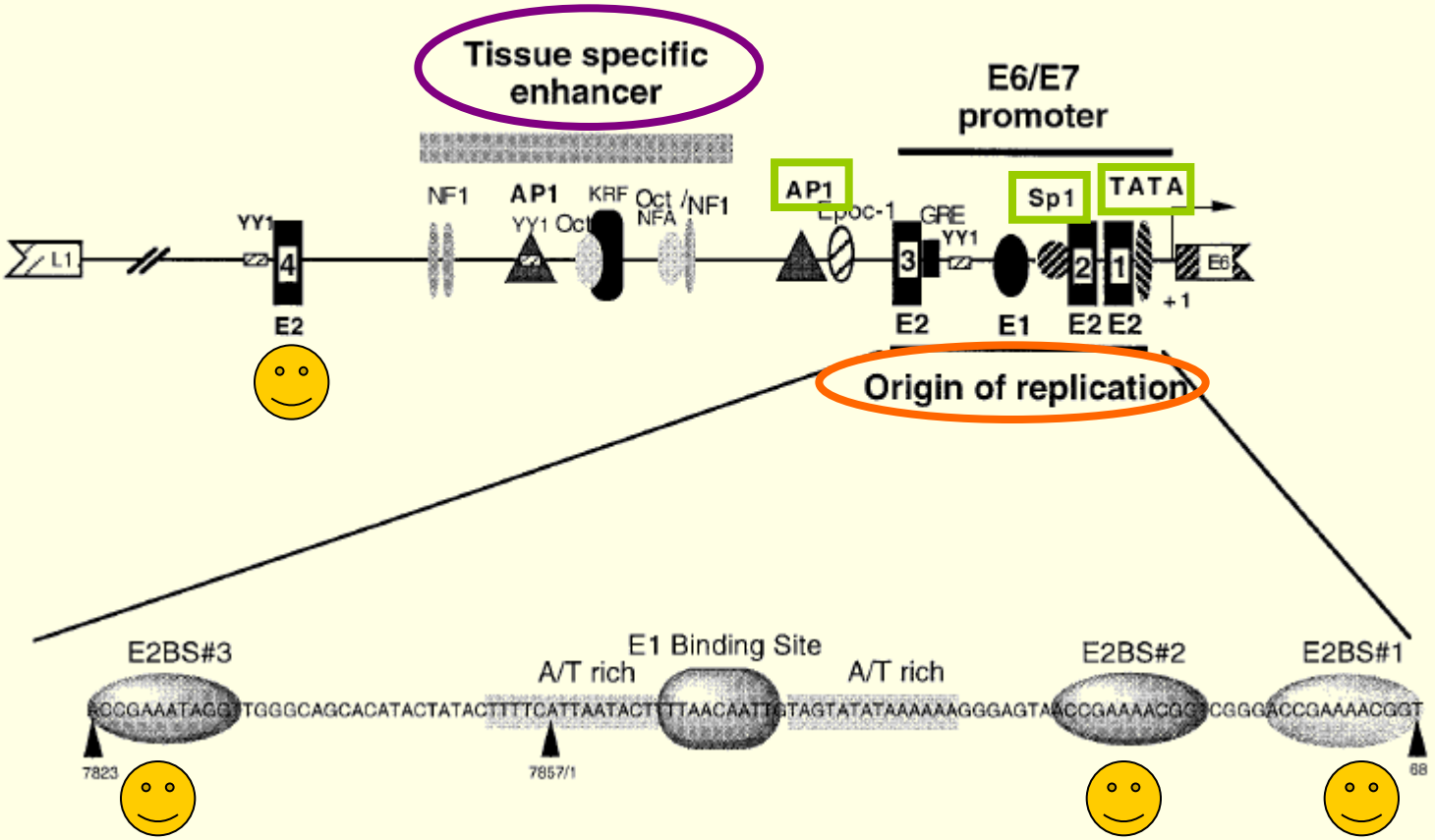
Adapted from Hamid N.A et al Cell. Mol. Life Sci. 66 (2009) 1700-1717

E2 gene

- 360 amino acids in length
- Contains 3 functional domains



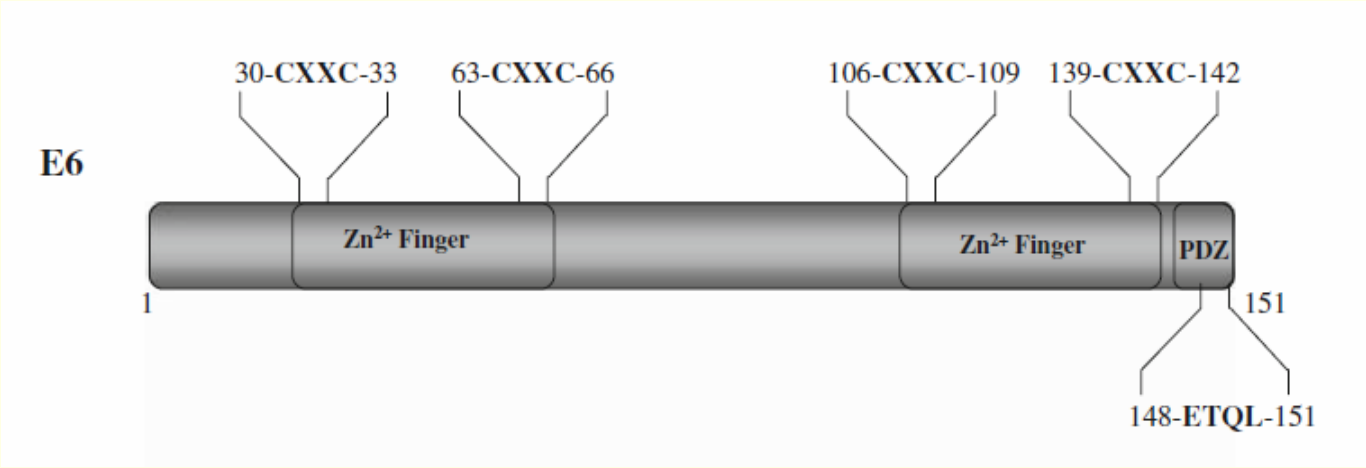
Organization of the Long Control Region



Adapted from Desaintes C et al., Cancer Biology 1996 (7) 339-347

E6 gene

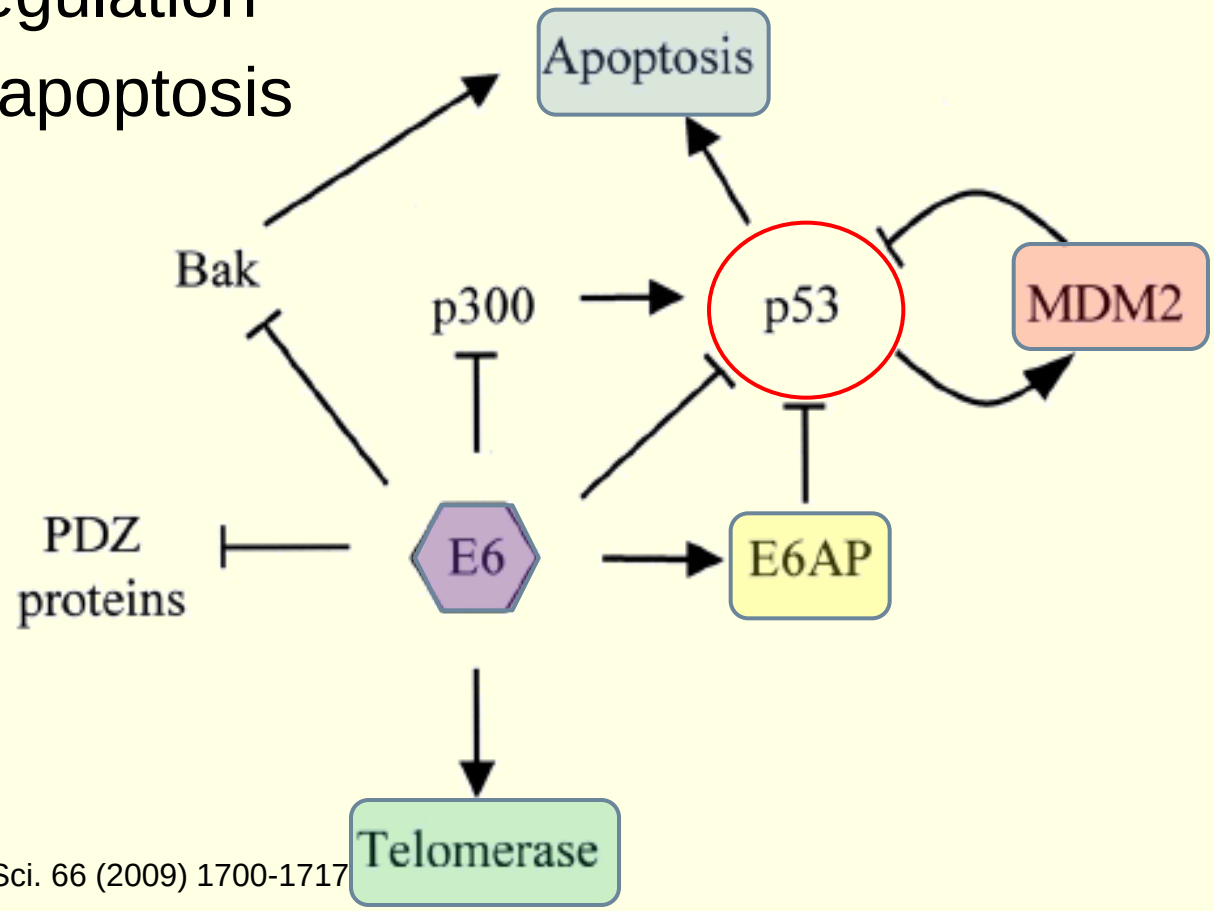
- 160 amino acids in length
- Transforming protein
- Contains 2 zinc-binding motifs
- A PDZ domain



Ghittoni R et al, Virus Genes (2009) DOI 10.007/s11262-0090412-8 published online

Targets of the E6 gene

- p53 is involved in multiple processes including:
  - Cell cycle regulation
  - Induction of apoptosis
  - DNA repair

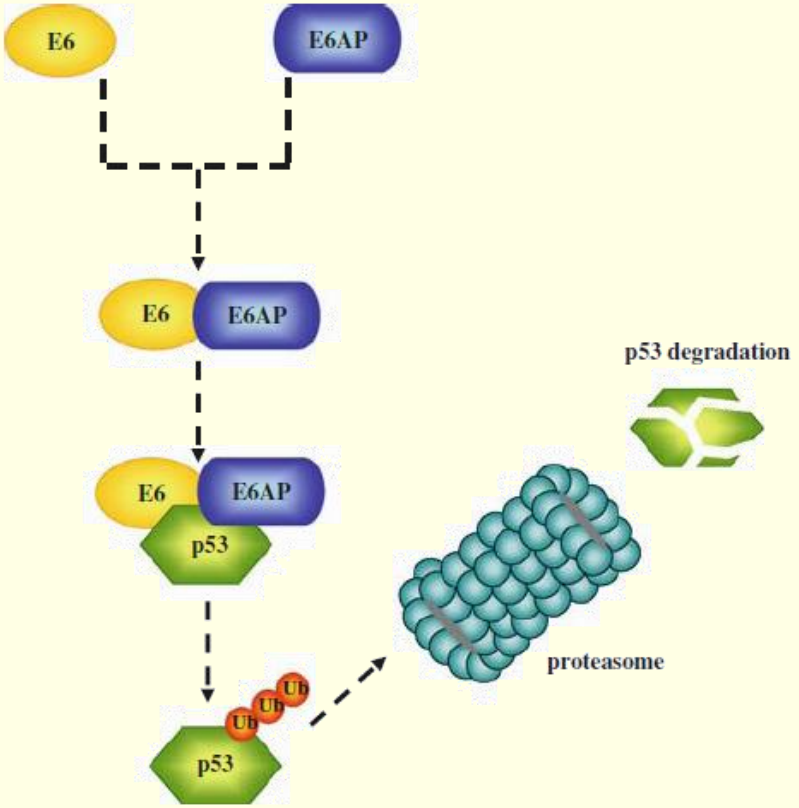


Adapted from Hamid N.A et al Cell. Mol. Life Sci. 66 (2009) 1700-1717

Targets of the E6 gene

- HrHPV e6 proteins bind to the p53 in conjunction with E6AP, a cellular ligase, that does not bind to p53 in the absence of E6

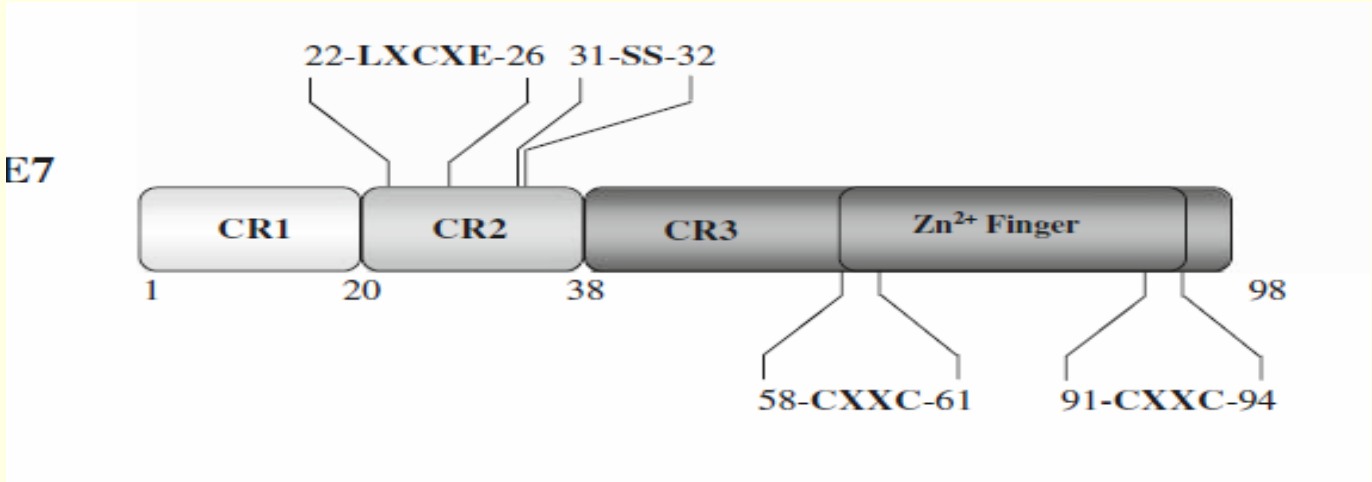
- This leads to the ubiquitination of p53 and its degradation



Ghittoni R et al, Virus Genes (2009) DOI 10.007/s11262-0090412-8 published online

E7 gene

- 98 amino acids in length
- Transforming protein
- Contains 3 conserved regions: CR1-3
- CR2 contains an LXCXE motif that mediates its binding to the pocket protein family pRb

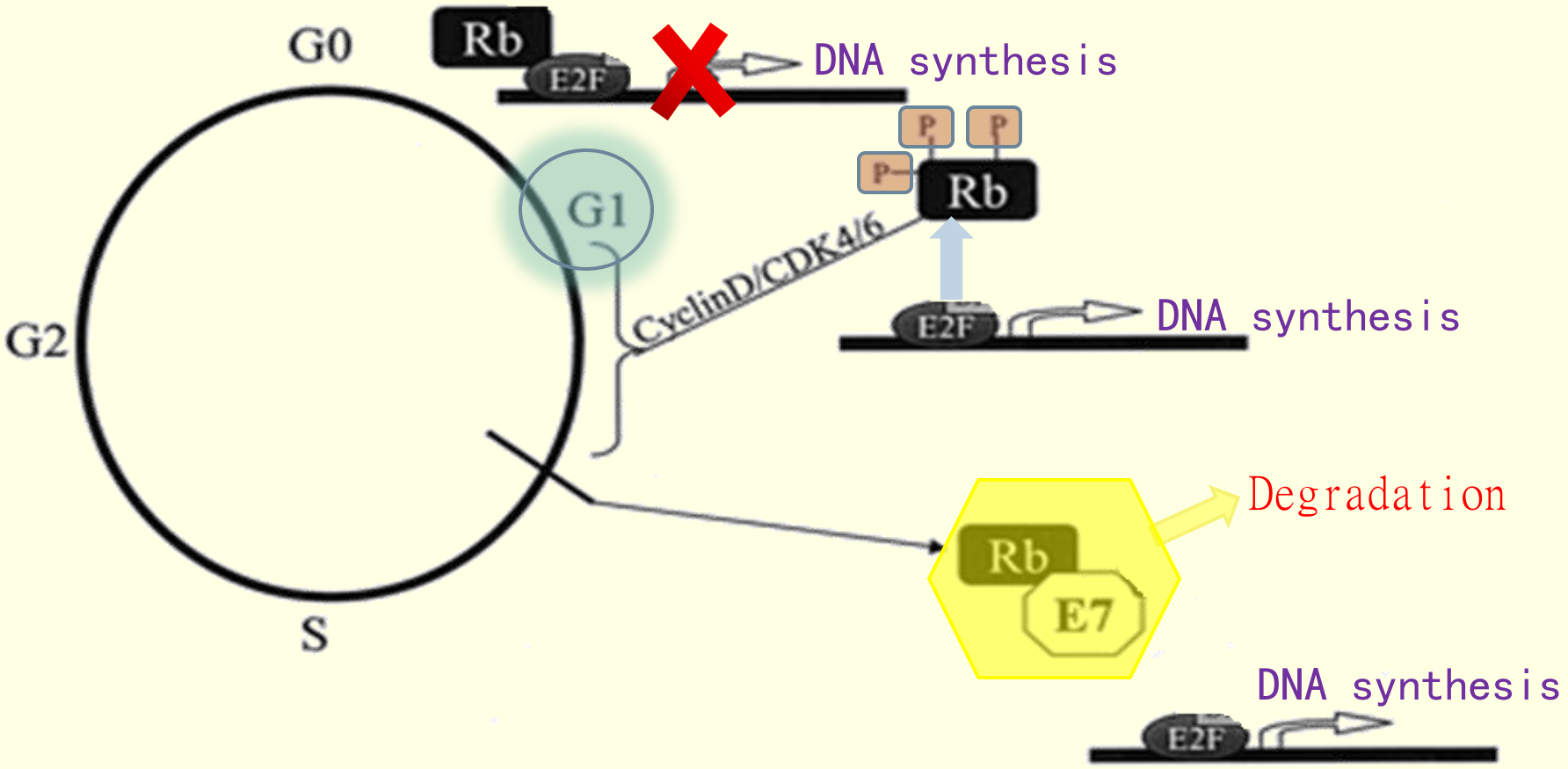


Ghittoni R et al, Virus Genes (2009) DOI 10.007/s11262-0090412-8 published online

Targets of the E7 gene

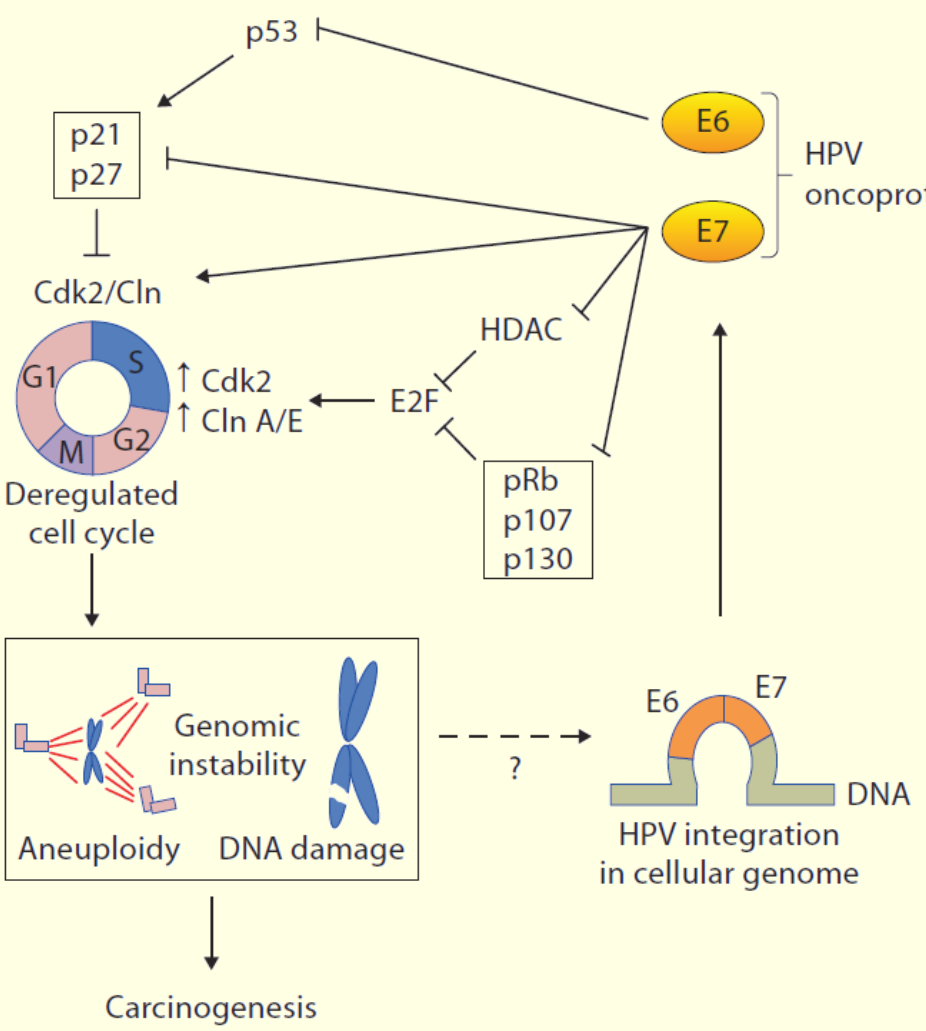
- pRb- key roles in:
  - DNA replication
  - DNA repair
  - Prevention of apoptosis, cell differentiation and cell senescence

Targets of the E7 gene



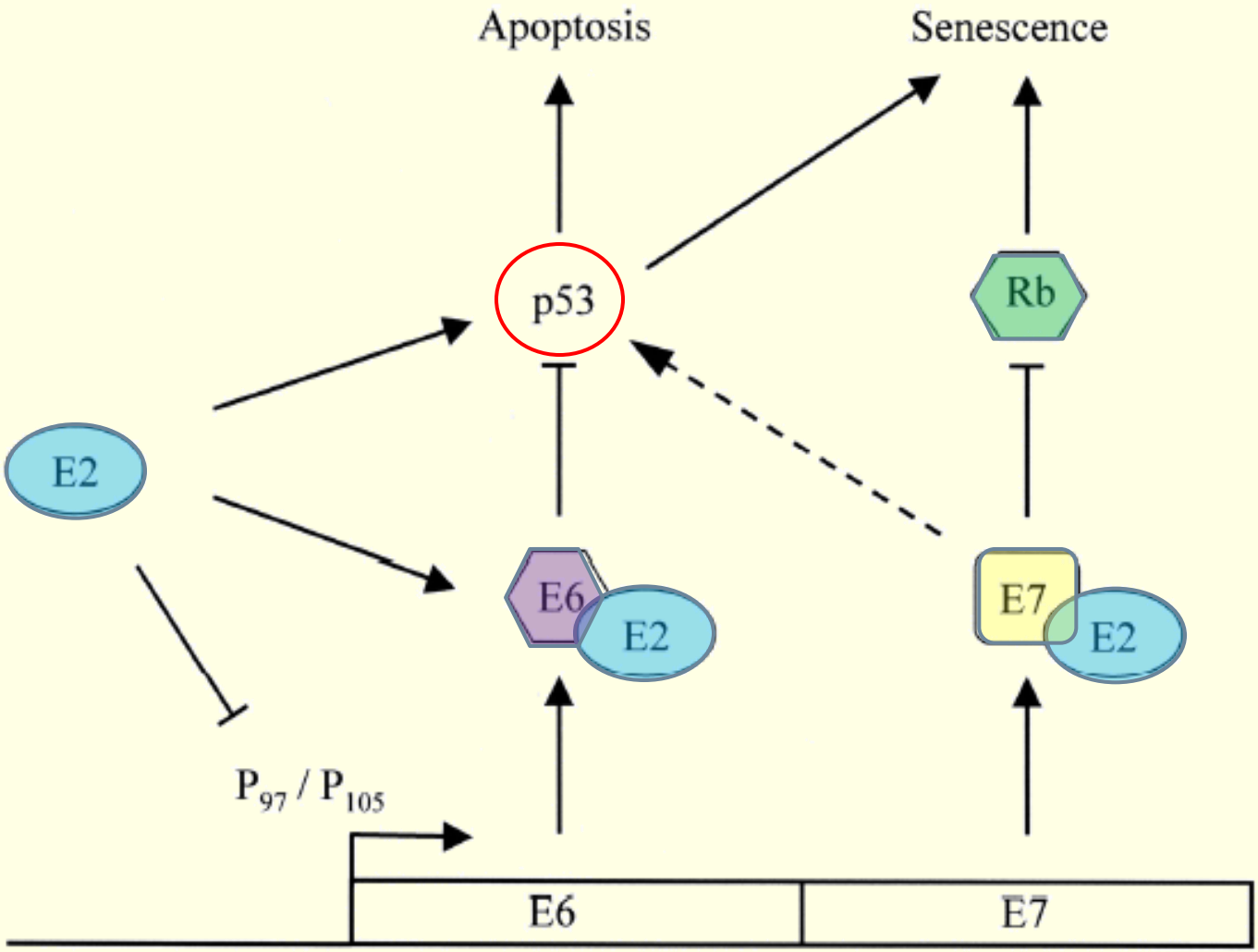
Adapted fromLongworth MS et al, Micobiology and Biology Reviews (2004) 362-372

Synergistic effect of E6, E7



Lehoux M et al, Public Health Genomics (2009) 12: 268-280

The interplay of the E2, E6 and E7 proteins



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Conclusions

- Completion of the viral life cycle requires the coordinate action of the HPV proteins
- Likely in viral infections E2 is subjected to regulation by E6 E7 and vice versa
- Operation of feedback loops that controls not only the expression of E6 and E7 but also their effects on cell proliferation and cell survival
- Complex interplay between multiple proteins is difficult to address
- Understanding how complex these interactions are exploited by the virus will require experimental approaches that do more than simply study the individual components