National Cervical Pathology Training Service

The role of HPV in the PATHOGENESIS of Cervical Cancer

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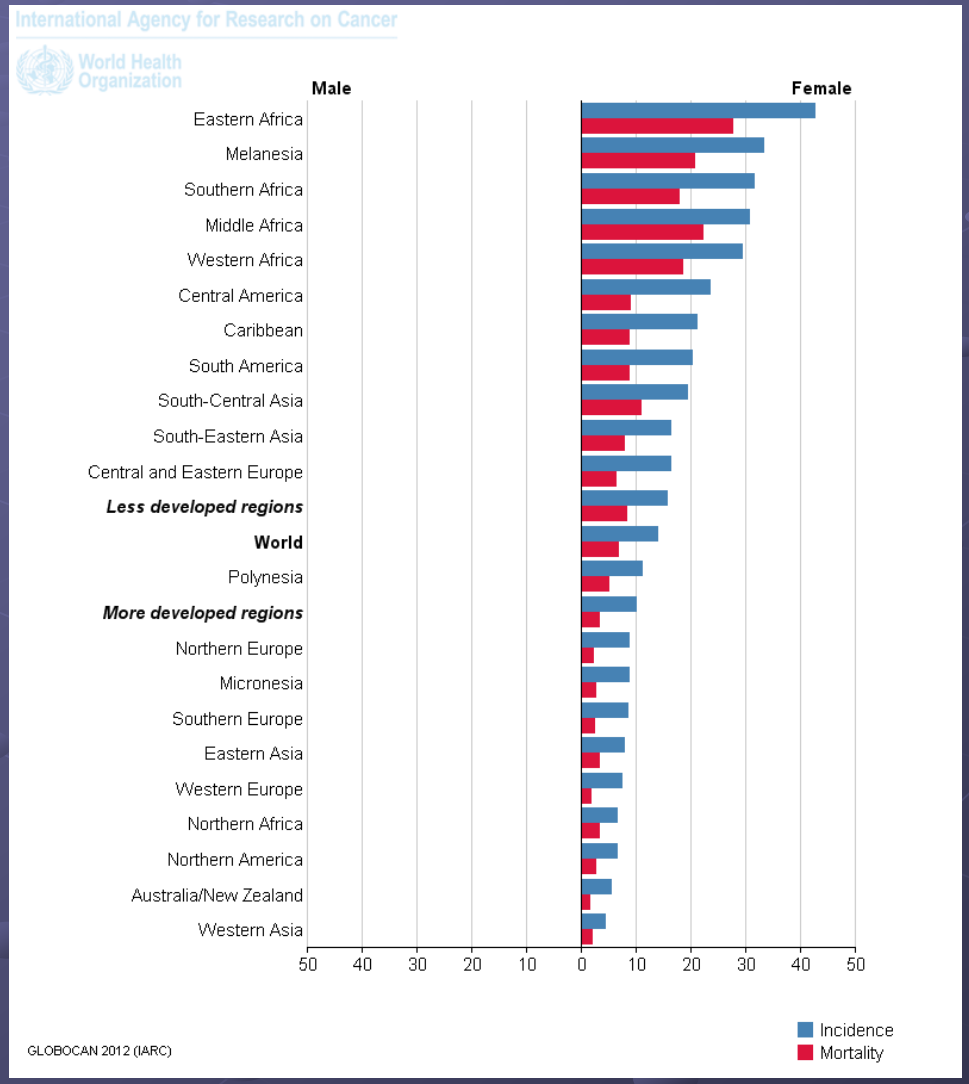
THE INCIDENCE AND MORTALITY OF CERVICAL CANCER

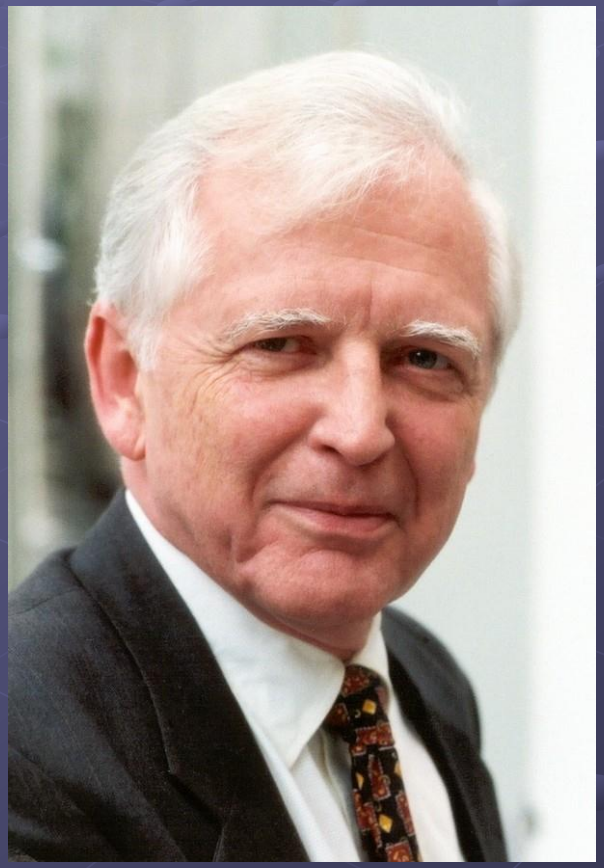


HPV

- CERVICAL CANCER IS THE THIRD MOST COMMON CANCER IN FEMALES WORLDWIDE
- THE LINK BETWEEN HPV AND CERVICAL CANCER WAS DEMONSTRATED BY HARALD ZU HAUSEN IN 1982

HPV

HARALD ZU HAUSEN

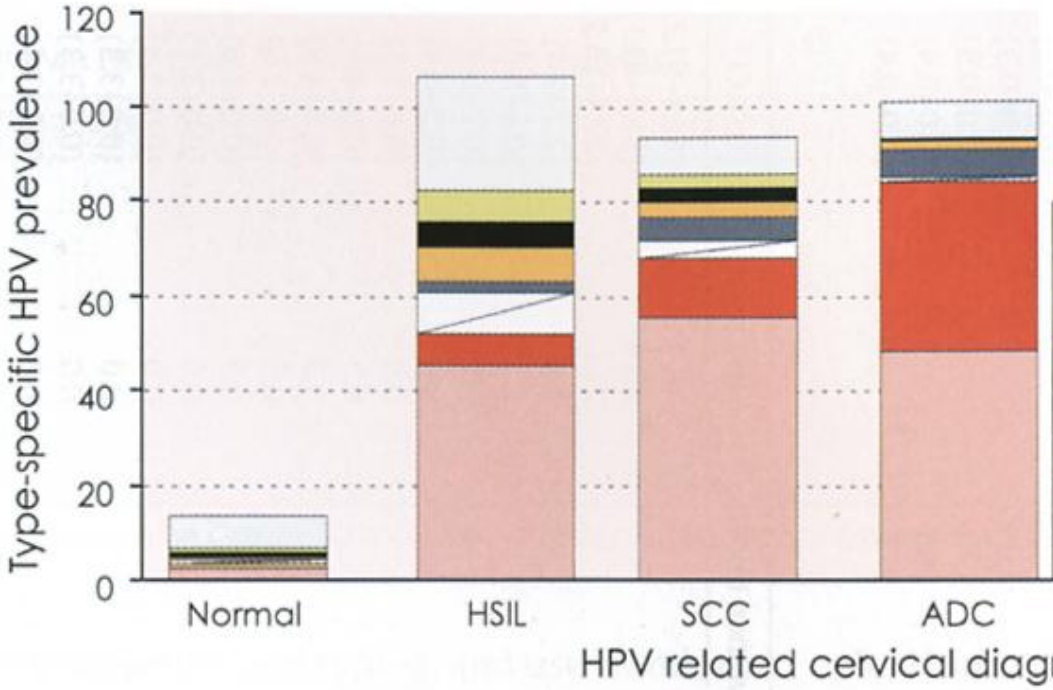


HPV

- HPV IS IMPLICATED IN 99.7% OF CERVICAL SQUAMOUS CELL CANCERS WORLDWIDE
- THE MOST COMMONLY SEXUALLY TRANSMITTED VIRUS
- 100 HPV TYPES ARE SPREAD SEXUALLY

HPV

F.X. Bosch et al. / Vaccine 26S (2008) K1–K16



	Normal	HSIL	SCC	ADC
HVP-16	2.6	45.3	55.2	48.4
HPV-18	0.9	6.9	12.8	36.3
HPV-31	0.6	8.6	3.8	0.7
HPV-45	0.4	2.3	4.6	5.8
HPV-33	0.5	7.3	3.7	2.0
HPV-52	0.9	5.1	2.9	0
HPV-58	0.9	7.0	2.8	0.7
Others	6.8	23.9	7.6	7.7

HSIL: High Grade Squamous Intraepithelial Lesion
SCC: Squamous Cell Carcinoma
ADC: Adenocarcinoma

HPV

- HPV IS TRANSMITTED BY CLOSE SEXUAL CONTACT OR SEXUAL INTERCOURSE

- RISK FACTORS FOR CERVICAL CANCER
  - EARLY AGE OF FIRST SEXUAL INTERCOUSE
  - LIFE-TIME AND RECENT NUMBER OF SEXUAL PARTNERS
  - LACK OF CONDOM USE
  - SMOKING AND ALCOHOL

SEXUALLY TRANSMITTED HPV LEADS TO THREE POSSIBLE OUTCOMES

ANOGENITAL WARTS

INACTIVE INFECTION

ACTIVE INFECTION

ANOGENITAL WARTS

- GENERALLY CAUSED BY HPV 6 AND 11
- DO NOT LEAD TO CANCER
- MOST RESOLVE SPONTANEOUSLY
- SOME INCREASE IN SIZE AND NUMBER
- TREATMENT: ABLATION

  EXCISION

  TOPICAL AGENTS

INACTIVE INFECTION

- NO NOTICEABLE SYMPTOMS
- INFECTED AREA REMAINS CYTOLOGICALLY NORMAL
- PRIMARILY CAUSED BY LOW RISK HPV 6 AND 11

ACTIVE INFECTION

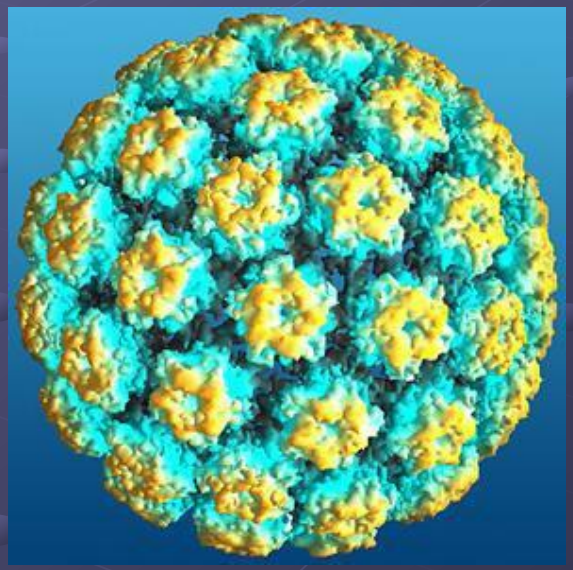
- THE HPV VIRUS CAUSES CHANGES IN INFECTED CELLS THAT MAY RESULT IN INTRAEPITHELIAL NEOPLASIA
- THE RISK OF PROGRESSION WITH HPV TYPES 16 AND 18 IS GREATEST

DIAGNOSIS IS MADE BY:

- CLINICAL INSPECTION
- COLPOSCOPY including ACETIC ACID STAINING
  (Highlights abnormal areas)
- CYTOLOGY
- BIOPSY

HPV VIRUS STRUCTURE

- SMALL
- NON-ENVELOPED
- ICOSAHEDRAL CAPSID (20 FACETS)
- COMPOSED OF 72 CAPSOMERES WHICH CONTAIN L1 AND L2

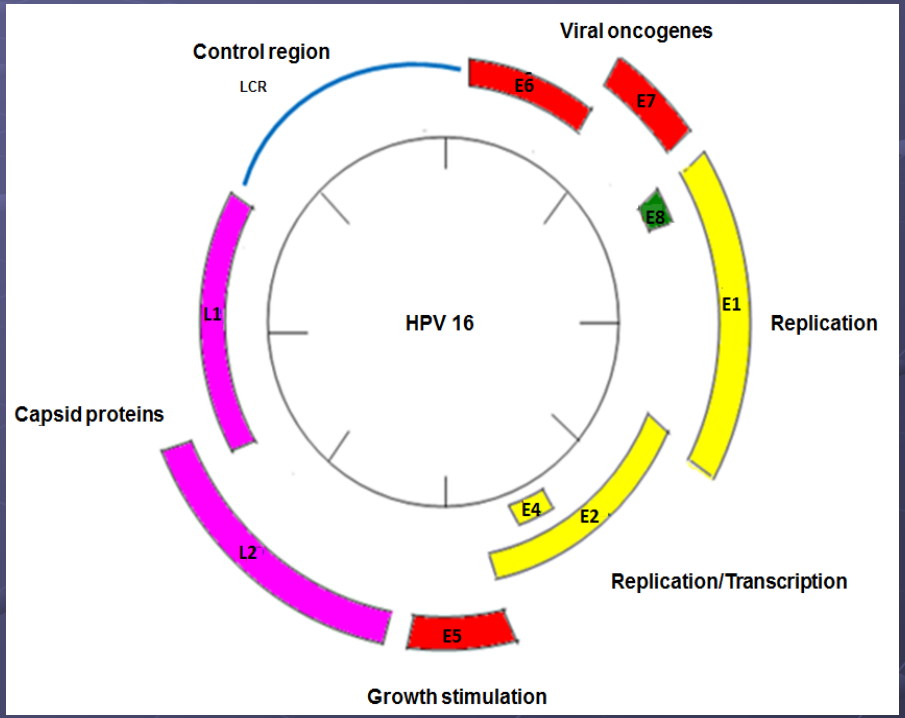


HPV VIRUS STRUCTURE

- Divided into 3 regions:
  - Early (E)
  - Late (L)
  - Long control region (LCR)

EARLY: expressed early and in non-productively infected cells

LATE: expressed in productively infected cells and encode the capsid



LIFE CYCLE

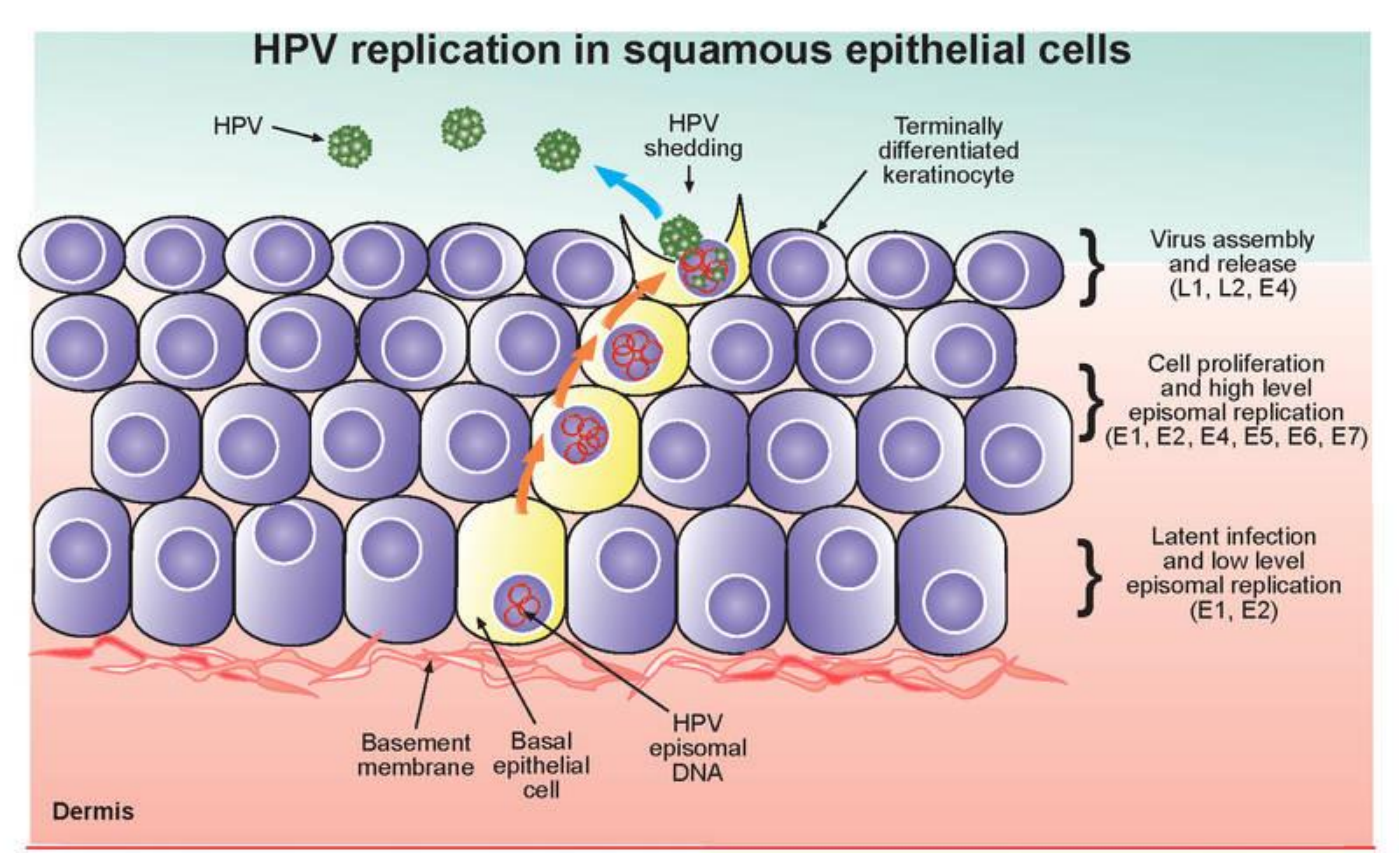
- TO ESTABLISH ITSELF THE VIRUS MUST INFECT MITOTICALLY ACTIVE CELLS.
- THIS EXPLAINS WHY BOTH GLANDULAR AND SQUAMOUS CARCINOMAS ARISE AT THE SQUAMO-COLUMNAR JUNCTION

LIFE CYCLE

ENTRY to the CELL:

- VIRUS INFECTS BASAL CELLS VIA MINOR ABRASIONS
- DURING WOUND REPAIR, RECEPTORS INTERACT WITH L1
- VIRUS ENTERS THE CELL BY ENDOCYTOSIS
- MIGRATES INTO THE NUCLEUS

HPV REPLICATION IN LOW GRADE LESIONS



http://immunopaedia.org.za/index.php?id=799

LIFE CYCLE

IN THE NUCLEUS: EXTRACHROMOSOMALLY

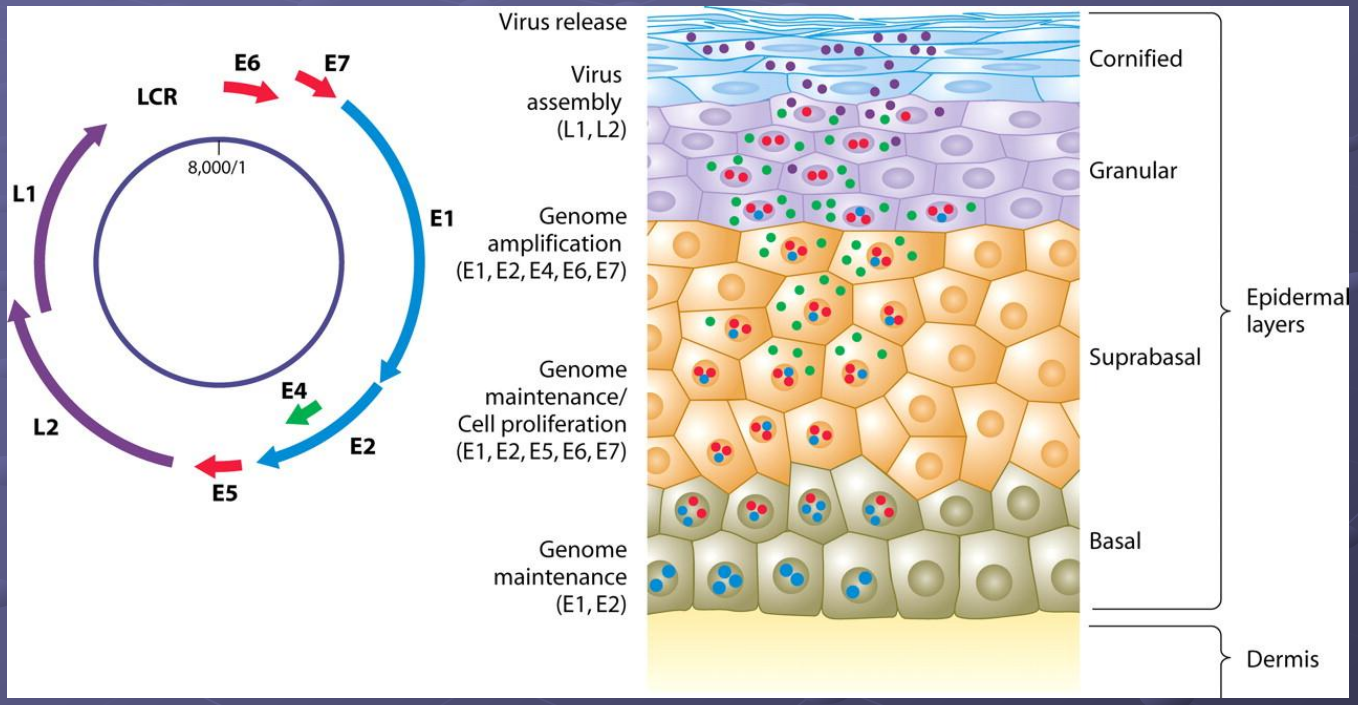
- HOST CELL FACTORS REGULATE VIRAL TRANSCRIPTION
- INTERACT WITH LCR
- BEGINS TRANSCRIPTION OF E6 AND E7 GENES
- MODIFICATION OF CELLULAR ENVIRONMENT OCCURS TO FACILITATE VIRAL REPLICATION

LIFE CYCLE IN BASAL CELLS

- THE VIRUS ESTABLISHES ITSELF AS A CIRCULAR EPISOME IN VERY LOW COPY NUMBERS
- USES THE HOST DNA MACHINERY TO SYNTHESIZE ITS OWN DNA (50-100 COPIES PER CELL)

- IN DIFFERENTIATED KERATINOCYTES, DNA REPLICATION INCREASES, RESULTING IN HIGH COPY NUMBERS

LIFE CYCLE



http://mmbr.asm.org/content/73/2/348/F2.expansion.html

LIFE CYCLE

- CELLULAR CHANGES PARALLEL MOLECULAR CHANGES
- VIRUS INTERFERES WITH THE MITOTIC SPINDLE AND CYTOKINESIS
- THIS RESULTS IN BI- AND MULTINUCLEATION, AS WELL AS CYTOLOGIC ATYPIA
- UNDER THE INFLUENCE OF E4, CELLS DEVELOP PERINUCLEAR HALOS VISIBLE IN DIAGNOSTIC KOILOCYTES

LIFE CYCLE

HOWEVER…..

LIFE CYCLE

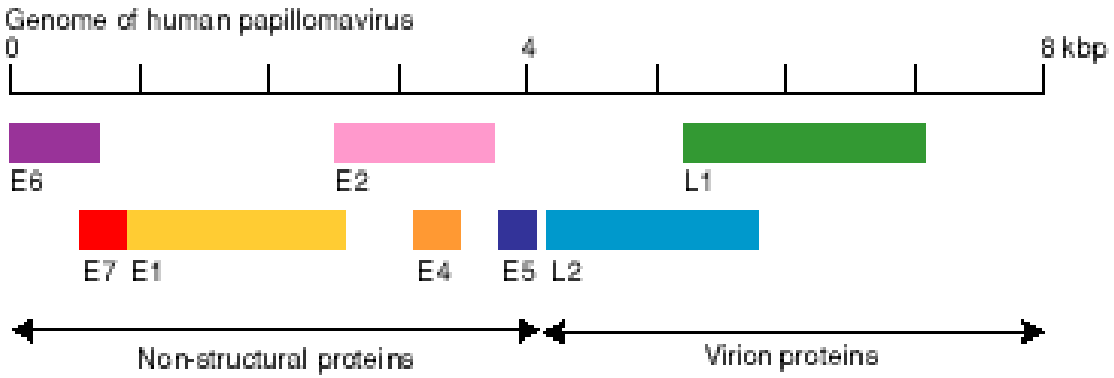
IN HIGH-GRADE INTRAEPITHELIAL NEOPLASIAS AND CANCERS, HPV DNA IS

INTEGRATED INTO THE HOST GENOME

HPV INTEGRATION

- THE VIRAL DNA BECOMES LINEAR INSTEAD OF CIRCULAR, ENABLING INTEGRATION WITH HOST DNA
- THE BREAK OCCURS IN THE E2 REGION
- E6 & E7 BIND WITH p53 AND pRB: THIS CAUSES INCREASED PROLIFERATION AND GENOMIC INSTABILITY
- THE HOST CELL ACCUMULATES MORE AND MORE DAMAGED DNA. THIS CANNOT BE REPAIRED
- MUTATIONS ACCUMULATE LEADING TO FULLY TRANSFORMED CANCEROUS CELLS

LINEARISATION

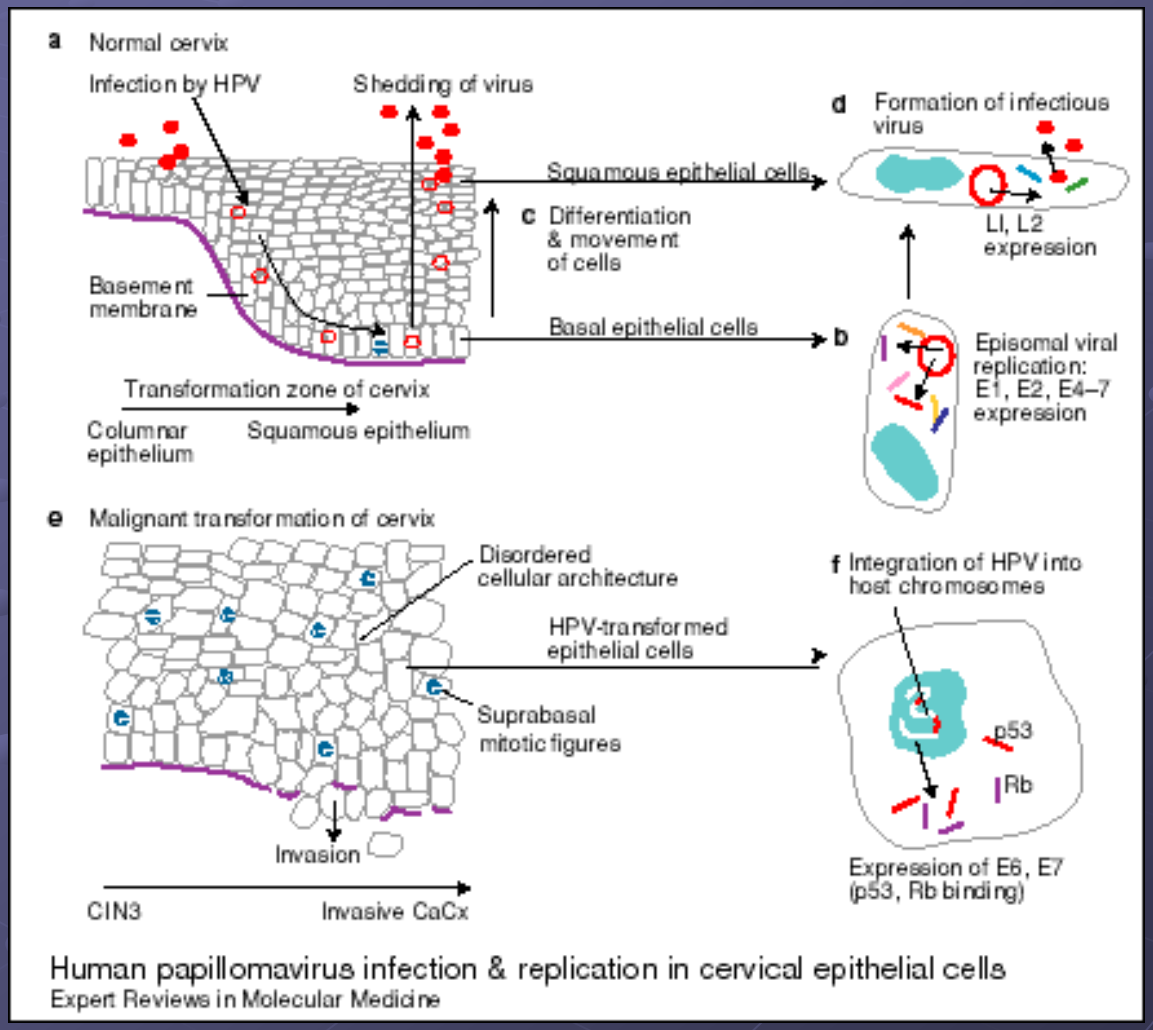


Simplified organisation (linearised) of human papillomavirus type 16 (HPV-16) genome

Expert Reviews in Molecular Medicine

http://journals.cambridge.org/fulltext_content/ERM/ERM1_05/S1462399498000210sup010.htm

HPV INTEGRATION



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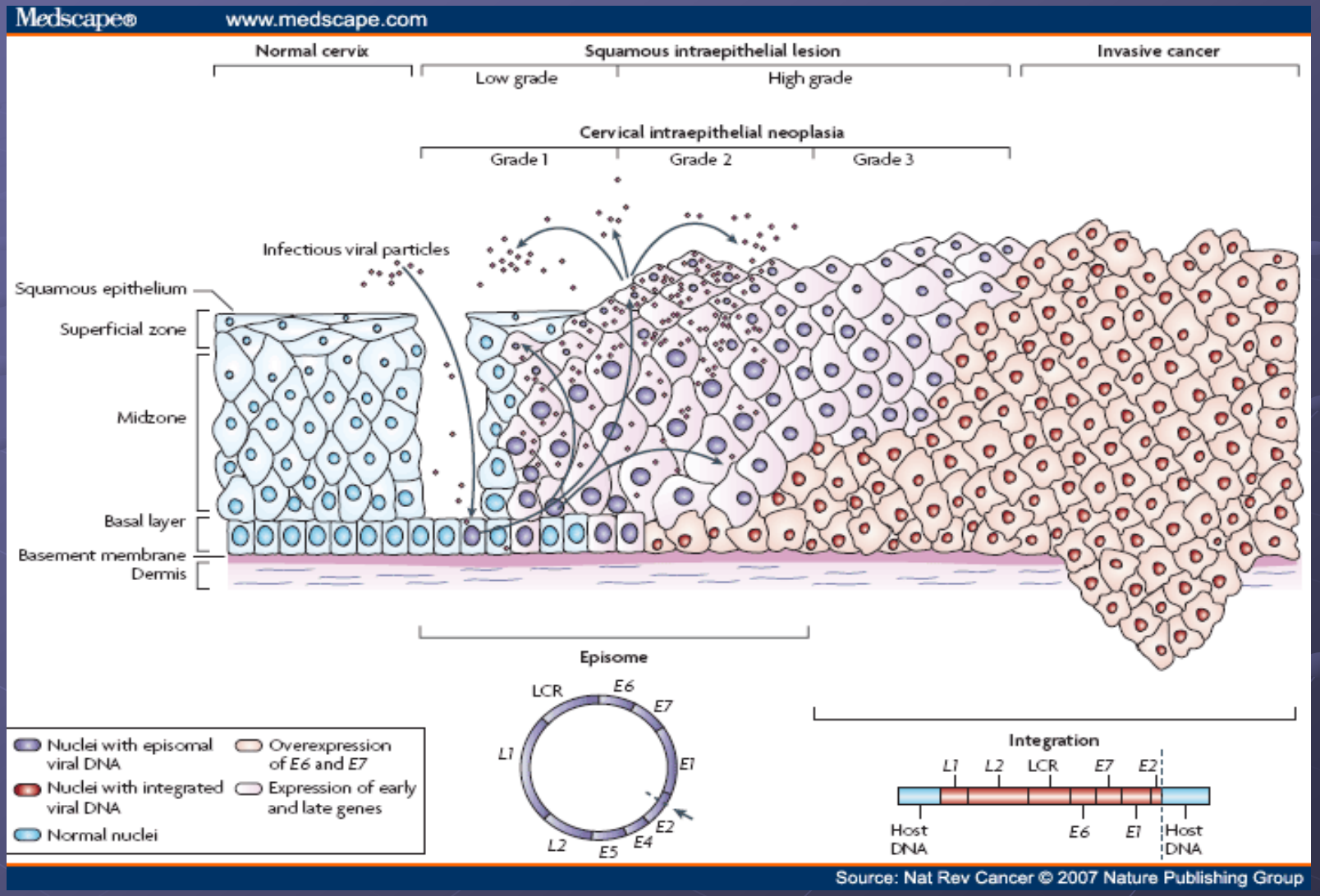
IN SUMMARY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Low grade
High grade
Invasive cancer
Cervical intraepithelial neoplasia
Grade 1
Grade 2
Grade 3
Infectious viral particles
Squamous epithelium
Superficial zone
Midzone
Basal layer
Basement membrane
Dermis
Episome
LCR
E6
E7
L1
E1
E2
L2
E5
E4
Integration
L1
L2
LCR
E7
E2
Host DNA
E6
E1
Host DNA
Nuclei with episomal viral DNA
Nuclei with integrated viral DNA
Normal nuclei
Overexpression of E6 and E7
Expression of early and late genes
Source: Nat Rev Cancer © 2007 Nature Publishing Group

IMMUNE RESPONSE

WHY DOES HPV REMAIN UNDETECTED BY THE IMMUNE SYSTEM FOR SO LONG?

IMMUNE RESPONSE

HPV HAS AN IMMUNE EVASION MECHANISM WHICH INHIBITS HOST DETECTION OF THE VIRUS

HOW?

IMMUNE RESPONSE

DURING MOST OF THE DURATION OF THE HPV INFECTIOUS CYCLE, THERE IS LITTLE OR NO RELEASE OF CYTOKINES TO ACTIVATE THE IMMUNE RESPONSE

AND

THE VIRUS INFECTS PRIMITIVE BASAL CELLS, BUT HIGH-LEVEL VIRAL EXPRESSION OF VIRAL PROTEINS AND VIRAL ASSEMBLY OCCUR ONLY IN THE UPPER LAYERS OF THE EPITHELIUM, REMOVED FROM STROMAL BLOOD VESSELS OF THE HOST

IMMUNE RESPONSE

- THE TIME BETWEEN INFECTION AND THE APPEARANCE OF A LESION IS A MINIMUM OF 4-6 WEEKS.

BUT

- IT CAN BE MONTHS TO YEARS – INDICATING THAT THE VIRUS CAN EFFECTIVELY EVADE THE IMMUNE SYSTEM

THANK YOU for your attention

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