VIRAL ONCOGENESIS

Microbial Pathogenesis MMIC 7050  2018/19
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Brief history of viral oncogenesis

- 1842 - Rigoni-Stern suggests a connection between sexual activity and cervical cancer
- 1901 - Ciuffo - Cell free transmission of genital warts
- 1908 - Hellerman and Bang 1908 - Transmission of chicken leukemia
- 1911 - Rous sarcoma virus isolated
- 1951 - Gross - Viral causation of murine leukemia
- 1964 - Epstein et al. - Epstein-Barr virus linked to human lymphomas
- ca. 1968 - Study on transformation by SV40 (Dulbecco, Baltimore and Temin) defines cancer as a genetic and molecular event
- ca. 1970 - Retroviruses integrate in the host genome
- 1976 - Vogt - Retroviral oncogenes are of cellular origin. The study of the mechanism of cell proliferation and cancer begins
- 1980 - Gallo - Human T-lymphotropic virus linked to T-cell leukemia
- 1981 - Chien - Hepatitis B virus linked to hepatocellular carcinoma
- 1983 - zur Hausen demonstrates that high risk, but not low risk, HPV types cause cervical cancer
- 1989 - Choo et al - hepatitis C linked to hepatocellular carcinoma
- 1994 - Chang et al - HHV-8 as the cause of Kaposi sarcoma
A tribute to oncogenic viruses

The following discoveries were made using oncogenic viruses (SV40 and animal retroviruses)

- Genetic etiology of cancer
- Discovery of oncogenes
- Discovery of tumor-suppressor genes
- Growth factors and their receptors
- Signal transduction pathways
- Mechanism of eukaryotic DNA replication
- Concept of protein functional domains
- Concept of transactivation of genes
- DNA supercoiling
### Infection-related cancers: worldwide estimates for 2002
(Parkin, IJC 2006)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cancer</th>
<th>Number of cases</th>
<th>% of all cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>Cervix</td>
<td>492,800</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Ano-genital</td>
<td>53,880</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>14,500</td>
<td></td>
</tr>
<tr>
<td>HBV and HCV</td>
<td>Liver</td>
<td>535,000</td>
<td>4.9</td>
</tr>
<tr>
<td>EBV</td>
<td>Nasopharynx</td>
<td>78,100</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
<td>28,600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt's lymphoma</td>
<td>6,700</td>
<td></td>
</tr>
<tr>
<td>HIV / HHV-8</td>
<td>Kaposi's sarcoma</td>
<td>66,200</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin's lymphoma</td>
<td>36,100</td>
<td></td>
</tr>
<tr>
<td>HTLV-I</td>
<td>ATL</td>
<td>3,300</td>
<td>0.03</td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. pylori</td>
<td>Stomach</td>
<td>592,000</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td>11,500</td>
<td></td>
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<tr>
<td>Helminths</td>
<td>Schistosomes</td>
<td></td>
<td></td>
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<td></td>
<td>Bladder</td>
<td>10,600</td>
<td>0.1</td>
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<tr>
<td></td>
<td>Liver flukes</td>
<td>2,500</td>
<td>0.02</td>
</tr>
<tr>
<td>All agents</td>
<td></td>
<td>1,932,800</td>
<td>17.8</td>
</tr>
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</table>
# Direct mechanism

<table>
<thead>
<tr>
<th>Virus</th>
<th>Most common malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillomaviruses</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>B-cell lymphomas</td>
</tr>
<tr>
<td>HHV-8 (KSHV)</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>T-cell leukemia</td>
</tr>
<tr>
<td>Merkel polyomavirus</td>
<td>Merkel cell carcinoma</td>
</tr>
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</table>
## Indirect (unknown) mechanism

<table>
<thead>
<tr>
<th>Virus</th>
<th>Most common malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>Hepatoma</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Hepatoma</td>
</tr>
<tr>
<td>HIV</td>
<td>Various malignancies (with other viruses)</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Cancer of the stomach and esophagus</td>
</tr>
<tr>
<td>Plasmodium</td>
<td>Burkitt lymphoma (with EBV)</td>
</tr>
</tbody>
</table>
Should cause human malignancies, but probably don’t

<table>
<thead>
<tr>
<th>Virus</th>
<th>Rumored malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV40</td>
<td>Non-Hodgkin lymphomas</td>
</tr>
<tr>
<td>BK and JC viruses</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>HTLV-2</td>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>None</td>
</tr>
</tbody>
</table>
Cancer epidemiology in two slides
Age-adjusted death rates in the US (2000 population); Source: American Cancer Society, Surveillance Research
Age-adjusted death rates in the US (2000 population); Source: American Cancer Society, Surveillance Research
How do we establish causality in human carcinogenesis?

(epidemiology meets molecular biology)
The Koch postulates
(Henle, 1884)

1. Isolate the organism from every case
2. Propagate in pure culture in vitro
3. Reproduce disease by injecting the organism into a suitable recipient
4. Re-isolate the organism
Molecular Koch’s postulates

1. The phenotype or property under investigation should be associated with pathogenic members of a genus or known pathogenic strains of the genus or species but be absent from nonpathogenic strain.

2. Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence. Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity.

3. The gene, which causes virulence must be expressed during infection.

4. Immunity must be protective.
HIV deniers

Human Immunodeficiency virus and acquired immunodeficiency syndrome: Correlation but not causation*

PETER H. DUESBERG

Department of Molecular Biology, Stanley Hall, University of California, Berkeley, CA 94720

Contributed by Peter H. Duesberg, June 14, 1988; revision received October 21, 1988

Abstract AIDS is an acquired immunodeficiency syndrome defined by a severe depletion of T cells and over 20 conventional degenerative and neoplastic diseases. In the U.S. and Europe, AIDS correlates to 95% with risk factors, such as about 8 years of promiscuous male homosexuality, intravenous drug use, or hemophilia. Since AIDS also correlates with antibody to a retrovirus,
IARC

International Agency for Research on Cancer (www.iarc.fr/)

Evaluates evidence on carcinogenic agents and publishes monographs identifying carcinogenic agents as:

- **Group 1**: Carcinogenic to humans
- **Group 2A**: Probably carcinogenic to humans
- **Group 2B**: Possibly carcinogenic to humans
- **Group 3**: Not classifiable as to its carcinogenicity to humans
- **Group 4**: Probably not carcinogenic to humans
Epidemiologic approaches used in assessing the evidence concerning the carcinogenicity of a suspected chemical, physical, or biological exposure or its circumstances (Adapted from Franco et al., SCB 2004)

<table>
<thead>
<tr>
<th>Type of epidemiologic evidence</th>
<th>Level of inference</th>
<th>Type of study</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td>Non-inferential, descriptive</td>
<td>Case reports</td>
<td>Suggestion of association</td>
</tr>
<tr>
<td>Population</td>
<td>Surveillance of incidence and mortality</td>
<td>Surveillance of incidence and mortality</td>
<td>Documentation of baseline disease burden, exploratory hypotheses</td>
</tr>
<tr>
<td></td>
<td>Ecologic (correlation or aggregate) studies</td>
<td>Ecologic (correlation or aggregate) studies</td>
<td>Coarse verification of correlation between exposure and disease burden</td>
</tr>
<tr>
<td>Individual</td>
<td>Cross-sectional studies</td>
<td>Cross-sectional studies</td>
<td>Correlation between exposure and disease (or marker) without regard to latency</td>
</tr>
<tr>
<td></td>
<td>Case-control studies</td>
<td>Case-control studies</td>
<td>Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare cancers</td>
</tr>
<tr>
<td></td>
<td>Cohort studies</td>
<td>Cohort studies</td>
<td>Correlation between exposure and disease (or marker) with improved understanding of latency; suitable for rare exposures</td>
</tr>
<tr>
<td>Experimental</td>
<td>Individual **</td>
<td>Randomized controlled trials of preventive intervention</td>
<td>Most unbiased assessment of correlation between exposure and disease (or marker)</td>
</tr>
</tbody>
</table>

** RCTs may target communities or providers as units of randomly allocated intervention. However, this is done for convenience of study design; in practical terms inference is at the individual level.
Non-epidemiologic approaches used in assessing the evidence concerning the carcinogenicity of a suspected chemical, physical, or biological exposure or its circumstances (Adapted from Franco et al., SCB 2004)

<table>
<thead>
<tr>
<th>Approach*</th>
<th>Type of scientific evidence</th>
<th>Level of inference</th>
<th>Type of study</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanistic</td>
<td>Analogy</td>
<td>Molecular structure</td>
<td>Structure-activity relationships</td>
<td>Useful to identify potentially carcinogenic compounds based their molecular similarity to known carcinogens</td>
</tr>
<tr>
<td>Toxicology</td>
<td>Experimental</td>
<td>DNA, cellular, organ</td>
<td>In vitro short-term genotoxicity assays</td>
<td>Rapid screening system for candidate compounds or exposures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ, whole organism</td>
<td>In vivo animal studies</td>
<td>Provides proof of principle and insights into dose-response effects</td>
</tr>
</tbody>
</table>

* Other supporting in vivo and in vitro data relevant to evaluation of carcinogenicity can also be used, particularly if they provide insights into mechanisms of absorption, metabolism, DNA binding or repair, hormonally-mediated effects, genetic damage, altered cell growth, loss of euploidy, cytopathic changes, and related biological effects.
Criteria to Establish Causality in Cancer (Hill, 1965)

Most important:
- Temporality
- Strength of association
- Biologic gradient (dose–response)
- Experimental evidence
- Consistency of studies

Least important:
- Coherence
- Plausibility
- Analogy
- Specificity
Why is it so difficult to establish causality of an agent for cancer?

Because:

• Cancer takes a long time to develop, so it is difficult to establish a temporal relationship.

• Development of cancer is a stochastic event.

• The probability is increased by the carcinogenic agent, but it is modified by host genetics, time of exposure, co-factors and bad luck.
Mechanisms of carcinogenesis
An overview
Cancer concepts

Cancer can be viewed as evolution of a cell lineage toward a invasive replication phenotype.

Evolution = mutations + replication + selection

Malignant transformation is due to an accumulation of mutations that increase the replication rate, longevity and invasiveness of the cells.

Mutations are by definition rare random events
Low probability that this will happen. We have trillions upon trillions of replicating cells, yet we get only about 0.3 - 0.4 cancers per lifetime.
Traits acquired during carcinogenesis

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Limitless replicative potential
- Evading apoptosis
- Tissue invasion and metastasis
- Sustained angiogenesis

From experimental studies: 4 to 7 mutational events are necessary

Control of cell proliferation in one slide

(TUMOR-SUPPRESSOR GENES)

Senescence → DNA repair → DNA damage
Apoptosis

Viral infection → p53

Care takers

Block of transcription factor
transcription

Gate keepers

ARF

Proto-oncogenes

Growth factors: sis

Receptors: fms, erbB, neu, ros

Signal transducers: src, yes, abl, fps, met, mos, ras

Transcription factors: myc, jun, fos, myn, ski, rel, N-myc

Cell division
The EXAMPLE of Familial Adenomatous Polyposis

**Tumor Initiation**

- Normal epithelium
- APC allele 1
- APC allele 2

**Dysplastic epithelium**

- Early adenomas
- Cell proliferation
- K-ras

**Intermediate adenoma**

- Late adenoma
- DCC/DPC4/JV18 (both alleles)
- P53 (both alleles)

**Carcinoma in situ**

- More mutations which increase invasiveness, deregulation, independence from growth factors

**Tumor Promotion and Progression**

- Invasive carcinoma

- 1st mutation (inherited)
- 2nd mutation - loss of the gatekeeper
- 3rd mutation - activation of oncogene
- 4th and 5th mutation - loss of caretaker
- 6th and 7th mutation - loss of apoptosis

Duration: 40 years
Fundamentals of viral carcinogenesis

Viral infection

Epidemiological factors

Cell proliferation

Viral mechanisms

Tumor initiation

Immune evasion and other viral mechanisms

Persistent infection

Environmental factors

Host factors

Tumor progression

Invasive cancer

Host factors
TIME
Oncogenesis by retroviruses

- **Transduction (acute transforming retroviruses):** they transduce a mutated form of a proto-oncogene (i.e. an oncogene).
- **Integration (non-acute transforming retroviruses):** they integrate next to a proto-oncogene and induce its abnormal expression.
- **Transformation by retroviral envelope proteins:** the viral Env activates directly some cellular oncogenes.
- **Oncogenesis by HTLV-1 (human):** use the viral oncogenic tax protein.
Transducing retroviruses
(Subfamily: Orthoretroviridae)

Genus: *Alpharetrovirus* - Simple retroviruses

Infect birds and mammals (no humans)
Examples: Rous sarcoma virus
Feline sarcoma virus
Murine leukemia virus
Avian leukemia virus
About 20-30 more
Oncogene acquisition

Integration

Transcription and removal of introns
Reverse-transcription and integration (mutations)
Recombination with cellular proto-oncogenes

Transcription, packaging (with the help of the original virus). Infection of an other cell.
Integrating retroviruses
(Subfamily: Orthoretroviridae)

Genus: *Betaretrovirus* - More complex genomes

Don’t tolerate insertions

Examples:
- Avian leukosis virus
- Mouse mammillary tumor virus
- Mouse leukosis virus
Transformation

The viral genome integrates near an oncogene
LTR induces overexpression of the oncogene
Cell division (tumor initiation), accumulation of additional
mutations (tumor progression)
Transformation by retroviral envelope proteins

- Friend’s spleen focus-forming virus, mouse (SFFV)
- Avian hemangioma virus, chicken (AHV)
- Jaagsiekt’s sheep retrovirus (JSRV)
- Enzootic nasal tumor virus, sheep (ENTV)

Oncogenic forms of Env interact with mitogenic signaling pathways, thereby inducing transformation
Mouse mammary tumor virus (MMTV)

- Its Env protein contains an immunoreceptor tyrosine-based activation motif (ITAM)
- Proteins containing ITAMs are involved in immune responses (e.g. B-cell Ag receptor)
- The K1 protein of Kaposi-Sarcoma herpesvirus and the LMP2 protein of Epstein-Barr virus also contain ITAM motifs.
HTLV (human T cell leukemia virus)

Subfamily: Orthoretroviridae
Genus: *Deltaretrovirus*

The only known human oncogenic retrovirus
Does not transduce oncogenes
Does not integrate next to oncogenes

Infects T cells

HTLV-1, HTLV-2, HTLV-3, HTLV-4
STLV-1, STLV-2, STLV-3 STLV-4
HTLV clades evolved independently and jumped species on at least 3 occasions
Epidemiology

Isolated in 1980 from a patient with T cell lymphoma in Japan
Infects an estimated 5-10 million people

Seropositivity (HTLV-1) varies and correlates with the incidence of ATLL, which develops in about 1-2 % of seropositive individuals:

- US 0.02%
- Canada 0.0014% (Nunavut cluster)
- Uganda 8%
- Iran 3%
- Okinawa 35%

HTLV-2

Rare, maybe causes hairy cell leukemia
More common in Amerindian population, Pygmy
In certain parts of Asia
Transmission

HTLV-1 is transmitted almost exclusively by direct cell-to-cell contact

- Mother to fetus, mother to newborn, breast milk
- Infected blood, blood products
- Increasing prevalence in IVDU and men-who-have-sex-with-men (MSMs)
- Man to woman by sexual intercourse
Diseases

- Asymptomatic
- 2-5% of infected people develop complications
  - Acute T-cell leukemia/lymphoma ATLL (0.8-2%, after 30 yrs)
  - HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) – After 3-10yrs
- Infective dermatitis, uveitis, arthritis
- Hyperinfection with *Strongyloides stercoralis* as a risk factor
Transformation

Two oncogenic proteins:
**Tax** is a transactivator of the viral promoter
**Tax** interacts with NF-κB and IF-κB causing an activation of NF-κB promoters (about 30 genes) in T cells.
Tumor progression may follow and is independent of Tax, but requires **HBZ**.
**HBZ** is a repressor of tax and an inducer of cell proliferation
Transformation by DNA viruses

Human Papillomavirus (HPV)
Epstein-Barr virus (EBV)
Kaposi-Sarcoma herpesvirus (KSHV, HHV-8)
Polyomaviruses (SV40, JCV, BKV, KI, WU, Merkel polyomavirus)
Adenoviruses

Commonalities:
- Persist in the host for 20+ years
- Cause cell division and inhibit apoptosis
- Inhibit Rb, the gatekeeper, and p53, the caretaker
- They co-evolved with the human species
Oncogenic DNA viruses induce cell proliferation as part of their life cycle

Polyoma and papillomaviruses require the cellular replication machinery for their own DNA replication.

EBV and KSHV infect primarily quiescent B lymphocytes that would not support the high metabolism required by these viruses. Cell replication staves off apoptosis.

Chance, other infections, host and environmental factors determine the probability of malignant transformation
Papillomaviruses

Circular, ds DNA genome, about 8kb in length

Non-enveloped icosahedral capsid made of 72 pentamers

Tropism for keratinized epithelia

Cause cell proliferation of the basal layer (papilloma)

The replication cycle is intimately connected with differentiation of the epithelium
Papilloma

Normal cervical epithelium

Cervical papilloma
The genome of papillomaviruses

Long control region

Fields Virology (2001)
Evolution of papillomaviruses

Classification of papillomaviruses
Human papillomaviruses

About 200 different ‘types”

Type definition: When the DNA sequence of the E6, E7 and L1 ORF has less than 90% homology to known HPV types.

Indeed, different types often have different epidemiology, pathogenesis and immunology.
Cutaneous HPV infections

Skin warts: HPV-1, HPV-2 and HPV-4
Flat warts: HPV-3, HPV-10 and HPV-28
Butcher wart: HPV-7
Epidermodysplasia verruciformis
Skin cancer (rare)
Skin warts
Epidermodysplasia verruciformis
Mucosal HPV infections

- Ano-genital warts (*condyloma acuminatum*): “low risk” types like HPV-6, HPV-11
- Cervical/vaginal infection: About 50 types
- Cervical dysplasia and cancer: “high risk” types like HPV-16, HPV-18, HPV-33, HPV-45, HPV-31
- Other genital cancers

- Recurrent respiratory papillomatosis: HPV-11, HPV-6

- Head and neck malignancies
Mucosal warts

Condyloma acuminatum (penis)
Condyloma acuminatum (vulva)
Laryngeal warts
Cervical infections

normal

dysplastic

cancer
Natural history of cervical cancer

10 - 30% of women are infected with one or more of the ~50 mucosal HPV types

\[ \Downarrow \]

Persistent infection (presence of “high risk” HPV DNA)

(1-3%)

\[ \Downarrow \]

HPV testing \[ \Rightarrow \] Pap screening

Transformation (abnormal cervical cytology)

(0.3 - 0.5%/year CIS)

\[ \Downarrow \]

Excisional biopsy

Progression (invasive cervical cancer)

Majority: HPV 16 and HPV 18 (70%)

Notables: HPV 45, HPV 33, HPV 31, HPV 59
Summary of oncogenic transformation by HPV “high risk” types

- E5 turns on the cellular oncogene pathway producing a mitotic signal
- E7 releases the inhibition of cell replication by Rb
- E6 releases the G1/S arrest by p53
- E6 prevents apoptosis
- Cell enters the S phase
- Cell keeps on replicating and accumulating mutations until it becomes cancerous
- Progression
The genome of papillomaviruses
“high risk” vs. “low risk”: epidemiology


<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Patients</th>
<th>Controls</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>%</td>
<td>no.</td>
</tr>
<tr>
<td>Negative for HPV</td>
<td>46</td>
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<tr>
<td>16</td>
<td>685</td>
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<td>18</td>
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<td>56</td>
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<tr>
<td>81</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>X††</td>
<td>47</td>
<td>3.5</td>
<td>34</td>
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“high risk” vs. “low risk”: Molecular genetics
“high risk” vs. “low risk”: Molecular biology

E6 transformation domains

<table>
<thead>
<tr>
<th></th>
<th>p53 degradation</th>
<th>p53 binding</th>
<th>MAGUK degradation</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>RRETQV 151</td>
</tr>
</tbody>
</table>

High Risk       Yes       Yes       Yes (required)
Low Risk        No        Yes       Missing
HR E6 induces degradation of p53

Elbel et al. (1997) Virology 239:132
Degradation of the MAGI protein by HR E6 protein

Dana Cabiles (2014) M.Sc. Thesis – University of Manitoba
Epstein - Barr Virus

EBV, HHV-4
A gamma herpesvirus

Discovered in 1964 associated with Burkitt lymphoma
Infects the majority of population worldwide

Transmitted through saliva, the first infection is usually asymptomatic
In young adults may cause infectious mononucleosis
Rarely:
• Chronic active mononucleosis
• EBV hepatitis
• X-linked lymphoproliferative syndrome
• Hemophagocytic syndrome
Type C - 184 kb

Genome

oriP

ori lyt

TR

IR1

IR2

IR3

IR4

TR
Infection

B cells, especially memory B cells.
Causes transformation in vivo and in vitro
Both lytic and latent infection
B cell proliferation in latent infection
Very strong T cell response

Nasopharyngeal epithelium
Latent and lytic infection, shedding in saliva
May cause tumors
Not very well understood
Mononucleosis
Malignancies

- B-cells lymphomas
  Early and late PTL (post-transplant lymphomas)
  In HIV infected individuals
  Rare normal individuals
- Burkitt lymphomas
- Nasopharyngeal carcinoma
  Transformation of epithelial cells.
  In HIV patients
  In normal patients
- Hodgkin’s lymphomas
  Peak of EBV-negative HL at 30 years of age in developed countries
  Most Hodgkins are EBV+ in developing countries
- Leiomyosarcomas
- Gastric carcinoma (Asia)
- T-cell lymphoma (Asia)
- Hepatoma (?), breast cancer (?)
Induction of proliferation

Requires:

- EBNA-1 maintains episomal replication (similarity with KSHV LANA)
- EBNA-2, EBNA-LP, EBNA 3A, 3B 3C. Transactivators.
- EBNA 3C inhibits and degrades Rb (PNAS 102:18562-18566. 2005)
- LMP-1- membrane protein that turns on the NFkB/Jun/AP-1 response.
- EBERs - Small RNAs of unknown function (they probably inhibit the interferon response).

Consequences:

- Proto-oncogenes pathways are turned on: the cell divides
- Anti-oncogenes pathways are turned off: apoptosis is inhibited
- Interferon response seems disabled (probably by EBERs)
Lytic cycle

• Like all herpesviruses EBV has a lytic cycle in which the genome is replicated by the viral proteins and more infectious virus is produced.
• This occurs in B cells and nasopharyngeal epithelia
• Leads to the host cell death
• Always occur at low level, most active during mononucleosis
Latency

The genome is present as an episome, replicated by the host machinery, needs oriP and EBNA-1
Only the latent proteins are expressed
Cell division is (usually) activated
Four types of latency:

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<td>Memory B cells</td>
<td>Endemic Burkitt</td>
<td>Hodgkin Nasopharyngiomas</td>
<td>Non endemic Burkitt Lymphoblastoid cell lines</td>
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Burkitt Lymphoma

- Endemic - Linked to malaria infection - 100 fold increased risk - 90% EBV+
- Sporadic - In Western countries - 30% EBV+
- AIDS-linked - In 10% of patients - 30-60% EBV+

Molecular features:
- EBV latency III - sporadic
- EBV latency I - endemic
- Translocation of c-myc under the control of the Ig long range enhancer
- Malaria infection causes massive replication of B cells
- Mutations in the c-myc regulatory regions
- Mutation in the p53 gene (in about 50% of tumors)
Kaposi Sarcoma Herpesvirus

Gamma herpesvirus (like EBV)
Large, linear ds DNA genome (145kb). Many genes.
Complex interaction with the host
A large number of genes that were “pirated” from the host
Sophisticated regulation of the host immunoresponse.
Asymptomatic first infection, followed by life long latency

Tumors are rare in immunocompetent individuals
More common in HIV patients.
Epidemiology

Wide variations in different populations (seroprevalence)
- > 5% in N. America and N. Europe
- 10-15% in the Mediterranean area (30% in Sardinia)
- 50% in sub-saharan Africa
- high in HIV at-risk groups, especially male homosexuals

Kaposi sarcoma incidence follows the prevalence of HHV-8
- mostly males in N. America (because of HIV)
- males and females endemic areas
- children in Africa
- risk greatly increased in immunosuppressed individuals
Transmission

Unclear
Anal intercourse
Saliva?
Blood borne transmission does not seem relevant
Kaposi Sarcoma
Latency

Latency is established in B cells (in culture and perhaps in vivo) and blood vessel cells (in vivo).

The following proteins have been shown to be expressed during latency:

• LANA (latency-associated nuclear antigen)
• v-cyclin
• v-FLIP
• v-IRF-2
• LANA-2

It is suspected that different types of latency exist in HHV-8 as in EBV
Transformation

Disruption of cell proliferation control
• LANA inhibits p53 and Rb
• v-cyclin is a pirated homolog of cellular cyclin
• v-FLIP activates the ras pathway
• And more

Cytokines and other pirated signals
• v-IL6 is an autocrine signal
• v-Bcl-2, v-IRF, v-IL6 prevent apoptosis
• And more
The End