Viruses and cancer

Daniel DiMaio
Department of Genetics
Tumor Viruses

Some naturally occurring tumors in animals are caused by viruses (1908)

Studies of tumor viruses have provided seminal insights into biology and carcinogenesis (e.g. oncogenes, p53)

Viruses are an important cause of cancer in humans

Anti-viral strategies can prevent or treat cancers
Expression of specific viral genes are sufficient to induce tumor formation

**Oncogenes**

RNA viruses – retroviruses

DNA viruses –
  polyomaviruses
  papillomaviruses
  herpesviruses
Many retroviral oncogenes encode proteins that comprise cellular growth signaling pathways.
Many of these oncogenes are implicated in human cancer.
These oncogene products are targets for therapy

v-Abl oncogene    Bcr-Abl translocation in chronic myelogenous leukemia
                 Gleevec inhibits tyrosine kinase activity and controls CML

v-ErbB1 oncogene   EGF receptor is mutated in lung cancer
                   Numerous TKI specific for mutant form of EGFR

Braf oncogene     Commonly mutated in melanoma
                   Vemurafemid in patients with these mutations

Responses tend to be short-lived
DNA virus oncogenes products modulate many of the same pathways by binding to cellular proteins
Some DNA virus oncoproteins transform cells by turning on cellular growth stimulatory proteins

Other DNA virus oncoproteins transform cells by turning off cellular growth inhibitory proteins

- Polyomavirus middle T
- Adenovirus E1A

Stimulatory signal (e.g. src) → Cell growth → Inhibitory signal (e.g. Rb)
Oncoproteins from multiple DNA tumor viruses bind and inactivate same tumor suppressor proteins

Retinoblastoma
- Adenovirus E1A
- Polyomavirus large T antigen
- High-risk HPV E7
- Low-risk HPV bind poorly

p53
- SV40 large T antigen
- Adenovirus E1B 55kDa
- Adenovirus E4orf6
- High-risk HPV E6
- Not low-risk HPV E6

These interactions are important for human cancer
Viruses and human cancer
Difficulties in identifying human tumor viruses

- Inefficient
- Slow
- Not sufficient
- No virus present
Human Tumor Viruses

In aggregate, ~15% of all cancer deaths worldwide are caused by virus infection

Adapted from Plummer et al, Lancet Glob Health 4: 609-16, 2016
Are other human tumors caused by viruses?

EBV
  Hodgkins disease
  Gastric carcinoma

HPV
  Skin cancers

Additional viruses?
Viral tumors are more prevalent in the developing world

- Poor nutritional and health status
- Infections more common
- Poor screening programs
- Different viral strains
- Different host genetics
How do viruses cause cancer?

Encode oncogenes (HPV, herpesviruses)
  - Stimulate cell growth
  - Induce genetic instability
  - Inhibit cell death (apoptosis)

Induce expression of cell oncogene
  (some retroviruses vectors used in gene therapy)

Induce chronic inflammation (HBV, HCV)
  - Injury, repair, proliferation, mutagenesis
Mechanism of carcinogenesis has important implications for prevention and treatment.
Some general principles

Most people infected with a tumor virus do not get cancer.

Progression to cancer often associated with immunosuppression or immunodeficiency.

It takes many years after infection before the cancer develops.

The cancer itself is not contagious.
HIV is an honorary tumor virus

Immunosuppression caused by HIV predisposes people to various cancers

AIDS-defining cancers
• Primarily virus-associated
  • Kaposi sarcoma - KSHV
  • Cervical - HPV
  • Aggressive B-cell lymphoma - EBV

Non-AIDS-defining cancers
  e.g. lung cancer
Viral etiology provides opportunities for understanding, prevention, and cure
Prevention

Prevent viral infection or spread by various public health measures
Prevent progression to carcinoma or spread of virus to new hosts by anti-viral strategies
Public health measures

Elimination of HBV and HCV from blood supply
Identification of HPV-induced cervical dysplasia by Pap screening and DNA testing
Vaccination against tumor virus infection
Vaccination against hepatitis B virus infection

Safe and effective hepatitis B vaccine that prevents infection and hepatitis
60% vaccine coverage of infants worldwide
>2/3 reduction of risk of hepatocellular cancer in vaccinated children
Treatment

Persistence of viral genes and proteins in cancer cells provide novel, well-defined targets for therapy.

Drugs that inhibit herpesvirus DNA replication can reduce numbers of Kaposi sarcoma lesions.

Will HCV cure reduce cancer risk?

Anti-viral drugs target viral proteins that are absent from uninfected cells.
Cervical carcinoma

Most common cause of cancer death in women in developing world

Incidence of invasive cervical cancer in U.S.A. - from SEER
Possible to eradicate most cases of cervical cancer based on an understanding of the infectious basis for this disease
Papillomaviruses

Small non-enveloped viruses
- 8000 base pairs of double-stranded DNA
- encode ~10 proteins

Many different HPV types
- Infect billions of people world-wide
- Specific types associated with specific diseases
- High-risk HPV types associated with cancer
Human Papillomavirus Particles
Virtually all cervical cancers contain HPV DNA

Harald zur Hausen
2008 Nobel Prize

~1000 cases
Bosch, et al., 2000
Epidemiological studies demonstrate that infection with high-risk HPV types confers a greatly elevated risk of cervical cancer.

- Many years pass between infection and cancer
- Most infected women do not get cancer

HPV infection is necessary but not sufficient.
It’s not just cervical cancer

HPV16 by far most prevalent HPV type in non-cervical cancer

Important that males are also vaccinated

Adapted from Van Dyne, et al., MMWR, 2018; https://www.cdc.gov/cancer/hpv/statistics/cases.htm
Two types of HPV vaccines

Prophylactic vaccine (Gardasil, cervarix)
- Generate antibodies to virus particles
- Prevent HPV infection

Therapeutic vaccine
- Generate killer T cells to viral E6/E7 proteins in cancer cells
- Treat HPV disease
Prophylactic HPV VLP vaccine

• Virus-like particle assembled from L1 protein
• Multiple HPV types in vaccine
• Contains no viral DNA
• Non-infectious, non-pathogenic
• Can induce robust antibody and cell-mediated immune response
• Prevents persistent HPV16 and HPV18 infection and cervical precancer

The first vaccine designed to prevent human cancer
HPV vaccination reduces incidence of precancerous cervical lesions
Decreased incidence of genital warts in heterosexual Australian men following HPV vaccine implementation in 2007


Herd immunity
In the US, HPV vaccination recommended for all boys and girls between 11 and 12 years old.

HPV Vaccination Rates of Adolescent Girls ages 13-17, by State

Completion of 3 dose HPV vaccine series among females ages 13-17, 2014

Vaccination rates even lower for boys

2014 U.S. average = 39.7%

NOTES: Share of females ages 13-17 who have received all 3 doses of the HPV vaccine series. *Statistically significant (p<.05) percentage point change from 2013.

What are main barriers to HPV vaccination?

Cost
General anti-vax attitude
Fear of side-effects
Social or religious stigma regarding sexually transmitted diseases
Lack of school-based or mandatory programs

Health care providers!
Limitations to prophylactic HPV VLP vaccine

VLPs expensive to produce and distribute
No benefit to women already infected
Vaccination rates low in much of the world
Not all high-risk HPV types are in vaccine and there is no cross-protection

Currently HPV16,18,6,11 and five other high-risk types
Cancer cells accumulate many mutations during carcinogenesis
E6 and E7 induce genetic instability

Karyotype of HeLa cells
Despite mutations, viral oncogenes are expressed in the cancers.

Do these mutations make the cancer cells independent of viral oncogenes?
Repression of HPV E6/E7 oncogenes activates p53 and Rb in cervical cancer cells
Repression of HPV oncogenes causes cervical cancer cells to stop growing.
PROLIFERATION OF CERVICAL CANCER CELLS REQUIRES EXPRESSION OF THE HPV ONCOGENES

• Cellular mutations accumulated during carcinogenic progression are not sufficient to maintain the malignant state

• Implies that drugs that inhibit the activity of viral proteins may be therapeutically useful
Strategies for controlling cervical cancer in the 21st century

Prevent infection
   prophylactic vaccination

Identification, monitoring, and treatment of carriers
   Pap smear and HPV DNA testing

Inhibit progression and transmission
   anti-viral drugs that inhibit viral replication

Immune-based treatment of cancer
   therapeutic vaccination

Mechanism-based treatment of cancer
   anti-viral treatments that inhibit expression or action of E6 and E7 proteins
Thank you!

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