LECTURE 15: Oncogenic Viruses and Antiviral Drugs & Viral Vaccines

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Part I: Oncogenic Viruses (Human Cancer Viruses)

Introduction

Cell Growth Regulation

Cell growth is the cell proliferation (the increase in cell numbers that occurs through repeated cell division).

Cell growth is regulated by **two groups of regulatory genes**:

A. Proto-oncogenes (cellular oncogene, c-onc)

- Are normal genes which control cell proliferation
- Have the potential to contribute to cancer development if their expression is altered (changed into oncogenes)
- **Oncogenes are genes that cause cancer**

B. Tumor Suppressor Genes

- Include genes that inhibit cell growth, fixing broken DNA or causing a cell to die
- **Examples:** P53, Rb (retinoblastoma)
- In normal cells, oncogenes are "switched off" or down-regulated by antioncogene proteins

Definition of Oncogenic Viruses

An oncovirus is a virus that can cause cancer.

- It refers to any virus with a **DNA or RNA genome** causing cancer
- Also called **"tumor virus"** or **"cancer virus"**
- Most viruses are **non-transforming** - however, they may play a role in reducing the host cell's ability to inhibit apoptosis

Oncogenic virus: A virus that is able to cause cancer is known as an oncogenic virus. Evidence that a virus is oncogenic includes the regular presence in the tumor cells of virus DNA, which might be all or a part of the virus. It is possible that the virus is just one of a number of carcinogenic factors that can give rise to these cancers.

Epidemiological Significance

- At least **15-20% of all human tumors worldwide** have a viral cause
- Viruses are etiologic factors in the development of several types of human tumors, including two of great significance worldwide: **cervical cancer** and **liver cancer**
- Many viruses can cause tumors in animals, either as a consequence of natural infection or after experimental inoculation

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Classes of Oncogenic Viruses

There are **two classes** of tumor viruses:

1. **DNA tumor viruses**
2. **RNA tumor viruses** (also referred to as Retroviruses)

DNA Tumor Viruses

1. Papovaviridae

- **Human papilloma virus** causes uterine (cervical) cancer

2. Polyomaviridae

- **JK, BK** causes solid tumor in rodents
- **Merkel Cell Polyoma virus** causes Merkel Cell Carcinoma (rare skin cancer)

3. Herpesviridae

a) Epstein-Barr Virus (EBV)

- Infection increases the risk of Burkitt lymphoma
- Nasopharyngeal carcinoma
- Some types of Hodgkin's and non-Hodgkin's lymphoma
- Stomach cancer

b) Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8)

- Associated with Kaposi's sarcoma, a type of skin cancer

c) Human cytomegalovirus (CMV or HHV-5)

- Associated with mucoepidermoid carcinoma and possibly other malignancies

4. Hepadnaviridae

- **Hepatitis B virus** causes hepatocellular carcinoma

5. Adenoviridae

- **Adenovirus** causes various solid tumor in rodents

6. Poxviridae

- **Smallpox; cowpox** causes various solid tumor

RNA Tumor Viruses

1. Retroviridae

- **Human T-cell leukemia virus (HTLV-1; HTLV-2)** causes Adult T-cell leukemia, Lymphoma

2. Flaviviridae

- **Hepatitis C Virus** causes Hepatocellular carcinoma

General Features of Viral Carcinogenesis

1. **Viruses can cause cancer in animals and humans**
2. **Tumor viruses frequently establish persistent infections in natural host**
3. **Viruses are seldom complete carcinogens**
4. **Host factors are important determinants of virus-induced tumorigenesis**
5. **Virus infections are more common than virus-related tumor formation**
6. **Long latent periods usually elapse between initial virus infection and tumor appearance**
7. **Viral strains may differ in oncogenic potential**
8. **Viruses may be either direct- or indirect-acting carcinogenic agents**
9. **Oncogenic viruses modulate growth control pathways in cells**
10. **Animal models may reveal mechanisms of viral carcinogenesis**

Part II: Antiviral Drugs

Definition and Overview

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses.

Challenges in Antiviral Drug Development

- **Designing safe and effective antiviral drugs is difficult** because viruses use the host's cells to replicate
- This makes it difficult to find targets for the drug that would interfere with the virus **without harming the host organism's cells**
- The **major difficulty** in developing vaccines and anti-viral drugs is due to **viral variation**

Limitations of Antiviral Drugs

The number of antiviral drugs is very small because:

1. **The virus is obligate intracellular parasite**, difficulty in obtaining selective toxicity against virus
2. **Relatively ineffective**, because many cycles of viral replication occur by the time the patients have systemic viral disease
3. **Some viruses remain latent in cells** e.g. Herpes virus family
4. **The emergence of viral drug resistance** - viruses mutate

Current Antiviral Targets

- Most of the antiviral drugs now available are designed to help deal with:
  - **HIV**
  - **Herpes viruses**
  - **Hepatitis B and C viruses**
  - **Influenza A and B viruses**
- Researchers are working to extend the range of antivirals to other families of pathogens

Mechanism of Action

Nucleotide/Nucleoside Analogues

- **Nucleotide analogues** are synthetic compounds which resemble nucleosides, but have an incomplete or abnormal deoxy-ribose and/or ribose group
- They look like the building blocks of **RNA or DNA**, but **deactivate the enzymes** that synthesize the RNA or DNA once the analogue is incorporated
- This approach is more commonly associated with the **inhibition of reverse transcriptase** (RNA to DNA)

Targets for Antiviral Chemotherapy

Stages in virus replication which are possible targets for chemotherapeutic agents:

1. **Attachment to host cell**
2. **Uncoating** - (Amantadine)
3. **Synthesis of viral mRNA**
4. **Translation of mRNA** (Interferon)
5. **Replication of viral RNA or DNA** (Interferon)
6. **Maturation of new virus proteins** (Protease inhibitors)

7. **Assembly, release** - Protease inhibitors can be developed to prevent the final maturation of viral proteins in viruses that use a polyprotein expression strategy

Examples of Antiviral Drugs

- **Rifampicin**
- **Tamiflu**

Part III: Viral Vaccines

Definition

Vaccine is a biological preparation that provides **active acquired immunity** to a particular disease. A vaccine typically contains an agent that resembles a disease-causing micro-organism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins.

Types of Vaccines

- **Prophylactic vaccines** (preventive)
- **Therapeutic vaccines** (e.g., vaccines against cancer)

Effectiveness and Limitations

- **Vaccines are very effective on stable viruses**
- **Limited use** in treating a patient who has already been infected
- **Difficult to successfully deploy** against rapidly mutating viruses, such as:
  - **Influenza** (the vaccine for which is updated every year)
  - **HIV**
- **Antiviral drugs are particularly useful** in these cases

Attributes of a Good Vaccine

1. **Ability to elicit the appropriate immune response** for the particular pathogen
2. **Long term protection**
3. **Safety**
4. **Stable**
5. **Inexpensive**

Types of Vaccines

1. Live, Attenuated Vaccines

- Vaccines contain **live, attenuated microorganisms**
- Many of these are active viruses that have been cultivated under conditions that **disable their virulent properties**
- Become less dangerous organisms to produce a **broad immune response**
- Although most attenuated vaccines are viral, some are bacterial in nature
- **Examples:** viral diseases measles, rubella, and mumps, and the bacterial disease typhoid

2. Inactivated Vaccines (Killed Vaccine)

- Vaccines contain **inactivated virus**, but previously virulent, micro-organisms
- Have been destroyed with **chemicals, heat, radiation, or antibiotics** without destroying the antigenicity of the virus
- **Examples:** influenza, cholera, hepatitis A, and rabies

3. Subunit Vaccines

- **Viral proteins or groups of proteins** are used
- These proteins can be purified directly from viral particles
- **Expensive**, since it is difficult to prepare virus in large enough quantities for protein purification
- **Potentially dangerous** since there is the possibility of contaminating virulent virus

4. DNA-Based Vaccines

- **Genes (DNA) encoding specific viral proteins** are injected into an animal (either in muscle or skin)
- The DNA is then taken up by cells, where it is **transcribed into mRNA** which is then **translated to give rise to the viral protein**
- This protein is expressed on the surface of cells, either alone or in association with **MHC molecules**
- It is recognized as a **foreign molecule** by the immune system, and elicits an immune response

5. Toxoid Vaccines

- For bacteria that secrete **toxins, or harmful chemicals**
- These vaccines are used when a **bacterial toxin is the main cause of illness**
- They can **inactivate toxins by treating them with formalin**
- Such "detoxified" toxins, called **toxoids**, are safe for use in vaccines

6. Recombinant Vector Vaccines

- **Immunogenic proteins** of virulent organisms may be synthesized artificially
- By introducing the **gene coding for the protein** into an expression vector, such as **E. coli or yeasts**

Study Questions

Q1: Enumerate types of viral vaccines?

Answer: The types of viral vaccines include:

1. **Live, attenuated vaccines** - contain live, weakened microorganisms
2. **Inactivated vaccines (killed vaccines)** - contain inactivated virus destroyed by chemicals, heat, radiation, or antibiotics
3. **Subunit vaccines** - use viral proteins or groups of proteins purified from viral particles
4. **DNA-based vaccines** - use genes encoding specific viral proteins injected into animals
5. **Toxoid vaccines** - use inactivated toxins for bacteria that secrete harmful chemicals
6. **Recombinant vector vaccines** - use artificially synthesized immunogenic proteins through gene insertion into expression vectors

Q2: Define Antiviral drugs?

Answer: Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses. They are designed to interfere with viral replication without harming the host organism's cells. However, developing safe and effective antiviral drugs is challenging because viruses use the host's cells to replicate, making it difficult to find selective targets that would affect the virus without damaging the host cells.

End of Lecture

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