Disorders of Cell Growth & Neoplasia

Lecture 5
Carcinogenic agents
Carcinogenic Agents

Oncogenic Viruses

- HPV, HBV, EBV, HTLV responsible for ~15% human cancer incidence.
- Oncogenic viruses are the 2nd most important risk factor (exceeded only by tobacco consumption).
- Oncogenic viruses documented more extensively in veterinary than human medicine.

General features of viral replication:
1. Virus attaches to a cell.
2. Virus penetrates cell membrane and injects nucleic acid (DNA or RNA) into cell.
3. Viral nucleic acid replicates using host cellular machinery.
4. New viral nucleic acids are packaged into viral particles and released from the cell. The host cell may be destroyed in the process.
Mechanisms of tumorigenesis by RNA retroviruses. Acute transforming RNA viruses contain a viral oncogene formed by transduction of a cellular protooncogene (meaning: acquisition by the viral genome of a gene, in this case a protooncogene, from a host cell). Infection of a cell by such a virus results in the integration and expression of the viral oncogene, potentially leading to neoplastic transformation. By contrast, slow transforming viruses do not contain a viral oncogene, but rather a promoter gene. The integration of this promoter gene misregulates the expression of a cellular protooncogene (a process called insertional mutagenesis), again potentially leading to neoplastic transformation. (source: Essential Pathology. Rubin & Farber. J.B. Lippincott Co., 2nd edition, 1995, Figure 5-17)
Oncogenic Viruses

1. Oncogenic RNA viruses

i) Slowly transforming retroviruses

- lack a viral oncogene.
- cause cancer in persistently infected animals (long latent period)
- replication-competent.

eg’s
- Feline leukemia virus
- Bovine leukemia virus
- Avian leukosis virus
- Human T-cell leukemia virus

Mechanisms of tumorigenesis by RNA retroviruses.
(source: Essential Pathology. Rubin & Farber. J.B. Lippincott Co., 2nd edition, 1995, Figure 5-17)
Lymphoma of various organs in cats, i.e. submandibular / parotid lymph nodes (upper left), kidney (upper right), intestine (lower left) and skin (lower right). Lymphoma (lymphosarcoma) is the most common malignancy of cats and in most cases the result of infection with FeLV. Most feline lymphomas are of T cell origin and are classified as “multicentric” (i.e. generalized involvement of lymph nodes, +/- liver, spleen, marrow, other), alimentary, thymic or miscellaneous (renal, ocular, cutaneous, etc), depending on which organs are involved.
Oncogenic Viruses

Oncogenic RNA viruses

ii) Rapidly transforming retroviruses

- carry their “own” oncogene (v-onc).
- cause cancer after a short latent period.
- replication-defective; need persistent infection by parent replication-competent retrovirus

eg. Feline sarcoma virus (+ FeLV).
Avian sarcoma virus (+ ALV)

Mechanisms of tumorigenesis by RNA retroviruses.
(source: Essential Pathology. Rubin & Farber. J.B. Lippincott Co., 2nd edition, 1995, Figure 5-17)
Multicentric fibrosarcoma in a ten month old domestic shorthaired cat. The paw is markedly swollen with multiple tumors. Additionally, a firm, pale gray mass ~ 4 x 3 x 2 cm’s is present in the right deltoid muscle and associated lymph node (note: each mass representing an separate tumor clone). [from Can Vet J 1984; 25: 207-210]
• infection of a cell by a DNA tumor virus has only one of two consequences:

➢ cell is transformed (integration), in which case the infection is non-productive.

➢ infection is productive, ie cell produces infectious viral particles but dies in process.

• transforming & productive infections can occur together in the same animal.

• other factors needed for malignant transformation, eg environmental carcinogens, diet, heredity, other infections, immunodeficiency, etc
Oncogenic Viruses

Oncogenic DNA viruses

- produce proteins that inactivate the products of tumor suppressor genes (also may enhance or mimic the activity of proto-oncogenes products).

- viruses may also act as mitogens of target cells via concurrent productive infection.

- continuous low-grade proliferation leads to cytogenetic rearrangement \( \rightarrow \) emergence of neoplastic clones.

Robbin’s Fig 7-43. Effect of HPV proteins E6 and E7 on the cell cycle. E6 and E7 enhance p53 degradation, causing a block in apoptosis and decreased activity of the p21 cell cycle inhibitor. E7 associates with p21 and prevents its inhibition of the Cyclin/CDK4 complex; E7 can bind to RB, removing cell cycle restriction. The net effect of HPV E6 and E7 proteins is to block apoptosis and remove the restraints to cell proliferation.
Oncogenic DNA viruses

i) Papilloma viruses

- A large number of *host-specific* papilloma viruses produce papillomas in vertebrates.
- HPV’s cause condyloma acuminata (genital warts) & cervical carcinoma.
- PV’s infections are common in vet med (mostly self-limited); exceptions.

Several *cutaneous papillomas* in a horse.
Multiple papillomas (papillomatosis) due to papilloma virus infection are most commonly seen in young dogs, cattle & horses. The size and number vary considerably and they are typically found on the skin or on the mucosal surfaces of the upper GI tract. It is generally a self-limiting disease, of varying duration. Images to the right shows single (top) and multiple (bottom) papillomas projecting from the mucosal surface of the esophagus.

Images from Noah’s arkive
Malignant neoplasms of the esophagus (right, top) and forestomachs (right, bottom) in ruminants are very rare. However, in several localities, squamous cell carcinoma (right) is relatively common in cattle, when an interaction between Bovine papillomavirus and ingestion of bracken fern (*Pteridium aquilinum*) occurs.

*Images from Noah’s arkive*
Equine Sarcoids (Fibropapillomas) are the most common skin tumor of the horse and are associated with infection by bovine papillomavirus.
Recent evidence suggests these relatively uncommon fibropapillomas (typically found on the head or distal limbs) are associated with bovine papillomavirus infection in the cat. (see Vet Pathol. 2001; 38: 291-6 and Vet Dermatol. 2003; 14: 47-56)
Oncogenic DNA viruses

ii) Herpesviruses

- Marek's disease virus + genetically susceptible chickens → T-cell lymphoma

The lymphoma of Marek's disease often shows an early “homing” for sciatic nerves often leading to paralysis (top, left). Compare affected left sciatic nerve (arrows) with the grossly unaffected right sciatic nerve. The liver shows multiple nodular lesions (top, right).
Hepatocellular carcinoma, liver, woodchuck

Hepatocellular carcinomas in woodchucks are usually associated with woodchuck hepatitis (WHV) virus infection.
• experimental models demonstrate the phenomenon of \textit{initiation} and \textit{promotion}.

\textit{initiation} - cells exposed to carcinogen (initiator) \rightarrow somatic mutations in DNA.

\textit{promotion} - promoters are not carcinogenic themselves but can induce tumors in initiated cells via cellular proliferation.

\textbf{Robbin’s Fig 7-41.} Classic experiments applying chemical compounds to mouse skin demonstrate the concept of initiation and promotion. Group 2: application of promoter repeated at twice-weekly intervals for several months. Group 3: application of promoter delayed for several months and then applied twice weekly. Group 6: promoter applied at monthly intervals.
Chemical Carcinogenesis

- mutagenic chemicals that initiate carcinogenesis are either:
  - direct acting carcinogens; do not require chemical transformation.
  - indirect-acting carcinogens; require metabolic activation → ultimate carcinogens.

### Direct-acting carcinogens

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<tr>
<th>Type</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Alkylating agents</td>
<td>Some anticancer drugs (e.g., cyclophosphamide), (\beta)-propiolactone, dimethyl sulfate, etc</td>
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<tr>
<td>Acylating agents</td>
<td>1-acetyl-imidazole, dimethylcarbamyl chloride</td>
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### Indirect-acting carcinogens

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<thead>
<tr>
<th>Type</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Polycyclic &amp; Heterocyclic Aromatic Hydrocarbons</td>
<td>Many produced in combustion of tobacco &amp; also in broiled / smoked meats, e.g., benzo(a)pyrene</td>
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<tr>
<td>Aromatic Amines, Amides, Azo Dyes</td>
<td>Aniline dye &amp; rubber industries (e.g., (\beta)-naphthylamine), food dyes (e.g., dimethylaminoazobenzene)</td>
</tr>
<tr>
<td>Natural Plant and Microbial Products</td>
<td>Aflatoxin B&lt;sub&gt;1&lt;/sub&gt;, Griseofulvin, Cycasin, Safrole, Betel nuts</td>
</tr>
<tr>
<td>Others (often occupational exposures)</td>
<td>Chromium, nickel, arsenic, asbestos, vinyl chloride, polychlorinated biphenyls (PCB’s), etc</td>
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Chemical Carcinogenesis

• mutagenic chemicals may form adducts (covalent bonding) between the carcinogen and DNA → **molecular damage.**

• outcome of cell damage can be:
  ① complete repair
  ② cell death
  ③ DNA mutation

• **initiation** requires at least one cell cycle for the mutation to become permanent.

• **Promoters** (chemicals / drugs, hormones, viruses) induce cell proliferation → additional mutations → neoplastic transformation.
Robbin’s Fig 7-42 General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter or other factors causes accumulation of additional mutations and emergence of a malignant tumor.