VIRUSES AND CANCER
2012

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VIRAL ONCOLOGY - LECTURE OUTLINE

1. Historical Review

2. Viruses Associated with Cancer

3. RNA Tumor Viruses

4. DNA Tumor Viruses

HISTORICAL REVIEW

Historical Review

1908 Ellerman and Bang : Leukemia induced in chickens by a cell-free extract (avian leukemia virus).

1911 Rous : Sarcoma induced in chickens by a cell-free tumor filtrate (Rous sarcoma virus).

1933 Shope : Papilloma virus from wild rabbits caused invasive tumors in domestic rabbits from which virus could be isolated.

1936 Bittner : Mammary tumors in mice caused by a factor in milk.

1951 Gross : Cell-free filtrates from AKR mice with leukemia caused leukemia in C3H mice.

1958 Stewart: Polyoma virus; as many as 10 different tumor types could be induced in a single mouse.

1970 Baltimore; Temin and Mizutani : Reverse transcriptase (RNA-dependent DNA polymerase) associated with RNA tumor viruses.

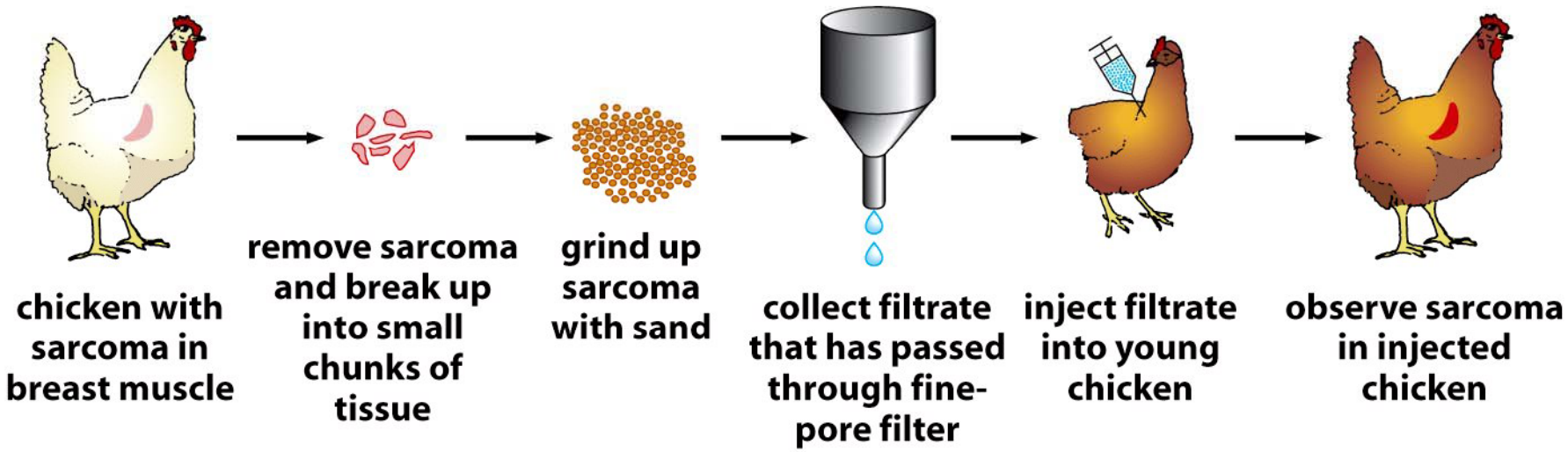

Figure 3-2 The Biology of Cancer (© Garland Science 2007)

Rous's protocol for inducing sarcomas in chickens

Retrovirus structure and typical genome

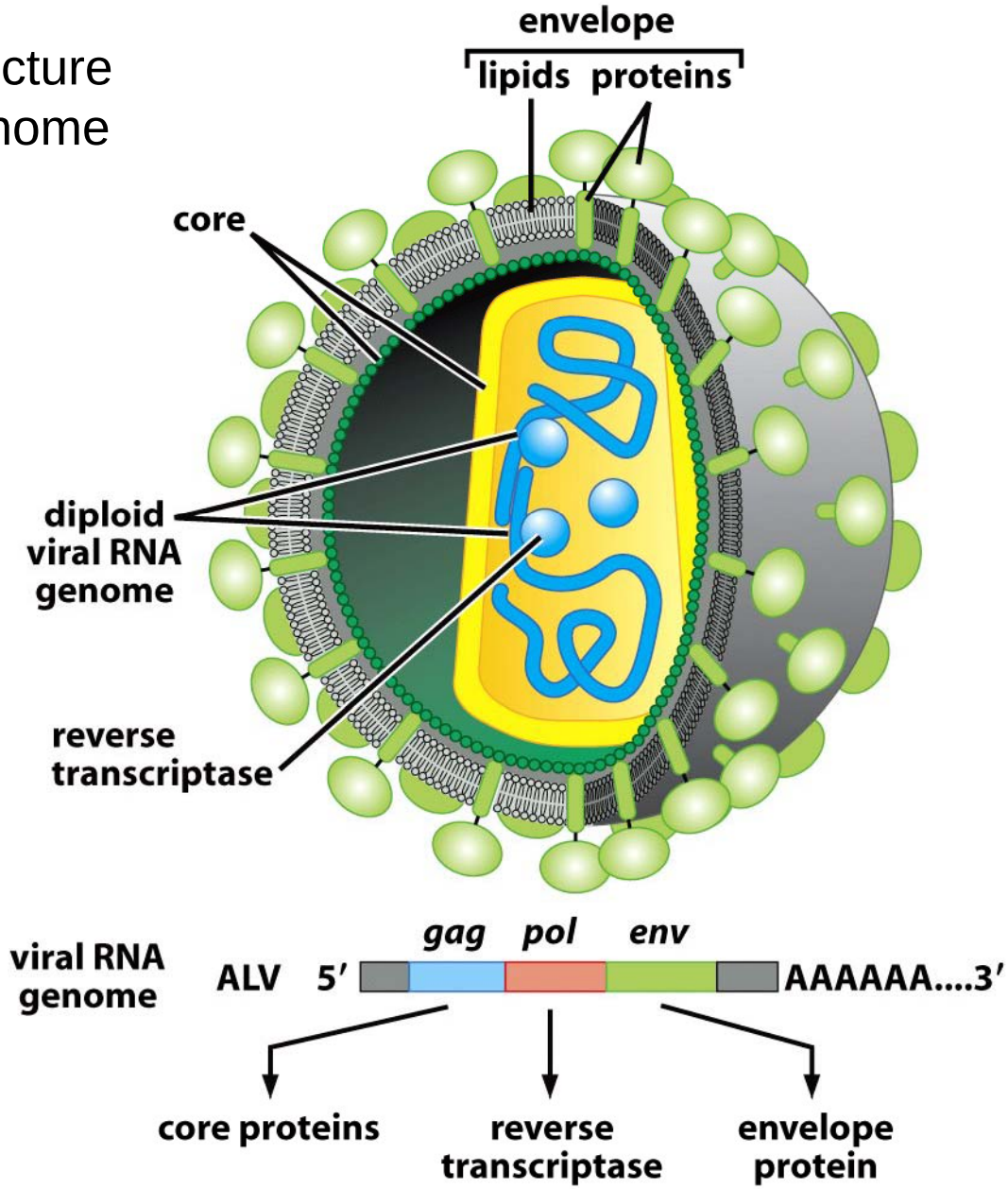

Figure 3-4a The Biology of Cancer (© Garland Science 2007)

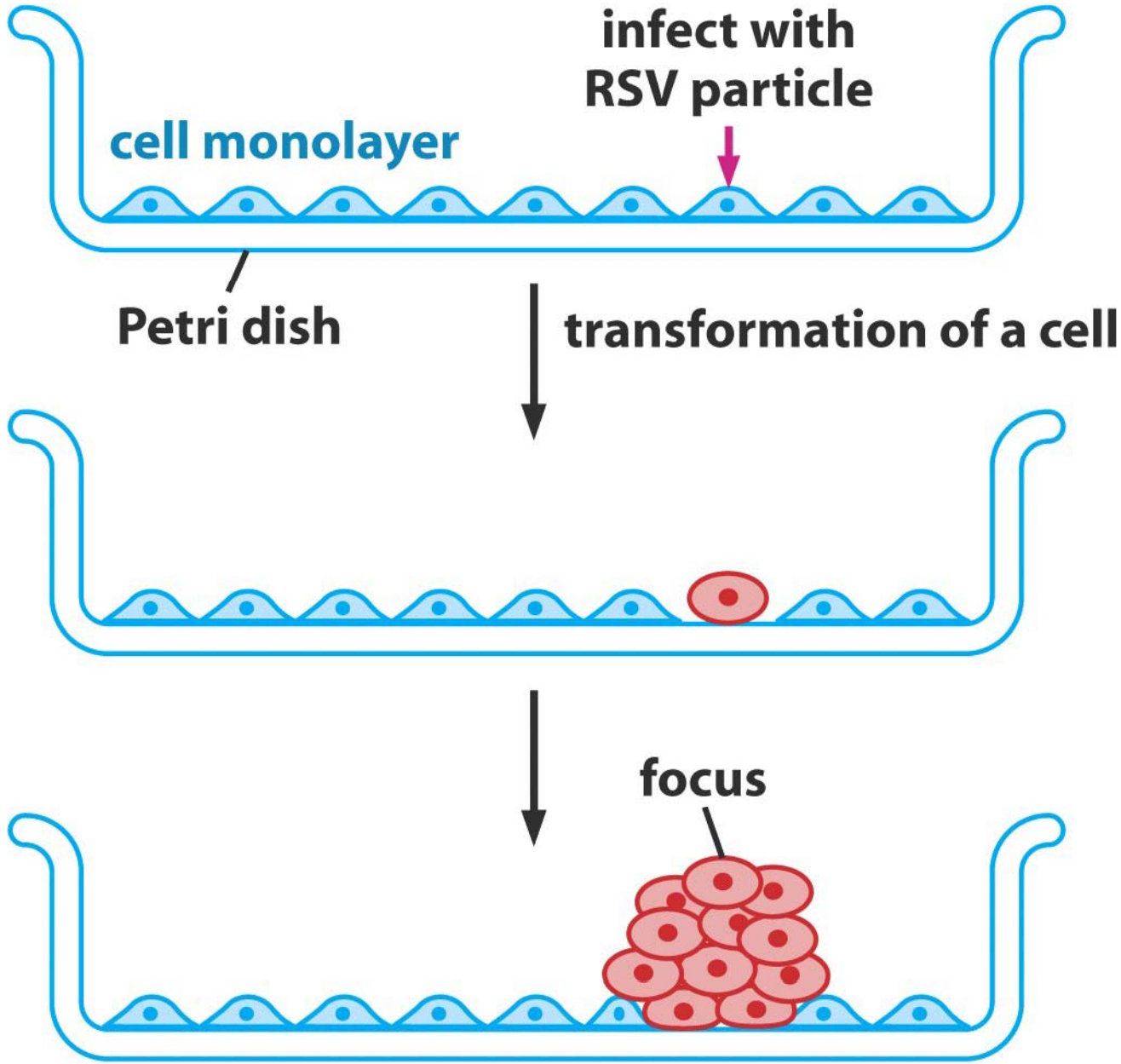

Figure 3-7a The Biology of Cancer (© Garland Science 2007)

Normal Chicken Embryo Fibroblasts Transformed by RSV

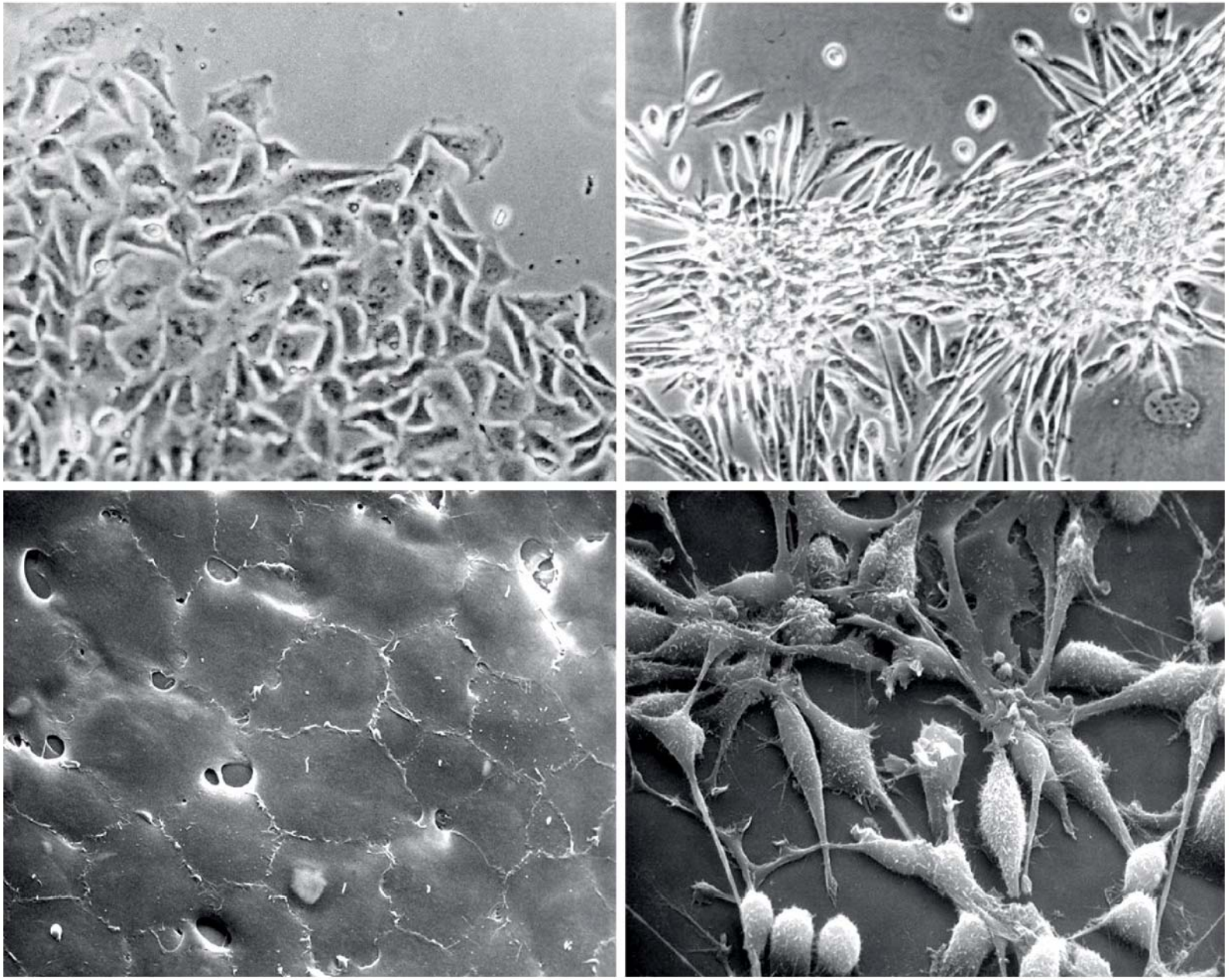

Figure 3-7b The Biology of Cancer (© Garland Science 2007)

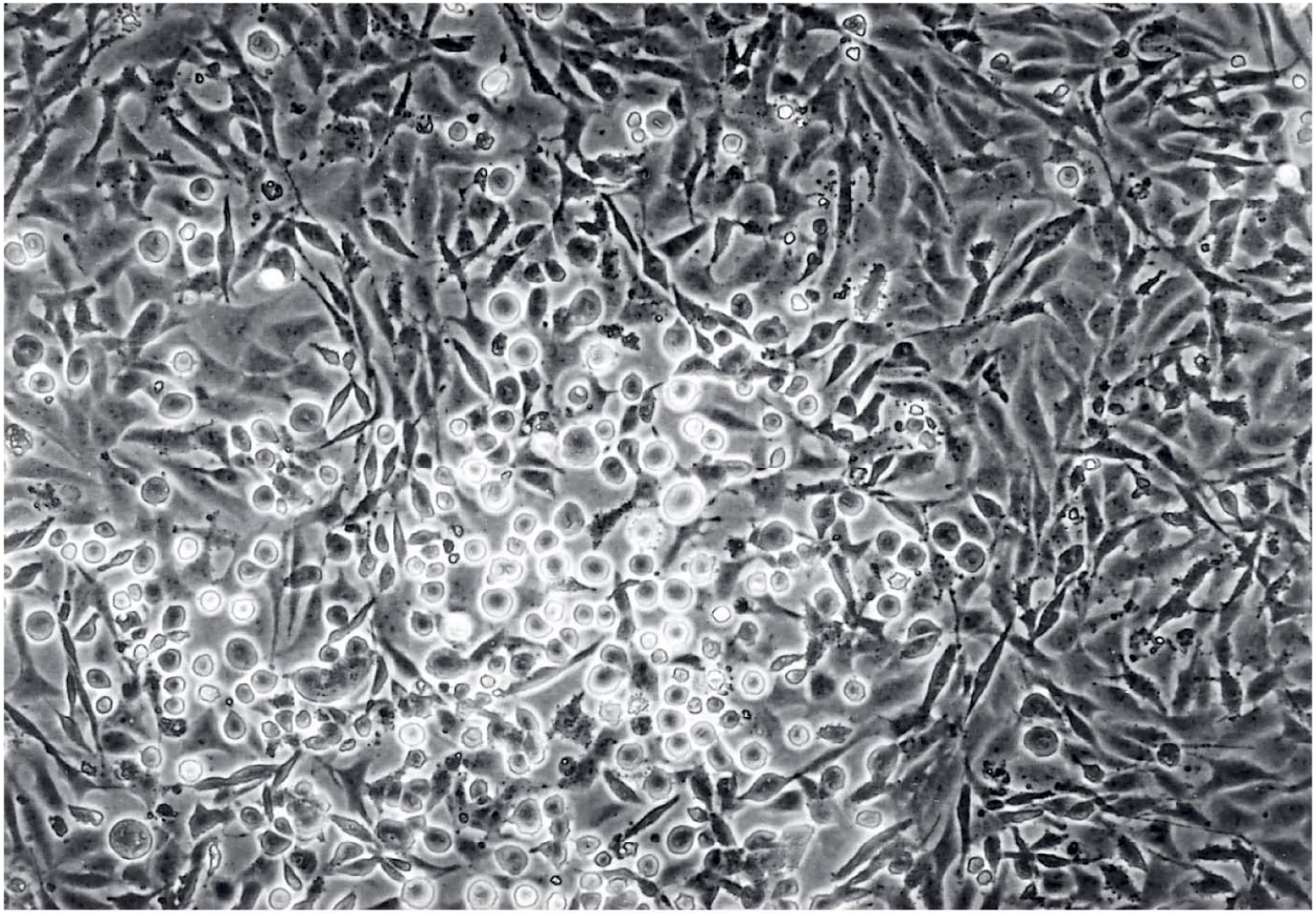

Figure 3-5 The Biology of Cancer (© Garland Science 2007)

A focus of chicken embryo fibroblasts transformed by RSV

ONCOGENIC VIRUSES

Oncogenic RNA Viruses

Retroviruses
- Sarcoma viruses
- Mammary tumor virus
- Leukosis viruses
- Human T cell leukemia viruses

Hepatitis C virus

Oncogenic DNA Viruses

Papovaviruses
- SV40
- Polyoma virus
- Shope papilloma virus
- Human papilloma viruses

Herpes viruses
- Epstein-Barr (EBV)
- Marek's disease virus (MDV)
- Herpes simplex viruses (HSV)

Adenoviruses

Hepadnaviruses
- Hepatitis B virus

Pox viruses
- Shope fibroma virus

VIRUSES ASSOCIATED WITH HUMAN CANCER

HBV and HCV:	Liver cancer
EBV:	Burkitt lymphoma
EBV:	Nasopharyngeal carcinoma
HTLV I:	Adult T-cell leukemia
HTLV II:	Hairy T-cell leukemia
HPV 16:	Cervical cancer
HIV:	Non-Hodgkin's lymphoma
KSHV (HHV-8):	Kaposi's sarcoma

VIRUS ASSOCIATED WITH SOME HUMAN PROSTATE CANCER

A retrovirus called XMRV (xenotropic murine leukemia virus-related virus) was detected in 40% of prostate tumors from men who were homozygous for an allelic variant of the RNASEL gene and in only 2% of tumors from men of other genotypes. The gene codes for RNase L, a ribonuclease required for the response to interferon. Activity is impaired in the allelic variant.

Reference: Dong et al., Proc. Nat. Acad. Sci. USA 104, 1655 (2007)

EPSTEIN-BARR VIRUS

Epstein-Barr virus was discovered by examining electron micrographs of cells cultured from Burkitt's lymphoma, a childhood tumor that is common in areas of sub-Saharan Africa where malaria is endemic.

EBV is implicated in the etiology of several different lymphoid and epithelial malignancies including nasopharyngeal cancer.

Immunosuppressed transplant patients are at risk of developing EBV-transformed B-cell proliferation presenting as "post-transplant lymphomas".

EBV-infected cells express a group of nuclear proteins that influence both viral and cellular transcription.

Reference: L.S. Young and A.B. Rickinson. Epstein-Barr virus: 40 years on. Nature Reviews Cancer 4: 757-768, 2004.

RNA TUMOR VIRUSES

These viruses have RNA as the genetic material. In order to transform cells RNA viruses must be integrated into the host cell genome. A DNA copy is integrated after reverse transcription. These viruses do not normally kill the host cell. Not all retroviruses cause cancer.

The enzyme reverse transcriptase catalyzes the production of a complementary DNA from the RNA genome and then catalyzes the formation of double stranded DNA from the single strand copy. The double stranded DNA is integrated into the host genome. Transformation can occur without viral replication which must be achieved using host mechanisms and may require a helper virus if the transforming virus is defective.

RNA TUMOR VIRUSES

The **avian leukosis virus** has the following genetic sequence:
LTR -- gag -- pol -- env -- LTR

in which the long terminal repeats (LTRs) have a promoting activity for transcription and may also facilitate viral integration. The gag and env genes code for viral structural proteins and the pol gene codes for reverse transcriptase.

RNA TUMOR VIRUSES

In the **Rous sarcoma virus** there is a transforming gene (src) between the env gene and the 3' LTR. Other transforming retroviruses may have one of the gag, pol or env genes replaced by a transforming gene known as an onc gene.

HTLV 1 has a gene known as the trans activating gene (tat) which can cause transcriptional activation of the virus and might activate cellular proto-oncogenes. There is a similar gene in the human immunodeficiency virus (HIV).

DNA TUMOR VIRUSES

The DNA viruses need not be incorporated into the host genome in order to replicate. In the case of hepatitis B virus in woodchucks there appears to be random integration into the host genome which may not be a prerequisite for transformation and can occur in normal cells of chronic virus carriers. On the other hand, transformation by DNA viruses is usually accompanied by integration of viral DNA into the genome of the host cell. DNA viruses tend to kill host cells.

DNA TUMOR VIRUSES

The papovaviruses have a circular genome.

The transforming region of the polyoma virus codes for three proteins (large, middle and small T antigens). The large T antigen elicits indefinite growth and diminishes the requirement for growth factors in serum. The middle T antigen is necessary for the maintenance of transformation. The **small T-antigen** protein is able to activate several cellular pathways which stimulate cell proliferation. Such as the mitogen-activated protein kinase (MAPK) pathway, and the stress-activated protein kinase (SAPK) pathway.

DNA TUMOR VIRUSES

The SV40 virus has two T antigens (large and small). The large T antigen of SV40 combines the functions of the large and middle T antigens of polyoma virus. The large T antigen of SV40 can bind a host nuclear protein known as p53. This represents the inactivation of a tumor suppressor protein.

DNA TUMOR VIRUSES

Herpes viruses have a linear double stranded DNA genome of 130-250 kb which could code for 100-200 proteins.

Adenoviruses cause a number of diseases in humans but historically were believed not to produce tumors in man. Leukemia has been seen is some patients receiving adenoviral vectors for gene therapy.

Transformation of cells by adenoviruses requires the combined action of two domains known as E1A and E1B. Each of these regions codes for two proteins. The E1A products cause indefinite growth of host cells and are proteins with a nuclear location like the large T antigens of polyoma and SV40.

SUGGESTED READING

1. Weinberg, R. The Biology of Cancer, Chapter 3, Garland Science, 2007

2. Gallo, R.C. and Reitz, M.S. RNA Tumor viruses. In: Hong et al (eds.) Holland-Frei Cancer Medicine (8th edition) Part II Scientific Foundations, Section 3 - Cancer Etiology, Chapter 20. (2010).

3. Cohen, J.I. Herpesviruses in Hong et al (eds.) Holland-Frei Cancer Medicine (8th edition) Part II Scientific Foundations, Section 3 - Cancer Etiology, Chapter 21 (2010).

4. Crum, C.P. and Chang, M.C. Papillomaviruses and Cervical Neoplasia in Hong et al (eds.) Holland-Frei Cancer Medicine (8th edition) Part II Scientific Foundations, Section 3 - Cancer Etiology, Chapter 22 (2010).