

7.013 Recitation 17 – 2013

Summary from Lectures 29 & 30

Cancer is the uncontrolled proliferation of a single cell that leads to a tumor, which is a mass of cells that are clonal descendents of that single cell. “Cancer” is a term for a group of many diseases that are caused by the accumulation of many mutations in both tumor suppressor genes and oncogenes. Mutations accumulate in cells throughout life due to the exposure to mutagens, such as those found in sun rays, the air, our food, and cigarette smoke. Cancer is a genetic disease in the sense that an accumulation of mutations in genes leads to cancer. Less than 10% of cancers are inherited, however. This is because most mutations leading to cancer occur in somatic cells.

Benign tumors are clumps of cells that may be growing but are not invading other tissues. Metastatic tumors are tumors that have had specific cells detached from the original tumor and travel to a second site in the body. Metastatic tumors can establish new sites of growth throughout the body and spread to multiple organs.

Cancer causing agents are called carcinogens and they are mostly mutagens or promutagens. These can be detected either by using the original Ames test (which detects mutagen) or modified Ames test (which can detect mutagens and also the promutagens).

Tumor suppressor genes and proto-oncogenes are normal genes that work in a regulated fashion in a normal cell to properly control the cell cycle. The wild-type function of a tumor suppressor gene is to inhibit the cell cycle in any cell that is not supposed to be actively growing and dividing. Both homologous versions of a tumor suppressor gene must lose their function to transform a normal cell to a cancerous type. The wild-type function of an oncogene is to promote the cell cycle in any cell that is supposed to be actively growing and dividing. One of the two homologous versions of an oncogene must gain a function or increase its function for a cell to become cancerous. Normal cellular counterparts of the oncogenes are called the proto-oncogenes. Some of these genes are carried by oncogenic viruses and are designated as v-oncogenes. The v-oncogenes can be linked to potent promoters that lead to their inappropriate and high level expression, leading to deregulated cell division. One example is the Rous sarcoma virus (RSV). This retrovirus infects the chickens, thereby causing them to acquire tumors. Here the viral genome contains a gene that it has stolen at some point from a host cell. This gene is an oncogene called src that is involved in cell signaling. The virus carries a mutant version of src that produces an overactive form of the normal cellular kinase src. When RSV infects a cell, the mutant src is transcribed and translated, creating an overactive cell signaling protein that promotes growth and division in chicken cells to form tumors. Other examples include the avian leukemia virus that causes leukemia and human papilloma virus responsible for cervical cancer.

Questions:

1. Why is cancer predominantly a disease of old age? What about the usual cause of cancer makes it more common in older people?
2. Why are the mutations that cause cancer generally not passed on to one's offspring? Why are almost all cancers sporadic as opposed to familial/inherited?

3. Describe the basic principal behind the standard Ames test. How is this different from modified Ames test?

4. What does it mean that a tumor is almost always clonal (or monoclonal)?

5. Why is it that cancer cells containing mutations in genes encoding ECM (extracellular matrix) proteins are more dangerous than cancer cells with normal ECM genes?

6. Weinberg's famous experiment: Ras was the first oncogene to be discovered. Ras is part of a cell signaling pathway. The input for this pathway is an extracellular protein growth factor, and the output is to induce transcription of genes necessary for the cell cycle to occur. Ras is a GTPase that is active in the GTP-bound form but inactive in the GDP-bound form. Ras was discovered in the Weinberg lab via the following experiment. Human tumor DNA was cut into pieces, and each different piece was put into a different mouse cell. The mouse cells were then grown in Petri plates. Only the mouse cell that took up the mutant allele of the oncogene could grow and divide enough to form a colony of cells.

- i. Do you think that the mouse cells had their own versions of Ras before the experiment began? If yes, do you think that the mouse versions of Ras were wild-type or mutant?
- ii. In this experiment, it seems that there was only one mutation necessary to make the mouse cells over-proliferate. We know, however, that cancer results from an accumulation of mutations. Why then did this experiment work?
- iii. If a patient had a tumor that was caused in part by mutations in Ras, do you think it would be a good therapeutic decision to treat the cancer patient with a drug that targets and inhibits Ras?
- iv. Do you think it would be a good therapeutic decision to provide this cancer patient with a wild-type copy of the Ras gene?
- v. Do you think that this experimental technique would work to identify tumor suppressor genes? Why or why not?

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7.013 Introductory Biology
Spring 2013

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