7.012 Recitation 14 - 2010

Questions:

1. Viruses can also cause cancer. One such example is the Rous sarcoma virus (RSV) that causes sarcoma, a cancer of connective tissues. The virus does so by inserting itself near the cellular c-Src gene, a non-receptor tyrosine kinase.

i. How does RSV convert the c-src to its mutated form?

Originally, the Avian leukosis virus inserted its genome into the normal cellular copy of the c-src proto- oncogene (a gene that encodes a protein that promotes cell division). With this insertion the normal c-src gene was mutated such that the kinase domain of the normal cellular src was expressed inappropriately. This mutated version of the src gene promoted the cell cycle in a unregulated way that lead to uncontrolled cell division. At some time later, the virus began a packaging step and in the process packaged the additional mutated part of the src gene. The new resulting virus was the RSV. All subsequent infection with RSV, deliver the oncogenic version of src to the host cells.

ii. How does the conversion of c-src to its mutated form help the virus?

Cells that express the oncogenic form of src proliferate in an uncontrolled fashion thereby producing more viruses.

2. 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?

Yes, they had wild-type versions of Ras gene before the experiment was done.

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?

A cell line is already immortalized and is therefore predisposed to transformation unlike the wild-type cells. Hence a single mutation is enough to transform it to a cancerous cell line.

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?

Most likely, yes, since oncogenic mutation is a gain-of-function mutation.

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?

No, since adding a wild-type copy of Ras gene cannot suppress the phenotype caused by the gain-of-function mutation.

v. Do you think that this experimental technique would work to identify tumor suppressor genes? Why or why not?

No, it would not work. A mutation in a tumor suppressor gene is a homozygous loss-of-function mutation. Therefore introducing a mutated copy of the tumor suppressor gene into the cells that have two wild-type copies of the same gene will not work (the effect of wild-type allele is dominant to the mutated allele).

3. Retinoblastoma is caused by a mutation in the retinoblastoma tumor suppressor gene. There are several mechanisms, which can cause a cell to lose its normal gene and thus be predisposed to develop into a tumor. These may result in a "loss of heterozygosity" or "LOH".

i. What do you mean by LOH? *Loss-of heterozygosity*

ii. Many clinicians and scientists are currently trying to develop cancer treatments that are more specific and targeted than chemotherapy. If a patient had a tumor that was caused in part by mutations in Rb do you think it would be a good therapeutic decision to provide this cancer patient with a wild-type copy of the Rb gene?

Yes, since mutations in the tumor suppressor genes are the loss-of-function mutations and providing a wild-type copy of the tumor suppressor gene would restore the cell to remain in its wild-type form.

4. Consider a patient who has CML, and answer the following questions.

i. Would the Philadelphia chromosomal translocation be present in all of the cells in the patient's body?

No, it is restricted to myeloid cells in the blood

ii. Would the Philadelphia chromosomal translocation be present in all of the cells in the patient's blood system?

Only in the cells of myeloid origin.

iii. How many independent times did the Philadelphia chromosomal translocation occur in the patient?

Only once, and all the cancerous cells originated as the clones of this mutated cell.

iv. Could the patient pass CML onto his/her kids?

No, this mutation has occurred in somatic cells and not in the germline cells.