Questions and Answers for Genetics and Genomics in Medicine Chapter 10

Question 1
There are more than 100 different cancers. What two key characteristics define these diseases?

Answer
- Unregulated cell proliferation.
- Abnormal cells that spread in the body by invading other tissues and by dissemination through the bloodstream or lymph ducts.

Question 2
The replication of DNA at the very ends of the telomeres of each of our chromosomes is problematic. Why is this, and what are the consequences?

Answer
DNA synthesis occurs in one direction only, the 5'→3' direction, and both strands of the DNA helix within a chromosome serve as templates for DNA synthesis. Because the 5'→3' direction of the two strands of the double helix are in opposite directions, the two new DNA strands that are synthesized will also be synthesized in opposite directions. As the replication fork advances, therefore, one new DNA strand (the leading strand) is synthesized in the same direction as the movement of the replication fork, but for the other new DNA strand (the lagging strand), the 5'→3' direction in which it must be synthesized is exactly the opposite of the direction of travel of the replication fork. The lagging strand is therefore synthesized in pieces starting from a direction *ahead of* the moving replication fork and moving back toward it. The pieces are joined together by a DNA ligase. At the very end of the telomere, however, there can be no DNA template ahead of the replication fork to complete the synthesis of the lagging strand, so the newly synthesized lagging strand will be shorter than the opposing complementary leading strand.

In short-lived vertebrates such as mice, a special reverse transcriptase, telomerase, is dedicated to solving the end-replication problem in somatic cells by offering an RNA template to make copies of telomere repeats. In long-lived vertebrates, such as humans, reverse transcriptase levels are kept very low in somatic cells; each time a cell divides it loses a few telomere repeats. Telomere shortening is also hastened by exonuclease nibbling from the protruding single strand. As a result, telomeres are eroded with each cell division. Telomeres are essential for protecting the integrity of the genome (when they are lost, chromosome instability ensues, with cycles of chromosome fusions and breakages). As a result, our somatic cells have an inbuilt mechanism that counts the number of replications a cell has undergone; after a certain number of cell divisions, when the telomeres have been reduced to a critically short length, the cells can no longer divide (cellular senescence). Most probably this developed as a major anti-cancer mechanism in long-lived organisms such as ourselves (but cancer cells get round this problem by finding some way or restoring telomere lengths so that they are above a certain critical length).

Question 3
One characteristic of cancer cells is that they can become immortal. How does this happen?

Answer
Normal human cells usually divide a finite number of times only, because the telomere sequences at the ends of each chromosome lose part of their sequence at each cell division. Ultimately a crisis state ensues in which chromosomes with very short telomere sequences undergo cycles of chromosome fusion and breaking. At the earliest stages of development, undifferentiated pluripotent cells express high levels of telomerase; however, as cells differentiate, telomerase expression is suppressed, except in a few cell types, including stem cells and germ cells. (By limiting the number of cell divisions that a cell can undergo, telomerase suppression is likely to be one of the defenses against cancer in long-lived organisms such as humans.)

In most cases, cancer cells reactivate telomerase expression to maintain telomerase lengths and enable the cells to divide indefinitely. However, in a significant minority of cancer cells a telomerase-independent method of telomere extension occurs that involves sequence exchange between individual telomere repeats, possibly by interchromosomal unequal crossover.

Question 4
Intratumor heterogeneity involves various types of functional differences between the cells of a tumor. How do these differences arise?

Answer
A single tumor is often composed of tumor cells proper (each of which has arisen from a single founder cell) plus a range of blood cells and other cells that have infiltrated from the stromal microenvironment, including various types of infiltrating immune cell (macrophages, mast cells, neutrophils, T cells, and B cells), activated tissue fibroblasts, endothelial cells, and pericytes. The latter cells are co-opted to support various tumor functions, such as mitogenesis, angiogenesis, tissue invasion, and metastasis (see Table 10.3).

The tumor cells proper within a tumor can become distinct from each other by the differential acquisition of genetic and/or epigenetic changes. New mutations in individual tumor cells can give rise to dominant new tumor subclones with different properties. Epigenetic changes can lead to the formation of cancer stem cells that can undergo differentiation to give different tumor cells with different levels of differentiation.

Question 5
DNA studies show that specific cancers are associated with distinctive mutational signatures. Give some examples.

Answer
- Lung cancer (due to tobacco carcinogens): preferential C>T transitions.
- Melanoma (due to excess irradiation with ultraviolet): preferential C>A transversions.

Question 6

Cancer whole-genome sequencing has enabled assays of the number of driver mutations in cancer genomes. Driver mutations can be assigned to specific gene loci according to whether distinctive types of mutation that might be expected to disturb gene expression are commonly identified in specific genes. However, the numbers of driver mutations identified can be quite small. In the breast cancer study shown in Figure 10.24, the number of driver mutations in 100 tumors, including both point mutations and changes in copy number, ranges from 0 to 6 per tumor. How do you interpret the small number of driver mutations identified?

Answer

There are two major limitations in using genome sequencing to identify driver genes in cancer. First, this method does not identify epigenetic changes at cancer-susceptibility loci. (They may arise as a consequence of mutation at some other locus, but that is not easily identified, or they may be independent of mutation, in which case they cannot be identified by genome sequencing.) Second, changes in copy number can be readily recorded for gene amplification events in oncogenes but may be less readily assigned to a specific gene locus if a very large chromosome region is involved. On that basis, the number of genes that make a causal contribution to tumorigenesis can be underestimated.

Question 7

The majority of clinical gene therapy trials are aimed at treating cancer, but unlike gene therapy for monogenic disorders, cancer gene therapy has been greatly disappointing. What factors make cancer gene therapy such a difficult prospect?

Answer

Aside from a low efficiency of gene delivery (which is a general problem with current gene therapy protocols), cancer gene therapy is beset by the problem of tumor regeneration. In cancer gene therapy, the focus has been on the selective killing of cancer cells, but with generally low efficiency of gene delivery it is very difficult to kill cancer cells directly (by transfecting suicide genes into cancer cells, for example), and the surviving cancer cells can quickly lead to the re-emergence of tumors. Modern cancer gene therapy trials have tended to focus on genetically modifying noncancer cells so as to stimulate the indirect killing of cancer cells through activated immune system cells.

Question 8

What is meant by targeted cancer therapies, and what advantages do they offer?

Answer

Standard cancer therapies are crude because the object is simply to remove tumors (by surgery) or to kill cancer cells by rather nonspecific means (chemotherapy, radiation therapy) that kill normal dividing cells in the vicinity as well as tumor cells (hence the harmful side effects of these therapies). In targeted cancer therapy, the aim is to inhibit a *specific* tumor protein (or other agent) that is crucial for the pathogenesis. The paradigm is inhibition of the hybrid BCR–ABL kinase that is formed

by a chromosomal translocation (the Philadelphia chromosome) and is the primary cause of the great majority of chronic myeloid leukemia cases. The drug imatinib (marketed as Gleevec™) is effective in inhibiting the BCR–ABL kinase and has been rather successful in extending 5-year survival rates.

A current problem with targeted cancer therapies is that drug resistance becomes evident after a while. At least in chronic myeloid leukemia, there are back-up drugs that can also target the mutant BCR–ABL kinase, notably the drugs nilotinib and dasatinib, and 5-year survival rates are now quite good. For other cancers, targeted cancer therapy has had less success, such as when using drugs aimed at countering the *BRAF* oncogene in melanoma, for which extended survival rates are measured in months rather than years.