

Chapter Twenty-Three: Cancer Genetics

COMPREHENSION QUESTIONS

Section 23.1

- *1. What types of evidence indicate that cancer arises from genetic changes?
Higher incidences of many types of cancer are associated with exposure to radiation and other environmental mutagens. In addition, the occurrence of some types of cancer runs in families, and a few cancers are linked to chromosomal abnormalities. Finally, the discovery of oncogenes and specific mutations that cause proto-oncogenes to become oncogenes, or inactivate tumor suppressor genes, proved that cancer has a genetic basis.
2. How is cancer different from most other types of genetic diseases?
Most cancers arise from genetic changes in somatic cells that arise during an individual's lifetime, whereas other types of genetic diseases are inherited through the germline.

Section 23.2

- *3. Outline Knudson's multistage theory of cancer and describe how it helps to explain unilateral and bilateral cases of retinoblastoma.
The multistage theory of cancer states that more than one mutation is required for most cancers to develop. Most retinoblastomas are unilateral because the likelihood of any cell acquiring two rare mutations is very low, and thus retinoblastomas develop in only one eye. Bilateral cases of retinoblastoma occur in people born with a predisposing mutation, so that as few as one additional mutational event can result in cancer. Thus, the probability of retinoblastoma is higher in these individuals and likely to occur in both eyes. Because the predisposing mutation is inherited, people with bilateral retinoblastoma have relatives with retinoblastoma.
4. Briefly explain how cancer arises through clonal evolution.
A mutation that relaxes growth control in a cell will cause it to divide and form a clone of cells that are growing or dividing more rapidly than their neighbors. Successive mutations that cause even more rapid growth, or the ability to invade and spread, each produce progeny cells with more aggressive, malignant properties that outgrow their predecessors and take over the original clone.
- *5. What is the difference between an oncogene and a tumor-suppressor gene? Give some examples of functions of proto-oncogenes and tumor suppressors in normal cells.
An oncogene stimulates cell division, whereas a tumor-suppressor gene puts the brakes on cell growth. Proto-oncogenes are normal cellular genes that function in cell growth and regulation of the cell cycle: from growth factors such as sis to

receptors like ErbA and ErbB, protein kinases such as src, and transcription factors like myc. Tumor suppressors inhibit cell cycle progression: RB and p53 are transcription factors and NF1 is a GTPase activator.

6. What is haploinsufficiency? How might it affect cancer risk?
Haploinsufficiency is a condition where a normally recessive trait affects a heterozygous individual. Haploinsufficiency arises in situations where a single functional copy of a gene is insufficient to produce a wild type phenotype. In most cases, haploinsufficiency reflects the need for a larger quantity of a gene product than is normally produced by a single wild-type allele. In the case of tumor-suppressor genes like RB, a single functional copy is often enough for the cell to have a normal phenotype, but leaves no “back-up” copy in reserve. In this case, the mutation of the single remaining wild-type allele in any one of the millions of cells in the retina will lead to formation of a cancer cell, hence the “predisposition to cancer” phenotype associated with haploinsufficiency of RB.
- *7. How do cyclins and CDKs differ? How do they interact in controlling the cell cycle?
The CDKs, or cyclin-dependent kinases, have enzymatic activity and phosphorylate multiple substrate molecules when activated by binding the appropriate cyclin. Cyclins are regulators of CDKs and have no enzymatic activity of their own. Each cyclin molecule binds to a single CDK molecule. Whereas CDK levels remain relatively stable, cyclin levels oscillate through the cell cycle.
8. Briefly outline the events that control the progression of cells through the G₁/S checkpoint in the cell cycle.
In G₁, cyclins D and E accumulate and bind to their respective CDKs. The cyclin D-CDK and cyclin E-CDK phosphorylate RB protein molecules. Phosphorylation of RB inactivates RB and releases active E2F protein. E2F protein transcribes genes required for DNA replication and progression into S phase.
9. Briefly outline the events that control the progression of cells through the G₂/M checkpoint of the cell cycle.
Cyclin B accumulates through G₂ and binds to its partner CDK, forming an inactive mitosis-promoting factor (MPF) which is activated by dephosphorylation. When enough MPF activity exceeds a threshold level, the cell commits to mitosis.
- *10. What is a signal-transduction pathway? Why are mutations in components of signal-transduction pathways often associated with cancer?
A signal-transduction pathway is the system that enables a cell to respond appropriately to an external signal. It begins with binding or perception of the external signal molecule, then proceeds through a cascade of intracellular events that relay and amplify the signal to bring about changes in transcription, metabolism, morphology, or other aspects of cell function. Since cell growth and division are regulated by external signals, mutations in signal-transduction components may cause the cell to grow and divide in the absence of external

growth stimuli, or may cause the cell to stop responding to external growth inhibitory signals.

11. How is the Ras protein activated and inactivated?
Ras protein with GDP bound is inactive. Exchanging GDP for GTP activates the Ras protein. This guanine nucleotide exchange is stimulated by adaptor proteins that bind to activated signal receptors.

12. Why do mutations in genes that encode DNA repair enzymes and chromosome segregation often produce a predisposition to cancer?
Mutations that affect DNA repair cause high rates of mutation that may convert proto-oncogenes into oncogenes or inactivate tumor-suppressor genes. Similarly, errors in chromosome segregation cause aneuploidy and chromosomal aberrations that cause loss of tumor-suppressor genes or add extra gene doses of proto-oncogenes.

- *13. What role do telomeres and telomerase play in cancer progression?
DNA polymerases are unable to replicate the ends of linear DNA molecules. Therefore, the ends of eukaryotic chromosomes shorten with every round of DNA replication, unless telomerase adds back special non-templated telomeric DNA sequences. Normally, somatic cells do not express telomerase; their telomeres progressively shorten with each cell division until vital genes are lost and the cells undergo apoptosis. Transformed cells (cancerous cells) induce the expression of the telomerase gene, in order to keep proliferating.

Section 23.3

- *14. Explain how chromosome deletions, inversions, and translocations may cause cancer.
Chromosomal rearrangements may inactivate tumor suppressor genes if the breakpoint occurs within the gene. Alternatively, rearrangements may juxtapose a strong promoter upstream of a proto-oncogene, causing overexpression or unregulated expression of the proto-oncogene. Finally, rearrangements may bring parts of two different genes together, causing the synthesis of a novel protein that is oncogenic.

15. Briefly outline how the Philadelphia chromosome leads to chronic myelogenous cancer.
The Philadelphia chromosome is a shortened chromosome 22 with a translocated tip of chromosome 9. A part of the c-ABL proto-oncogene from chromosome 9 is fused with BCR gene on chromosome 22. The resulting fusion protein is more active at promoting cell proliferation than the normal c-ABL protein, and causes leukemia.

16. What is genomic instability? Give some ways in which genomic instability may arise.

Genomic instability is a condition or process that leads to numerous chromosomal rearrangements and aneuploidy, often found in cells of advanced tumors. Mutations that affect the mitotic spindle checkpoint may cause a high frequency of aneuploidy. Other mutations, such as mutations in the APC gene, may affect the spindle itself or other aspects of the chromosome segregation mechanism. Still other mutations that affect centrosome duplication, such as some p53 mutations, could also lead to aneuploidy.

Section 23.4

- *17. How do viruses contribute to cancer?

Retroviruses have strong promoters. Upon integration into the host genome, the retrovirus promoter may drive overexpression of a cellular proto-oncogene. Alternatively, integration of the retrovirus may inactivate a tumor-suppressor gene. A few retroviruses carry oncogenes that are altered versions of host proto-oncogenes. Other viruses, such as human papilloma virus, express gene products (proteins or RNA molecules) that interact with the host cell cycle machinery and inactivate tumor-suppressor proteins.

Section 23.5

18. How is an epigenetic change different from a mutation?

Unlike mutations, epigenetic changes do not alter the sequence of nucleotides in the DNA. Although epigenetic changes are usually transmitted to mitotic progeny cells, epigenetic changes are more readily reversible than mutations.

19. How is DNA methylation related to cancer?

DNA methylation is associated with transcriptional repression. Methylation and silencing of tumor-suppressor genes would increase the risk of cancer; demethylation and activation of proto-oncogenes would also increase the risk of cancer. Hypomethylation (loss of DNA methylation) may also increase the risk of cancer by increasing genomic instability, by mechanisms that are not yet clear.

Section 23.6

20. Briefly outline some of the genetic changes that are commonly associated with the progression of colorectal cancer.

Colorectal cancer begins as benign tumors, called polyps, that enlarge and acquire further mutations that turn them malignant and, finally, invasive and metastatic. These progressive changes are associated with multiple mutations. One common sequence in colorectal cancer is mutation of the APC gene leads to faster cell division and polyp formation. Oncogenic mutations of the ras gene are found in cells from larger polyps. Then mutations in p53 and other genes are found in

malignant tumor cells, which may lead to genomic instability and additional changes that lead to greater malignancy and invasiveness.

APPLICATION QUESTIONS AND PROBLEMS

Section 23.1

- *21. The *palladin* gene, which plays a role in pancreatic cancer (see the introduction to this chapter), is said to be an oncogene. Which of its characteristics suggest that it is an oncogene rather than a tumor-suppressor gene?

Because oncogenes promote cell proliferation, they act in a dominant manner. In contrast, mutations in tumor suppressor genes cause loss of function and act in a recessive manner. The mutated palladin gene caused increased cell migration when introduced into cells that contain wild-type palladin genes. Such a dominant effect suggests that palladin is an oncogene.

22. If cancer is fundamentally a genetic disease, how might an environmental factor such as smoking cause cancer?

Environmental factors can cause cancer by acting as mutagens. Higher rates of mutation will lead to higher rates of inactivation of tumor-suppressor genes or conversion of proto-oncogenes to oncogenes.

23. Both genes and environmental factors contribute to cancer. Table 23.2 shows that prostate cancer is 30 times as common among Caucasians from Utah as among Chinese from Shanghai. Briefly outline how you might go about determining if these differences in the incidence of prostate cancer are due to differences in the genetic makeup of two populations or to differences in their environments.

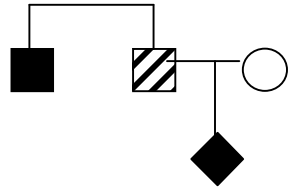
If the differences in cancer rates are due to genetic differences in the two populations, then people who migrated from Utah or Shanghai to other locations would have similar rates of cancer incidence as people who stayed in Utah or Shanghai. Moreover, different ethnic groups in Utah or Shanghai would have different rates of cancer. If the cancer rates are due to environmental factors, then people who migrated from Utah or Shanghai would have rates of cancer determined by their location and not by their place of origin, and different ethnic groups in the same location would have similar rates of cancer.

Section 23.2

- *24. A couple has one child with bilateral retinoblastoma. The mother is free from cancer, but the father had unilateral retinoblastoma and he has a brother who has bilateral retinoblastoma.

- a. If the couple has another child, what is the probability that this next child will have retinoblastoma?

First, we summarize the information with a pedigree. The shaded boxes represent bilateral retinoblastoma; the striped box represents unilateral retinoblastoma.



Familial retinoblastoma is caused by mutation of the RB tumor-suppressor gene. Because the loss of a functional RB allele means that only one additional mutation event will completely eliminate RB function and lead to retinoblastoma, loss-of-function RB mutations have dominant effects with regard to retinoblastoma. If the father with unilateral retinoblastoma is heterozygous for an RB mutation, then the chance of another child inheriting the mutant RB allele is $\frac{1}{2}$. Note that the father is almost certainly not homozygous for the RB mutation because he has only unilateral retinoblastoma and because individuals homozygous for RB mutations would be extremely susceptible to multiple types of cancer at early age.

- b.** *If the next child has retinoblastoma, is it likely to be bilateral or unilateral? Because retinoblastoma in this family is most likely an inherited disorder, a child with retinoblastoma will more likely have bilateral retinoblastoma. Unilateral retinoblastomas are usually spontaneous in origin, requiring two independent mutations in a single somatic retinal cell. Familial retinoblastomas occur in family members that inherited one of the two mutations required for retinoblastoma. As only one additional mutation is required in the somatic retinal cells, retinoblastoma occurs in both eyes and at earlier ages than spontaneous unilateral retinoblastomas.*

- c.** *Propose an explanation for why the father's case of retinoblastoma was unilateral, while his son's and brother's cases were bilateral. The father may have unilateral retinoblastoma because of variable expressivity of the mutation in the RB gene. Alleles at another locus or multiple other loci may have contributed to resistance to retinoblastoma in the father, so that he suffered retinoblastoma in only one eye. Alternatively, it may have been just good fortune (random chance) that one of his eyes was spared the second mutation event that led to retinoblastoma in his other eye.*

25. *Mutations in the RB gene are often associated with cancer. Explain how a mutation that results in a nonfunctional RB protein contributes to cancer. RB protein is a tumor suppressor, acting at the G₁/S checkpoint to prevent cells from beginning DNA replication. Without functional RB protein, cells are more prone to begin a round of cell division.*
26. *Cells in a tumor contain mutated copies of a particular gene that promotes tumor growth. Gene therapy can be used to introduce a normal copy of this gene into the tumor cells. Would you expect this therapy to be effective if the mutated gene were an oncogene? A tumor-suppressor gene? Explain your reasoning.*

Gene therapy to introduce a normal copy of the gene into tumor cells will not work for oncogenes because oncogenes are dominant, activating mutations of proto-oncogenes. Gene therapy may work if the tumor arises from a mutation that inactivates a tumor-suppressor gene. Loss-of-function mutations are recessive; therefore, a normal copy of the gene will be dominant and restore regulation of cell proliferation in the tumor cells. However, one would have to insert and express the tumor suppressor gene in all tumor cells, which is not possible at this time.

- *27. Genes in cancer cells are frequently amplified, meaning that the gene exists in many copies. Would you expect to see gene amplification in oncogenes, proto-oncogenes, or both? Explain your answer.

Gene amplification in cancer cells would most likely affect proto-oncogenes. Oncogenes are altered forms proto-oncogenes with greater activity or lack of regulation. Amplification of oncogenes may have little additional effect for a cancer cell. However, amplification of proto-oncogenes would mimic the effect of an oncogene, and therefore may be frequent in cancer cells.

28. David Seligson and his colleagues examined levels of histone protein modification in prostate tumors and their association with clinical outcomes (D. B. Seligson et al. 2005. *Nature* 435:1262–1266). They used antibodies to stain for acetylation at three different sites and for methylation at two different sites on histone proteins. They found that the degree of histone acetylation and methylation helped predict whether prostate cancer would return within 10 years in the patients who had a prostate tumor removed. Explain how acetylation and methylation might be associated with tumor recurrence in prostate cancer. (Hint: See Chapter 17)

Histone acetylation and methylation patterns are associated with varying transcriptional states of chromatin. Histone modifications may determine whether particular tumor suppressor genes or proto-oncogenes important for prostate cancer are transcribed. Modifications that shut down transcription of tumor suppressors or activate transcription of proto-oncogenes would promote the recurrence of tumors, whereas modifications that activate transcription of tumor suppressor genes or suppress transcription of proto-oncogenes would inhibit the recurrence of tumors.

29. Radiation is known to cause cancer, yet radiation is often used as treatment for some types of cancer. How can radiation be a contributor to both the cause and the treatment of cancer?

Radiation can cause mutations that lead to cancer, such as inactivating a tumor-suppressor gene or causing an oncogenic mutation in a proto-oncogene. On the other hand, radiation will preferentially kill rapidly proliferating cells, such as cancer cells, that are actively replicating their DNA and lack tumor-suppressor functions that ensure DNA damage is repaired before DNA is replicated or before the cell divides.

Section 23.3

30. Some cancers are consistently associated with the deletion of a particular part of a chromosome. Does the deleted region contain an oncogene or a tumor-suppressor gene? Explain.

The deleted region contains a tumor-suppressor gene. Tumor suppressors act as brakes on cell proliferation. The deletion of tumor-suppressor genes will therefore permit the uncontrolled cell proliferation that is characteristic of cancer.

Oncogenes, on the other hand, function as stimulators of cell division. Deletion of oncogenes will therefore prevent cell proliferation, and usually cannot cause cancer.

Section 23.5

31. Some cancers have been treated with drugs that demethylate DNA. Propose an explanation for how these drugs might work. Do you think the genes causing cancers that respond to the demethylation are likely to be oncogenes or tumor-suppressor genes? Explain your reasoning.

Drugs that demethylate DNA would presumably activate expression of demethylated genes. Cancer growth and progression may be inhibited if these drugs are able to turn on expression of tumor suppressor genes that had been silenced by DNA methylation. If DNA demethylation turned on expression of oncogenes, cancer growth and progression would be accelerated.

CHALLENGE QUESTIONS

Section 23.2

32. Many cancer cells are immortal (will divide indefinitely) because they have mutations that allow telomerase to be expressed. How might this knowledge be used to design anticancer drugs?

Because cancer cells depend on telomerase activity to preserve their telomeres, drugs that target telomerase enzymatic activity may limit the ability of cancer cells to divide indefinitely.

33. Bloom syndrome is an autosomal recessive disease that exhibits haploinsufficiency. As described on p. 631 a recent survey showed that people heterozygous for mutations at the *BLM* locus are at increased risk of colon cancer. Suppose you are a genetic counselor. A young woman whose mother has Bloom syndrome is referred to you; the young woman's father has no family history of Bloom syndrome. The young woman asks whether she is likely to experience any other health problems associated with her family history of Bloom syndrome. What advice would you give her?

*The young woman must be heterozygous for the mutation at the *BLM* locus because her mother was homozygous for the mutation. Although the young woman does not have Bloom syndrome, haploinsufficiency at this locus will result in some increased*

risk of colon cancer. Her cells will have a reduced amount of the BLM helicase involved in DNA double-strand break repair and will be more susceptible to mutations that may lead to cancer.

34. Imagine that you discover a large family in which bladder cancer is inherited as an autosomal dominant trait. Briefly outline a series of studies that you might conduct to identify the gene that causes bladder cancer in this family.
- Because this cancer is inherited as a dominant trait, the cause is most likely an oncogenic mutation, rather than inactivation of a tumor-suppressor gene. One possible approach to identify the bladder cancer oncogene would be to isolate DNA from bladder cancer cells and transfect cultured normal cells from a distinct genetic background. Isolate any colonies of transformed cells that arise and determine which common chromosomal region has been taken up by the transformed cell lines. The region of the gene could be further refined by transfection with subfragments of that region. Genes within this transforming region would be sequenced to identify mutations. Finally, candidate mutations would be tested by genetically engineering cells to carry that precise mutation to see if such cells become cancerous.*