16.7: Cancer and Gene Regulation

Skills to Develop

- Describe how changes to gene expression can cause cancer
- Explain how changes to gene expression at different levels can disrupt the cell cycle
- Discuss how understanding regulation of gene expression can lead to better drug design

Cancer is not a single disease but includes many different diseases. In cancer cells, mutations modify cell-cycle control and cells don’t stop growing as they normally would. Mutations can also alter the growth rate or the progression of the cell through the cell cycle. One example of a gene modification that alters the growth rate is increased phosphorylation of cyclin B, a protein that controls the progression of a cell through the cell cycle and serves as a cell-cycle checkpoint protein.

For cells to move through each phase of the cell cycle, the cell must pass through checkpoints. This ensures that the cell has properly completed the step and has not encountered any mutation that will alter its function. Many proteins, including cyclin B, control these checkpoints. The phosphorylation of cyclin B, a post-translational event, alters its function. As a result, cells can progress through the cell cycle unimpeded, even if mutations exist in the cell and its growth should be terminated. This post-translational change of cyclin B prevents it from controlling the cell cycle and contributes to the development of cancer.

Cancer: Disease of Altered Gene Expression

Cancer can be described as a disease of altered gene expression. There are many proteins that are turned on or off (gene activation or gene silencing) that dramatically alter the overall activity of the cell. A gene that is not normally expressed in that cell can be switched on and expressed at high levels. This can be the result of gene mutation or changes in gene regulation (epigenetic, transcription, post-transcription, translation, or post-translation).
Changes in epigenetic regulation, transcription, RNA stability, protein translation, and post-translational control can be detected in cancer. While these changes don’t occur simultaneously in one cancer, changes at each of these levels can be detected when observing cancer at different sites in different individuals. Therefore, changes in histone acetylation (epigenetic modification that leads to gene silencing), activation of transcription factors by phosphorylation, increased RNA stability, increased translational control, and protein modification can all be detected at some point in various cancer cells. Scientists are working to understand the common changes that give rise to certain types of cancer or how a modification might be exploited to destroy a tumor cell.

Tumor Suppressor Genes, Oncogenes, and Cancer

In normal cells, some genes function to prevent excess, inappropriate cell growth. These are tumor suppressor genes, which are active in normal cells to prevent uncontrolled cell growth. There are many tumor suppressor genes in cells. The most studied tumor suppressor gene is p53, which is mutated in over 50 percent of all cancer types. The p53 protein itself functions as a transcription factor. It can bind to sites in the promoters of genes to initiate transcription. Therefore, the mutation of p53 in cancer will dramatically alter the transcriptional activity of its target genes.

Proto-oncogenes are positive cell-cycle regulators. When mutated, proto-oncogenes can become oncogenes and cause cancer. Overexpression of the oncogene can lead to uncontrolled cell growth. This is because oncogenes can alter transcriptional activity, stability, or protein translation of another gene that directly or indirectly controls cell growth. An example of an oncogene involved in cancer is a protein called myc. Myc is a transcription factor that is aberrantly activated in Burkett’s Lymphoma, a cancer of the lymph system. Overexpression of myc transforms normal B cells into cancerous cells that continue to grow uncontrollably. High B-cell numbers can result in tumors that can interfere with normal bodily function. Patients with Burkett’s lymphoma can develop tumors on their jaw or in their mouth that interfere with the ability to eat.

Cancer and Epigenetic Alterations

Silencing genes through epigenetic mechanisms is also very common in cancer cells. There are characteristic modifications to histone proteins and DNA that are associated with silenced genes. In cancer cells, the DNA in the promoter region of silenced genes is methylated on cytosine DNA residues in CpG islands. Histone proteins that
surround that region lack the acetylation modification that is present when the genes are expressed in normal cells. This combination of DNA methylation and histone deacetylation (epigenetic modifications that lead to gene silencing) is commonly found in cancer. When these modifications occur, the gene present in that chromosomal region is silenced. Increasingly, scientists understand how epigenetic changes are altered in cancer. Because these changes are temporary and can be reversed—for example, by preventing the action of the histone deacetylase protein that removes acetyl groups, or by DNA methyl transferase enzymes that add methyl groups to cytosines in DNA—it is possible to design new drugs and new therapies to take advantage of the reversible nature of these processes. Indeed, many researchers are testing how a silenced gene can be switched back on in a cancer cell to help re-establish normal growth patterns.

Genes involved in the development of many other illnesses, ranging from allergies to inflammation to autism, are thought to be regulated by epigenetic mechanisms. As our knowledge of how genes are controlled deepens, new ways to treat diseases like cancer will emerge.

Cancer and Transcriptional Control

Alterations in cells that give rise to cancer can affect the transcriptional control of gene expression. Mutations that activate transcription factors, such as increased phosphorylation, can increase the binding of a transcription factor to its binding site in a promoter. This could lead to increased transcriptional activation of that gene that results in modified cell growth. Alternatively, a mutation in the DNA of a promoter or enhancer region can increase the binding ability of a transcription factor. This could also lead to the increased transcription and aberrant gene expression that is seen in cancer cells.

Researchers have been investigating how to control the transcriptional activation of gene expression in cancer. Identifying how a transcription factor binds, or a pathway that activates where a gene can be turned off, has led to new drugs and new ways to treat cancer. In breast cancer, for example, many proteins are overexpressed. This can lead to increased phosphorylation of key transcription factors that increase transcription. One such example is the overexpression of the epidermal growth factor receptor (EGFR) in a subset of breast cancers. The EGFR pathway activates many protein kinases that, in turn, activate many transcription factors that control genes involved in cell growth. New drugs that prevent the activation of EGFR have been developed and are used to treat these cancers.

Cancer and Post-transcriptional Control

Changes in the post-transcriptional control of a gene can also result in cancer. Recently, several groups of researchers have shown that specific cancers have altered expression of miRNAs. Because miRNAs bind to the 3' UTR of RNA molecules to degrade them, overexpression of these miRNAs could be detrimental to normal cellular activity. Too many miRNAs could dramatically decrease the RNA population leading to a decrease in protein expression. Several studies have demonstrated a change in the miRNA population in specific cancer types. It appears that the subset of miRNAs expressed in breast cancer cells is quite different from the subset expressed in lung cancer cells or even from normal breast cells. This suggests that alterations in miRNA activity can contribute to the growth of breast cancer cells. These types of studies also suggest that if some miRNAs are specifically expressed only in cancer cells, they could be potential drug targets. It would, therefore, be conceivable that new drugs that turn off miRNA expression in cancer could be an effective method to treat cancer.
Cancer and Translational/Post-translational Control

There are many examples of how translational or post-translational modifications of proteins arise in cancer. Modifications are found in cancer cells from the increased translation of a protein to changes in protein phosphorylation to alternative splice variants of a protein. An example of how the expression of an alternative form of a protein can have dramatically different outcomes is seen in colon cancer cells. The c-Flip protein, a protein involved in mediating the cell death pathway, comes in two forms: long (c-FLIPL) and short (c-FLIPS). Both forms appear to be involved in initiating controlled cell death mechanisms in normal cells. However, in colon cancer cells, expression of the long form results in increased cell growth instead of cell death. Clearly, the expression of the wrong protein dramatically alters cell function and contributes to the development of cancer.

New Drugs to Combat Cancer: Targeted Therapies

Scientists are using what is known about the regulation of gene expression in disease states, including cancer, to develop new ways to treat and prevent disease development. Many scientists are designing drugs on the basis of the gene expression patterns within individual tumors. This idea, that therapy and medicines can be tailored to an individual, has given rise to the field of personalized medicine. With an increased understanding of gene regulation and gene function, medicines can be designed to specifically target diseased cells without harming healthy cells. Some new medicines, called targeted therapies, have exploited the overexpression of a specific protein or the mutation of a gene to develop a new medication to treat disease. One such example is the use of anti-EGF receptor medications to treat the subset of breast cancer tumors that have very high levels of the EGF protein. Undoubtedly, more targeted therapies will be developed as scientists learn more about how gene expression changes can cause cancer.

Career Connection

Clinical Trial Coordinator

A clinical trial coordinator is the person managing the proceedings of the clinical trial. This job includes coordinating patient schedules and appointments, maintaining detailed notes, building the database to track patients (especially for long-term follow-up studies), ensuring proper documentation has been acquired and accepted, and working with the nurses and doctors to facilitate the trial and publication of the results. A clinical trial coordinator may have a science background, like a nursing degree, or other certification. People who have worked in science labs or in clinical offices are also qualified to become a clinical trial coordinator. These jobs are generally in hospitals; however, some clinics and doctor’s offices also conduct clinical trials and may hire a coordinator.

Summary

Cancer can be described as a disease of altered gene expression. Changes at every level of eukaryotic gene expression can be detected in some form of cancer at some point in time. In order to understand how changes to gene expression can cause cancer, it is critical to understand how each stage of gene regulation works in normal cells. By understanding the mechanisms of control in normal, non-diseased cells, it will be easier for scientists to understand what goes wrong in disease states including complex ones like cancer.
Review Questions

Cancer causing genes are called ________.

1. transformation genes
2. tumor suppressor genes
3. oncogenes
4. mutated genes

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Targeted therapies are used in patients with a set gene expression pattern. A targeted therapy that prevents the activation of the estrogen receptor in breast cancer would be beneficial to which type of patient?

1. patients who express the EGFR receptor in normal cells
2. patients with a mutation that inactivates the estrogen receptor
3. patients with lots of the estrogen receptor expressed in their tumor
4. patients that have no estrogen receptor expressed in their tumor

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Free Response

New drugs are being developed that decrease DNA methylation and prevent the removal of acetyl groups from histone proteins. Explain how these drugs could affect gene expression to help kill tumor cells.

These drugs will keep the histone proteins and the DNA methylation patterns in the open chromosomal configuration so that transcription is feasible. If a gene is silenced, these drugs could reverse the epigenetic configuration to re-express the gene.

How can understanding the gene expression pattern in a cancer cell tell you something about that specific form of cancer?

Understanding which genes are expressed in a cancer cell can help diagnose the specific form of cancer. It can also help identify treatment options for that patient. For example, if a breast cancer tumor expresses the EGFR in high numbers, it might respond to specific anti-EGFR therapy. If that receptor is not expressed, it would not respond to that therapy.

Glossary

DNA methylation
epigenetic modification that leads to gene silencing; commonly found in cancer cells

Histone acetylation
epigenetic modification that leads to gene silencing; commonly found in cancer cells found in cancer cells


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myc oncogene that causes cancer in many cancer cells

Contributors

- Connie Rye (East Mississippi Community College), Robert Wise (University of Wisconsin, Oshkosh), Vladimir Jurukovski (Suffolk County Community College), Jean DeSaix (University of North Carolina at Chapel Hill), Jung Choi (Georgia Institute of Technology), Yael Avissar (Rhode Island College) among other contributing authors. The OpenStax College name, OpenStax College logo, OpenStax College book covers, OpenStax CNX name, and OpenStax CNX logo are not subject to the creative commons license and may not be reproduced without the prior and express written consent of Rice University. For questions regarding this license, please contact partners@openstaxcollege.org. Download for free at http://cnx.org/contents/185cbf87-c72...f21b5eabd@9.87.