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Mary Beckerle's Lecture Part 1:

Introduction to Cancer Biology

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1. Keywords and Terms

Cancer, growth factor signaling, integrins, cell adhesion, Ras, oncogenes, extracellular matrix, focal adhesion, actin cytoskeleton

2. Lecture Notes

Cancer is a disease that affects an extremely large number of people within the general population. Some cancers can be prevented (for example, through not smoking, limiting sun exposure, HPV vaccine). Moreover, early detection of cancer via screening significantly improves our ability to treat the disease.

Healthy tissue has well-organized cells and controlled cell growth, both of which are disturbed in cancer.

Hallmarks of cancer:

Briefly described within the lecture:

1. Insensitivity to anti-growth signals
2. Self-sufficiency in growth signals
3. Evading apoptosis (programmed cell death)

Not discussed in the lecture:

1. Limitless replicative potential
2. Tissue invasion and metastasis
3. Sustained angiogenesis

Each human cell has 23 pairs of chromosomes, containing genetic material/DNA organized into approximately 30,000 genes, which direct all cellular behavior. Alterations in genes, through either inherited or acquired damage, are the early changes that lead to cancer.

Examples of human cancer susceptibility genes

Colon cancer: APC

Breast cancer: BRCA1/2

Melanoma: p16

A genetic understanding of cancer can better allow for screening, early intervention, tailored therapy, and/or prevention. Molecular analysis of the activities of all 30,000 human genes (by a technique called microarray) indicates that different genes are turned on/off in different kinds of cancers, as well as within tumors of the same type. Thus, cancer is NOT a single disease with a single treatment.

Example of a cellular circuit mutated in cancer: Growth factor signaling

Cancer cells can acquire self-sufficiency in growth signaling in many ways, including:

1. Increased production of growth factors
2. Altered growth factor receptor profile of activity
3. Altered/activated downstream elements in the growth factor signaling pathway
4. Influencing cofactors

Integrin Receptors: an example of a cofactor involved in growth factor signaling

Integrins are:

- transmembrane, heterodimeric receptors for extracellular matrix
- concentrated at specialized cell-substratum adhesion sites called focal adhesions
- a link between the extracellular matrix and the actin cytoskeleton
- bidirectional signaling receptor molecules
- modulators of cell migration, proliferation and survival

Importantly, integrin-dependent adhesion is required for normal growth factor response. The crosstalk between integrin signaling and growth factor signaling can occur at many levels. Through this crosstalk, agents that affect integrin function can impinge upon cell growth/proliferation. For example, an anti-integrin antibody can inhibit the proliferation of ovarian tumor cells. Indeed, integrin inhibitors are in clinical trials for numerous cancer applications.

3. Recommended Reading

“The Biology of Cancer” by Robert Weinberg (Garland Science 2006) is a textbook that broadly covers many aspects of cancer biology.

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell (2000)100; 57-70.

4. Review Questions

1. What are three examples of behaviors that can help prevent cancer?
2. What are six hallmarks of cancer?
3. What general molecular defect leads to all forms of cancer?
4. What are 2 general ways in which a person can come to have genes that are damaged?
5. What are some examples of cancer susceptibility genes?
6. True or False: All breast tumors have the same complement of active and inactive genes.
7. Give an example of a cancer that acquires self-sufficiency in growth factor signaling by increasing the production of a growth factor.
8. True or False: Integrin-dependent cell adhesion is required in order for growth factor signaling to occur properly.
9. Integrin receptors span the plasma membrane to link what two structural components inside and outside of the cell?
10. What is the term for integrin-rich sites of cell-substratum attachment?

5. Answers to Review Questions

1. Avoiding smoking, limiting sun exposure, and getting HPV vaccine were presented, but there are many others
2. Self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis

3. Alterations/mutations in genes
4. Inherited damage and acquired damage
5. APC, BRCA1/2, p16, and Ras are specifically mentioned, but there are many others.
6. False
7. Two examples presented: glioblastomas producing PDGF, and sarcomas producing TGF-alpha
8. True
9. Extracellular matrix and the actin cytoskeleton
10. focal adhesions

6. Discussion Questions

1. Why is there unlikely to be a single, “magic bullet” cure for cancer?
2. Mutations in genes that normally function to promote cell proliferation can cause cancer. These are called oncogenes. For example, mutations in the Ras oncogene can allow for constitutive growth factor signaling and the inappropriate cell proliferation characteristic of tumors. Conversely, mutations in genes that normally function to restrict proliferation can also cause cancer. These are called tumor suppressor genes. An example is Retinoblastoma (Rb), which normally functions to prevent excessive cell growth by inhibiting cell cycle progression. How must the nature of mutations in oncogenes and tumor suppressor genes differ, in order for both groups to promote tumor growth?
3. If a person inherits a heterozygous mutation in the tumor suppressor gene APC, they still have one functioning, normal copy of this gene. However, all of these individuals develop colon polyps, and nearly all go on to develop colon cancer at a young age (in the absence of treatment). How does this occur?
4. Why does cancer tend to be more prevalent in elderly populations than among the young?

5. Anoikis is a type of apoptosis (programmed cell death) that takes place when normal integrin-based cell attachments are lost. How might anoikis contribute to cancer progression?

7. Answers to Discussion Questions

1. Cancer is not a single disease with a single cause. Rather, a multitude of genetic alterations can give rise to uncontrolled cell growth. A single agent cannot be expected to correct or prevent every kind of cellular defect that leads to cancer.
2. Cancer causing mutations in oncogenes in some way increase the expression or activity of their gene product. Often these are dominant mutations that require only a single copy to produce an effect. Mutations in tumor suppressor genes tend to be loss-of-function mutations. Often, both copies of these genes need to be mutated in order to observe an effect on cell growth.
3. Loss of heterozygosity. The remaining copy of the tumor suppressor gene can be inactivated—ie: by a point mutation, deletion, truncation—leaving no tumor suppressor gene remaining to protect the body.
4. Alterations in genes, through either inherited or acquired damage, lead to cancer. Setting aside the contribution of mutations inherited at birth, the longer we are alive, the more mutations we have the opportunity to acquire. It is acquired mutations that contribute more significantly to cancer in the elderly.
5. In cancer, cellular architecture becomes disorganized within the tumor. In the absence of normal attachment to the ECM, some of these disorganized cells may be destroyed through anoikis pathways. Moreover, metastatic cancer cells that exit the primary tumor are also likely to be destroyed as they detach from the ECM of the tumor and move into a different ECM environment elsewhere within the body. Hence, anoikis helps to restrict tumor progression and metastasis. Anoikis pathways must be circumvented in order for metastatic lesions to develop.

8. Explain or Teach These Concepts to a Friend

1. Explain and give examples of three broad classes of molecular mechanisms by which the uncontrolled cell growth characteristic of cancer can arise.
2. How standard growth factor signaling pathways transmit extracellular growth signals into a cell proliferation response.
3. How does microarray analysis work? What information can it provide? What are its drawbacks? (This will require some background reading beyond the lecture.)

9. Research the Literature on Your Own

1. Describe one way in which retinoic acid (mentioned briefly in the lecture) is used in the targeted treatment of cancer.
2. Using the diagram of “Cellular circuits mutated in cancer” presented in the lecture as a starting point, choose a protein shown in red, and research and present its role in cancer development.
3. One could imagine that loss of integrin expression could promote metastasis because tumor cells more easily detach from the primary tumor. Conversely, overexpression or mis-expression of integrins might also promote metastasis by allowing tumor cells to migrate and survive in a wider variety of ECM environments. Find evidence in the literature to either support or refute these two hypotheses. Are they mutually exclusive?