Cancer

Attributes of Cancerous Tumors

- Unregulated cell division and growth (defects in cell cycle regulation).
- Failure to undergo apoptosis in response to inappropriate division.
- Cell migration (metastasis): alterations in Cell-to-Cell Interactions Are Associated with Malignancy. Metastatic cells break their contacts with other cells and the ECM in their tissue of origin, and as a result, metastatic cells can invade adjoining tissue or enter the circulation and establish themselves in a distant site.
- Angiogenesis (formation of new blood vessels): tumor growth requires formation of new blood vessels to supply tumors with blood. Many tumors produce growth factors that stimulate angiogenesis.

Cancer is an extraordinarily rare event

About 1 in 10 people will contract cancer at some point in their lives, and most of us have some sort of personal experience with someone we know having cancer. As such, we tend to think of cancer as common, and of course, it is a very serious disease. However, when one considers it in a developmental context, cancer is actually a very rare occurrence. First of all, cancer is rare before the age of forty. Then when one considers all the billions of cell divisions that occur under proper regulation, it is truly amazing how rarely a cell becomes malignant.

Because of the dire consequences of inappropriate cell proliferation, cells have evolved elaborate failsafe mechanisms to eliminate cells that divide when they are not supposed to. This is the reason for the rarity of cancer. Normal cells require growth factor signals to instruct the cells to divide and not to undergo apoptosis. Links between the cell cycle and apoptotic machinery promote cell death for inappropriately dividing cells. For cancer to occur requires the failure of the apoptotic safeguard mechanisms as well as the deregulation of the cell cycle. Thus, most cancers require 2 or more mutations to deregulate the cell cycle and to overcome the apoptotic safeguards against inappropriate division.

Links between Apoptosis and the Cell Cycle

One of the factors that contributes to the rarity of cancers is the tight linkage between the cell cycle and apoptosis. Factors that promote cell division also tend to promote apoptosis. Factors that inhibit apoptosis also tend to inhibit cell division. There is a particularly tight relationship between the control of cell cycle checkpoints and apoptosis.

p53 forms one of the key links between cell cycle regulation and apoptosis. Cell damage induces p53. p53 inhibits cell division by activating transcription of the CKI p21. p53 also induces apoptosis by inhibiting the expression of Bcl2 and activating the expression of Bax and Fas.

P53→ apoptosis
P53-- | cell cycle
p53 knockout mice are viable and cells can be induced to undergo apoptosis by other means indicating that p53 does not have a direct role in apoptosis. However p53 mice nearly always die of cancer indicating that p53 is a tumor suppressor.

Rb, the inhibitor of G1-S progression also inhibits apoptosis. Mice that are deficient in Rb die because of widespread apoptosis. Lack of p53 suppresses the apoptosis in Rb deficient cells indicating that Rb functions to suppress p53 dependent apoptosis. Rb is one of the targets of degradation by caspases during apoptosis.

\[ \text{Rb} \rightarrow \text{cell cycle} \]

\[ \text{Rb} \rightarrow \text{apoptosis} \]

Myc is a transcription factor and proto-oncogene. Myc is required at the G1-S transition and for quiescent cells to enter the cell cycle. Myc activates transcription of the cdc25 phosphatase which activates CDK. Thus Myc promotes cell division and in combination with the appropriate growth factors is an important component of normal cell proliferation. However, in the absence of growth factors, cells sense Myc induced cell division as inappropriate and undergo apoptosis. This is because Myc also induces p53.

\[ \text{Myc} \rightarrow \text{cell cycle} \]
\[ \text{Myc} \rightarrow \text{apoptosis} \]

The apoptotic regulator Bcl2 also feeds back to inhibit the cell cycle by an unknown mechanism.

\[ \text{Bcl2} \rightarrow \text{apoptosis} \]
\[ \text{Bcl2} \rightarrow \text{exit to quiescence} \]
\[ \text{Bcl2} \rightarrow \text{re-entry to cell cycle} \]

**Genetic Basis of Cancer**

Most cancers have a genetic basis. Exceptions include cancers caused by things like asbestos that are thought to cause cancer by disrupting normal cell interactions. Virally induced cancers, while not necessarily the result of a mutation, still have a genetic basis in that they cause the misregulation of genes that control the cell cycle or apoptosis.

There are 2 general classes of genes associated with cancers—oncogenes and tumor suppressor genes. Gain-of-function mutations in proto-oncogenes convert them to oncogenes (cancer causing). Loss-of-function mutations in tumor suppressor genes can also cause cancer.

**Oncogenes**

Arise through gain-of-function mutations in Proto-oncogenes.

Proto-oncogenes generally encode factors that function to promote cell division or inhibit apoptosis.

Examples of Proto-oncogenes:

- Growth factor signaling molecules (Growth factors, GF receptors, signal transduction molecules like ras, MAPK, etc.)
- Transcription factors, such as myc
- Apoptosis inhibitors such as Bcl2
At least three mechanisms can produce gain-of-function mutations to generate oncogenes from the corresponding proto-oncogenes.

- Point mutations in a proto-oncogene that result in a constitutively acting protein product
- Localized reduplication (gene amplification) of a DNA segment that includes a proto-oncogene, leading to overexpression of the encoded protein
- Chromosomal translocation that brings a growth-regulatory gene under the control of a different promoter and that causes inappropriate expression of the gene

In addition, oncogenes may be incorporated into viral genomes to generate tumor viruses.

**Tumor Suppressor Genes**
Discovered because fusing cancer cells with some non-cancer cells inhibits tumor growth unless a particular chromosome is lost. In general, they inhibit cell cycle progression or promote apoptosis. Loss-of-function mutations in tumor suppressor genes can also cause cancer.

Four broad classes of proteins are generally recognized as products of tumor-suppressor genes:

- Intracellular proteins that regulate or inhibit cell cycle. Examples include:
  - Retinoblastoma (Rb)
  - p53
  - CKIs
- Receptors or signal transduction molecules for paracrine factors (e.g. TGF-β) that inhibit cell proliferation
- Proteins that promote apoptosis
  - Death receptors and signal transduction molecules
  - Bax
- Enzymes that participate in cell / DNA repair

**Some Examples of Genetic Defects Common in Cancers**
Many cancers involve defects in the factors that regulate the cell cycle or induce apoptosis in response to inappropriate cell proliferation. Several examples follow:

Deregulated Myc expression is associated with a number of cancers, but Myc alone is not sufficient to cause cancer. As mentioned, Myc alone induces apoptosis. However, if Ras is also deregulated then cancer can occur. Ras is a signal transduction molecule that acts downstream of growth factor receptors and deregulated Ras substitutes for the growth factor requirement.

*It is thought that deregulation of Rb is a ubiquitous feature of all cancers.* This makes sense since Rb blocks the cell cycle at start. For cancer to occur, cells must get past this point somehow.
Overexpression of Bcl2 causes increased tumorogenesis by oversuppressing apoptosis. Similarly, deficiencies in Bax are common in many types of cancer including colon cancer because these cells are defective in apoptosis initiation.

Defects in death receptor signaling are associated with some cancers. For example, mutations in the FasR gene for the Fas receptor increase the frequency of Hodgkin’s lymphoma.

As mentioned, p53 is a tumor suppressor. Cells mutant for p53 no longer undergo apoptosis or cell cycle arrest in response to cellular damage. This makes these cells susceptible to accumulating genetic defects that could result in cancerous proliferation. Mice lacking p53 are viable and healthy, except for a predisposition to develop multiple types of tumors.

**Oncogenic Viruses**

Retroviruses
- Contain an RNA genome
- Reverse transcription produces a DNA copy that integrates into the host genome
- Host genes occasionally get incorporated into the viral genome
- Infection by a retrovirus containing an incorporated oncogene can cause cancer.

DNA viruses
- Do not integrate into the host genome
- Only a few examples of tumorogenic DNA viruses
- human papillomavirus (HPV) is tumorogenic
- encodes viral gene products that interfere with normal cellular regulation
  - One HPV protein, E7, binds to and inhibits Rb
  - another, E6, inhibits p53
  - E5 protein causes sustained activation of the PDGF receptor
  - Together these proteins induce transformation and proliferation of the host cells
- transformation occurs in the absence of mutations to cell regulatory proteins

**Cancer Therapy**

There are 4 major types of cancer therapy.
- Chemotherapy
- Radiation Therapy
- Angiogenesis suppression
- Gene therapy:

Many cancer therapies depend on induction of apoptosis by causing cellular damage. For example, radiation therapy causes damage to cells and dividing cells are the most sensitive. The idea is that actively dividing cancer cells will be induced to undergo apoptosis. Many other therapeutic agents work by similar means. However, some tumors become insensitive to therapy because of defects in the apoptotic machinery.
One of the most common examples is defects in p53. Since p53 is the central regulator in damage induced apoptosis and cell cycle arrest, cells with defects in p53 no longer respond to agents such as radiation or certain drugs. Since tumors require angiogenesis for a blood supply to support tumor growth, some therapies target this process. The most common strategy is to develop and use inhibitors of growth factors that promote blood vessel development. The idea behind gene therapy is conceptually simple: replace a defective gene (such as P53) with a functional copy. Of course technically this is a huge challenge. How to get the functional gene into every cancer cell? Engineered viruses are the most promising vector right now. Yes, some of the same families of viruses that can cause cancer may be manipulated to deliver cancer suppressor genes to the defective cells.