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Cancer

- 2nd leading cause of death in the US
- 4th leading cause of death in young adults
- TABLE 1.1 Some Common Forms of Cancer
- 1 in 2 males develop cancer
- 1 in 3 females develop cancer
- Mortality rates have decreased by 21%

Cancer cells

- Abnormal forms of the body’s own cells that multiply uncontrollably
- Due to altered genetic content, normal control mechanisms are disrupted in cancer cells
- Genetic disease
- Cancer cells ignore their genetic programming and become less specialized

Cells

- TABLE 1.2 Functions of Some Common Structures in a Human Cell
- 30 trillion cells
- As the cell divides, signals from nearby cells instruct the cell to turn off certain sets of instructions in the DNA and turn on others
- Results in specialized cells
- Acquire materials to manufacture energy and materials for transport
- Work performed by enzymes

Enzymes

- Form an assembly line to produce a particular product
- The product of the enzymes upstream is the substrate of the enzymes downstream

A change n the DNA can alter the shape and thus the function of a protein

- This alteration can cause a cell to become cancerous

Cell division

- Interphase

- Cell performs normal functions but also prepare for M phase
- G1 phase
- First growth phase
- S phase
- DNA is replicated or synthesized
- G2 phase
- Second growth phase
- Cells that don’t actively divided enter the G0 phase (resting phase)
- Checkpoints
- Ensures DNA is ready for cell division
- G1 assesses DNA integrity
- G2 assesses copying of DNA (was it done correctly)
- M phase checkpoint assesses if DNA was separated correctly
- If the checkpoints don't work properly the cell may become cancerous
- M phase
- Cell division occurs here
- Mitosis
- cytokinesis
- Not all cells go through the cell cycle at the same rate

Telomeres

- Repetitive nucleotides
- Each time the cell goes through the cell cycle the telomeres shorten
- Length can determine age cells
- When telomeres get too short the cell is targeted for destruction

Continually dividing cells

- S phase
- DNA replication occurs
- Each homologous chromosome is copied
- Produces an identical structure = sister chromatids
- Sister chromatids held together by centromere
- Centrosomes are replicated

Mutations

- Silent mutations

- No mutation
- His -> His
- Missense mutation
- Glu -> Val
- Nonsense mutation
- Glu -> Stop

Cell cycle regulation genes

- tumor-suppressor genes
- Prevent unregulated cell growth
- Slow progression of cell in cell cycle
- Both copies of the genes need to be mutated to cause cancer
- Examples
- Proteins that examine the DNA for damage during the G1 checkpoint
- P53
- BRCA1
- Rb
- Proto-oncogenes
- Precursor to a gene that is associated with cancer
- Accelerate cell cycle
- Proteins are involved in signaling pathways that promote growth and cellular development
- External growth factor binds to a receptor initiating a signaling pathway that causes cell growth
- Become an oncogene when a mutation causes it to be actives without the influence of the external growth factor
- Only need one copy of the gene to be defective for cells to become cancerous
- Specific example
- ERBB2 gene that produces the protein HER-2 (a receptor that assists in the growth of breast tissue
- 25% of all breast cancers have a mutation that causes an overexpression of HER-2 protein

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Cancer

- Cellular disease
- Starts with a single cell that divides over and over again continuously
- Genetic disease

- Mutations disrupt normal cell cycle control mechanisms
- Over time more and more mutations are acquired

Identifying cancer cells

- Abnormal forms of the body’s own cells that multiply continuously uncontrollably

Characteristics of cancer cells

- Different appearance
- Irregular shape
- Dysplasia
- Nuclei are typically larger, have an irregular shape and are darker
- Due to the increased amount of DNA in the nucleus
- Immortal
- Telomerase repairs the end of chromosomes
- Less specialized
- Genetic programming is reversed
- Originally set of genes are turned on while others are turned off
- Loss of specialization = abnormal shape
- They steal the nutrients the need to grow
- No longer functions as part of the surrounding tissue
- If the cancer cells continue to divided a mass of unspecialized tissue will form
- This is called a tumor
- Benign tumor
- Localized to one tissue type
- Cells often closely resemle those in the surrounding tissue
- Less dangerous
- Malignant tumor
- Has the ability to invade other tissues or organs and move to other locations in the body
- Cells do not resemble other cells of the tissue
- Cells are very unspecialized
- Cells within the tumor are diverse in appearance
- Most dangerous form

Angiogenesis

- Cells in the middle of the tumor release growth factors
- Causes the local capillaries to grow towards the tumor and deliver oxygen and nutrients

- These capillaries can then move cancer cells from their original location to another location in the body
- Cancer cells can also move through lymphatic vessels
- Cancer releases proteinase at the new site

Metastasis

- Malignant tumor
- Distant tumor

Stages of cancer

- How large is the tumor
- Has the tumor spread / invaded other tissues
- Is the cancer in nearby lymph nodes
- Has the cancer moved to other organs
- Stage 0
- Early detection
- Cancer cells are located in a small area
- Cells have not begun to invade any surrounding tissue
- More than one tissue in one organ
- Stage 1
- Cancer cells have begun to invade surrounding tissue
- 1A: tumor is small, less than 2cm
- 1B: tumor is smaller than 2cm
- Stage 2
- Cancer cells are considered invasive
- Tumor is large but still inside of the one organ
- 2A: tumor is smaller than 2 cm and found in multiple lymph nodes
- 2B: tumor is between 2 - 5 cm and found in lymph nodes
- Stage 3
- Cancer cells are more invasive
- Breast tissue affected
- Surrounding tissues are affected
- Not yet spread to distant tissues or organs
- 3A: less than 2 cm and spread to more than 4 lymph nodes
- Larger than 5c and spread to only nearby lymph nodes
- 3B: tumor spread to the wall of the organ and 9 lymph nodes
- 3C: tumor has spread to nearby bones or more than 10 lymph nodes

- Stage 4
- Cancer has fully metastasized and spread to outside organs
- For breast cancer this includes spreading to the lungs, heart, brain, and liver
- This stage is considered incurable
- Medical advances are being made to extend the life of individuals with stage 4 cancer

TMN Classification of cancer

- Second classification used by pathologists
- T = size of the tumor
- T1 < T2 < T3 < T4
- N = number of lymph nodes cancer is detected
- N3 = cancer cells found in 3 lymph nodes
- M = metastasis of cancer
- M0 = no metastasis
- M1 = cancer has moved to distant organs or tissues

Cancer causes death by disrupting our physiology

- Tumors take up space in organ
- Tumors take nutrients and oxygen from healthy cells
- Tumors alter body chemistry
- Homeostasis
- Maintenance of a stable environment
- Internal temp is 37 C
- Internal pH is set at 7.4
- Optimal environment for our enzymes
- Dynamic steady state in which changes that occur are minimized by compensatory physiological responses
- Control systems
- Negative feedback mechanism
- Restores homeostasis by reducing the stimulus at the start
- Disrupted by homeostasis

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Determining cancer susceptibility

- Genetic testing

- Isolate DNA from white blood cells from blood sample
- Copy DNA region we are interested in using PCR
- Denaturation
- Annealing
- Extension
- Sequence the copied DNA
- Identify the order of nucleotides in a sequence using fluorescent dyes

TABLE 3.1 Types of Mutations in BRCA!

Cancer identification

- Blood tests
- Quantifies number of blood cells in a sample
- Complete blood count (CBC)
- Can identify metastasized cells in the blood
- Blood chemistry test determines if homeostasis is maintained
- Liver enzymes
- Ions
- Proteins
- Antibodies
- Scans
- Mammogram
- X-ray of breast tissue
- Screening
- Diagnostic
- Computerized tomography (CT)
- Contrast dye injected into blood
- X-rays used to look at the organs from different angles
- Computer generates 3D view of the internal organs
- Sometimes called CAT scans
- Used to detect spread of to determine treatment effectiveness
- Positron emission tomography (PET)
- Sugar containing a small amount of radioactive tracer injected into blood
- Cells that are more active will take up more sugar
- X-rays used to identify cells using the sugar
- Used to determine if breast cancer has spread to nearby lymph nodes or tissues
- Magnetic resonance imaging (MRI)

- Does not use radiation
- Uses radio waves and magnets to generate a detailed image of the body
- Used to detect if cancer has spread in high-risk individuals
- Biopsies
- Noninvasive procedure in which a small section of tissue is removed to look for the presence of cancer cells
- Tissue sent to pathologist to look for characteristics of cancer cells

Traditional cancer treatments

- Surgery
- Local removal of tumor cells
- Some cancer cells can be left behind
- Radiation
- Local killing of tumor cells by DNA damage
- Radiation can damage the DNA of normal cells
- Movement of energy in the form of either waves or particles
- Radiation waves
- Based on their wavelengths in the EM spectrum
- Long wavelength = less energy
- Oncologists use x-rays and gamma rays
- Radiation particles
- High energy pieces of atoms
- Alpha and beta particles
- External radiation treatment
- Most commonly used form
- Not if cancer has metastasized
- Patient placed in position to maximize energy beam effectiveness
- Used in combo with CT scan
- Use x-rays or higher energy gamma rays
- Multiple rounds
- Performed over a couple of weeks
- Internal radiation treatment
- Small deposits of radioactive material placed inside the body
- Placed in body using needle or catheter
- Not used if cancer has metastasized
- Referred to as “seeds”
- Radioactive material releases radiation the damages DNA of cancer cells

- Healthy cells can be damaged
- Also referred to as brachytherapy
- Interstitial brachytherapy
- Intracavitary brachytherapy
- Systemic radiation treatment
- Variation of internal radiation therapy
- Instead of being placed the radioactive substance is ingested or injected into the blood
- Targeted to cancer cells by
- Specific radioactive elements
- Radioactive iodine (I-131) used to treat thyroid cancer)
- Targeting molecules
- Combine radioactive compound to antibodies that targets the cancer cell
- Antibodies can be made to bind to a specific protein on a cancer cell.
- Chemotherapy
- Can damage normal cells
- Drugs used to treat cancer, control the spread of cancer or reduce the symptoms caused by cancer
- Targets the fast-growing characteristic of cancer cells
- Alkylating agents
- Damages DNA of rapidly dividing cells
- Prevents the cell from replicating
- Ex. cyclophosphamide
- Consequences
- Nucleotides become alkylated
- Can cause DNA strand breakage
- Forms covalent links between adjacent nucleic acid strands
- Prevent separation of strands during DNA replication
- Alkylated nucleotides result in miscoding through abnormal base pairing
- Introduction of mutations
- Alkaloids and taxanes
- Naturally produced by plants
- Referred to as mitotic inhibitors
- Can cause nerve damage
- Alkaloids inhibit the formation of the spindle fibers
- Spindle fibers attach to sister chromatids during mitosis
- Ex. vincristine
- Taxanes prevent the breakdown of spindle fibers

- Spindle fibers breakdown during separation of sister chromatids
- Antimetabolites
- Compounds that mimic nucleotides or folic acid
- Purine and pyrimidine analogues can be integrated into DNA strand
- Interfere with DNA replication
- Ex. methotrexate
- Antitumor antibiotics
- Isolated from the bacteria Streptomyces
- Not used to treat bacterial infection
- Prevent functioning of enzymes involved in DNA replication or DNA transcription
- Ex. doxorubicin
- Topoisomerase inhibitors
- Inhibit the enzyme topoisomerase
- Side effects
- Rapidly dividing cells are sensitive to chemotherapy and account for the many undesirable side effects
- Hair follicles
- Bone marrow
- Intestinal epithelium

Future cancer treatments

- Immunotherapy
- Use our immune cells to fight cancer
- Interferon and interleukins signal white blood cells to activate
- Convince our immune cells that cancer cells are foreign and then use the existing immune mechanisms to target those cells for destruction
- Identify subtle differences between cancer cells and normal cells
- Antigens
- Cancer vaccine
- White blood cells removed
- Genetically modified
- Antigen is displayed
- Cells are returned to the body
- Initiate attack of cytotoxic T cells
- CRISPR/Cas9 technology

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