Cancer

Cancer = Occurs when there is dysregulation of checkpoints of cell division or cells escape the cell cycle control mechanism, leading to uncontrolled cell division
Tumour = mass of genetically identical cells derived from a single genetically altered cell
Malignant tumour = Fast growing tumour which can be carried and spread to other parts of the body via blood or lymphatic system
Benign tumour = Slower-growing tumour that usually does not spread

Characteristics of cancer cells

1. Uncontrolled, rapid cell division (Rate of cell division exceeds rate of cell death)
2. Promotes **angiogenesis** (i.e. Growth of blood capillaries) into tumour
3. No **contact inhibition** → Able to infiltrate surrounding tissue
    - Normal cells: Cell division slows when cells come into contact with other cells
4. No **apoptosis** (Programmed cell death)
5. Able to **metastasise** by entering lymphatic and blood circulation to invade other tissues to form secondary tumours
6. Have oncogenes → Proto-oncogenes which have undergone gain-in-function mutation
7. Absent/mutated tumour suppressor genes
8. Undifferentiated and unspecialised (Unable to carry out normal cell functions)
9. Can detach from surrounding cells
10. High nucleo-cytoplasmic ratio

Proto-oncogene (e.g. ras gene)

- Codes for proteins involved in <u>regulation of normal cell growth and proliferation</u>
    - e.g. Ras protein (a G protein involved in signal transduction pathway)
        - Signal transduction: Binding of growth factor to extracellular ligand binding site of receptor (RTK) causes the dimerisation of the 2 receptor subunits ⇒ Conformational change in intracellular domain of the receptor ⇒ Activates intrinsic tyrosine kinase activity of intracellular domain ⇒ Autophosphorylation of tyrosine residues by tyrosine kinase where kinases on 1 subunit cross-phosphorylate the tyrosine residues on the other subunit ⇒ Triggers <u>signal transduction pathway</u> ⇒ Activates receptor
        - Activation of receptor results in binding of GTP to inactive Ras protein ⇒ Ras protein activated ⇒ Phosphorylation cascade ⇒ Production of specific transcription factor (activator) ⇒ Increased cell division
        - Ras protein will become inactive again due to intrinsic GTPase activity
- Mutation: Oncogenes = Mutated form of proto-oncogene
    - Gain-in-function mutation
    - Dominant mutation
        - Mutation in just one copy of the gene results in increased cell growth and

proliferation

- Leads to excessive cell growth and proliferation ⇒ Cancer by:
  - ↑ Amount of proto-oncogene products
    - **Point mutation** in base sequences of <u>regulatory elements</u> ⇒ ↑ Transcription and excess production of growth-stimulating protein
    - **Gene amplification**: Normal DNA replication process is flawed ⇒ ↑ no. of proto-oncogenes ⇒ Excessive production of proto-oncogene protein product
    - **Chromosomal translocation**: Unusual exchange between chromosomes ⇒ Proto-oncogene under control of an <u>enhancer</u> ⇒ Up-regulation of transcription of proto-oncogene
    - **Retroviral integration** by
      - Inactivating <u>silencer</u> of proto-oncogene ⇒ Expression of proto-oncogene cannot be turned off
      - Inserting its own <u>enhancer</u> ⇒ Up-regulating transcription of the proto-oncogene
      - Inserting <u>homologue</u> of the proto-oncogene which codes for a <u>stronger inducer of cell proliferation</u> ⇒ Excessive production of proto-oncogene protein product
  - ↑ Intrinsic activity of the protein's product
    - **Point mutation** within <u>proto-oncogene</u> ⇒ Change in amino acid sequence of proto-oncogene protein ⇒ Hyperactive protein/More resistant to degradation/Constitutively active Ras protein with GTP permanently bound to it
- How to explain mutation mechanisms
  1. The proto-oncogene is a normal gene that expresses normal amount of protein
  2. Explain mechanism by which proto-oncogene becomes oncogene
  3. This results in high level of transcription of the gene to produce excessive amount of the protein
  4. State that this is a gain-in-function mutation
  5. Excessive amount of protein stimulates cells to undergo greater cell division leading to tumour formation
  6. Dominant mutation as a mutation in just one copy of the gene results in increased cell growth and proliferation

Tumour suppressor genes

- Codes for products that <u>inhibit cell division</u> and <u>prevent uncontrolled cell division</u>
  - e.g. p53 gene codes for specific transcription factor (activator) that binds to enhancer region to activate genes involved in:
    - Activating cell cycle arrest
      - Halts cell cycle ⇒ Gives time for cell to repair its damaged DNA +

prevent production of mutant daughter cells
        - Activating DNA repair
            - Preserves genomic integrity and prevents mutations that may lead to formation of oncogenes/inactivation of other tumour suppressor genes
        - Initiating apoptosis when DNA damage is beyond repair
            - Removes damaged cells with the potential to cause cancer
- Mutation
    - Loss-of-function mutation
    - Recessive mutation
        - Requires mutation in both genes
        - If only 1 copy mutated, other non-mutant copy still produces functional gene product ⇒ Tumour suppression
    - Leads to inability to inhibit cell cycle, repair damaged DNA and promote apoptosis ⇒ Cancer by:
        - **Point mutation**, **chromosomal translocation** or **retroviral integration** ⇒ Defective p53 protein which does not restrict cell growth and proliferation

Factors that increase chance of cancer

- Exposure to ultraviolet light/radioactivity/ionising radiations
- Carcinogens such as tar in tobacco smoking/asbestos/benzene/formaldehyde/ethidium bromide
- Viruses such as avian sarcoma virus/human papilloma virus/hepatitis b virus
- Spontaneous mutation of proto-oncogenes/tumour suppressor genes
- Lifestyle and diet
    - Tobacco Smoking
    - Alcohol
    - Carcenogenic food
- Genetic predisposition
- Age

****Explain how one named factor can increase the chances of a cancerous growth/Why is development of cancer a multi-step process (possible essay)**

1. (For first question) State one of the first 3 factors ⇒ Causative agent increases the chance of DNA damage and mutations in the genes which <u>control regulatory checkpoints</u> of the cell cycle in a single cell.
2. Development of cancer requires the <u>accumulation of mutations</u> in the genes which <u>control **regulatory checkpoints** of the cell cycle</u> in a single cell ⇒ Disrupts normal cell cycle ⇒ Uncontrolled cell division ⇒ Excessive cell growth and proliferation
3. <u>Loss-of-function mutation</u> of <u>**tumour suppressor genes**</u> ⇒ Inability to inhibit cell

cycle, repair damaged DNA and promote apoptosis

4. Gain-in-function mutation of **proto-oncogenes** to form **oncogenes** ⇒ Over-expression of protein products OR production of hyperactive/degradation resistant protein products
5. Upregulation/Activation of genes coding for **telomerase** ⇒ Telomeres lengthened and cell can divide indefinitely
6. Loss of contact inhibition enables cells to grow into a tumour
7. **Angiogenesis** → Blood vessels formed can transport oxygen and nutrients for its growth
8. Tumour must be malignant where cells can **metastasise** to spread to other parts of the body via the blood stream to form secondary tumours
9. Takes years to accumulate these mutations ⇒ Multi-step process