Introduction to Oncogenes, Types, and Mode of Action

1. What are Oncogenes?

Oncogenes are genes that have the potential to cause cancer when mutated or abnormally expressed. They originate from normal cellular genes called **proto-oncogenes**, which regulate cell growth and division. When mutated, proto-oncogenes become oncogenes and promote uncontrolled cell proliferation, leading to tumor formation.

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2. Types of Oncogenes

Oncogenes can be classified based on their function in cellular signaling pathways and mechanisms of action:

a. Growth Factors (Mitogens)

- These oncogenes encode proteins that stimulate cell proliferation.
- **Example**: *sis* (encodes Platelet-Derived Growth Factor, PDGF) in some sarcomas.

b. Growth Factor Receptors

- Mutations in these genes lead to constant activation of signaling pathways, even without external signals.
- **Example**: *HER2/neu* (overexpressed in breast cancer).

c. Intracellular Signal Transducers

- These oncogenes encode proteins involved in intracellular signaling cascades.
- **Example**: *RAS* (a small GTPase involved in MAPK signaling, frequently mutated in pancreatic and lung cancer).

d. Transcription Factors

- These proteins regulate gene expression and can drive cancer when mutated or overexpressed.
- **Example**: *MYC* (involved in Burkitt's lymphoma and other cancers).

e. Anti-Apoptotic Proteins

- Oncogenes in this category help cancer cells evade apoptosis (programmed cell death).
- **Example**: *BCL-2* (overexpressed in B-cell lymphoma, preventing cell death).

f. Cell Cycle Regulators

- These oncogenes promote uncontrolled cell division by bypassing normal cell cycle checkpoints.
- **Example**: *Cyclin D1* (CCND1, overexpressed in breast cancer and lymphoma).

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3. Mode of Action of Oncogenes

Oncogenes drive cancer by disrupting normal cellular signaling and regulatory mechanisms. The key modes of action include:

a. Mutation-Induced Activation

- **Point mutations** in oncogenes can result in constitutively active proteins.
- Example: *RAS* mutations lead to continuous cell growth signaling.

b. Gene Amplification

- Extra copies of oncogenes lead to excessive protein production.
- Example: *HER2* gene amplification in breast cancer leads to aggressive tumor growth.

c. Chromosomal Translocation

- Parts of two different chromosomes swap places, leading to abnormal oncogene expression.
- Example: *BCR-ABL* fusion in chronic myeloid leukemia (CML) results from the **Philadelphia chromosome**.

d. Insertional Mutagenesis

- Viral DNA integrates near proto-oncogenes, leading to their overexpression.
- Example: HPV integration leading to *MYC* oncogene activation in cervical cancer.

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4. Oncogene Addiction and Targeted Therapy

Some cancers rely heavily on specific oncogenes for survival, a concept known as **oncogene addiction**. Targeted therapies exploit this dependence:

- **HER2 inhibitors** (e.g., Trastuzumab) for HER2-positive breast cancer.
- **BCR-ABL inhibitors** (e.g., Imatinib) for chronic myeloid leukemia.
- **EGFR inhibitors** (e.g., Erlotinib) for lung cancer.

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5. Conclusion

Oncogenes play a crucial role in cancer development by promoting uncontrolled cell growth and survival. Understanding their types and mechanisms has led to significant advances in targeted cancer therapies, improving patient outcomes.