Enzyme-Linked Receptors: Types, Mechanisms, and Signaling Pathways

Types of Enzyme-Linked Receptors

- Receptor Tyrosine Kinases (RTK)
  - RTKs possess intrinsic kinase activity within the receptor itself.
  - They undergo autophosphorylation upon ligand binding, activating signaling cascades.
  - Commonly involved in growth factor signaling and cellular responses.
- Non-Receptor Tyrosine Kinases (NRTK)
  - NRTKs are not part of the receptor structure but associate non-covalently with receptors.
  - They require ligand binding to the receptor for activation.
  - They play a crucial role in various signaling pathways, including those related to cytokines.

Similarities Between RTK and NRTK

- Shared Characteristics
  - Both types of receptors are involved in tyrosine phosphorylation.
  - They activate downstream signaling molecules, leading to cellular responses.
  - Phosphorylation serves as a mechanism for signal transduction.

Differences Between RTK and NRTK

- Structural Differences
  - RTKs have intrinsic kinase activity, while NRTKs do not.
  - NRTKs require receptor association for activation, which is non-covalent.
- Functional Differences
  - RTKs directly phosphorylate themselves upon activation.
  - NRTKs rely on RTKs or other kinases for phosphorylation.

Mechanism of Action of Receptor Tyrosine Kinases

- Dimerization and Autophosphorylation
  - Ligand binding induces receptor dimerization, leading to autophosphorylation.
  - This process activates the receptor and creates docking sites for downstream signaling proteins.
- Phosphorylation Cascade
  - Autophosphorylation increases kinase activity and creates binding sites for other proteins.
  - Phosphate groups facilitate electrostatic interactions with target proteins.

Effects of Autophosphorylation

- Increased Kinase Activity
  - Autophosphorylation enhances the enzymatic activity of the receptor.
  - It promotes further phosphorylation of downstream signaling proteins.
- Creation of Docking Sites
  - Phosphorylated tyrosine residues serve as docking sites for additional signaling molecules.
  - This interaction leads to the localization of proteins to the plasma membrane.

Cytokine Signaling and the JAK/STAT Pathway

- Role of Cytokines
  - Cytokines are small proteins that regulate immune and blood cell activity.
  - They bind to cytokine receptors, activating the JAK/STAT signaling pathway.
- Mechanism of JAK/STAT Activation
  - Ligand binding induces receptor dimerization and JAK activation.
  - JAK phosphorylates STAT proteins, which then dimerize and translocate to the nucleus to activate gene transcription.

Summary of Key Concepts

- RTKs and NRTKs play crucial roles in cellular signaling through phosphorylation.
- The JAK/STAT pathway is vital for cytokine signaling, while integrins mediate cell adhesion and signaling.
- RAS and PI3-kinase pathways are essential for regulating cell proliferation and survival.
- Crosstalk between pathways ensures balanced cellular responses, influenced by the specific receptor and signaling molecule combinations present in different cell types.

Cell-Specific Responses to Signaling

- Distinct Receptor Combinations
  - Different cell types express unique combinations of receptors and signaling molecules.
  - This diversity allows for varied responses to the same ligand.
- Mechanisms of Differential Response
  - Cells may respond differently to the same hormone due to variations in receptor types or downstream effectors.
  - The chromatin structure also influences gene expression, affecting cellular responses.

Crosstalk Between Signaling Pathways

- Interaction of RAS and PI3-Kinase Pathways
  - RAS activates PI3-kinase, while Akt can inhibit Raf, balancing signaling activity.
  - This crosstalk ensures that signaling pathways do not become overactive.

PI3-Kinase/Akt Pathway

- Activation of PI3-Kinase
  - PI3-kinase is recruited to activated RTKs and converts PIP2 to PIP3.
  - PIP3 serves as a binding site for Akt, which is then phosphorylated and activated.
- Role of Akt in Cell Survival
  - Akt phosphorylates proteins that inhibit apoptosis, promoting cell survival.
  - It also regulates metabolic pathways and protein translation.

The Ras/Raf/MAPK Signaling Pathway

- Signaling Cascade
  - Growth factor binding activates RTKs, leading to autophosphorylation.
  - Phosphorylated sites recruit docking proteins that activate RAS.
  - RAS activates Raf, which phosphorylates MEK, leading to ERK activation.
  - ERK phosphorylates various target proteins, promoting cell proliferation and survival.

RAS Signaling Pathway

- Overview of RAS
  - RAS is a small GTPase that acts as a molecular switch in signaling pathways.
  - It is activated by GTP binding and plays a critical role in cell proliferation and survival.
- RAS Activation and Inhibition
  - RAS is activated by guanine nucleotide exchange factors (GEFs) and inhibited by GTPase-activating proteins (GAPs).
  - Mutations in RAS can lead to oncogenic activity, contributing to cancer progression.

Integrin Signaling

- Integrin Activation
  - Integrins bind to the extracellular matrix, leading to clustering and activation of focal adhesion kinase (FAK).
  - FAK undergoes autophosphorylation, creating docking sites for downstream signaling molecules.
- Role of Src Kinase
  - Src kinase binds to phosphorylated FAK and further phosphorylates it.
  - This amplifies signaling pathways that regulate cell movement and morphology.