Journal of Cellular and Molecular Pharmacology

Aditi, J Cell Mol Pharmacol 2024, 8:6

Case Study Open Access

Tyrosine Kinase Receptors: Mechanisms, Functions, and Therapeutic Implications

Aditi Mishra*

Department of Chemistry, Institute of Molecular Biology, India

Abstract

Tyrosine kinase receptors (TKRs) are crucial components of cellular signaling that regulate a wide range of physiological processes such as cell growth, differentiation, metabolism, and survival. These receptors, which are present on the cell membrane, become activated upon ligand binding, triggering downstream signaling cascades through the phosphorylation of tyrosine residues in their cytoplasmic domains. Abnormal activation of TKRs is implicated in various diseases, particularly cancer, where they can drive tumorigenesis. This article explores the molecular mechanisms underlying TKR activation, their role in cellular signaling, and their involvement in disease pathogenesis. Additionally, it discusses the therapeutic strategies targeting TKRs, with a focus on receptor tyrosine kinase inhibitors (RTKIs) used in clinical practice.

Keywords: Tyrosine kinase receptors; Receptor tyrosine kinases; Signal transduction; Cancer; Cellular signalling; Therapeutic targeting; RTK inhibitors; Growth factors; Oncogenesis

Introduction

Tyrosine kinase receptors (TKRs) are integral membrane proteins that play a central role in the regulation of cellular functions, including cell growth, differentiation, metabolism, and survival. These receptors are activated by the binding of specific ligands [1], such as growth factors, cytokines, and hormones. Upon activation, TKRs undergo autophosphorylation on specific tyrosine residues in their intracellular domain, initiating a cascade of downstream signaling events that regulate a variety of cellular processes.

TKRs are critical for normal cellular functions, but when dysregulated, they can contribute to the pathogenesis of numerous diseases, particularly cancer. Abnormal activation or overexpression of receptor tyrosine kinases (RTKs) often leads to uncontrolled cell division, survival, and migration, hallmark features of tumorigenesis. Given the central role of TKRs in disease [2], they have become important targets for therapeutic intervention, with several receptor tyrosine kinase inhibitors (RTKIs) now in clinical use.

This article provides an overview of the mechanisms by which tyrosine kinase receptors function, their involvement in disease, and the therapeutic implications of targeting these receptors in various conditions.

Mechanisms of Tyrosine Kinase Receptor Activation

Tyrosine kinase receptors are membrane-bound proteins that possess an extracellular ligand-binding domain, a single transmembrane helix, and a cytoplasmic tyrosine kinase domain [3]. Upon ligand binding, TKRs undergo a conformational change that activates their intracellular kinase activity. This process typically occurs in the following steps:

Ligand binding and dimerization: The activation of TKRs begins when a specific ligand binds to the extracellular domain of the receptor. This binding induces receptor dimerization or oligomerization, a process in which two or more receptor monomers associate to form a functional complex. Ligand binding also induces a conformational change that brings the intracellular kinase domains of the receptor into proximity, allowing for cross-phosphorylation of tyrosine residues.

Autophosphorylation and activation of downstream signaling: Once dimerization occurs, the kinase domains of the receptor become active and catalyze the transfer of phosphate groups from ATP to specific tyrosine residues within the intracellular domain. This autophosphorylation creates docking sites for a variety of signaling proteins [4] containing phosphotyrosine-binding domains, such as Src homology 2 (SH2) or phosphotyrosine-binding (PTB) domains. These docking proteins then initiate downstream signaling pathways that regulate cellular processes like gene expression, cell cycle progression, and survival.

Activation of key signaling pathways: Tyrosine phosphorylation activates several major intracellular signaling cascades, including the Ras-MAPK pathway (mitogen-activated protein kinase), the PI3K-AKT pathway (phosphoinositide 3-kinase), and the JAK-STAT pathway (Janus kinase-signal transducer and activator of transcription). These pathways control key cellular processes such as proliferation, differentiation, survival, and metabolism. Disruption of these pathways can lead to abnormal cellular behavior, contributing to disease.

Types of Tyrosine Kinase Receptors

There are several families of receptor tyrosine kinases, each associated with specific ligands and cellular functions:

Epidermal growth factor receptor (EGFR) Family: The EGFR family includes EGFR (HER1), HER2, HER3, and HER4 receptors [5]. These receptors regulate processes such as cell growth, differentiation, and survival. Overexpression or mutations of EGFR, particularly in HER2 (found in many breast cancers), can lead to uncontrolled cellular proliferation and tumorigenesis.

***Corresponding author:** Aditi Mishra, Department of Chemistry, Institute of Molecular Biology, India, E-mail: aditi_m@gmail.com

Received: 02-Dec-2024, Manuscript No: jcmp-25-158294, **Editor Assigned:** 04-Dec-2024, pre QC No: jcmp-25-158294 (PQ), **Reviewed:** 18-Dec-2024, QC No jcmp-25-158294, **Revised:** 23-Dec-2024, Manuscript No: jcmp-25-158294 (R), **Published:** 30-Dec-2024; DOI: 10.4172/jcmp.1000253

Citation: Aditi M (2024) Tyrosine Kinase Receptors: Mechanisms, Functions, and Therapeutic Implications. J Cell Mol Pharmacol 8: 253.

Fibroblast growth factor receptor (FGFR) family: FGFRs are involved in embryonic development, wound healing, and angiogenesis. Mutations or dysregulation of FGFR signalling [6] are implicated in various cancers, as well as skeletal disorders and developmental defects.

Insulin-like growth factor receptor (IGFR) family: IGFRs, particularly IGF1R, are involved in regulating growth and development by modulating cell survival and metabolism. Altered IGFR signaling can contribute to cancer, metabolic disorders, and age-related diseases.

Platelet-derived growth factor receptor (PDGFR) family: PDGFRs are involved in the regulation of cell proliferation, survival, and migration. PDGFR signaling plays a critical role in wound healing, tissue repair, and angiogenesis. Aberrant activation of PDGFRs is associated with various cancers, including gliomas and sarcomas.

Vascular endothelial growth factor receptor (VEGFR) family: VEGFRs are key regulators of angiogenesis, the process by which new blood vessels form [7]. Overexpression of VEGFR signaling can contribute to tumor growth and metastasis by promoting the development of a blood supply to tumors.

Tyrosine Kinase Receptors in Disease

Cancer: Abnormal activation of TKRs is one of the primary drivers of cancer. Mutations in receptors like EGFR, HER2, and FGFR, or their ligands, often result in uncontrolled cell proliferation and survival, leading to tumorigenesis. The overexpression of certain RTKs can promote resistance to apoptosis, facilitate metastasis, and enable the acquisition of resistance to chemotherapy [8]. Targeting these receptors with specific inhibitors has become a central strategy in cancer therapy.

Neurological disorders: Abnormal TKR signaling also plays a role in neurological conditions. For instance, the dysfunction of Trk receptors, which are activated by nerve growth factor (NGF), has been implicated in neurodegenerative diseases like Alzheimer's disease. Disrupting TKR signaling in neurons can lead to impaired survival and function of these cells.

Cardiovascular diseases: Tyrosine kinase receptors, such as VEGFRs and PDGFRs, are involved in vascular development and repair [9]. Dysregulation of these pathways can contribute to cardiovascular diseases, including atherosclerosis and ischemic heart disease.

Therapeutic Targeting of Tyrosine Kinase Receptors

Given their central role in disease, TKRs have become important targets for therapeutic intervention, particularly in cancer. Several receptor tyrosine kinase inhibitors (RTKIs) have been developed to block the activity of overactive receptors:

Small molecule inhibitors: These drugs, such as imatinib (targeting BCR-ABL in chronic myelogenous leukemia) and gefitinib (targeting EGFR in non-small [10] cell lung cancer), inhibit the kinase activity of specific RTKs, thereby preventing their activation and downstream signaling.

Monoclonal antibodies: Monoclonal antibodies, such as trastuzumab (Herceptin) for HER2-positive breast cancer, bind to the extracellular domain of the receptor, preventing ligand binding and receptor activation.

Combination therapies: In many cases, RTKIs are used in combination with other therapies, such as chemotherapy or immunotherapy, to enhance treatment efficacy and overcome resistance.

Conclusion

Tyrosine kinase receptors are essential mediators of cellular signaling, regulating processes like cell growth, differentiation, and survival. Their dysregulation is implicated in numerous diseases, particularly cancer, where aberrant activation of these receptors promotes tumorigenesis. The development of targeted therapies, including receptor tyrosine kinase inhibitors and monoclonal antibodies, has revolutionized the treatment of cancer and other diseases associated with TKR dysregulation. Continued research into the molecular mechanisms governing TKR signaling holds the promise for more effective and personalized treatments in the future.

References

1. Leung DW, Cachianes G, Kuang WJ (1989) Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 246: 1306-1309.
2. Olofsson B, Pajusola K, Kaipainen A (1996) Vascular endothelial growth factor B, a novel growth factor for endothelial cells. Proc Natl Acad Sci USA 93: 2576-2581.
3. Joukov V, Pajusola K, Kaipainen A, Chilov D (1996) novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. EMBO J 15: 290-298.
4. Yamada Y, Nezu J, Shimane M (1997) Molecular cloning of a novel vascular endothelial growth factor. VEGF DGenomics 42: 483-488.
5. Olsson AK, Dimberg A, Kreuger J (2006) VEGF receptor signalling in control of vascular function. Nat Rev Mol Cell Biol 7: 359-371.
6. Araújo AP, Mesak C, Montalvão MF (2019) Anti-cancer drugs in aquatic environment can cause cancer insight about mutagenicity in tadpoles. Sci Total Environ 650: 2284-2293.
7. Barros S, Coimbra AM, Alves N (2020) Chronic exposure to environmentally relevant levels osimvastatin disrupts zebrafish brain gene signaling involved in energy metabolism. J Toxic Environ Health A 83: 113-125.
8. Ben I, Zvi S, Langevitz P (2019) Hydroxychloroquine from malaria to autoimmunity.Clin Rev Allergy Immunol 42: 145-153.
9. Bergqvist Y, Hed C, Funding L (1985) Determination of chloroquine and its metabolites in urine a field method based on ion-pair. Bull World Health Organ 63: 893-898.
10. Burkina V, Zlabek V, Zamarats G (2015) Effects of pharmaceuticals present in aquatic environment on Phase I metabolism in fish. Environ Toxicol Pharmacol 40: 430-444.