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MECHANISM OF ACTION OF TYROSINE KINASE INHIBITORS

Kamola Anvarjon qizi Almirzayeva
Tashkent Pharmaceutical Institute, Tashkent, Republic of Uzbekistan
E-mail: almirzayevak@gmail.com

Annotation: This thesis explores the molecular mechanisms of action of tyrosine kinase inhibitors (TKIs) and their role in targeted cancer therapy. It examines their effects on intracellular signaling pathways, including RAS–RAF–MEK–ERK, PI3K–AKT–mTOR, and JAK–STAT, and their therapeutic applications in various malignancies. Particular attention is given to the mechanisms of drug resistance, including kinase-domain mutations and activation of alternative signaling pathways. The review also highlights recent advances in the development of selective inhibitors and combination therapies to improve treatment efficacy and support personalized cancer management.

Keywords: tyrosine kinase inhibitors, molecular mechanisms, targeted therapy, cancer, signal transduction, drug resistance.

Relevance: Tyrosine kinase inhibitors (TKIs) have become essential agents in modern targeted cancer therapy because they selectively interfere with molecular pathways responsible for tumor growth and progression. Tyrosine kinases regulate cell proliferation, differentiation, survival, migration, and angiogenesis through phosphorylation of intracellular proteins. However, mutations, overexpression, or abnormal activation of these enzymes may lead to uncontrolled cellular signaling and malignant transformation. Unlike conventional chemotherapy, TKIs target specific molecular abnormalities, potentially improving therapeutic selectivity and reducing damage to normal cells. Recent advances have expanded their clinical application in chronic myeloid leukemia, lung cancer, breast cancer, renal cell carcinoma, and other malignancies. Nevertheless, acquired drug resistance and treatment-related adverse effects remain important challenges, making the investigation of their mechanisms of action particularly relevant [1–4].

Aim: To investigate the molecular mechanisms of action of tyrosine kinase inhibitors, explain their effects on intracellular signaling pathways, and evaluate their therapeutic significance and major mechanisms of resistance in cancer treatment.

Methods: A narrative literature review was conducted using scientific publications concerning tyrosine kinase inhibitors, receptor tyrosine kinase signaling, targeted cancer therapy, and drug resistance. The analysis included foundational research on kinase inhibition and recent reviews published in 2024 and 2025. The selected literature was comparatively evaluated to identify the principal molecular targets, mechanisms of action, therapeutic applications, and biological factors contributing to treatment failure.

Results: Tyrosine kinase inhibitors (TKIs) suppress the activity of protein kinases involved in tumor growth and progression. Receptor tyrosine kinases, including EGFR, HER2, VEGFR, and FGFR, regulate cellular proliferation, survival, and angiogenesis. Their abnormal activation can lead to uncontrolled cell growth and resistance to apoptosis [1, 2].

Most TKIs competitively bind to the adenosine triphosphate (ATP)-binding site of kinase domains, preventing phosphorylation and inhibiting intracellular signaling pathways such as RAS–RAF–MEK–ERK, PI3K–AKT–mTOR, and JAK–STAT. Consequently, they can reduce tumor-cell proliferation, promote apoptosis, and suppress angiogenesis [1–3].

The therapeutic efficacy of TKIs depends on the molecular characteristics of the tumor. Imatinib inhibits the BCR::ABL1 fusion protein in chronic myeloid leukemia (CML), while gefitinib and

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osimertinib target specific EGFR alterations in non-small-cell lung cancer. HER2- and VEGFR-targeted inhibitors are also used in selected malignancies [1, 3, 5].

Despite their effectiveness, TKIs may encounter resistance due to kinase-domain mutations, activation of alternative signaling pathways, and tumor heterogeneity. For example, the BCR::ABL1 T315I mutation can reduce sensitivity to certain inhibitors. These mechanisms highlight the limitations of targeting a single molecular pathway [3, 4].

Recent research focuses on developing next-generation inhibitors, identifying resistance mechanisms, and combining targeted therapies. Although TKIs have improved cancer treatment, adverse effects such as gastrointestinal disturbances, skin reactions, hypertension, and liver toxicity may occur. Therefore, appropriate patient selection, dose management, and treatment monitoring are essential for optimizing therapeutic outcomes [1, 3, 4].

Conclusion: Tyrosine kinase inhibitors represent a major advancement in precision oncology because they interfere with molecular mechanisms that sustain malignant growth. Their principal mechanism involves the inhibition of kinase-dependent phosphorylation and suppression of oncogenic signaling pathways, leading to reduced proliferation, increased apoptosis, and, in some cancers, decreased angiogenesis. Nevertheless, genetic mutations, alternative signaling pathways, and tumor heterogeneity can limit their long-term effectiveness. Further investigation of resistance mechanisms and the development of more selective inhibitors and rational combination therapies may improve treatment outcomes and support more individualized cancer management.

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