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Mechanistic Analysis of Protein-Protein Interactions in Oncogenic Signaling Pathways and Their Role in Targeted Cancer Therapy

Ahmed Al-Farsi, Olga Petrovna, Pierre Dupont, Katarzyna Nowak

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ABSTRACT
Protein-protein interactions (PPIs) play a fundamental role in oncogenic signaling, influencing cell proliferation, survival, and metastasis. Dysregulation of PPIs contributes to cancer progression, making them attractive targets for therapeutic intervention. This study provides a mechanistic analysis of PPIs in key oncogenic pathways, including the Ras-MAPK, PI3K-Akt, and JAK-STAT pathways. We explore the structural and functional dynamics of PPIs, their role in cancer development, and strategies for targeting these interactions using small molecules, monoclonal antibodies, and peptide-based inhibitors. The review highlights emerging computational and experimental approaches in PPI-targeted therapy and discusses future prospects for improving therapeutic efficacy.

INTRODUCTION:

Protein-protein interactions (PPIs) are critical regulators of intracellular signaling networks, governing cellular processes such as proliferation, differentiation, and apoptosis. In cancer, aberrant PPIs disrupt signaling homeostasis, leading to uncontrolled cell growth and resistance to apoptosis. Oncogenic pathways, including the Ras-MAPK, PI3K-Akt, and JAK-STAT cascades, are driven by specific PPIs that serve as potential therapeutic targets. Understanding the mechanistic basis of PPIs in these pathways is essential for developing novel cancer therapeutics. This review examines the structural principles underlying PPIs in oncogenic signaling and their implications for targeted therapy.

Key Oncogenic Signaling Pathways and PPIs

Ras-MAPK Pathway:

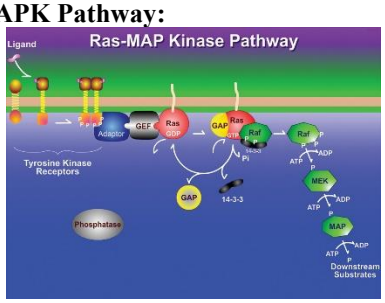

Fig.Ras-MAPK Pathway

The Ras-MAPK pathway regulates cell growth and

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differentiation through a cascade of kinase activations. Ras's proteins interact with Raf kinases, initiating a phosphorylation sequence leading to ERK activation. Mutations in Ras (e.g., KRAS G12D) enhance its affinity for Raf, sustaining aberrant signaling. Structure-based drug design efforts have targeted the Ras-Raf interaction, yielding inhibitors such as sotorasib for KRAS-driven cancers.

PI3K-Akt Pathway:

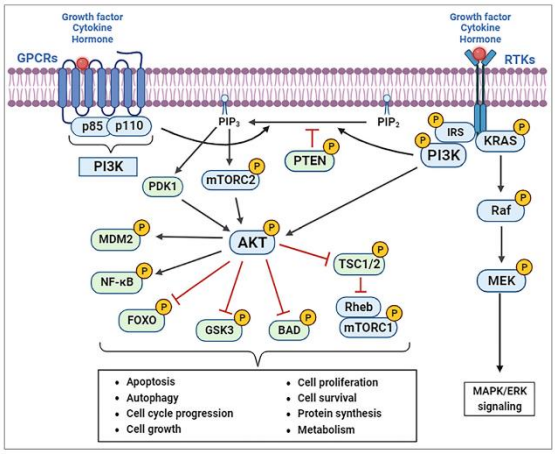

Fig.PI3K-Akt Pathway

The PI3K-Akt pathway promotes cell survival and metabolism. PI3K interacts with receptor tyrosine kinases (RTKs) to activate Akt via PDK1 phosphorylation. Dysregulated PI3K-Akt signaling, common in breast and prostate cancers, is often due to mutations in PIK3CA or PTEN loss. Small molecules like alpelisib disrupt PI3K-Akt PPIs, offering therapeutic benefits.

JAK-STAT Pathway:

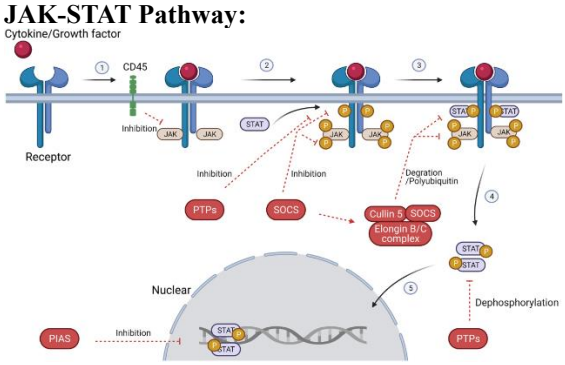

Fig.JAK-STAT Pathway

Cytokine receptors engage JAK kinases, which phosphorylate STAT proteins, driving oncogenic transcription programs. Constitutive STAT3/STAT5 activation is prevalent in leukemia and lymphoma. Disrupting JAK-STAT PPIs using inhibitors such as ruxolitinib has demonstrated efficacy in myeloproliferative disorders.

Structural Basis of PPIs in Oncogenic Signaling
Protein Interface Characteristics:
PPIs in oncogenic pathways are characterized by large, hydrophobic interaction surfaces. Structural studies using X-ray crystallography and cryo-EM have identified key binding motifs, such as the Ras switch regions involved in Raf binding. Understanding these interfaces is critical for designing inhibitors.

Computational Modeling and Molecular Docking:
Molecular dynamics simulations and AI-driven docking studies predict PPI binding affinities and conformational changes upon inhibitor binding. Advances in structure-based drug design (SBDD) have led to rational drug discovery efforts targeting oncogenic PPIs.

Therapeutic Strategies Targeting PPIs:
Small Molecule Inhibitors:
Small molecules targeting PPIs disrupt oncogenic signaling by interfering with protein interfaces. Examples include AMG 510 (sotorasib) for KRAS G12C inhibition and navitoclax, which disrupts Bcl-2/Bax interactions in apoptosis regulation.

Monoclonal Antibodies:
Monoclonal antibodies (mAbs) block extracellular PPIs, such as RTK-ligand interactions. Trastuzumab inhibits HER2 dimerization, reducing downstream oncogenic signaling in breast cancer.

Peptide-Based Inhibitors:
Peptidomimetics and stapled peptides mimic native PPI interfaces, offering specificity in targeting intracellular PPIs. Strategies like helix-mimetic inhibitors of MDM2-p53 interactions are under clinical investigation.

Challenges and Future Directions: Despite progress, targeting PPIs remains challenging due to large, flat interaction surfaces. Advances in proteolysis-targeting chimeras (PROTACs) and AI-driven drug design hold promise for overcoming these hurdles. Future research should focus on improving PPI-targeting drug stability, selectivity, and bioavailability.

CONCLUSION: PPIs are central to oncogenic signaling and cancer progression, making them crucial targets for therapy. Mechanistic insights into PPI dynamics and structural features have facilitated the development of novel inhibitors. Continued advancements in computational modeling and experimental approaches will enhance our ability to design effective PPI-targeted cancer therapies.

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