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Overlapping Pathways in Oncological disease Progression and Therapy

Tantiago Antonio*

Department of Pathology, National and Kapodistrian University of Athens, 11527 Athens, Greece

Introduction

The intricate web of cellular signalling pathways plays a pivotal role in the development and progression of cancer. Among these, the intersecting pathways where different signalling routes converge or influence each other are crucial in shaping tumour biology and therapeutic responses. Understanding how these pathways interact provides valuable insights into cancer mechanisms and unveils novel strategies for treatment. Cancer development is driven by a complex interplay of multiple signalling pathways that regulate cellular processes such as growth, survival, differentiation, and migration. Pathways like the Fibroblast Growth Factor Receptor (FGFR) signalling and the NOTCH signalling system are prominent examples of how distinct molecular routes can intersect and contribute to tumour genesis.

Description

FGFR signalling, known for its role in cell proliferation and survival, often intersects with NOTCH signalling, which is essential for cell fate determination and tissue homeostasis. These intersecting pathways not only influence the cellular behaviour of tumour cells but also impact their response to therapy. For instance, aberrations in one pathway can affect the activity of another, potentially leading to resistance to targeted treatments. By elucidating the mechanisms through which these pathways interact, researchers can identify novel therapeutic targets and develop more effective treatment strategies. This introduction sets the stage for a deeper exploration of how intersecting signalling pathways contribute to cancer development and treatment. By examining these interactions, we can enhance our understanding of tumour biology and improve therapeutic approaches, ultimately advancing the field of oncology. FGFR2 is a member of the fibroblast growth factor receptor family, which consists of receptor tyrosine kinases. These receptors are activated by binding to Fibroblast Growth Factors (FGFs), leading to receptor dimerization and auto phosphorylation. This activation triggers downstream signalling pathways, such as the MAPK/ERK, PI3K/AKT and PLC pathways, which are involved in cell proliferation, survival and differentiation [1,2]. Aberrant FGFR2 signalling has been implicated in various cancers, including breast, gastric and lung cancers. Mutations, amplifications and fusions of the FGFR2 gene can lead to its constitutive activation, promoting ontogenesis. Targeting FGFR2 with specific inhibitors has shown promise in clinical trials, highlighting its potential as a therapeutic target [3].

Signalling pathway

The signalling pathway is a highly conserved cell signalling system present in most multicellular organisms. NOTCH1, one of the four NOTCH receptors in mammals, is activated by binding to its ligands (Delta-like and jagged families). Upon ligand binding, NOTCH1 undergoes photolytic cleavage, releasing the Intra Cellular Domain (NICD). The NICD translocate to the nucleus, where it regulates the transcription of target genes involved in cell fate determination, differentiation and proliferation. NOTCH1 plays a dual role in cancer, acting as either an oncogene or a tumour suppressor, depending on the context. In certain cancers, such as T-cell Acute Lymphoblastic Leukemic (T-ALL), NOTCH1 is frequently mutated, leading to its activation and promoting cancer cell survival and proliferation. Conversely, in other cancers, NOTCH1 functions as a tumour suppressor and its loss contributes to tumour genesis [4]. Emerging evidence suggests a complex interplay between FGFR2 and NOTCH1 signalling pathways. This crosstalk can influence various cellular outcomes and has significant implications for cancer therapy.

Mechanisms of interaction

Regulation of gene expression: FGFR2 activation can influence the expression of NOTCH1 ligands, thereby modulating NOTCH1 signalling. Conversely, NOTCH1 signalling can affect the expression of FGFR2 and its downstream targets.

Shared downstream effectors: Both FGFR2 and NOTCH1 pathways converge on common downstream effectors such as: the MAPK/ERK pathway. Crosstalk at this level can amplify or dampen signalling outputs, affecting cell fate decisions.

Post-translational modifications: FGFR2 and NOTCH1 can undergo post-translational modifications, such as phosphorylation and ubiquitination, that affect their stability and activity. Crosstalk between these pathways can modulate these modifications, altering the signalling dynamics.

Implications for cancer therapy

Understanding the molecular interactions between FGFR2 and NOTCH1 provides new avenues for therapeutic intervention. Several strategies can be envisioned:

Combination therapies: Targeting both FGFR2 and NOTCH1 pathways simultaneously may produce synergistic effects, enhancing therapeutic efficacy and overcoming resistance to single-agent therapies.

Biomarker development: Identifying biomarkers that reflect the status of FGFR2 and NOTCH1 signalling can guide the selection of patients who are most likely to benefit from targeted therapies.

Context-specific interventions: Given the context-dependent roles of FGFR2 and NOTCH1 in cancer, therapies need to be tailored to the specific genetic and molecular landscape of each tumour.

Current therapeutic approaches

FGFR2 inhibitors: Several FGFR2 inhibitors are currently in clinical development or have received regulatory approval. These include small molecule tyrosine kinase inhibitors, monoclonal antibodies and FGF ligand traps. Clinical trials have shown promising results, particularly in cancers with FGFR2 alterations [5].

NOTCH1 inhibitors: NOTCH1 inhibitors, including γ-Secretase Inhibitors (GSIs) and monoclonal antibodies targeting NOTCH1 ligands, have been investigated in preclinical and clinical studies. While these inhibitors have shown efficacy in certain cancers, challenges such as toxicity and resistance need to be addressed.

***Address for Correspondence:** Tantiago Antonio, Department of Pathology, National and Kapodistrian University of Athens, 11527 Athens, Greece; E-mail: antonio@Tantiago.uoa.gr*

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Challenges and future directions

Despite the promising therapeutic potential of targeting FGFR2 and NOTCH1, several challenges remain:

1. **Resistance mechanisms**: Cancer cells can develop resistance to FGFR2 and NOTCH1 inhibitors through various mechanisms, such as secondary mutations and activation of compensatory pathways. Understanding these resistance mechanisms is crucial for developing effective combination therapies.

2. **Toxicity**: Inhibition of FGFR2 and NOTCH1 signalling can lead to adverse effects, given their roles in normal tissue homeostasis. Strategies to minimize toxicity while maintaining therapeutic efficacy are needed.

3. **Biomarker identification**: Reliable biomarkers are essential for patient stratification and monitoring therapeutic responses. Advances in genomics and proteomics hold promise for identifying such biomarkers.

Conclusion

The intricate molecular interactions between FGFR2 and NOTCH1 have profound implications for cancer therapy. By elucidating the mechanisms of crosstalk and developing targeted interventions, we can improve therapeutic outcomes for patients with cancers driven by aberrant FGFR2 and NOTCH1 signalling. Future research should focus on overcoming the challenges of resistance, toxicity and biomarker identification to fully realize the potential of targeting these pathways in cancer therapy.

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Conflict of Interest

None.

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