Multiscale Modeling in High-Grade Gliomas

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Title Slide

Title: Multi-scale Signaling and Tumor Evolution in High-Grade Gliomas

Focus: How PTPN11, a key protein, plays a central role in driving brain tumors, specifically high-grade gliomas

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Introduction to High-Grade Gliomas (HGGs)

- About HGGs: These are very aggressive brain tumors, including glioblastomas and grade 4 IDH-mutant astrocytomas, with extremely low 5-year survival rates (under 5%).
- Challenge: Even though we already know a lot about their genetic makeup, treatment success is still limited.
- Study Focus: This study integrates multi-scale molecular data to understand how HGGs grow and resist treatment, focusing especially on the role of PTPN11.

Study Objectives

- To integrate data from different levels (genomic, proteomic, metabolomic) to get a full picture of HGGs.
- To identify core regulatory networks that influence tumor behavior, particularly those that drive growth and recurrence.
- To zero in on PTPN11 as a target because of its major role in these tumor processes.

Methodology

- Sample Cohort:
  - Study involved 228 tumor samples: 212 glioblastomas (GBMs) and 16 IDH-mutant astrocytomas (grade 4), including both primary and recurrent (after treatment) cases, and normal brain samples for comparison.
- Data Types:
  - Genomic: Whole exome and genome sequencing (WES, WGS)
  - Epigenetic: DNA methylation
  - Transcriptomic: mRNA, miRNA, and single-nuclei RNA sequencing
  - Proteomic: Phosphoproteome, acetylome, and glycoproteome
  - Metabolomic: Lipidome and metabolome

Key Findings — HGG Molecular Scale

- Upstream Alterations & Downstream Events: Despite heterogeneity in genomic alterations, common downstream events drive tumor progression.
- Protein-Protein Interactions (PPIs): Tumor recurrence is associated with changes in PPIs, glycosylation sites, and metabolic pathways.
- Central Role of PTPN11: This study suggests PTPN11 serves as a core signaling hub connecting multiple oncogenic pathways.

PTPN11 Signaling Hub

- Key Role of PTPN11:
  - PTPN11 functions as a central signaling hub that coordinates pathways relevant to tumor growth and survival.
  - PTPN11 alterations (mutations or post-translational modifications) impact various downstream pathways, reinforcing its role in glioma progression.
- Key Pathways Linked to PTPN11:
  - EGFR and PDGFR Pathways: These growth factor receptors are commonly altered in HGGs and are integrated by PTPN11 into downstream signaling.
  - IDH1 Pathway: IDH1 mutations, seen in astrocytomas, also feed into PTPN11-regulated pathways, indicating its cross-subtype relevance.
- Conclusion: Extensive involvement of PTPN11 in HGG signaling highlights it as a key node for potential therapeutic targeting to disrupt core oncogenic networks.

Effects of PTPN11 Alterations

- Direct (Cis) Effects:
  - PTPN11 mutations impact RNA and protein expression levels of PTPN11 itself.
  - Alterations also influence PTPN11's own post-translational modifications, notably phosphorylation at residues Y62 and Y546.
- Distant (Trans) Effects:
  - PTPN11 mutations drive distal changes in other molecular events, influencing key pathways such as PI3K/AKT and MAPK.
  - Phosphorylation at Y62: Associated with decreased PI3K/AKT pathway activity (inhibitory).
  - Phosphorylation at Y546: Strongly activates MAPK signaling (activating), which supports tumor progression.
- Implication: Cis and trans effects highlight potential strategies to modulate PTPN11 signaling to inhibit tumor growth and spread.

Tumor Evolution and Recurrence Patterns

- Changes Over Time:
  - Tumors change their protein and cell composition over time, especially when they come back after treatment.
  - Recurrence is often linked to stress-response and repair pathways, making these tumors more resistant.
- Microenvironment Changes:
  - Recurrent tumors have fewer blood vessels and more immune-suppressing cells, making them more difficult to treat.
- Takeaway: Targeting these evolving features could prevent or slow recurrence.

Metabolomic and Glycoproteomic Insights

- IDH1-Mutant Tumors:
  - Tumors with IDH1 mutations have distinct metabolic and glycoprotein changes, including increased levels of 2-hydroxyglutarate (2-HG), an oncometabolite, and high-mannose glycans due to incomplete glycosylation.
  - Key glycoproteins, such as CNTN2 and ASAH1, are identified as recurrence markers.
- Glycosylation Pathway:
  - High-mannose glycans indicate disrupted glycosylation, potentially promoting tumor progression.
  - High expression of glycosylation enzymes (e.g., STT3A/B, GANAB) in HGGs further underscores glycoproteomic pathway alterations.
- Implication: Glycoproteomic profiles may serve as biomarkers for tumor aggressiveness and recurrence, offering targets for novel therapies.

Clinical Implications

- PTPN11 as a Therapeutic Target:
  - With its central role, PTPN11 is a promising target for novel therapies in HGG, with potential to disrupt multiple oncogenic pathways.
  - Modulation of PTPN11 phosphorylation sites (Y62, Y546) could offer new ways to help prevent recurrence or make tumors more sensitive to treatments.
- Glycoproteins as Biomarkers:
  - Specific glycoproteins identified in this study, such as CNTN2, may be effective biomarkers for tracking recurrence or prognosis.
- Next Steps: Developing clinical trials for PTPN11-targeted treatments and validating these biomarkers.

Conclusion and Future Directions

- Summary:
  - PTPN11 is a key player in glioma growth and progression.
  - This study helps us understand how it controls other pathways, and why targeting it might work.
- Future Work:
  - Develop PTPN11-targeted drugs and test them in trials.
  - Use glycoprotein markers to detect and monitor high-risk tumors.

References

1. Liu J, Cao S, Imbach KJ, et al. (2024). Multi-scale signaling and tumor evolution in high-grade gliomas. Cancer Cell. 2024 Jul 8;42(7):1217-1238.e19. doi: 10.1016/j.ccell.2024.06.004. PMID: 38981438; PMCID: PMC11337243.