

## Hyperactivation of a YAP-driven Rho-GTPase Switch Drives Invasive Spread and Confers Poor Prognosis in Glioblastoma

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### Introduction

Progression of infiltrative cancers such as glioblastoma results from defects in the molecular pathways linking cell migration and invasion into surrounding tissue. This tightly governed process integrates various extracellular cues into intracellular signaling pathways by finely tuning small Rho-GTPases to modulate cell dispersal. Insight into these mechanistic links can help identify important molecular components, whose activity can determine the outcome of cell migration dependent events in development and progression of cancer, including subsequent recurrence. In this study, we delineated the molecular components that dictate invasive spread of glioblastoma, the most common malignant brain tumor.

### Methods

Migration speed was assessed using live single cell imaging of patient-derived glioblastoma cells. Evaluation of molecular regulation was conducted using western blot, PCR, chIP-seq, chIP-luciferase using patient-derived glioblastoma cells and tissues. GSEA, bioinformatics, and Kaplan-Meier analyses of patient data-sets such as REMBRANDT and TCGA was performed. Genetic manipulations were performed using lentiviral-based shRNA and overexpression constructs. In vivo invasive spread was conducted using intracranial glioblastoma xenograft models.

### Results

This study suggests a central and widespread role for YAP in controlling the migratory speed and invasiveness of glioblastoma. Using patient-derived glioblastoma cells and tissues and murine intracranial glioblastoma xenograft models, we demonstrate that YAP binds an enhancer region and promotes transcription of TRIO, a guanine nucleotide exchange factor (GEF) protein that can regulate Rho-family GTPases. YAP-mediated TRIO up-regulation activates Rac1 and inhibits RhoA to increase migration speed. In addition, an increase in YAP-mediated TRIO expression leads to activation of STAT3 to confer invasive potential. Furthermore, our studies indicate that hyperactivation of YAP-TRIO-STAT3 signaling confers poor patient outcome and that YAP can regulate the Mesenchymal subtype of glioblastoma, suggesting a new signature in clinical prognosis of this aggressive and infiltrative cancer.

### Conclusions

YAP-dependent infiltrative cell migration and spread is enhanced in a patient specific way in glioblastoma, where hyperactivation of the YAP-mediated TRIO and STAT3 network also confers poor patient outcome and up-regulation of genes associated with the Mesenchymal subtype of glioblastoma. Our analysis suggests that the YAP-TRIO-STAT3 signaling network identified in this study is a ubiquitous regulator of invasive cell spread in a variety of pathological contexts.

### Learning Objectives

By the conclusion of this session, participants should be able to: 1) understand the molecular basis for cellular migration and invasive spread of glioblastoma. 2) understand how invasive spread is intimately linked to tumor progression. 3) Identify molecular components with prognostic and therapeutic power for clinical use.

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