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Network of mutually repressive metastasis regulators can promote cell heterogeneity and metastatic transitions[1] GABOR BALAZSI, Department of Systems Biology - Unit 950, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA, EUN-JIN KIM, School of Mathematics and Statistics, University of Sheffield, Sheffield, S3 7RH, UK, MARSHA ROSNER, Ben May Department for Cancer Research, The University of Chicago, Chicago, IL 60637, USA — The sources and consequences of nongenetic variability in metastatic progression are largely unknown. To address these questions, we characterize the transcriptional regulatory network around the metastasis suppressor Raf Kinase Inhibitory Protein (RKIP). It was previously shown that RKIP negatively regulates the transcription factor BACH1, which promotes breast cancer metastasis. Here we demonstrate that BACH1 acts in a double negative (overall positive) feedback loop to inhibit RKIP transcription in breast cancer cells. BACH1 also negatively regulates its own transcription. Analysis of the RKIP-BACH1 network reveals the existence of an inverse relationship between BACH1 and RKIP involving both monostable and bistable transitions between "low BACH1, high RKIP" and "high BACH1, low RKIP" cellular states that can potentially give rise to nongenetic variability. Single cell analysis confirmed the antagonistic relationship between RKIP and BACH1, and showed cell line-dependent signatures consistent with bistable behavior. Together, our results suggest that the mutually repressive relationship between metastatic regulators such as RKIP and BACH1 can play a key role in determining metastatic progression in cancer.

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