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Research Article

# Cell Cycle-dependent Tumor Engraftment and Migration are Enabled by Aurora A

Tony L.H. Chu, Marisa Connell, Lixin Zhou, Zhengcheng He, Jennifer R Won, Seyed M Rahavi, Helen Chen, Pooja Mohan, Oksana Nemirovsky, Abbas Fotovati, Miguel Angel Pujana, Gregor SD Reid, Torsten O. Nielsen, Nelly Pante, and Christopher A. Maxwell

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## Abstract

Abstract:Cell cycle progression and the acquisition of a migratory phenotype are hallmarks of human carcinoma cells that are perceived as independent processes but may be interconnected by molecular pathways that control microtubule nucleation at centrosomes. Here, cell cycle progression dramatically impacts the engraftment kinetics of 4T1-luciferase2 breast cancer cells in immunocompetent BALB/c or immunocompromised NOD-SCID gamma (NSG) mice. Multi-parameter imaging of wound closure assays was used to track cell cycle progression, cell migration, and associated phenotypes in epithelial cells or carcinoma cells expressing a fluorescence ubiquitin cell cycle indicator. Cell migration occurred with an elevated velocity and directionality during the S/G2-phase of the cell cycle, and cells in this phase possess front-polarized centrosomes with augmented microtubule nucleation capacity. Inhibition of Aurora Kinase-A (AURKA/Aurora-A) dampens these phenotypes without altering cell cycle progression. During G2-phase, the level of phosphorylated Aurora-A at centrosomes is reduced in hyaluronan mediated motility receptor (HMMR)-silenced cells as is the nuclear transport of TPX2, an Aurora-A activating protein. TPX2 nuclear transport depends upon HMMR-T703, which releases TPX2 from a complex with importin-alpha (KPNA2) at the nuclear envelope. Finally, the abundance of phosphorylated HMMR-T703, a substrate for Aurora-A,

predicts breast cancer-specific survival and relapse-free survival in patients with estrogen receptor (ER)-negative (n= 941), triple negative (TNBC) phenotype (n= 538), or basal-like subtype (n= 293) breast cancers, but not in those patients with ER-positive breast cancer (n= 2,218). Together, these data demonstrate an Aurora-A/TPX2/HMMR molecular axis that intersects cell cycle progression and cell migration. Implications: Tumor cell engraftment, migration, and cell cycle progression share common regulation of the microtubule cytoskeleton through the Aurora-A/TPX2/HMMR axis, which has the potential to influence the survival of patients with estrogen receptor negative breast tumors.

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