ACTIVATION OF THE HIPPO TUMOR SUPPRESSOR PATHWAY LIMITS THE PROLIFERATION OF GENOMICALLY UNSTABLE TETRAPLOID CELLS

Neil J. Ganem[1], Hauke Cornils[1], Kevin P. O'Rourke[1], Kirsten Lundquist[1], and David Pellman[1]

[1]Howard Hughes Medical Institute, Department of Pediatric Oncology, Dana-Farber Cancer Institute, Children's Hospital, Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA.

Tetraploid cells, which are a common byproduct of cell division failures, are genetically unstable and have the capacity to facilitate tumorigenesis. Approximately 20% of all solid tumors exhibit a near-tetraploid karyotype, suggesting that tetraploidy plays significant roles in both the development and/or progression of human malignancies. Countering this oncogenic effect of tetraploidy is a p53-dependent tumor suppression mechanism that limits the proliferation of tetraploid cells by promoting a durable G_1 cell cycle arrest and cellular senescence. However, unlike other pathways that activate p53 and promote G_1 arrest in response to stress, such as the DNA damage response, the cellular defects and corresponding signaling mechanisms that trigger G_1 arrest in tetraploid cells are poorly understood. To address this fundamental unresolved aspect of cancer biology, we developed a novel genome-wide RNAi screening assay to identify proteins that are necessary to activate G_1 cell cycle arrest in tetraploid cells. As a complementary approach, we also performed *in vitro* evolution experiments to identify physiologically relevant adaptations made by rare tetraploid cells that enable their sustained proliferation. We demonstrate that cytoskeletal stress imparted by cytokinesis failure leads to activation of the Hippo tumor suppressor pathway in tetraploid cells both *in vitro* and *in vivo*. Hippo pathway induction in tetraploid cells is triggered by functionally reduced intracellular tension and is mediated by activation of Lats2 kinase. Notably, analysis of a broad spectrum of human cancers reveals that high-ploidy tumors frequently adapt to overcome Hippo signaling, suggesting that functional inactivation or bypass of this pathway may be a prerequisite for the development of such tumors. Understanding the adaptations acquired by tetraploid cells in order to sustain their proliferation may provide new therapeutic avenues to selectively kill abnormal high-ploidy cancer cells while sparing normal healthy diploids (*ploidy-specific lethality*).