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Effects of anticancer drugs on Chromosome Instability (CIN) and new clinical implications for tumor-suppressing therapies

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Whole-chromosomal instability (CIN), manifested as unequal chromosome distribution during cell division, is a distinguishing feature of most cancer types. CIN is generally considered to drive tumorigenesis, but a threshold level exists whereby further increases in CIN frequency in fact hinder tumor growth. While this attribute is appealing for therapeutic exploitation, drugs that increase CIN beyond this therapeutic threshold are currently limited. In our previous work, we developed a quantitative assay for measuring CIN based on the use of a non-essential human artificial chromosome (HAC) carrying a constitutively expressed EGFP transgene. Here, we used this assay to rank 62 different anticancer drugs with respect to their effects on chromosome transmission fidelity. Drugs with various mechanisms of action such as antimicrotubule activity, histone deacetylase (HDAC) inhibition, mitotic checkpoint inhibition, and targeting of DNA replication and damage responses were included in the analysis. Ranking of the drugs based on their ability to induce HAC loss revealed that paclitaxel, gemcitabine, dactylolide, LMP400, talazoparib, olaparib, peloruside A, GW843682, VX-680, and cisplatin were the top ten drugs demonstrating HAC loss at a high frequency. Therefore, identification of currently used compounds that greatly increase chromosome mis-segregation rates should expedite the development of new therapeutic strategies to target and leverage the CIN phenotype in cancer cells.

Biography:

Natalay Kouprina received her M.Sc. in physical chemistry from the St. Petersburg State University, Russia, and her Ph.D. and Dr.Sc. in cell biology from the Institute of Cytology, Russian Academy of Sciences. While in Russia, she worked on the identification of genes that control the replication and segregation of chromosomes in budding yeast. In 1991 she moved to the United States and focused her interests on human genome. Her current interest is to combine a transformation-associated recombination (TAR) cloning technology for selective isolation of a large segments from complex genomes with the human artificial chromosome (HAC) –based vectors to develop a novel system for delivery and expression of full-length mammalian genes for functional genomics that has a great potential for gene therapy. At present she is a staff scientist at the National Cancer Institute, NIH, USA. She has 101 publications in many leading international journals and 7 US patents. She is an editorial board member of several international journals. She was an Invited Guest Editor of special issues of few journals. Natalia Kouprina was a co-organizer of several international conferences.