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Research Area Changes in genome structure and sequence underlie tumorigensis. Genes that maintain genome structure are evolutionarily conserved and are often somatically mutated in cancer. Thus, mutations that cause genome instability are considered important predisposing events that contribute to the initiation and/or progression of cancer. Our general approach is to develop and apply genetic and biochemical methodologies in the model organism, Saccharomyces cerevisiae (bakers yeast), to obtain an understanding of molecular components required for chromosome transmission, with the overarching goal of relating our work in yeast to human cancer. We have established an extensive genome instability

gene catalog in yeast that provides a resource to identify cross species, candidate human genes that are somatically mutated and could cause chromosome instability (CIN) in cancer. Our functional studies of selected CIN genes in yeast have elucidated mechanistic insights into various aspects of the chromosome cycle, including sister chromatid cohesion, kinetochores, DNA replication and repair, and cell cycle checkpoints. We have also developed a strategy to identify genes in yeast synthetic lethal (SL) interaction networks as a means for identifying novel cancer drug targets. By definition, mutations that cause CIN in cancer cells produce “sub-lethal” deficiencies in an essential cellular process (chromosome maintenance) and therefore may represent genetic vulnerabilities in tumor cells that could be exploited for therapeutic benefit in the treatment of cancer. To identify candidate drug targets, we have been testing synthetic lethal interactions, predicted in yeast, using RNAi, gene knockouts, and mutants in both C. elegans and mammalian cell culture, to identify evolutionarily conserved SL gene pairs involving CIN genes somatically mutated in cancer. Our research involves a direct path from identification and mechanistic studies of CIN genes in yeast, to mining sequence data for orthologs mutated in cancer, to interrogation of the function of somatic variants and finally the identification of (1) therapeutic target genes defined by synthetic lethality and (2) small-molecule inhibitors of those targets.
