2016-17
MCB Distinguished Speaker Series

Dr. Philip Hieter

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"Chromosome instability and synthetic lethality in yeast and cancer"

Wed. Nov 16, 2016
SSC 1511 @ 10:30 am

Genes that maintain chromosome stability (CIN genes) are conserved in eukaryotes and are often somatically mutated in cancer. We have been identifying synthetic lethal partner genes, in yeast synthetic lethal (SL) interaction networks, that are highly connected with sets of CIN genes somatically mutated or overexpressed in cancer. This identifies hub proteins and processes that are candidate targets for synthetic lethal killing of cancer cells with defined CIN gene somatic alterations. For example, the protein product of FEN1 (encoding flap endonuclease) was used as a target for small-molecule inhibitor screening using a fluorescence-based assay for enzyme activity. Inhibitors of FEN1 activity in vitro were shown to selectively inhibit the proliferation of cultured cancer cells carrying inactivating mutations in CDC4, or knockdown or inhibition of MRE11A, two genes frequently mutated in a variety of cancers.

To determine the role of gene over-expression on chromosome instability (CIN), we performed genome-wide screens in the budding yeast for yeast genes that cause CIN when over-expressed, a phenotype we refer to as dosage CIN (dCIN), and identified 245 yeast dCIN genes. This catalogue of dCIN genes reveals human orthologs known to be recurrently over-expressed and/or amplified in tumors. We show that two genes, *TDP1* and *TAF12,* cause CIN when over-expressed in human cell lines. Rhabdomyosarcoma lines with elevated human Tdp1 levels also exhibit CIN that can be partially rescued by siRNA-mediated knockdown of *TDP1*.

Over-expression of dCIN genes represents a genetic vulnerability that could be leveraged for selective killing of cancer cells through targeting of an unlinked synthetic dosage lethal (SDL) partner. Using SDL screens in yeast, we identified a set of genes that when deleted, specifically kill cells with high levels of Tdp1. In some cases, we were able to recapitulate the SDL interaction in rhabdomyosarcoma lines with elevated human Tdp1 levels using small molecule inhibitors of the corresponding human synthetic lethal partner, suggesting potential therapeutic agents for tumors with elevated levels of hTdp1. The catalog of dCIN genes provides a candidate list to identify genes that cause CIN when over-expressed in cancer, which can then be leveraged through SDL to selectively target tumors.

(Philip Hieter, Supipi Duffy, Hok Khim Fam, Melanie Bailey, Derek van Pel, Cornelius Boerkoel, and Nigel O'Neil)

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*** ALL WELCOME TO ATTEND ***

*** COFFEE, TEA AND TIMBITS ***

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