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A gene signature that predicts deficiency of homologous recombination DNA repair in cancer

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Abstract

Homologous recombination (HR)-mediated DNA repair predisposes to cancer development, but also provides therapeutic opportunities: for example, poly-ADP ribose polymerase (PARP) inhibitors are synthetically lethal with HR repair deficiency in cancer cells. We identified an “HR-defect” gene signature that predicted HR repair deficiency in cells, predicted clinical outcomes of multiple human cancers, and predicted sensitivity of human cancer cells to PARP inhibitors. HR repair deficiency leads to genomic instability and often promotes accumulation of additional mutations. Our gene signature analysis further revealed that combinatorial effects of co-existing genetic changes such as loss of both BRCA1 and PTEN may extensively rewire the HR repair network and confer resistance to PARP inhibitor treatment. To combat PARP inhibitor resistance, furthermore, we successfully used our HR-defect gene signature as a drug discovery tool and found that TTK, mTOR and PI3K inhibitors could induce HR repair deficiency and sensitize cancer cells to PARP inhibitor treatment. Collectively, our findings demonstrate that gene expression profiling can be used to define the functional status of the HR repair network in cells, which has multiple clinical implications.

Biography

Professor Shiaw-Yih Lin has studied DNA damage response in cancer for 10+ years, during which time he has authored more than 40 peer-reviewed reports. He has served on the editorial boards for the *World Journal of Clinical Oncology*, *American Journal of Cancer Research*, *Frontiers in Molecular and Cellular Oncology*, *World Journal of Translational Medicine*, and *Experimental Hematology & Oncology*. Dr. Lin is a member of the International Scientific Advisory Board for International Institute of Anticancer Research, and he has served on numerous review committees for the NIH, DOD and Susan G. Komen for the Cure.