

Synthetic lethal targeting of RAD54B-deficient colorectal cancer cells

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Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. Novel insight into the aberrant biology that contributes to the pathogenic origins of the disease is in dire need so that new therapeutic approaches can be developed that exploit these origins. Synthetic lethality refers to the lethal combination of two independently viable mutations and has been extensively studied in model organisms. Recently, synthetic lethality has been applied in cancer contexts and has begun to show tremendous potential as it exploits somatic mutations that drive *tumorigenesis*. RAD54B is an excellent candidate for therapeutic targeting as it is mutated in numerous tumor types, including CRC. RAD54B is an evolutionarily conserved protein that functions in DNA repair and is essential for chromosome stability. RAD54B deficiencies cause chromosome instability, which we believe can be exploited via a synthetic lethal approach. Utilizing a cross-species candidate gene approach, 80 candidate synthetic lethal interactors of RAD54B were subjected to an RNAi-based high-content screen. Subsequent direct tests validated a synthetic lethal interaction between RAD54B and superoxide dismutase 1 (SOD1) in both CRC cells and immortalized fibroblasts. Chemical inhibitors and real-time cell analyses confirmed the selective targeting of RAD54B-deficient cells and determined the decrease in cell numbers is due to cellular cytotoxicity associated with increases in DNA damage. Thus, we have identified a novel candidate therapeutic target for the treatment of RAD54B-deficient CRCs that requires further pre-clinical study. Furthermore, these data have far reaching implications as RAD54B defects have been identified in numerous tumor types including, prostate, ovarian, bladder and breast.

Biography

Kirk J. McManus received his PhD in 2004 from the University of Alberta, Canada and performed his postdoctoral studies in the Michael Smith Laboratories at the University of British Columbia, Canada. He is currently an Assistant Professor at the University of Manitoba and a Senior Scientist within the Manitoba Institute of Cell Biology. He has published more than 20 papers and has served on various national grant review panels.

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