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Selective killing of RAD54B-deficient colorectal cancer cells through SOD1 inhibition

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Abstract

Colorectal cancer (CRC) affects both males and females, and is the second leading cause of cancer-related deaths in North America. Novel insight into the disease is highly warranted so that new therapeutic approaches can be developed. Synthetic lethality refers to the lethal combination of 2 independently viable mutations and has been extensively studied in model organisms such as yeast. Recently, synthetic lethality has been applied in cancer contexts and is beginning to show potential as a new therapeutic modality. *RAD54B* is an excellent candidate for therapeutic targeting as it is mutated in CRC and numerous other tumor types. 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 targeted through a synthetic lethal approach. Utilizing cross-species approaches, 80 candidate synthetic lethal interactors of *RAD54B* were subjected to an RNAi-based high-content screen in human cells. Subsequent direct tests validated an interaction between *RAD54B* and superoxide dismutase 1 (*SOD1*) in both CRC cells and immortalized fibroblasts. Real-time cell analyses showed that chemical inhibitors are able to selectively kill *RAD54B*-deficient cells and demonstrated the decreases in cell numbers observed is due to cellular cytotoxicity rather than cell cycle arrest. Thus, we have identified and validated SOD1 as a novel candidate therapeutic target for the treatment of *RAD54B*-deficient CRCs cells. These data have far reaching implications as *RAD54B* defects have been identified in numerous tumor types including, prostate, ovarian, bladder and breast.

Biography

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.