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Targeting cellular survival responses to replication stress in cancer

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The key to successful targeted therapy for cancer is to identify intrinsic features that distinguish cancer cells from normal cells. Replication stress is a characteristic feature of cancer cells. Atearly phases of the tumorigenesis process,excessive growth signals resulting from activation of oncogenes or loss of tumor suppressors lead to intensive replication stress, which is a characterized feature that distinguishes premalignant and malignant cells from normal cells. It remains unclear how these cells cope with increased replication-associated DNA lesions caused by replication stress and maintain a high rate of DNA replication to allow for aggressive and malignant growth. To develop effective targeted therapeutic strategies, our long-term goal is to identify and target the essential mechanism by which premalignant and malignant cells adapt and survive under conditions of replication stress.

To achieve this goal, in our current studies, we took two approaches to systematically identify genetic and chemical regulators of homologous recombination (HR)-mediated DNA repair, which plays a fundamental role to repair double-strand DNA breaks, the predominant replication stress-induced DNA lesions. First, we utilized a proteomic analysis to identify protein components that preferentially associated with replication forks in the presence of oncogene-induced replication stress. We have reported that human nuclease/helicase DNA2 is recruited to replication lesions in response to replication stress, enhances HR repair of replication-associated DSBs, and there by counteracts replication stress to promote tumorigenesis. Moreover, our study has revealed important clinical relevance of DNA2 in cancer. Our study implicates DNA2 as a potential preventive and therapeutic target to develop small molecule inhibitors. Second, we took a chemical screening approach to identify inhibitors of HR repair with selectivity against cells with oncogene-induced replication stress. Together, it is our hope to identify effective prevention strategies that selectively kill premaliganant/malignant cells by small molecules targeting cellular survival responses to replication stress.

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