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EDITORIALS

Repressing DNA Repair to Enhance Chemotherapy: Targeting MyD88 in Colon Cancer

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The more a cell divides, the more unstable its DNA is and the more DNA damage it sustains during replication. Thus, cells often require DNA repair to simply progress through a DNA replication cycle. Cancer cells are especially sensitive to this requirement for DNA repair because they replicate their DNA without most of the controls normal cells have. Thus, cancer cells subvert DNA repair pathways to maintain replication, and prevent apoptosis from mitotic catastrophe [reviewed in (1)]. This enhancement of DNA repair is further selected for by cancer therapy and commonly leads to resistance. The paradox of this is that many cancers have defects in DNA repair that lead to their original genomic instability and transformation to malignancy in the first place.

Cancer cells resolve this paradox by becoming increasingly reliant on, indeed addicted to, alternative DNA repair pathways for replication (1). Targeting these alternative DNA repair pathways can lead to not only decreases in proliferation but also increases in de novo DNA lesions during replication and ultimately apoptosis. Such targeting of DNA repair is one form of synthetic lethality, which is one of the most promising drug development concepts in the last decade (1). Synthetic lethality is especially intriguing in malignancies that are less responsive to classic cytotoxic chemotherapy, such as colon cancer.

In this issue of the Journal, Kfoury and colleagues demonstrated that MyD88 is a novel target for synthetic lethality in colon cancer (2). They found that repressing MyD88 induced de novo DNA damage from replication alone without exposure to any external agent and this increased damage produced more apoptosis (2). The hypothesis behind this work is intriguing: Many studies have shown that individuals with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, have an increased risk of colon cancer (3,4). This gut mucosal inflammatory response is mediated by signaling cascades initiated from Toll-like receptors (TLRs) and the interleukin 1 receptor (IL-1R). Persistence of this inflammatory signaling cascade in the colonic mucosal cell may be the key to the development of cancer in inflammatory bowel disease patients (5). However, the mechanism by which persistent inflammasome signaling results in neoplastic transformation has not been well described (5).

Previously Renno, Kfoury, and colleagues in this group found that MyD88 acts as a bridge between the inflammatory signaling pathways from the TLR/IL-1R and the Ras oncogenic signaling pathway (6). Activation of TLR/IL-1R led to activation of Ras, and its effector ERK, by MyD88. MyD88 is known to be required for Ras-dependent signaling and transformation (6). Other studies found that expression of MyD88 is increased in several types of malignancies (7,8). Kfoury et al. report here that inhibiting MyD88 expression reduced colon cancer cell line and murine xenograft colon cancer proliferation, increased apoptosis, and increased sensitivity to the DNA cross-linker cisplatin (2). These studies demonstrate that MyD88 inhibition produces synthetic lethality in colon cancer cells, which often rely on Ras for proliferative signals (2,6).

Kfoury et al. performed their experiments in colon cancer cell lines with activating Ras mutations. In these colon cancer cell lines, a decrease in MyD88 protein produced an increase in the expression of both p53 and its target p21, indicating that the p53 pathway was activated in response to MyD88 reduction. When these experiments were repeated in cells deficient in p53, no apoptosis was observed upon MyD88 silencing, demonstrating that functional p53 was required for initiation of apoptosis.

How is the increase in de novo DNA damage, and therefore apoptosis, being mediated? The Ras pathway promotes increased transcription of ERCC1, an essential component of the nucleotide excision repair machinery (9,10). Consistent with MyD88 enhancing Ras activation, Kfoury and colleagues found that indeed repressing MyD88 reduced ERCC1 expression, which resulted in increased DNA damage from replication. Adding back a vector that forced expression of ERCC1 reduced the de novo replicative DNA damage back down to normal levels.

Although interesting, these in vitro observations needed to be confirmed by in vivo studies to have any clinical relevance. For this, Kfoury et al. engineered colon cancer cell lines to have doxycycline-inducible repression of MyD88 and implanted these cells subcutaneously in nude mice. In this xenograft system, the MyD88-deficient tumors were 5 times smaller than the control MyD88-expressing tumors and had increased de novo apoptosis.

Importantly, the MyD88-deficient tumors were also more sensitive to cisplatin, probably because of the decrease in Ras-mediated expression of ERCC1. ERCC1 is an essential component of the nucleotide excision DNA repair machinery, a system that assists in removing cisplatin DNA adducts (11). There are reports that low expression of ERCC1 is a good prognostic indicator, implying that it might be a therapeutic target (12,13). Kfoury et al. provided further evidence that this effect of MyD88 on cisplatin sensitivity is mediated by ERCC1 by showing that MyD88 silencing did not increase the sensitivity of the cells to etoposide (a topoisomerase II inhibitor) or paclitaxel (a tubulin-disrupting agent). Resistance to these agents does not require ERCC1 or the NER pathway (14,15). One would assume that MyD88 would have the same effect on oxaliplatin, a drug more commonly used for colon cancer than cisplatin, and that repressing MyD88 would also increase sensitivity to oxaliplatin.

These findings are biologically significant on two levels. First, they provide insight into how chronic inflammatory signaling might generate colonic neoplastic transformation. These studies link inflammasome signaling to Ras activation, a known driver of colonic oncogenesis, by MyD88. Because Ras has proven difficult to target, perhaps disrupting an upstream step above Ras, such as MyD88, might prove more effective. Perhaps MyD88 inhibition might decrease transformation rates in colonic mucosa harboring constant TLR/IL-1R activation.

Second, this work defines MyD88/Ras signaling as a mediator of resistance to DNA cross-linking chemotherapy by enhanced expression of ERCC1. Targeting MyD88 as opposed to ERCC1 during colon cancer therapy is especially attractive because it might also slow proliferative rates by reducing Ras activation upstream of ERCC1. Thus, this work defines MyD88 as a novel and clinically significant synthetic lethal target in colon cancer.

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Protecting Human Research Participants: Reading vs Understanding the Consent Form

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In 1998, in this Journal, Davis and colleagues (1) published their findings on a comparative study of a standard vs a simplified consent form (CF) in 53 patients with cancer and 130 individuals who were apparently healthy. Interviews conducted with the participants after reading a standard Southwestern Oncology Group CF and a shortened version of the same CF in varying sequence indicated an overwhelming preference for the simplified form (1). The standard form was 7 pages, contained 3438 words with sentences that averaged 21 words, and was without graphics. Application of Flesch–Kincaid methodology indicated a 12th grade reading level. By contrast, the shortened version was prepared as a 7-page booklet that contained 524 words with an average sentence length of 12.5 words, culturally sensitive instructional graphics, and colored headers. Readability was determined at a 5th grade level. CF preference was independent of race but varied by reading and educational level. Surprisingly, participant responses to 10 comprehension questions, which included key elements of study design, drug allocation, and risk, showed that their understanding of the basic information was very low, irrespective of form preference. The authors, supported by editorial comment by Taylor et al. (2) in the same issue of the Journal, concluded that there are serious questions regarding the adequacy of the design of written informed consent documents for