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Targeting DNA mismatch repair deficiency as a therapeutic target in cancer

Sarah A. Martin
Queen Mary University of London, UK

The potential of developing a therapy based on targeting the underlying genetic defects, is that it may cause highly selective killing of tumor cells while sparing normal cells, resulting in both increased efficacy and reduced toxicity. The identification of synthetic lethal interactions represents an attractive approach for targeting these deficiencies. Two genes are said to be synthetically lethal if a mutation in either gene alone is compatible with viability but mutation of both causes cell death. This approach has been successfully exploited in the clinic using PARP inhibitors in the treatment of patients with germ line mutations in BRCA1/2. When the genes that mediate the DNA mismatch repair (MMR) pathway, such as MLH1, MSH2 and MSH6 are mutated or epigenetically silenced, the predisposition to cancer is vastly increased. Previously, we have shown that silencing of specific DNA polymerases are synthetically lethal with MMR deficiency via an accumulation of oxidative DNA damage. It has been previously shown that mutations in the MMR gene MSH6 can arise in glioblastomas during temozolomide (TMZ) treatment and can mediate resistance to the drug. Recently, we have identified the thiazole antibiotic, Thiostrepton as synthetically lethal with MSH6 deficiency in our TMZ resistant glioblastoma cells. Our data suggests that this re-sensitization of the TMZ resistant cells is due to a novel regulation of FOXM1, a target of thiostrepton, by MSH6. These synthetic lethal approaches highlight how an understanding of DNA repair processes can be used in the development of novel cancer treatments.

Biography

Sarah Martin completed her Ph.D. in 2003 from the National University of Ireland, Galway and completed postdoctoral studies from Mount Sinai School of Medicine, New York and the Institute of Cancer Research in London. She joined Barts Cancer Institute as a principal investigator in 2010, where she is investigating nuclear and mitochondrial DNA repair as a therapeutic strategy. She has published numerous papers in the area of synthetic lethal targeting and DNA repair deficiency and contributed to many review articles in this area.

sarah.martin@qmul.ac.uk