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A novel approach for overcoming drug resistance in gastrointestinal cancers

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Background: The combined annual mortality from pancreatic cancer (PC) and colon cancer (CC) is estimated to 88,170 deaths which surpasses the toll from breast and prostate cancer combined (72,280 deaths), and it represents the second leading cause of death after lung cancer (157,300 deaths), with no cure in sight, which is in part due to both intrinsic (de novo) and extrinsic (acquired) resistance to conventional therapeutics. This disappointing outcome is in part due to our inability to kill cancer cells that have undergone the Epithelial-to-Mesenchymal Transition (EMT) reminiscent of cancer stem/stem-like cells (CSCs) which are resistant to conventional therapeutics. The aggressiveness of PC, and recurrence of CC (affects nearly 50% of patients treated by conventional therapeutics), is in part due to the re-emergence of chemotherapy-resistant CSCs. If these cells are the "root" of treatment failure, then elucidation of their intracellular signaling processes and discovering ways to target those events would be of immense importance for overcoming drug resistance especially by killing those resistant cells.

Methods: Our working hypothesis was that treatment failure in PC and CC is primarily due to therapeutic resistance contributed by the presence or enrichment of EMT-phenotype cells or CSCs, which must be eliminated to eradicate tumor and prevent tumor recurrence. We tested our hypothesis in preclinical (in vitro and in vivo) studies using both PC and CC cells by investigating whether our newly developed small molecule CDF, derived from a natural agentcurcumin, could be useful in killing drug resistant cells. We also investigated whether specific microRNAs (miRNAs) may in part be responsible for the killing of drug resistant cells by CDF alone or in combination with conventional therapeutics.

Results: We found that CDF could up-regulate the expression of miR-200 (low expression is the "hallmark" of CSCs and drug resistance) and reduced the expression of miR-21 (high expression is the "hallmark" of CSCs and drug resistance associated with tumor aggressiveness) in gemcitabine-resistant PC cells. Down regulation of miR-21 by CDF resulted in the induction of PTEN, an endogenous negative regulator Akt signaling. We also found decreased expression of EZH2 and increased expression of a panel of tumor-suppressive miRNAs (let-7a, b, c, d, miR-26a, miR-101, miR-146a, and miR-200b, c that are typically lost in PC) by CDF. Mechanistic investigation showed that the re-expression of miR-101 by CDF led to decreased expression of EZH2 and the killing of CSCs. We also found that CDF in combination with 5-fluorouracil and oxaliplatin (5-FU + Ox) were able to kill the CSCs derived from CC cells. Moreover, we found that the expression of miR-34a and miR-34c was down-regulated in CC specimens compared to normal colonic mucosa and the loss of expression was consistent with data from CC cell lines.

Conclusions: Our results suggest that deregulation of miRNAs and their targets by CDF is mechanistically associated with overcoming drug resistance in both PC and CC. Moreover, CDF could become a novel demethylating agent for restoring the expression of miR-34 family and potentially other miRNAs, and thus CDF could become a newer therapeutic agent for the treatment of both PC and CC, which could be largely due to the killing of CSCs, resulting in overcoming drug resistance and tumor recurrence.

Biography

Fazlul D Sarkar has completed his PhD from Banaras Hindu University and continued Post-doctoral studies at Memorial Sloan-Kettering Cancer Institute in New York. He has published 555 peer-reviewed research articles and review articles, and also published 50 book chapters. He edited four books and he is an Academic Editor for PLoS One, and also serves on the editorial board of 10 cancer journals. His basic science research led to drug discovery and he is an expert in conducting translational research including clinical trials.

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