Human RAD51, genomic instability and Barrett’s adenocarcinoma

Masood A. Shammas
Harvard (Dana Farber) Cancer Institute, USA

A prominent feature of Barrett’s adenocarcinoma (BAC) is significant genomic instability leading to genetic changes which ultimately result in acquisition of drug resistance and progression of disease. We have evaluated the role of recombinase (hsRAD51) and homologous recombination (HR), key components of repair and genome maintenance, in genomic instability in BAC. We also show that RAD51 and HR activity are elevated in BAC cells and a moderate (≤50%) suppression of RAD51 in BAC cells leads to a significant reduction in genomic evolution (P<0.02), without affecting growth in vitro. The mutational frequency of chromosomes correlated strongly with their Alu frequency, indicating that these repetitive sequences may serve as substrates for elevated HR and may be targeted to prevent genomic instability. We also show that unlike moderate suppression, strong or complete suppression of RAD51, activates ATM-chk2 mediated DNA damage response and reduces proliferation rate of BAC cells in vitro. Wortmannin, a PI3K inhibitor, impairs ATR-chk1 damage response pathway in these cells. Simultaneous suppression of PI3K and RAD51 targets chk1 and chk2 checkpoints, increases telomere attrition, and inhibits the growth of BAC cells in culture or as tumors in mice. Our data therefore show that elevated RAD51 contributes to both the genomic instability and survival of BAC cells.

Biography

Dr. Masood Shammas is a Scientist at Harvard (Dana Farber) Cancer Institute, Boston. He completed his doctorate in Biochemistry and Molecular Biology at University of Arkansas for Medical Sciences (UAMS) and postdoctoral trainings at Arkansas Cancer Research Center and UAMS. From 2001-2006, he worked as Instructor at Harvard Medical School and DFCI. In 2006 he accepted a position as Director, Surgical Oncology And Developmental Therapeutics at Wayne State University, Detroit, USA. In 2009, he moved back to Harvard. He has published ~42 peer reviewed research papers, 2 book chapters, and serves as reviewer for several scientific journals.