OMICS Group Conferences
Accelerating Scientific Discovery

2nd World Congress on
Cancer Science & Therapy

September 10-12, 2012 Hilton San Antonio Airport, USA

Polyploid cells rewire DNA damage response networks to overcome replication stress-induced barriers for tumor progression

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Mutations in genes involved in DNA replication, such as flap endonuclease 1 (FEN1), can cause single-stranded DNA breaks (SSBs) and subsequent collapse of DNA replication forks leading to DNA replication stresses. Persistent replication stresses normally induce p53-mediated senescence or apoptosis to prevent tumor progression. It is unclear how some mutant cells can overcome persistent replication stresses and bypass the p53-mediated pathways to develop malignancy. Here we show that polyploidy, which is often observed in human cancers, leads to overexpression of BRCA1, p19arf and other DNA repair genes in FEN1 mutant cells. This overexpression triggers SSB repair and non-homologous end-joining pathways to increase DNA repair activity, but at the cost of frequent chromosomal translocations. Meanwhile, DNA methylation silences p53 target genes to bypass the p53-mediated senescence and apoptosis. These molecular changes rewire DNA damage response and repair gene networks in polyploid tumour cells, enabling them to escape replication stress-induced senescence barriers.

Biography

Dr. Shen is a professor/chair of the Department of Radiation Cancer Biology and co-leader of Molecular Oncology Program of the NCI-designated Comprehensive Cancer Center at City of Hope. He has published nearby 100 papers on DNA replication/repair nucleases in reputed journals including Zheng et al., 2007 Nature Medicine; Guo et al., 2010, Nature Chemical Biology; Zheng et al., 2012, Nature Communications in relevance to the topic of his lecture.

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