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The effect of Fhit loss on genome instability and cancer development

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Abstract

Fhit gene is frequently lost or reduced in expression in various human cancers. Fhit loss initiates DNA double-strand breaks (DSBs) and subsequent genome instability. Down-regulation of thymidine kinase 1 (TK1), due to loss of Fhit, causes dNTP imbalance, resulting in spontaneous replication stress that leads to chromosomal aberrations, allele copy number variations, small insertions/deletions and single-base substitutions (SBSs). Therefore, to confirm the role of the Fhit-TK1 pathway in promoting genome stability, we asked if Fhit-deficient cells exhibit decreased levels of DNA damage upon addition of a continuous supply of thymidine, the substrate for TK1, despite the low TK1 protein expression of Fhit−/− cells. We first assessed spontaneous levels of DNA damage by quantifying nuclear γH2AX foci, marker of DSBs, by indirect immunofluorescence in early passage Fhit+/+ and −/− kidney cell lines. The Fhit−/− cells exhibited ~2-fold increases in γH2AX positive foci *vs* Fhit+/+ cells. Levels of DNA damage prior to thymidine supplementation were also measured in these cells by neutral comet assay. We observed a significant elevated levels of DNA damage in Fhit−/− *vs*+/+ cells. Low level concentration (10 μM) thymidine supplementation suppressed DSB formation and accumulation of DNA damage in Fhit−/− cells. We also demonstrated that Fhit regulates dTTP levels and suggested that this occurs through scavenger decapping of TK1 mRNA. These results revealed that TK1 down-regulation by Fhit loss is a transient step initiating genome instability in preneoplastic lesions. The cause of Fhit-deficient DSBs: thymidine deficiency-induced replication stress, can be resolved with thymidine supplementation.

Keywords: Fhit, Genome Instability, Replication Stress, Thymidine Deficiency, Thymidine Kinase 1

Biography:

Bahadir Batar is an assistant professor at Tekirdag Namik Kemal University Medical School in Turkey. He received his Ph.D. from Cerrahpasa Medical School of Istanbul University in 2013, Turkey. He has worked as a postdoctoral fellow at The Ohio State University Comprehensive Cancer Center during the 2014-2016. His primary research interest is in the area of molecular biology and genetics of cancers. Dr. Batar has been working on projects to understand the role of loss of the FHIT and WWOX fragile genes in initiation and progression of several cancers and therapeutic resistance.

Speaker Publications:

1. "DNA repair and apoptosis: Roles in radiotherapy-related acute reactions in breast cancer patients."; Cell Mol Biol (Noisy-le-grand)/ 2018/ 64(4):64-70
2. "Decreased DNA repair gene XRCC1 expression is associated with radiotherapy-induced acute side effects in breast cancer patients"; j.gene / 2016/ 582(1):33-7

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