OMICS Group Conferences
Accelerating Scientific Discovery

2nd World Congress on
Cancer Science & Therapy

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

Exposure to heavy ion space radiation enhances risk of colorectal cancer in $Apc^{min/+}$ mouse model

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Risk of colorectal cancer (CRC) increases after exposure to ionizing radiation (IR). However, CRC risk prediction following heavy ion space radiation exposure is hindered due to scarcity of *in vivo* mechanistic understanding. Therefore, intestinal tumorigenesis and mechanisms of tumorigenesis were studied after 1.6 Gy of ^{56}Fe radiation (energy: 1000 MeV/nucleon) exposure in $APC^{Min/+}$ and wild type C57BL/6J mice (n=20; 6 to 8 wks old; female) and results were compared to equitoxic 2 Gy γ radiation. For tumorigenesis study, $APC^{Min/+}$ mice were humanely sacrificed between 100 and 110 days after radiation exposure, intestine surgically removed, lumen washed and cut open along the length, tumors counted, and tissues preserved for molecular analysis. Because chronic oxidative stress is implicated in carcinogenesis, we also assessed reactive oxygen species, mitochondrial status, and antioxidant activity in wild type mouse intestine 1-year after radiation exposure. In $APC^{Min/+}$ mice, relative to controls and γ-rays, intestinal tumor frequency was higher after ^{56}Fe. Staining for phospho-histone H3 indicating proliferation was more and alcian blue staining indicating differentiation was less in ^{56}Fe than γ tumors. Activation of β-catenin was more in ^{56}Fe-irradiated normal and tumor tissues. When considered with higher levels of cyclin-D1, we concluded that relative to γ radiation high-energy 56Fe irradiation led to higher intestinal tumorigenesis, tumor proliferative index, and reduced tumor cell differentiation due to preferentially greater activation of β-catenin and its downstream effectors. In wild type mice, long-term functional dysregulation of mitochondria and increased NADPH oxidase activity are major contributing factors towards heavy ion radiation-induced persistent oxidative stress in IEC with potential for neoplastic transformation.

Biography

Dr. Kamal Datta has completed his M.D. in Biochemistry at the All India Institute of Medical Sciences (AIIMS), New Delhi and did postdoctoral studies from the National Institutes of Health. He is the Assistant Professor of Biochemistry at the Georgetown University Medical Cancer. He has published more than 25 papers in reputed peer-reviewed journals including PNAS, Blood, Cancer Research, International Journal of Cancer and Cancer Gene Therapy and serving as an editorial board member of the Journal of Carcinogenesis and Mutagenesis.

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