High LET radiation produces sustained DNA damage signaling and changes cellular homeostasis in hippocampal neuronal cells

Ramesh Kandimalla, Xiaobing Tang, Tiedong Wang and Huichen Wang*

Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA 30322

High linear energy transfer (LET) radiation induces clustered DNA damage and delayed oxidative stress which prolongs their response signaling to the progeny of irradiated cells, leading to alteration of homeostasis, including cell death program (apoptosis, autophagy and senescence) and cell growth. Here we investigated the molecular and cellular mechanism of persistent DNA damage response, cell survival and cell death of hippocampal neuronal cells following exposure to heavy ion particles and proton. We found that DNA damage response signaling persists longer in hippocampal neuronal cells exposed to high LET radiation (^{56}Fe (1Gev/n)) than to low LET radiation (proton (1Gev/n)). High LET radiation induced higher phosphorylation of Tip60, expression of p53, p21 and PUMA than low LET radiation. GSK3 inhibitors reduced Tip60 phosphoryaltion, p53 and PUMA expression. Inhibition of GSK3 activity reduced the cell killing of hippocampal neuronal cells following exposure to high LET radiation. High LET radiation induced more apoptosis, senescence and autophagy than low LET radiation. This suggests that high LET radiation may sustain DNA damage signaling and change cellular homeostasis of energy and growth, implying the risk to the central nervous system (CNS).

This work is supported by NASA space radiation program NNX08BA08G.

Key words: CNS, high LET radiation, DNA damage.