Technical Report

The c-Abl signaling network in the radioadaptive response

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Zhi-Min Yuan, UTHSCSA

Introduction

Assessment of the health risk of low-level radiation exposure has been hampered by the lack of means for the direct measurement of low-dose IR exposure, resulting in great uncertainties about its health risk. Currently, a linear no-threshold (LNT) dose model is used to predict low-dose IR-induced biological effects, which assumes that the underlying biological processes induced by low-dose IR are essentially the same as those triggered by higher-dose IR, and thus extrapolates the effects from high-dose to low-dose radiation. Based on this model, any amount of radiation could cause harm no matter how small the dose. Studies have shown however, the existence of adaptive dose-response relationships with low doses being protective and high doses causing detrimental effects, contradicting the LNT model. This adaptive response is in fact part of a general cellular response to stress that is evolutionally conserved. Hence, many have argued that the use of the LNT model has led to unfounded levels of public fear regarding low levels of radiation exposure, and misunderstandings about the safety of diagnostic imaging for medical use. However, the controversy remains unresolved due to a lack of understanding of the molecular mechanisms underlying the adaptive stress response and there is insufficient scientific evidence to warrant a change from the LNT model.

Research Summary

The radioadaptive response, or radiation hormesis, i.e. a low dose of radiation can protect cells and organisms from the effects of a subsequent higher dose, is a widely recognized phenomenon. Mechanisms underlying such radiation hormesis, however, remain largely unclear. Preliminary studies indicate an important role of c-Abl signaling in mediating the radioadaptive response. We propose to investigate how c-Abl regulates the crosstalk between p53 and NFκB in response to low doses irradiation. We found in our recent study that low dose IR induces a reciprocal p53 suppression and NFκB activation, which induces HIF-a and subsequently a metabolic reprogramming resulting in a transition from oxidative phosphorylation to glycolysis. Of importance is that this glycolytic switch is essential for the radioadaptive response. This low-dose radiation-induced HIF1α activation was in sharp contrast with the high-dose IR-induced p53 activation and HIF1α inhibition. HIF1α and p53 seem to play distinct roles in mediating the radiation dose-dependent metabolic response. The induction of HIF1α-mediated glycolysis is restricted to a low dose range of radiation, which may have important implications in assessing the level of radiation exposure and its potential health risk. Our results support a dose-dependent metabolic response to IR. When IR doses are below the threshold of causing detectable DNA damage (<0.2Gy) and thus little p53 activation, HIF1α is induced resulting in induction of glycolysis and increased radiation resistance. When the radiation dose reaches levels eliciting DNA damage, p53 is activated and diminishes the activity of HIF1α and glycolysis, leading to the induction of cell death. Our work challenges the LNT model of radiation exposure risk and provides a metabolic mechanism of radioadaptive response. The study supports a need for determining the p53

and HIF1α activity as a potential reliable biological readout of radiation exposure in humans. The exquisite sensitivity of cellular metabolism to low doses of radiation could also serve as a valuable biomarker for estimating the health effects of low-level radiation exposure.

Publications

Rajuli Lall[1,5], Suthakar Ganapathy[2,5], Mei Yang[2], Shaowen Xiao[1,6], Teng Xu[1], Hang Su[1], Miriam Shadfan[1], John M. Asara[3,4], Chul S. Ha[1], Issam Ben-Sahra[2], Brendan D. Manning[2], John B. Little[2] and Zhi-Min Yuan[2*] Low-dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response. 2014, Cell Death & Differentiation. In press.