A functional interaction of the c-Abl and heat shock response pathways in radio-adaptive response

Hang Su & Zhi-Min Yuan. Department of Radiation Oncology, UTHSCSA

The radio-adaptive response, i.e. a low dose of radiation can protect cells and organisms from the effects of a subsequent higher dose, is a phenomenon that has been widely recognized. However, mechanisms underlying such radiation hormesis remain largely unclear. Our preliminary studies have uncovered a crucial role for the c-Abl tyrosine kinase as evidenced by that c-Abl-deficient cells exhibited a compromised radio-adaptive response. To test the hypothesis that c-Abl mediates the radio-adaptive response by coordinating multiple cellular processes/pathways, we recently employed a proteomic approach to analyze the global tyrosine phosphorylation events in cells triggered by the activation of c-Abl. We identified 207 phosphotyrosine sites within 133 putative substrates, among which there are a number of heat shock proteins. While heat shock proteins have been implicated in radio-adaptive response, the underlying biology remains largely unknown. We made an attempt to address this by establishing a number of cell models that express, under the ER inducible promoter, either constitutive or dominant negative mutant of heat shock transcription factor (HSF-1). We assessed radio-adaptive response under the condition the HSF activity was altered; either suppression or stimulation based on the basal level of HSF activity in different cell lines tested. Our preliminary data indicate an important role for the heat shock response pathway in radio-adaptive response, though with different extents when different cell types were tested. We also examined the potential interaction between the c-Abl and heat shock response pathways. Of interest is the observation that expression of the dominant negative HSF1 mutant resulted in inhibition of c-Abl-mediated radio-adaptive response, implicating a functional interaction between these two pathways in regulation of radio-adaptive response. To gain insight into the role of HSF-1, we measured the miRNA expression profile to explore a potential contribution of HSF-1 regulated miRNA in radio-adaptive response. The differentially expressed miRNAs will be assessed for their role in radio-adaptive response. The identified miRNAs' biological roles and regulation will be fully characterized. When successfully completed, our study is expected to shed new light on the mechanisms for radio-adaptive response. (This work is supported by DOE 110976).