

Radiation induced Apoptosis in the Developing Brain

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The developing brain is very sensitive to ionizing radiation. The detrimental effect of radiation has typically been attributed to its ability to cause DNA damage. Fortunately cells possess complex and efficient DNA repair mechanisms capable of repairing most genomic damage. However, occasionally, damaged DNA is mis-repaired or incompletely repaired. This can result in the triggering of apoptotic cell response. In the developing nervous system, apoptosis results in naturally occurring cell death, a process that eliminates neurons that have made faulty synapses or have not reached appropriate targets. Apoptosis is also a response to many stimuli like ionizing radiation and factors into many neurodegenerative diseases. The aim of this work is to understand the effect of low dose ionizing radiation on brain development and to estimate the radiation induced apoptotic response. Apoptosis requires the expression of several specific genes among which the Trp53 gene. The analysis of those expressed genes by quantitative PCR and by DNA microchips array will help in unraveling the molecular aspect of the radiation induced apoptosis. We performed qPCR and cDNA microarray analysis at embryonic day E 13 after in utero exposure to 50cGy x-radiation of both wild-type and p53 knock-out mice in irradiated and non-irradiated conditions. Only genes with identified function and a minimal 2 fold amplification were further considered. Our results indicate that genes activated in p53 +/+ and in p53-/- mice appear quite different. It revealed that the main activated pathways in irradiated wild type embryos are involved in the regulation of a p53 mediated pathway that may lead to cell cycle arrest and increased level of apoptosis. To define whether the transcriptional radiation response was solely p53 mediated, we analyzed the expression of cell cycle regulating genes in a Trp53 null mutant. The modulated expression of cell cycle regulating genes such as cyclins and Cdk genes indicated the induction of a cell cycle arrest, without evidence for the onset of apoptosis. Additional gene expression studies have shown that various E2F transcription factors may be involved in this event. Together these results provide a detailed view of the different p53-related mechanisms that are triggered in response to ionizing radiation in the developing brain.