G-1

Differences of SRE (Serum Responsive Element) Activity and Gene Expression between AT5BIVA and LM217 Cells

Eun Kyung Choi*, You-Jin Kim[1], Yun-Hee Rhee[1], Hyesook Chang and Kun-Koo Park[1]
College of Medicine, Ulsan University and [1]Asan Institute for Life Sciences

The human genetic disorder ataxia-telangiectasia (A-T) is a multisystem disease characterized by extreme radiosensitivity. The recent identification of the gene mutated in A-T, ATM, and the demonstration that it encodes a homologous of phosphatidylinositol 3-kinase (PI3-K), the catalytic subunit of an enzyme involved in transmitting signals from the cell surface to the nucleus, provides support for a role for this gene in signal transduction. Potential downstream effectors of ATM may be the Rel/NFkB, AP-1, CREB or Elk1 family of transcription factors. Although the ionizing radiation was known to induce c-fos transcription, nothing is known about how ATM mediated signal transduction pathway modulates the c-fos gene transcription and gene expression. Here we have studied whether the c-fos transcription is differentially regulated in normal human fibroblast cells (LM217) and in ATM mutated cells (AT5BIVA) and cloned differentially expressed genes between both cell lines. We found that c-fos transcription as well as c-Fos protein expression was severely impaired in cells from individuals with ataxia-telangiectasia. SRE (Serum Responsive Element), p62TCF/elk-1 (ternary complex factor) were significantly reduced in AT5BIVA cells in comparing with normal fibroblast cells. Futhermore, SRE activity was strongly induced by treatment of serum in normal cells, but not in AT cells. Consistent with this, constitutively activated MEKK-induced SRE activity was reduced in AT cells suggesting impaired function of MAPK (mitogene activated protein kinase). We also found reduced TRE CAT, NFkB luciferase reporter gene activity as well as reduced TRE, NFkB or CRE binding activity in AT5BIVA cells. Furthermore we cloned differentially expressed genes between AT and LM cells. The data provide evidence for novel transcriptional differences between LM217 and AT5BIVA cells and the cloned gene may contribute to biological phenotypes such as radiation-induced apoptosis of AT cells.