144 Molecular analysis of human p53 gene promoter element and its nuclear binding proteins.

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By the dissection of 2.4kb of human p53 promoter, we have identified the 21bp of novel sequence (PE21), located about 50 bases upstream to the putative transcription start site, was responsible for human p53 gene basal and UV-inducible transcriptions. PE21 by itself directed transcriptional start when it was inserted adjacent upstream to the luciferase gene. Deletions of three parts of the sequence from the promoter completely abrogated the gene expression as well as UV-induction. Neighboring NFkB binding site did not contribute to both the basal and UV-inducible transcription in normal human fibroblasts. We also detected PE21 binding nuclear protein(s) by gel shift and southwestern analyses. Since the PE21 sequence does not show any homology to conventional promoter core, our results suggest that p53 gene expression is controlled by unique mechanisms.

145 **Restoration of Mutant p53 to Normal p53 Activity by Glycerol**

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We have previously reported that heat stress induces *WAF1* expression only in a wild-type p53 cell line (A-172) of human glioblastoma. Transfection of A-172 cells with mutant *p53* (m*p53*) vector abolished the heat-induced *WAF1* expression, demonstrating the dominant negative nature of this p53 mutant over the endogenous wtp53. We examined whether glycerol can act as a chemical chaperone to change the mp53 conformation. No *WAF1* expression was induced in this transformant. A human osteosarcoma cell line (Saos-2) is deficient in *p53* gene and m*p53*-transfected Saos-2 did not response to Waf1 induction after heating or glycerol treatment alone. In contrast, A-172 cells and Saos-2 cells transfected with m*p53* showed *WAF1* expression, when heated in the presence of glycerol at 0.6 M or 1.2 M. These results suggested that glycerol is effective in restoring several p53 mutants to normal p53 function leading to normal *WAF1* expression after heat stress. We have been studying the molecular mechanism of conformational change of mp53 by glycerol. This observation provides a novel tool for correction of mutant p53 conformation and may be applicable for p53-targeted cancer therapy.

146 Interaction between Maternally and Paternally Derived Genomes and Induction of Genetic Instability in Mice

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We have reported previously that radiation induced germline mutation at a mouse minisatellite locus, Ms6hm/ Pc-1, is likely caused indirectly by genetic instability, because the frequency of the mutation was at least two orders of magnitude higher than to be expected from the number of DNA damage inflicted by irradiation. In addition, we have shown that minisatellite mutation can at the locus be induced at the maternally derived allele in F1 mice born to irradiated spermatozoa. This clearly demonstrates that DNA damage introduced by irradiated sperm induces genetic instability in fertilized egg which then operates equally on the paternally as well as the maternally derived alleles. In this study, we studied the molecular pathway involved in interaction between male and female genmes and the subsequent genetic instability in F1 mice. Results of the study using early stage mouse embryos with several knockout backgrounds will be presented.