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Transcriptional Activation of the p53 Tumor Suppressor Gene Provides a Rapid Protective Mechanism against DNA Damage during S-phase of the Cell Cycle

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p53 functions as a DNA-binding factor that regulates genes required to initiate cell cycle checkpoints or apoptosis in response to ionizing radiation, UV light or other types of DNA damage. Countless studies over the past 20 years indicate that mutant forms of p53 found in tumor cells, which are highly expressing in cancers, lose their DNA-damage checkpoint activities and often function as cancer promoting oncogenes. Thus mutant p53 serve to contribute to tumorigenesis.

Since first demonstrated by Reed et al., [1] that p53 expression is induced upon entry of cells, the molecular mechanisms responsible for this gene activation as well as it's biological significance has remained unexplained. Elevated expression of p53 during S-phase presented a dilemma in light of our understanding of the role that p53 plays as a both an inhibitor of DNA synthesis and inducer of apoptosis. Since elevated levels of p53 protein lead to either growth arrest or apoptosis in response to DNA damage, it might seem surprising that activation of the p53 gene is induced upon entry of cells into S-phase. Recent evidence describes both the mechanism of cell cycle regulation of p53 and the role that p53 expression plays in promoting the DNA damage response during the S-phase. With regard to mechanism, numerous studies have demonstrated that p53 gene expression is induced during early S-phase in cells progressing from G0/G1 into S via the coordinated regulation of two well studied transcription factors, RBP-Jκ and C/EBPβ-2. These two proteins act as a repressor and activator of p53 gene expression, respectively, by binding to the identical site on the p53 promoter. By measuring the rates of induction of p53 target genes such as p21 and Bax and the rate of induction of apoptosis, results indicate that the induction occurs to provide a sufficient level of p53 mRNA in order to promote a rapid response to DNA damage. For example, results demonstrate that Bax expression was up regulated after DNA damage by 4h in exponentially growing cells and within 1h in cells in S-phase. Likewise, p21 expression began to elevate by 6h after drug treatment in exponential cells, and by 4h in cells both in S-phase. With respect to apoptosis, the activity of caspases 3 and 7 (a measure of cellular apoptosis) was observed between 3 and 6h in exponentially growing cells and between 0 and 3h in S-phase. These findings are in full agreement with results published some time ago by Mosner et al. [2] demonstrating a very rapid elevation of p53 protein after DNA damage in cells in S phase. All this points to a remarkable cellular protective mechanism whereby induction of p53 expression tales place in S-phase in order to provide sufficient p53 mRNA to prime the cells for DNA damage, this ensuring a much more rapid DNA damage response before the cells are able to exit S-phase.

In summary then, p53 has long been characterized as the "guardian of the genome". This label resulted from the gene being induced in response to DNA damage and leading to either cell cycle arrest or apoptosis. The presumptive goal of p53 activation is to destroy cells that have sustained genetic damage thus eliminating cells that may eventually become genetically unstable and ultimately oncogenic. This 'guardian of the genome' activity is not only employed upon exposure to external DNA damaging agents resulting in genetic insults. The observations discussed above point to the importance of p53 in normal cell division, that is, cells synthesize p53 mRNA during S-phase. Since S phase occurs within a limited period of time (usually around 8 hrs), cells that sustain damage or errors in replication need to respond quickly before cells exit S-phase and thus pass damage to daughter cells. Having p53 mRNA prepared and ready to translate into protein appears to be a mechanism that provides a rapid response and helps to insure genetic integrity [3-8].

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