PHOSPHORYLATION OF eIF-4E REGULATES p53 PROTEIN SYNTHESIS FOLLOWING DNA DAMAGE

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ABSTRACT

The eukaryotic translation initiation factor 4E (eIF-4E) is essential for efficient cap-dependent protein translation. eIF-4E is known to be regulated by its inhibitory binding proteins (4E-BPs) and by its own phosphorylation. However, the role of eIF-4E phosphorylation in protein translation is still unclear. The tumor suppressor protein p53 plays a critical role in suppressing cell transformation and maintaining genetic integrity. These functions are achieved by accumulation of p53 protein after DNA damage and by p53-induced activation of genes that mediate either cell growth arrest or cell death. Although there is clear evidence indicating that p53 induction is regulated by protein synthesis following DNA damage, the mechanism for the translational regulation of p53 is poorly understood. Our results show that etoposide treatment caused a rapid increase in eIF-4E phosphorylation as well as increased p53 protein synthesis. The addition of CGP57380 (CGP), a specific inhibitor of the eIF-4E kinase Mnk1, not only inhibited eIF-4E phosphorylation but also resulted in reduced synthesis of p53 protein. 35S-labelling experiments further demonstrated that the accumulation of p53 protein was accompanied by an increase in the de novo p53 protein synthesis following etoposide treatment, whereas addition of CGP led to a decrease of p53 induction. Our findings provide the first evidence that phosphorylation of eIF-4E by Mnk1 is critical for increased p53 protein synthesis in response to DNA damage.