

**P007** Proteasome-mediated generation of a dephosphorylated fragment of the protein synthesis inhibitor 4E-BP1 that binds to eIF4E in cells with activated p53

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Inhibition of protein synthesis caused by the activation of the tumour suppressor protein p53 is associated with dephosphorylation and proteolytic cleavage of polypeptide chain initiation factor eIF4G1 and the inhibitor of mRNA cap-dependent polypeptide chain initiation, 4E-BP1. As a consequence, binding of the cap recognition factor eIF4E to eIF4G1, required for formation of the eIF4F initiation complex, is impaired. Here we show that the 4E-BP1 cleavage product is almost completely dephosphorylated at the four sites known to regulate its activity and becomes bound to eIF4E in preference to the remaining full-length 4E-BP1 in the same cells. In contrast to situations where the induction of apoptosis leads to cleavage of 4E-BP1 in a caspase-dependent manner, the p53-induced processing of 4E-BP1 cannot be prevented by the broad specificity caspase inhibitor z-VAD.FMK. However, combined treatment of cells with z-VAD.FMK and the proteasome inhibitor MG132 does block 4E-BP1 cleavage in cells with activated p53. These data suggest that 4E-BP1 is cleaved in a site-specific manner as a result of p53-dependent activation of the proteasome.