

P046 Ubiquitination and degradation of the eIF4E-binding protein 4E-BP1 and its regulation by TRAIL

Androulla Elia, Ian W. Jeffrey and Michael J. Clemens
Translational Control Group, Centre for Molecular and Metabolic Signalling, Division of Basic Medical Sciences, St George's, University of London

The relative levels of and activities of polypeptide chain initiation factor eIF4E and its inhibitory binding protein 4E-BP1 can have a major impact on protein synthesis and cellular phenotype. Overexpression of eIF4E is associated with cell transformation and resistance to apoptosis whereas 4E-BP1 is both pro-apoptotic and anti-oncogenic. We have shown that in cells treated with the pro-apoptotic cytokine TRAIL, 4E-BP1 becomes hypophosphorylated and also accumulates to a considerably higher level. The latter effect does not require new protein synthesis, suggesting that the protein is stabilised under these conditions. Western blots of extracts from control and TRAIL-treated Jurkat cells have revealed that TRAIL induces the appearance of a ladder of modified forms of 4E-BP1. In addition, immunoprecipitation of 4E-BP1 from mouse fibroblasts yields a ca. 50 kDa protein that is recognized by anti-ubiquitin antibodies on Western blots whereas anti-ubiquitin immunoprecipitates a protein of similar mass that is recognized by anti-4E-BP1. Collectively these data suggest that 4E-BP1 can be ubiquitinated and may be degraded by the proteasome. We suggest that TRAIL inhibits this degradation by impairing proteasomal function, leading to the accumulation of 4E-BP1 in both unmodified and ubiquitinated forms.