

P008 Regulation of protein synthesis in human tumour cells by treatment with interferon- α and TRAIL

Ian W. Jeffrey, Stéphanie Bornes, Vivienne Tilleray and Michael J. Clemens

Translational Control Group, Dept. of Basic Medical Sciences, St George's Hospital Medical School, London

Tumour cells are often sensitized to the death-inducing effects of tumour necrosis factor α -related death-inducing ligand (TRAIL) by treatment with interferons. TRAIL also has a strong inhibitory effect on protein synthesis which is dependent on caspase activity. We have therefore examined the effects of prior treatment with interferon- α on the sensitization of translation to such regulation by TRAIL. Interferon treatment sensitizes MCF-7 and HeLa cells to down-regulation of translation by TRAIL. The inhibition is characterized by changes in the phosphorylation of the α subunit of initiation factor eIF2, with strong enhancement in MCF-7 cells but only modest increases in HeLa cells. In MCF-7 cells the phosphorylation of eIF2 α is associated with caspase-mediated cleavage and activation of the protein kinase PKR. TRAIL causes marked dephosphorylation and accumulation of the eIF4E-binding protein 4E-BP1; this is associated with decreased binding of eIF4G1 to eIF4E in the eIF4F complex. Consistent with its effects on the regulation of overall translation by TRAIL, interferon sensitizes MCF-7 and HeLa cells to the effects of TRAIL on the phosphorylation of 4E-BP1. Our data suggest that the inhibition of protein synthesis by TRAIL and the changes in sensitivity of cells to such inhibition following prior interferon treatment are due primarily to regulation of the 4E-BP1/eIF4E system rather than to the phosphorylation of eIF2 α .