TRANSLATIONAL CONTROL AND CANCER

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Control of protein synthesis is an important part of the overall regulation of gene expression, and disregulation contributes to oncogenesis. The rate-limiting step of protein synthesis occurs during the initiation phase, where most regulation occurs. Initiation involves the binding of methionyl-tRNA and mRNA to the ribosome and the pathway is promoted by at least 12 initiation factors in human cells. The basic mechanism for how initiation proceeds will be reviewed. The initiation factors contribute to translational control through variations in their cellular levels or activities, the latter frequently determined by their phosphorylation states. Regulation also may occur through the action of *trans*-factors which can be either proteins or non-coding small RNAs. Many tumors have enhanced or decreased cellular levels of initiation factors, suggesting a link between protein synthesis and cancer. Activation of protein synthesis through changes in initiation factors that promote methionyl-tRNA (eIF2) or mRNA (eIF4E, eIF4G) binding results in the malignant transformation of immortal human cells. Recently, eIF3, the most complex of initiation factors, also has been implicated. eIF3 comprises 13 non-identical subunits (named a to l) present in a complex of about 800 kDa. The structure of human eIF3 was shown to be a 5-lobed structure by cryo-electron microscopy and protein subunit-subunit interactions have been elucidated by mass spectrometry. Five eIF3 subunits (a, b, c, h and i) when overexpressed individually stimulate protein synthesis and are oncogenic. Down-regulation of eIF3h in prostate cancer cells reduces their malignant phenotypes. It is proposed that when protein synthesis is activated, weak mRNAs encoding proteins involved in cell proliferation are translated relatively more efficiently, leading to an imbalance of gene expression and to cancer.