The role of eukaryotic initiation factor 5A in the control of cell proliferation and apoptosis

Review Article

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Summary. In the past years, the attention of scientists has mainly focused on the study of the genetic information and alterations that regulate eukaryotic cell proliferation and that lead to neoplastic transformation. An increasing series of data are emerging about the involvement of the initiation phase of translational processes in the control of cell proliferation. In this paper we review the novel insights on the biochemical and molecular events leading to the initiation and its involvement in cell proliferation and tumourigenesis. We describe the structure, regulation and proposed functions of the eukaryotic initiation factor 5A (eIF-5A) focusing the attention on its involvement in the regulation of apoptosis and cell proliferation. Moreover, we describe the modulation of its activity (through the reduction of hypusine synthesis) in apoptosis induced either by tissue transglutaminase or interferon α. Finally, we propose eIF-5A as an additional target of anti-cancer strategies.

Keywords: Amino acids – eIF-5A – Hypusine – tTGase – Apoptosis – IFNα – Tumour cells

Abbreviations: IF, initiation factor; eIF, eukaryotic IF; PHAS, phosphorylated heat and acid stable protein; 5′ UTR, 5′ untranslated region; EGF, epidermal growth factor; S6K, ribosomal S6 kinase; ERK, extracellular signal regulated kinase; PE, pseudomonas exotoxin A, TAA, tumour associated antigen; MAb, monoclonal antibody; JNK-1, NH2 terminal Jun Kinase-1

Introduction

In the past years, protein synthesis has not been considered as fundamental in the control of cell proliferation. However, data are emerging on the involve-
ment of this process in cell growth and tumourigenesis. Protein biosynthesis is a central process in all living cells. It is one of the last steps in the transmission of genetic information stored in DNA on the basis of which proteins are produced to maintain the specific biological function of a given cell. Protein synthesis takes place on ribosomal particles where the genetic information transcribed into mRNA is translated into protein. The process of protein synthesis on the ribosome consists of three phases: initiation, elongation and termination. The initiation phase appears to be the main target of regulatory messages within the cell and therefore is critical for the modulation of the species of mRNA transcripts (see also below). Here we briefly describe the molecular mechanisms involved in the initiation phase of protein synthesis.

**Biochemical bases of the initiation phase**

In prokaryotic protein biosynthesis the initiation phase is controlled by a small number of initiation factors (IFs), IF-1, IF-2 and IF-3. Among these, IF-2 is the most likely to form a ternary complex with GTP and initiator tRNA\(^{\text{Met}}\). All three factors are involved in assembling the initiation complex of initiation factors, initiator tRNA\(^{\text{Met}}\), the ribosomal subunits and mRNA. Eukaryotic initiation is much more complex and involves a large number of eukaryotic initiation factors (Hershey, 1991; Merrick, 1992; Pain, 1996). The 80S ribosomes dissociate, and 40S subunits are captured for initiation by binding eIF1A and eIF3; the size of the latter causes the particle to sediment at 43S (Gaspar et al., 1994; Hannig et al., 1993). Initiator tRNA binds, in the form of a ternary complex with eIF2 and GTP, to produce the 43S preinitiation complex (Gaspar et al., 1994; Hannig et al., 1993). The 43S preinitiation complex binds to mRNA at the 5’-end and migration along the mRNA towards the AUG initiation codon (Gaspar et al., 1994; Hannig et al., 1993). The initial binding involves the factors eIF4E, eIF4G and eIF4A, which assemble at the 5’-end of mRNA, thus creating the conditions that allow the melting of intramolecular secondary structures within the mRNA that would otherwise prevent the binding of the 43S preinitiation complex (Hershey, 1991; Pain, 1996; Rhoads, 1993; Merrick, 1994; Rhoads et al., 1994). The term 48S preinitiation complex is frequently used, and refers to the 43S – globin ~ mRNA complex formed in the reticulocyte lysate (Bommer et al., 1991). When the 43S preinitiation complex stops at the initiation codon, the GTP molecule introduced as part of the eIF2 complex is hydrolysed to GDP, and this gives energy for the ejection of the initiation factors bound to the 40S ribosomal subunit (Price et al., 1992). The initiation factor eIF5 is involved in this process which is likely to accelerate the hydrolysis of GTP (Price et al., 1992). The release of these factors allows the association of a native 60S ribosomal subunit, to reconstitute a 80S ribosome at the initiation codon positioned to commence the elongation stage of translation. The continuity of initiation events requires the recycling of initiation factor molecules. eIF2 is released as a binary complex with GDP and requires a guanine nucleotide exchange factor, eIF2B, to