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Review

Translational regulation mechanisms of AP-1 proteins

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ABSTRACT

The activator protein 1 (AP-1) transcription factor is assembled from jun-jun, jun-fos, or jun-atf family protein homo- or heterodimers. AP-1 belongs to the class of basic leucine zipper (bZIP) transcription factors. It binds to promoters of its target genes in a sequence-specific manner, and transactivates or represses them. AP-1 proteins are implicated in the regulation of a variety of cellular processes including proliferation and survival, differentiation, growth, apoptosis, cell migration, and transformation. The decision if a given AP-1 factor is positively or negatively regulating a specific target gene is made upon abundance of dimerization partners, dimer-composition, post-translational regulation, and interaction with accessory proteins. In this review we describe translational control mechanisms that can regulate the abundance of AP-1 proteins. The *Atf4/5*, and *JunD* (mRNAs) are regulated by upORF dependent mechanisms. *JUNB* (mRNA) translation is controlled via mTOR. Translation efficiency of the unstable *c-Fos* (mRNA) can be decreased by the miRNA mir7B, while its perinuclear translation might facilitate efficient nuclear c-fos protein import. *c-Jun* (mRNA) appears to be regulated by both, m7G cap (CAP)-dependent and CAP-independent translational control mechanisms, via putative internal ribosome entry segments (IRES). IRES elements were also proposed to play a role in the regulation of *JunD* (mRNA). We conclude that in addition to transcriptional and post-translational control mechanisms translational regulation contributes to the balanced production of AP-1 proteins, in order to maintain physiological cellular conditions.

Contents

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1. Introduction

Activator protein 1 (AP-1) family proteins are basic leucine zipper (bZIP) transcription factors that are implicated in the regulation of a variety of cellular processes including proliferation and survival, growth, differentiation, apoptosis, cell migration, and transformation. They represent sequence-specific DNA-binding transcription factors and consist of homo- or heterodimers, which are formed by jun (c-jun, junB, junD), fos (c-fos, fra-1, fra-2), or atf proteins, in mammalian cells. In yeast, a jun homologue, Gcn4p, recognizes the same DNA response element, namely the 12-O-tetradecanoylphorbol-13-acetate (TPA) response element (TRE), and also forms dimers. AP-1 factors play important roles in malignant processes. Often, increased AP-1 levels lead to increased transactivation of target gene expression. Regulation of AP-1 activity is critical for the decision of cell fate and occurs at various levels, including dimer-composition, transcriptional and post-translational events, and interaction with accessory proteins [1]. Surprisingly, research regarding regulation at the level of translation has long been neglected, despite its high potential to influence AP-1 abundance and thereby activity. Recently, it has been shown that the fusion tyrosine kinase oncoprotein, npm-alk, of Anaplastic Large Cell Lymphoma (ALCL) (for an excellent review, see [2]) contributes to neoplastic transformation by inducing more effective translation of the AP-1 transcription factor junB, via an increased number of ribosomes bound to the *JUNB* mRNA [3]. To our knowledge, no other study directly relates AP-1 factor translation efficiency with human neoplasia or disease. However, a growing number of reports describe various mechanisms implicated in translational regulation of AP-1 factors.

Before going into specific details of AP-1 translational regulation, we will look at general concepts of translational regulation and their underlying principles. During and after their transcription most pre-mRNAs are spliced and further processed in messenger ribonucleoprotein particles (mRNPs). Factors that build up mRNPs are continuously changing throughout the life of an mRNA. The CAP is formed at the 5′-end of the mRNA in a process dependent on guanylyl transferase [4]. Nuclear CAP-binding factor (cbc20/80) binds and accompanies the mRNA until getting displaced by the cytoplasmic CAP-binding protein, eIF4E. The 3′-end of the mRNA is processed by cleavage/polyadenylation factors, and the growing poly A-tail is formed by poly-A polymerase and bound by nuclear poly-A binding protein (pabN1). After export of the mRNA through the nuclear porous complex, papN1 gets displaced by cytoplasmic poly A-binding factors (pabCs). mRNP factors such as Y-box proteins that are assembled along the length of the mRNA are possibly displaced during the first pioneering round of translation in the cytoplasm. During this process, the mRNA's CAP is probably still attached to cbc20/80 instead of the cytoplasmic CAP-binding protein eIF4E [5–7].

During the mRNA maturation process the dynamic nature of the mRNP might be of utmost importance for key translational regulatory mechanisms. There are three important cytoplasmic mRNP based structures:

(i) Polysomes, structures in which an mRNA is translated via various ribosomes, leading to efficient protein production (following the general idea, the more ribosomes bound to one mRNA, the more protein generated from this specific mRNA.
(ii) P-bodies, structures in the cytoplasm where mRNA decay occurs and many translationally silent mRNPs (possibly mediated by miRNAs) are aggregated.
(iii) Stress granuli (SG). Under stress conditions, in which house-keeping proteins are not required, their messages (mRNAs) reversibly accumulate in SG via tia-1 and tiaR binding. For more detailed information on the lives of mRNAs, see [6,7] and references therein.

Translation of AP-1 proteins is reportedly regulated by a set of mechanisms that can be roughly divided into CAP-dependent and CAP-independent. See Fig. 1.

2. CAP-dependent translational regulation

Translation is most often regulated during its initiation step [8,9]. Activation for translation of m7G capped mRNA's includes cooperative binding of the core initiation factors eIF4E, eIF4G (the scaffold at which translation initiation factors attach) and eIF4A (the catalytic RNA helicase subunit). Many eukaryotic mRNAs have highly structured 5′-UTRs, and therefore the helicase activity of eIF4A might be of great importance to facilitate the small (40s)

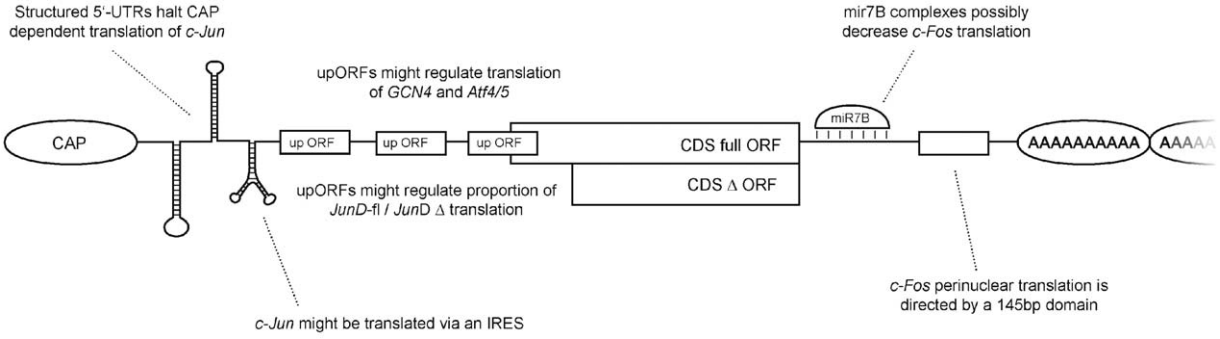

Fig. 1. Translational control mechanisms of AP-1 mRNAs that were experimentally fully or in part deciphered are depicted in the figure. *c-Jun* (mRNA) translation was proposed to be regulated via its highly structured 5′-UTR that inhibits the scanning process of the small ribosomal subunit. However, *c-Jun* (mRNA) might be translated by internal initiation via an IRES dependent mechanism. The *JunD* (mRNA) produces two protein isoforms, junD-fl and junD-delta. The ratio of one to the other was found to be regulated via upORFs in the *JunD* (mRNA). The yeast *GCN4* (mRNA) is a classical example of translational regulation via upORFs. Not surprisingly the *Atf4/5* (mRNAs) that share structural features with *GCN4* (mRNA) are regulated in a similar manner. *c-Fos* (mRNA) translation is possibly regulated in two different ways. Either via translational suppression by miR7B or in a positive manner by a sequence within a 145 bp stretch in its 3′-UTR that confers its perinuclear translation. With kind permission from Pesole, G [10].