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Review

Stress-mediated translational control in cancer cells ☆

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ABSTRACT

Tumor cells are continually subjected to diverse stress conditions of the tumor microenvironment, including hypoxia, nutrient deprivation, and oxidative or genotoxic stress. Tumor cells must evolve adaptive mechanisms to survive these conditions to ultimately drive tumor progression. Tight control of mRNA translation is critical for this response and the adaptation of tumor cells to such stress forms. This proceeds though a translational reprogramming process which restrains overall translation activity to preserve energy and nutrients, but which also stimulates the selective synthesis of major stress adaptor proteins. Here we present the different regulatory signaling pathways which coordinate mRNA translation in the response to different stress forms, including those regulating eIF2α, mTORC1 and eEF2K, and we explain how tumor cells hijack these pathways for survival under stress. Finally, mechanisms for selective mRNA translation under stress, including the utilization of upstream open reading frames (uORFs) and internal ribosome entry sites (IRESes) are discussed in the context of cell stress. This article is part of a Special Issue entitled: Translation and Cancer.

1. Introduction

Tumors often grow within hostile microenvironments characterized by different stress conditions such as hypoxia and nutrient deprivation (ND) due to defective tumor vasculature, or genotoxic and oxidative stress induced by rapid cell division or therapy [1–4]. Tumor cells must manage these and other stresses, and their ability to respond to each stress form will determine tumor progression and ultimately patient outcome. At the cellular level, the stress response relies on both energy preservation and the generation of an adaptive response, which combine to maintain cell survival. However, the mechanisms of stress adaptation proceed at the expense of tumor proliferation, representing a dilemma for tumor cells during tumor progression.

One major path to adaptively respond to stress is through the tight control of mRNA translation [2,4]. Indeed, mRNA translation is a highly energy-consuming process [5] which is typically inhibited in response to a number of stress forms in most tumor cells [1,2], allowing them to preserve energetic balance. In addition to saving energy, reducing overall mRNA translation prevents the synthesis of proteins that would otherwise interfere with the adaptive stress response [6]. However, the global decrease in translation occurs in conjunction with the selective synthesis of specific proteins which are involved in the adaptive response to stress [1,2]. Reduced mRNA translation activity under stress occurs predominantly at the initiation step [2,7], which is the rate-limiting step of mRNA translation, but in few notable cases it occurs at the elongation step [8–11]. In this review we will discuss how tumor cells control overall protein synthesis in response to various stresses, as compared to normal cells.

1.1. Stress signaling pathways and translational control

There are several highly conserved signaling pathways which control mRNA translation activity to couple overall translation rates to rapid changes in the extracellular milieu, and which tumor cells hijack to adapt to stress. These regulatory pathways orchestrate adaptive responses to stress by restraining overall translation and by stimulating selective synthesis of stress adaptive proteins [1,2]. Historically, most of the current understanding of translational control under cell stress has been from earlier investigations of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). ER stress is induced by an accumulation of unfolded or misfolded proteins in the ER lumen [12]. This leads to activation of the UPR, which collectively induces three parallel signaling pathways to effectively decrease global mRNA translation, degrade misfolded proteins, and increase synthesis of molecular chaperones and other factors in order to reduce ER stress and regain protein folding homeostasis [12,13]. The UPR induces three main effectors, namely the three ER transmembrane proteins, protein kinase RNA-like endoplasmic reticulum kinase (PERK), activating transcription

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factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1), which collaborate to reprogram gene expression to increase protein quality control capacity through selective synthesis of chaperones, 78 kDa glucose-regulated protein (GRP78)/binding immunoglobulin protein (BiP), X-box binding protein 1 (XBP1), CCAAT-enhancer-binding protein homologous protein (CHOP), ATF4, and other factors, as has been expertly reviewed elsewhere [12,14]. If ER stress is severe and the UPR cannot compensate, this can lead to apoptosis, such as occurs with enhanced protein synthesis rates accompanying rapid proliferative rates, or as a result of high mutational burden in tumor cells. Indeed, ER stress is induced following diverse stress forms [15–17], and is increasingly viewed as a convergent downstream consequence of multiple stress types [18]. Therefore we will not further discuss ER stress in this review, focusing instead on other microenvironmental stress forms that can act upstream to induce ER stress, including hypoxia and nutrient deprivation, as well as oxidative and genotoxic stress.

Common to the regulation of mRNA translation under different stress types, including ER stress, is the translation initiation factor, eukaryotic translation initiation factor 2α (eIF2α). The activity of eIF2α is directly restricted by four stress-sensing kinases, namely PERK, which as mentioned is activated under ER stress as part of the UPR, as well as protein kinase RNA-activated (PKR), general control non-derepressible 2 (Gcn2) and heme-regulated inhibitor (HRI), each of which senses and responds to specific cellular stresses such as ER stress, hypoxia, ND, and oxidative stress [1,15]. Activation of these kinases directly leads to phosphorylation of eIF2α, in turn reducing the ability of this protein to recruit methionyl-initiator tRNA to the 40S ribosomal subunit, thus compromising the assembly of the translation initiation complex [19]. Paradoxically, eIF2α phosphorylation favors the selective translation of subsets of transcripts, depending on the stress type, through alternative translation regulatory mechanisms (see below) [1]. Another common and critical regulator of mRNA translation under stress is mammalian target of rapamycin complex 1 (mTORC1), which stimulates cap-dependent translation initiation by preventing the binding of eIF4E binding protein (4EBP) to the translation initiation factor eIF4E, and by inducing the phosphoprotein 70 ribosomal protein S6 kinase (p70S6K) which controls ribosomal protein S6 activity [20]. The mTORC1 complex is inactivated by nutrient deprivation, hypoxia and oxidative and genotoxic stress through different mechanisms, which restricts global protein synthesis [21]. However, the reduction in cap-dependent translation activity that occurs as a consequence of mTORC1 inhibition promotes cap-independent translation to support selective mRNA translation [22]. Finally, the other major regulator of protein synthesis in response to stress is the eukaryotic elongation factor 2 (eEF2) kinase (eEF2K) which directly controls the activity of the translation elongation factor eEF2 [23–25]. In response to ND, hypoxia and oxidative and genotoxic stress, eEF2K is activated, leading to phosphorylation and inactivation of eEF2, in turn preventing protein synthesis [26]. This pathway allows for the strict regulation of mRNA translation specifically at the elongation step in response to cell stress.

1.2. Selective translation mechanisms under cell stress

Several alternative translation mechanisms have emerged to circumvent the overall translation arrest that occurs under cell stress, in order to support the selective synthesis of stress adaptive proteins [1,2,4,27,28]. This translational reprogramming is exploited by tumor cells to enhance their protection against stress [22,29,30]. One key mRNA which undergoes selective translation is ATF4, a ER stress-induced transcription factor that activates transcription of downstream stress-response genes such as CHOP, components of the endoplasmic-reticulum-associated protein degradation (ERAD) machinery, and molecular chaperones [14,31]. Translational inhibition due to eIF2α phosphorylation leads to selective translation of ATF4, therefore reprogramming gene expression under stress. Analysis of the mechanism led to the identification of upstream open reading frames (uORFs) in the 5′ untranslated region (UTR) of the ATF4 message [27]. It is now estimated that ~50% of mammalian transcripts may possess at least one uORF [32,33]. In general, under homeostatic conditions, uORFs are inhibitory by preventing the scanning ribosomes from translating the main ORFs [34,35]. However, under stress conditions, for some uORF-containing mRNAs, ribosomes can bypass the uORFs via a reinitiation mechanism to allow translation of the main ORF [34–36]. Mechanistically, stress-mediated phosphorylation of eIF2α lowers the pool of functional eIF2, thereby allowing time for reinitiating ribosomes to assemble a translation initiation complex after scanning past the uORFs [34,35]. As a consequence, increased numbers of ribosomes are available to initiate translation from downstream main ORFs.

Other uORF-containing mRNAs are also selectively translated under stress, such as GADD34, CHOP and ATF5 [34,37,38]. For some mRNAs, translation proceeds via a re-initiation mechanism such as for ATF4, which is regulated by two uORFs in its 5′UTR. However, other mRNAs such as GADD34 are regulated by a single uORF, thus precluding the use of a re-initiation mechanism [37]. How can scanning ribosomes bypass a regulatory uORF within a 5′UTR? It has been proposed that the single uORF within the 5′UTR may use a leaky scanning whereby scanning ribosomes may under certain conditions circumvent the AUG start codon of the uORF and proceed to initiate translation at the main ORF [14]. Alternatively, a recent paper revealed that density regulated protein (DENR) and multiple copies in T-cell lymphoma-1 (MCT-1) factors can promote re-initiation of uORFs, thus providing another mechanism of uORF ribosome bypass [39]. Moreover, it was shown that DENR and MCT-1 factors are required for proliferation and control translation of a subset of uORF-containing mRNAs [39]. It remains to be seen whether DENR and MCT-1 proteins have a wider role in the translation of other uORF-containing mRNAs during cellular stress. In contrast, some uORFs are selectively translated under specific conditions such as genotoxic and oxidative stress, although the mechanisms remain unknown [8,40].

Another key mechanism of alternative translation in response to stress is through cap-independent translation using an internal ribosome-entry site (IRES). Such elements are present in the 5′UTRs of specific transcripts such as cellular inhibitor of apoptosis protein-1 (cIAP1), X-linked inhibitor of apoptosis protein (XIAP), and p53. These elements allow direct recruitment of ribosome subunits without requiring the presence of certain cap-dependent initiation factors such as eIF4E [1,6,41]. Even though some authors support that 3-5% of all cellular mRNAs may contain IRES elements [42], their ability to support efficient translation in eukaryotes is still a matter of debate [43–45]. Under stress conditions when cap-dependent translation is blocked (due to mTORC1 inhibition), cap-independent translation may become prevalent [2,22]. Together, such mechanisms allow tumor cells to synthesize proteins required for stress adaptation, even though overall translation is attenuated [46–48]. In this review, we will focus on translational control that occurs under stress forms induced within the tumor microenvironment, namely hypoxia, nutrient deprivation, and oxidative and genotoxic stress. For these stress forms, each of which can induce ER stress, we will describe their impact on overall translation activity as well as the signaling pathways which link stress sensing to the control of mRNA translation. Finally, the selective translation mechanisms employed under each of stress type will be presented.

2. Control of translation under hypoxia

The translational response to prototypical stress forms is exemplified by growth of cells under reduced oxygen tension, or hypoxia, and so we will first discuss the effects of hypoxia on tumor cell mRNA translation.

2.1. Tumor hypoxia

Hypoxia is a common feature of the tumor microenvironment and one which tumors must manage in order to progress. At early stages