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Review

Roles of the translation initiation factor eIF2α serine 51 phosphorylation in cancer formation and treatment☆

Antonis E. Koromilas *

Lady Davis Institute for Medical Research-McGill University, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec H3T 1E2, Canada
Department of Oncology, Faculty of Medicine, McGill University, Montreal, Quebec H2W 1S6, Canada

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ABSTRACT

Cells respond to various forms of stress by activating anti-proliferative pathways, which allow them to correct the damage caused by stress before re-entering proliferation. If the damage, however, is beyond repair, stressed cells are eliminated from the host by undergoing death. The balance between cell survival and death is essential for cancer formation and is determined by several key pathways that impact on different stages of gene expression. In recent years, it has become evident that phosphorylation of the alpha (α) subunit of the translation initiation factor eIF2 at serine 51 (eIF2αS51P) is an important determinant of cell fate in response to stress. Induction of eIF2αS51P is mediated by a family of four kinases namely, HRI, PKR, PERK and GCN2, each of which responds to distinct forms of stress. Increased eIF2αS51P results in a global inhibition of protein synthesis but at the same time enhances the translation of select mRNAs encoding for proteins that control cell adaptation to stress. Short-term induction of eIF2αS51P has been associated with cell survival whereas long-term induction with cell death. Studies in mouse and human models of cancer have provided compelling evidence that eIF2αS51P plays an essential role in stress-induced tumorigenesis. Increased eIF2αS51P exhibits cell autonomous as well as immune regulatory effects, which can influence tumor growth and the efficacy of anti-tumor therapies. The findings suggest that eIF2αS51P may be of prognostic value and a suitable target for the design and implementation of effective anti-tumor therapies. This article is part of a Special Issue entitled: Translation and Cancer.

1. eIF2α serine 51 phosphorylation in mRNA translation under stress

Global rates of protein synthesis can alter by various intracellular and extracellular influences that range from normal physiological changes in response to growth factor, hormone and/or cytokine stimulation to pathological conditions caused by various forms of stress [58,120]. In recent years, there has been very strong evidence to suggest that the polypeptide chain translation initiation factor eIF2 is a frequent target of regulation and its activity is often rate-limiting for protein synthesis [120,135]. eIF2 consists of three subunits α, β and γ; increased phosphorylation of the smallest α subunit at serine 51 (herein referred to as eIF2αS51P) is a widely used mechanism of translational control in cells exposed to stress in many organisms. Initiation of mRNA translation requires eIF2 bound to GTP and the initiator methionyl-tRNA leading to formation of a ternary complex, which is associated with the small (40S) ribosomal subunit and the initiation factors eIF1, eIF1A and eIF3 resulting in the formation of the 43S pre-initiation complex [82,120] (Fig. 1). The 43S pre-initiation complex binds to an mRNA near the 5′ cap structure and scans in a 3′ direction towards a start codon. During this process, GTP bound to eIF2 is hydrolyzed to GDP and P_i; start codon recognition releases P_i from eIF2 resulting in the formation of eIF2.GDP complex, which dissociates from the 40S subunit [82]. For another round of initiation to occur, GDP bound to eIF2 is replaced by GTP, a reaction mediated by the guanine exchange activity (GEF) of eIF2B [103]. In cells exposed to stress, increased eIF2αS51P switches eIF2 from a substrate to a competitive inhibitor of eIF2B resulting in a global inhibition of protein synthesis [103] (Fig. 1). Paradoxically, increased eIF2αS51P can also promote translation of select mRNAs that are inefficiently translated in the absence of stress including mRNAs encoding for the general control non-derepressible 4 (GCN4) in yeast or activating transcription factor 4 (ATF4) and ATF5 in mammalian cells [36,84,130,149]. These mRNAs contain upstream open reading frames (uORFs) in their 5′ untranslated region (5′ UTR), which impede translation under normal conditions. Increased eIF2αS51P bypasses the inhibitory effects of uORFs leading to delayed translation re-initiation at the correct AUG [120]. Increased eIF2αS51P can also enhance translation of certain mRNAs containing an internal ribosome entry site (IRES) in their 5′ UTR [120]. Stimulation of translation of select mRNAs by eIF2αS51P results in the synthesis of proteins that contribute to cell adaptation to stress [44,142].

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* Corresponding author at: *Lady Davis* Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, Room F508, 3999 Cote Ste-Catherine Road, Montreal, Quebec H3T 1E2, Canada. Tel.: +1 514 340 8222local3697; fax: +1 514 340 7576.
E-mail address: antonis.koromilas@mcgill.ca.

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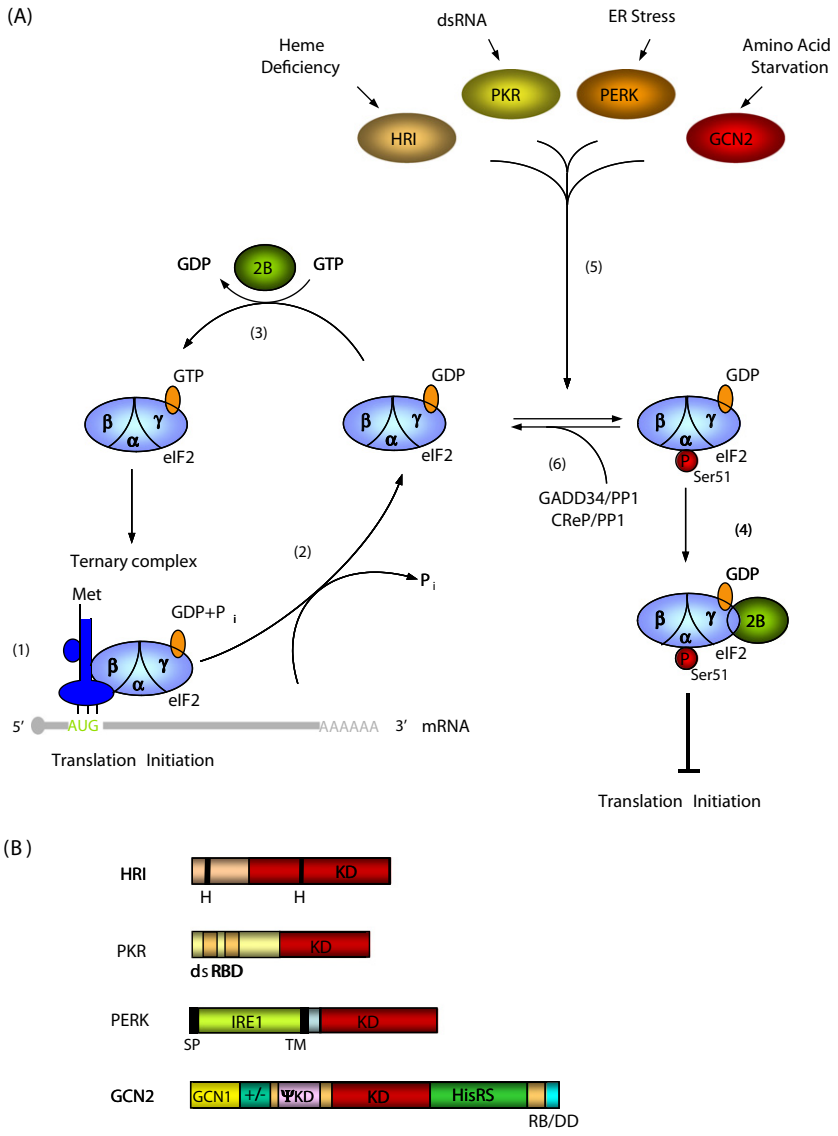

Fig. 1. Regulation of mRNA translation initiation by eIF2αS51P. (A) Initiation of translation requires recognition of initiation codon AUG by the eIF2–GTP–Met-tRNA$_i^{Met}$ ternary complex bound to the 43S pre-initiation complex (not shown for simplicity). eIF2 binds to Met-tRNA$_i^{Met}$ in its active GTP-bound state to form the ternary complex (1). GTP is hydrolyzed to GDP and P_i during the scanning of the 5′ UTR; upon recognition of the start codon (AUG) P_i is released and eIF2–GDP dissociates from the 43S pre-initiation complex (2). The guanine nucleotide exchange factor eIF2B replaces GDP by GTP in order to reconstitute a functional ternary complex for a new round of translation initiation (3). Phosphorylation of the α subunit of eIF2 at Ser51 (eIF2αS51P) results in sequestering eIF2B in an inactive complex and as a result GDP–GTP exchange can no longer occur and global mRNA translation is inhibited (4). Four kinases phosphorylate eIF2α in response to distinct stress conditions as indicated resulting in inhibition of protein synthesis (5). eIF2αS51P is negatively regulated by GADD34/PP1 and CreP/PP1 holoenzyme complexes (6). (B) The structures of the eIF2α kinases are presented. The conserved kinase domains (KD) are depicted in red. The two heme-binding sites in HRI are marked in black. The dsRNA binding domains (dsRBDs) in PKR are shown in orange. The N-terminal half of PERK, which resembles the corresponding domain of the ER stress-responsive IRE1 kinase, signal peptide (SP) and transmembrane (TM) domain of PERK are indicated. GCN2 structure consist of N-terminal GCN1 binding domain, charged region (+/−), pseudokinase domain (ψKD), the regulatory histidyl-tRNA synthetase (HisRS) domain and the C-terminal ribosome binding and dimerization domain (RB/DD).

In mammalian cells, induction of eIF2αS51P is mediated by a family of four kinases each of which responds to distinct stress stimulus [135] (Fig. 1). The family includes the heme-regulated inhibitor (HRI), which becomes activated by heme deficiency and controls globin synthesis in erythroid cells [46]; the general control non-derepressible-2 (GCN2), which is activated by uncharged t-RNA caused by amino acid deficiency [23]; the RNA-dependent protein kinase PKR, an interferon (IFN)-inducible protein which becomes activated by binding to double-stranded (ds)RNA [88]; and the PKR-like endoplasmic reticulum (ER)-resident protein kinase PERK, whose activity is induced by the accumulation of misfolded proteins in the ER [51]. These enzymes consist of distinct regulatory domains but exhibit significant sequence similarities in the protein kinase domain, which can account for their specificity towards eIF2α [135] (Fig. 1). eIF2αS51P is negatively regulated by the protein phosphatase1 regulatory subunit 15A (PPP1r15a), which is also known as growth arrest and DNA damage-inducible protein (GADD34), and the constitutive repressor of eIF2 phosphorylation (CreP) or PP1r15b, which are regulatory subunits of protein phosphatase 1 (PP1) [27,52,64,96] (Fig. 1). In addition, the Src homology (SH) domain-containing adaptor Nck is part of PP1/CreP holo-phosphatase complex that interacts with eIF2β to mediate eIF2αS51P dephosphorylation [79].

To date, it remains a mystery how a single phosphorylation event can act as an integrator of diverse stress stimuli and orchestrate so different biological outcomes in stressed cells. Increased eIF2αS51P is associated with several pathophysiological conditions including virus infection, neurodegeneration, inflammation, diabetes, obesity and cancer [57,97,132]. Herein, we review the connection of eIF2αS51P to cancer and focus on PKR, PERK and GCN2 given that the role of HRI in tumorigenesis has yet to be established.