Advances in Clinical and Medical Research

Genesis-ACMR-5(1)-73
Volume 5 | Issue 1
Open Access
ISSN: 2583-2778

Role of elf2 Signaling in Cancer and its Relationship with Coronavirus

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Citation: Tanabe S. (2024) Role of eIF2 signaling in cancer and its relationship with coronavirus. Adv Clin Med Res. 5(1):1-3.

Received: December 7, 2023 | **Published**: January 12, 2024

Abstract

Several signaling pathways are involved in corona virus infection and cancer. The translation of mRNA is initiated by eukaryotic initiation factor 2 (eIF2). Endoplasmic Reticulum (ER) stress induced by hypoxia in cancer activates signaling pathways involving eIF2. The stress responses of cells play important roles mainly in protecting cells, while the prolonged responses and involvement of microRNAs may cause cell transition. The precise mechanism of eIF2 signaling pathways and involvement of microRNAs to respond to the stresses in cancer is not fully elucidated. In this Editorial, the relationship between eIF2 signaling and corona virus and its role in cancer are focused.

Keywords

eIF2; Coronavirus; Cancer; mRNAs

The Role of Eukaryotic Initiation Factor 2 (eIF2)

Eukaryotic initiation factor 2 (eIF2) promotes initiation of translation of eukaryotic mRNAs [1]. Translation is controlled by eIF2 phosphorylation, which is implicated in learning and memory, neurodegenerative

diseases, and cancer [1]. Phosphorylation of eIF2α converts eIF2-guanine diphosphate (GDP) into a competitive inhibitor of the guanine nucleotide exchange factor eIF2B, then decreases ternary complex (TC) assembly [1]. eIF2TC formation plays a central role in integrated stress response (ISR), which is a central signaling network that responds to protein homeostasis defects [2]. TC formation is regulated by eIF2 phosphorylation [2].

eIF2 Signaling and Coronavirus

eIF2 signaling plays an important role in ISR when the viruses enter the host cells [3]. eIF2 is phosphorylated to inhibit guanine nucleotide-exchange factor EIF2B. Heme-regulated eIF2α kinase (HRI), general control non-derepressible 2 (GCN2), and PKR-like ER kinase (PERK) sense the stress factors such as hypoxia, amino acid deprivation, glucose deprivation or accumulation of unfolded proteins in the endoplasmic reticulum (ER) [3]. Various stresses including ER stress may induce the phosphorylation of the eIF2α, which has significant impact on the translation initiation. Corona virus has several types of structural proteins and accessory proteins (AcPs), which are involved in the inhibition of ISR [3].

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) induced eIF2-pathway-mediated beta cell trans differentiation [4]. The phenotype where the trans differentiation of human isletβ cells occurs can be reversed with a trans-integrated stress response inhibitor (trans-ISRIB) [4]. Trans-ISRIB can reverse the effects of eIF2α phosphorylation [5]. eIF2 signaling is involved in cell fate change upon SARS-CoV-2 infection [4]. Although molecular mechanisms underlying islet cell phenotypic changes have been investigated with single cell RNAseq technologies, further investigation is needed [6].

eIF2 Signaling and MicroRNAs (miRNAs)in Cancer

Phosphorylation level of eIF2α is increased in the condition of the Endoplasmic Reticulum (ER) stress induced by hypoxia, which results in the promotion of a pro-adaptive signaling pathway, while prolonged ER stress induces apoptotic cell death [7]. The ER stress induces activation of Unfolded Protein Response (UPR) pathways through induction of protein kinase RNA-like endoplasmic reticulum kinase (PERK), which leads to the phosphorylation of eIF2α [7]. Since hypoxia is closely associated with cancer progression and induction of metastasis, targeting UPR pathways may contribute to overcoming resistance to anti-cancer drugs of cancer [7].

The UPR network relates to tumor dormancy, where UPR-triggered eIF2α phosphorylation induces repression of protein translation in relation to cyclin D1 that controls G1/S transition [7-8]. eIF2α is a target of miRNA (miR)-30b-5p and miR-30c-5p, which is essential to the anti-apoptotic function of the miRNAs [9]. Up-regulation of miR-30b-5p and miR-30c-5p suppresses the phosphorylated eIF2α/Activated Transcription Factor 4 (ATF4)/CCAAT/Enhancer-Binding Protein (C/EBP) Homologous Protein (CHOP) pro-apoptotic pathway [9]. An interesting finding is that translation of mRNA is regulated by miRNAs with an involvement of a translation initiating factor eIF4G. eIF4G-poly(A)-binding protein (PABP) interaction stimulates translation [10]. The interaction is suggested to interfere with let-7 miRNA-mediated mRNA deadenylation [10]. The eIF-miRNA network may play an important role in cancer progression.

Conclusion

In stress response, the eIF2 signaling and its phosphorylation are crucial in terms of translation of mRNAs. Several miRNAs regulate the eIF2 signaling pathways and are involved in cancer progression. Investigation of ISR in corona virus-associated phenomena as well as identification of targets in eIF2 signaling to overcome the resistance of anti-cancer drugs would be interesting targets in future.

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DOI: https://doi.org/10.52793/ACMR.2024.5(1)-73