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REGULAR ARTICLE

Blocking IRES-mediated translation pathway as a new method to treat Alzheimer's disease

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Abstract Scientists theorized that β-amyloid (Aβ) plaques and tau tangles are involved in the development of Alzheimer's disease (AD), and amyloid precursor protein (APP) produces Aβ to trigger the disease process. However, the normal synaptic function of APP itself is not fully understood. Several findings cast APP as a potential key player in learning and memory under normal condition. Nevertheless, the regular operation of APP will be disrupted by abnormal accumulation of Aβ under cellular pathological conditions. Herein, there is a hypothesis that AD could be treated by attenuating APP synthesis during cellular pathophysiological stress. In virtue of a previous study, it was speculated that cells could not decrease APP synthesis via self-protection maybe because APP is synthesized via internal ribosome entry segment (IRES)-mediated translation. Consequently, the blockage of this translation might be a new inoffensive and high-level specificity treatment.

Introduction

Aβ and APP

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of aggregates of β-amyloid (Aβ) and intraneuronal neurofibrillary tangles (NFTs) with tau protein [1]. Therefore, there are usually two typical pathological hallmarks in AD patient brain: First, Aβ plaques outside of neurons are produced via the accumulation of Aβ, and then NFTs inside them are formed via tau protein phosphorylation. In addition, the NFTs mostly occur after Aβ plaques have developed. It is believed that Aβ plaques ignite the fuse to trigger the disease process. Furthermore, Aβ is derived from amyloid precursor protein (APP) via two proteases, β-secretase and γ-secretase [2]. Notwithstanding, the normal functions of uncleaved APP in the brain are still unknown, a few studies also suggested that full-length APP with nonamyloidogenic pathway as a potential key player in learning and memory through the promotion of synaptic activity, synapse formation, and dendritic spine formation [3–6]. In addition, Ma and colleagues found further that Aβ levels exceeding the

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normal range may initiate abnormalities in synaptic function [7]. Therefore, there is a premise that a certain amount of Aβ is required for physiological function regulations in the neurons. However, under pathological stress conditions, the increase in Aβ concentration produces pathological effects, including decreased presynaptic neurotransmitter release, reduced postsynaptic responsiveness, long-term potentiation (LTP) impairment, and long-term depression (LTD) facilitation (see Ref. [8] for a recent review). As a result, the concentration of Aβ (APP) must be maintained within a normal physiological range in order to treating AD.

IRES-mediated translation

The majority of mRNAs in eukaryotic cells are translated via the methylguanosine cap at the 5′ end of the mRNA with eukaryotic initiation factors (eIFs). In general, many of the eIFs (eIF2α, eIF4GI, eIF4GII, eIF3j) involved in this process are degraded and become less active under a number of pathophysiological stress conditions or apoptosis, thus attenuating protein synthesis [9]. Scientists subsequently found that a number of proteins (e.g., XIAP, c-Myc, and DAP5), involved in cell death, are still synthesized via cap-independent translation during apoptosis [10–12]. The initiation of cap-independent translation involved a complex RNA structural element known as internal ribosome entry segment (IRES) to recruit ribosomes [13–15]. This structural element in the 5′-untranslated region (UTR) plays a pivotal role in cell's relieving and recovery from stress condition as usual. As we know, eIF2α phosphorylation will increase under cell death, but how can the IRES-dependent translation bypass the limitation of protein synthesis such as eIF2α phosphorylation under physiological and pathophysiological stress? With respect to this new challenge, scientists proposed some meaningful hypothesis [16]. On the basis of a few eIF2-independent modes of translation of viral RNAs [17,18], recently, Nehal Thakor and Martin Holcik have theorized that the IRES-mediated translation of X-linked inhibitor of apoptosis protein (XIAP) is more likely to be dependent upon eIF2α during normal growth condition and then switches to eIF5B-dependent mode when eIF2α is phosphorylated under cellular stress. Interestingly, these results cater for previous hypothesis, however, they also noticed that not all cellular IRES operate with an eIF5B-dependent mode [19].

APP and IRES-dependent translation

Salubrinal, an inhibitor of eIF2α-P dephosphorylation, is used for inducing eIF2α phosphorylation to promote cell survival under endoplasmic reticulum (ER) stress [20]. Although some groups tried to treat AD by altering the level of eIF2α phosphorylation using salubrinal [21,22], the results were less effective than kainic acid injury-induced cell death [23] and cerebral stroke [24]. As a result, it is suggested that the short-term treatment of salubrinal, with no alterations in phosphorylated eIF2α levels, protects against Aβ neurotoxicity through inhibition of the NF-κB pathway rather than through inhibition of ER stress. However, after long-term incubation (1 week) with salubrinal, the eIF2α phosphorylation levels were markedly higher following further repression of global translation and reduction of synaptic proteins that resulted in severe neuronal loss and significantly accelerating disease. Herein, we can conclude that Aβ-induced cell death has little correlation with eIF2α phosphorylation level. In addition, Leslie A. Krushel and coworkers found that APP could also be synthesized through IRES-mediated translation. Besides, they suggested that the APP 5′-leader consists three regions including 5′50 nt, the internal 44 nt and 3′53 nt, furthermore, the region of 5′50 nt is sufficient to internally initiate translation (i.e., this region is sufficient to exhibit IRES activity, although total IRES activity was reduced by approximately half of the full-length APP leader) [25]. Given all that, I suggested that this kind of translation manner via eIF2α-independent mode can make APP synthesis resistant to the limitation of cell respond phosphorylating subunits of eIFs under ER stress or other pathophysiological stress.

Proposal and evaluation of hypothesis

Hypothesis

In this article, I proposed two methods as a potential treatment. A: RNA editing on 50 nt of the APP 5′-UTR [25]. B: Editing/removing the IERS element within longer 5′-UTR [26].

Evaluation of hypothesis

First, there is a significant necessity for research operation mechanism of IERS-mediated translation of APP via avidin–biotin RNA affinity chromatography and additional biochemical, molecular biological, and cell culture methods to ensure the validity of the eIF2α-independent mode of APP synthesis [19]. Subsequently, the effects of the two methods should be tested by identifying apoptotic neurons and the viability of the neurons. In order to verify successfully, the appropriate infected cell mode and three experimental groups (A, B, A + B) should be set. The two methods also should be tested to know whether they influence traditional translation. In practice, method B should not be considered unless method A is ineffectual. The intrinsic mechanisms of hypothesis: Under normal condition, if hypothesis make good, this kind of treatment will not obstruct the normal levels synthesis of APP to keep APP operate normal functions because the translations of APP are conducted via traditional manner predominantly this moment. On the other hand, under pathological stress conditions, APP synthesis can be performed neither traditional translation (eIF2α-dependent manner) due to eIFs phosphorylation and cleavage nor IRES-translation (eIF2α-independent manner) because of lack IRES activity after treatment. In this way, cell can attenuate synthesis of APP and then Aβ to prevent Aβ concentration from exceeding the normal range (Fig. 1).

Discussion

The hypothesis in this article is a treatment method for AD by controlling the IRES-mediated translation of APP intrinsically. In virtue of this rule, a few RNA-binding proteins repressing IRES activity as potential treatments still lack stability and reliability [27–29]. In addition, Martin Holcik suggested that initiation complex formed on the XIAP IRES RNA is indeed translation competent. Therefore, I also try to explore targeting translation initiation factors such as eIF5B

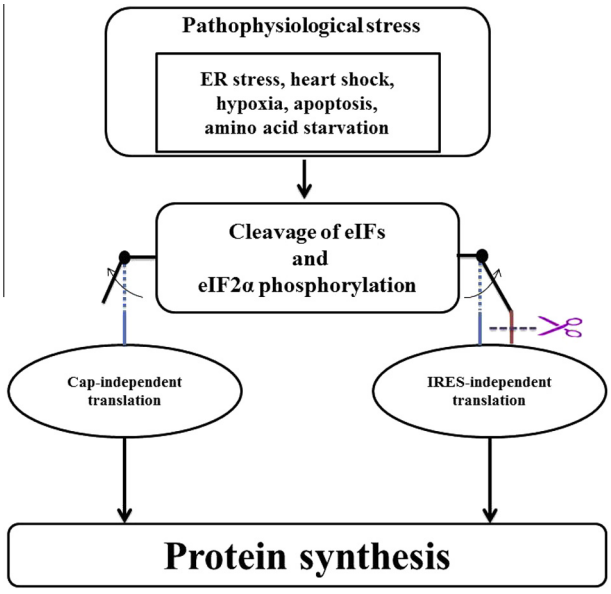

Fig. 1 The diagram of operation mechanism, the blue lines mean the eIF2α-dependent pathway and the red line means the eIF2α-independent pathway. The effects of cellular stress trigger a switch-like in circuit diagram, stopping the cap-independent translation with only one route completely, however, do not blocking IRES-independent translation due to the other route (IRES-translation managers preferentially perform an eIf2α-dependent under normal condition). Herein, the treatment aims to cut the second route response to APP synthesis.

to block the initiation of IRES-mediated translation, however, translations of other proteins and even normal functions of cells are easy to be influenced by lack of enough available translation initiation factors. The treatment in hypothesis is an effective solution of a goal that treatments should maintain the concentration of Aβ within a normal physiological range proposed from the review above [8] and consider the high-level specificity for target protein (APP in this article). Once hypothesis make good, the nerve cells can be survived by self-preservation phosphorylating subunits of eIFs. In this way, treatments will have only minor side effect.

Overview box

First Question: What do we already know about the subject?

The amyloid precursor protein (APP) is most commonly known as the source of the Aβ that accumulate in the brains of patients with Alzheimer's disease (AD). Scientists found that nerve cells could not decrease APP synthesis via self-protection under pathophysiological stress. Most recently, it has been shown that APP synthesis may be performed via a new translation mechanism called as internal ribosome entry segment (IRES)-mediated translation. According to the results, IRES-mediated translation allows proteins to continue translating via an eIF2α-independent manner under pathophysiological stress.

Second question: What does your proposed theory add to the current knowledge available and what benefits does it have?

Although some studies focus on repressing IRES activity as a potential treatment for AD via controlling a few RNA-binding proteins, this method could still cause potential damage for the whole cell due to lack of safety and high-level specificity. If the theory in this article proves to be effective, a safer way to treat AD would be set.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

In order to evaluate whether RNA editing is an effective treatment for AD, first, studies which focus on the operation mechanism of IRES-mediated translation of APP should be conducted. In the next stage, animal testing (using mice) should be further designed. If encouraging results are shown, a study in humans should be considered.

Conflict of interest

The authors report no conflicts of interest.

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