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Eukaryotic initiation factor 4A (eIF4A) during viral infections

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Abstract
The helicase eIF4A is part of the cellular eIF4F translation initiation complex. The main functions of eIF4A are to remove secondary complex structures within the 5′-untranslated region and to displace proteins attached to mRNA. As intracellular parasites, viruses regulate the processes involved in protein synthesis, and different mechanisms related to controlling translation factors, such as eIF4A, have been found. The inhibitors of this factor are currently known; these substances could be used in the near future as part of antiviral pharmacological therapies in instances of replication cycles in which eIF4A is required. In this review, the particularities of how some viruses make use of this initiation factor to synthesize their proteins are discussed.

Keywords eIF4A · Translation · Virus · Initiation

Introduction

Viruses require viral proteins to form new particles. This process depends on the cellular translational machinery; therefore, viruses have developed mechanisms that favor the synthesis of their proteins over cellular protein synthesis [1, 2]. Different studies have suggested the possible roles of translation initiation factors during viral infections, and the eIF4F complex is one of the most widely studied translation initiation factors and is commonly used by certain viruses [3–5].

Consistent with the above statement, the eIF4A protein, which is part of the eIF4F complex, can be regulated during viral infection [6], but the way in which this regulation is accomplished tends to be different in each case, which means that viruses can either use it or not use it at all, or they may alternate between requiring and not requiring the protein.

The eIF4A factor and its role in translation initiation

The synthesis of proteins or translation is divided into three phases—initiation, elongation, and termination—and the objective is to translate the information contained in the mRNA [7, 8]. According to the form of initiation, the translation has been classified as cap-dependent or cap-independent [7].

The cellular mRNAs are characterized by having a structure at the 5′ end, called cap. At the 3′ end, they contain a polyadenylated tract (poly A) bound to the poly(A)-binding protein (PABP) [7, 9, 10]. In the cap-dependent mechanism, the mRNA is recruited to a protein complex called eIF4F, which is composed of three proteins: eIF4E, a cap-binding protein; eIF4A, which is a helicase; and eIF4G, which in turn joins eIF4E and eIF4A and other initiation factors like eIF3 [11–13]. Another complex that participates in the initiation phase is called 43S, formed by the small 40S ribosomal subunit, the eIF3 factor, and the ternary complex formed in turn by eIF2, GTP, and tRNA-methionine-initiator (Met-tRNAi). The eIF4F complex recruits the 43S complex

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through the interaction of eIF3 [12, 14]. The 40S ribosomal subunit carries the eIF2-GTP-Met-tRNAi complex to the start codon AUG, where the 40S and 60S ribosomal subunits bind, giving rise to the full 80S ribosome. The eIF2 protein is released together with GDP and the elongation step is started (Fig. 1) [11, 12, 15, 16].

The eIF4A factor is a DEAD-box helicase, which is composed of two recA-like domains and a flexible central hinge region [17–19]. This factor is part of the eIF4F complex, which is also composed of eIF4G and eIF4E [12, 13, 20]. This complex has been described as a key element in the cap-dependent translation initiation process, which is a highly regulated step [12]. One of the functions of eIF4F is to recruit mRNA for translation; however, eukaryotic mRNA presents secondary structures in the 5′-untranslated region (5′-UTR) that can make translation difficult due to their ability to prevent the assembly of the 40S ribosomal subunit, and they complicate scanning near the start codon [21]. The role of eIF4A helicase activity is to unwind 5′ UTR structures [22].

A number of studies suggest that eIF4A by itself has weak helicase activity. Such activity is stimulated when eIF4B or eIF4H initiation factors are present. In addition, eIF4A removes adhered proteins and heterogeneous ribonucleoprotein molecules from the cellular nucleus that commonly coat mRNA [21, 23, 24].

Until recently, eIF4A was considered to solely could remove structures within mRNA during protein biosynthesis, but recently, specific research has found that eIF4A can be of higher importance and that it can even function as a regulator at different levels [25, 26]. One of the events in which eIF4A participates is in the assembly of stress granules (SGs). These granules are cytoplasmic aggregates in which cellular translation is arrested under stress conditions (reviewed in [27]). Initially, SGs were suggested to be assembled as a response to the phosphorylation of the translation factor eIF2 [28]. However, more recent studies have shown that SGs are also formed as a consequence of eIF4A inactivation [26]. After the discovery that the drug Pateamine A, which favors the binding of eIF4A to mRNA in such a way that functionality is inhibited [29] and that SGs are formed as a result [26], it was proposed that eIF4A is important for protein synthesis control, and consequently, for regulation of gene expression at the translational level. Recently, different research teams have used this initiation factor as therapeutic target in cancer or

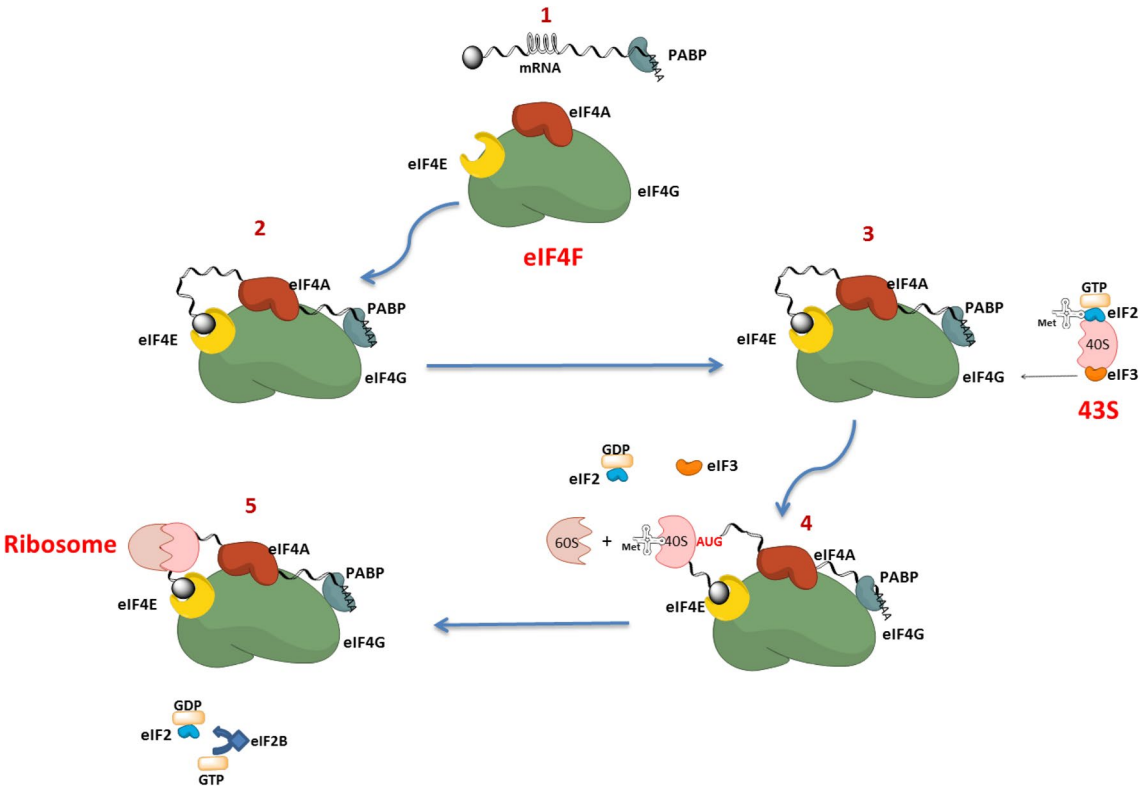

Fig. 1 Initiation of translation. **1** The eIF4F complex—which contains eIF4E, eIF4A, and eIF4G—**2** recruits mRNA through the interaction of eIF4G with the poly(A)-binding protein (PABP), while eIF4E binds to the mRNA 5′ cap. **3** The 43S complex, which contains the small 40S ribosomal subunit, **4** binds eIF4G through eIF3 to carry out the scanning of the mRNA to the start codon, **5** and the full 80S ribosome is subsequently formed. Then the GDP-eIF2 complex is released and gives rise to the elongation phase

during viral infections and have obtained promising and interesting results [30, 31].

In the mechanism known as cap-independent, the presence of a structure known as internal ribosome entry site (IRES) within the 5′-UTR is important for the translation of mRNA. This mechanism was initially described as a trait of the picornavirus family; however, it is now known that IRESs are not found exclusively in viral mRNAs [32, 33]. It has been observed that, in this initiation form, an mRNA with IRES can become translated without requiring any canonical initiation factor—as happens in the cricket paralysis virus (family: Dicistroviridae, genus: Cripavirus) [34]—but may have to be translated with one or more canonical factors such as eIF4A or by using cellular proteins, known as IRES trans-acting factors (ITAFs) [35–37], which have already been described for some viral IRESs [38].

Viral translational mechanisms that benefit from eIF4A

Some viruses employ translational mechanisms for their mRNAs that are similar to those used by cellular mRNAs. For this reason, these viruses draw on mechanisms that ensure or stabilize the formation of eIF4F. One example is cytomegalovirus, which codes for a protein known as pUL69 whose target is eIF4A (Fig. 2a). It has been demonstrated in vitro that pUL69-eIF4A binding ensures that eIF4E remains recruited within eIF4F, and thus, eIF4E is prevented from being sequestered by the regulating protein 4EBP [39]. In addition, to ensure the formation of eIF4F, cytomegalovirus stimulates the synthesis of all components of this complex [40].

The influenza virus, known for having mRNAs with characteristics similar to cellular mRNAs, uses eIF4A to synthesize its proteins. In experimental models, both in vitro and in vivo, there has been evidence of the virus needing, in addition to eIF4A, eIF4G but not eIF4E (Fig. 2b) [41].

The principal function of eIF4A is to remove complex secondary structures in mRNA regardless of the way that

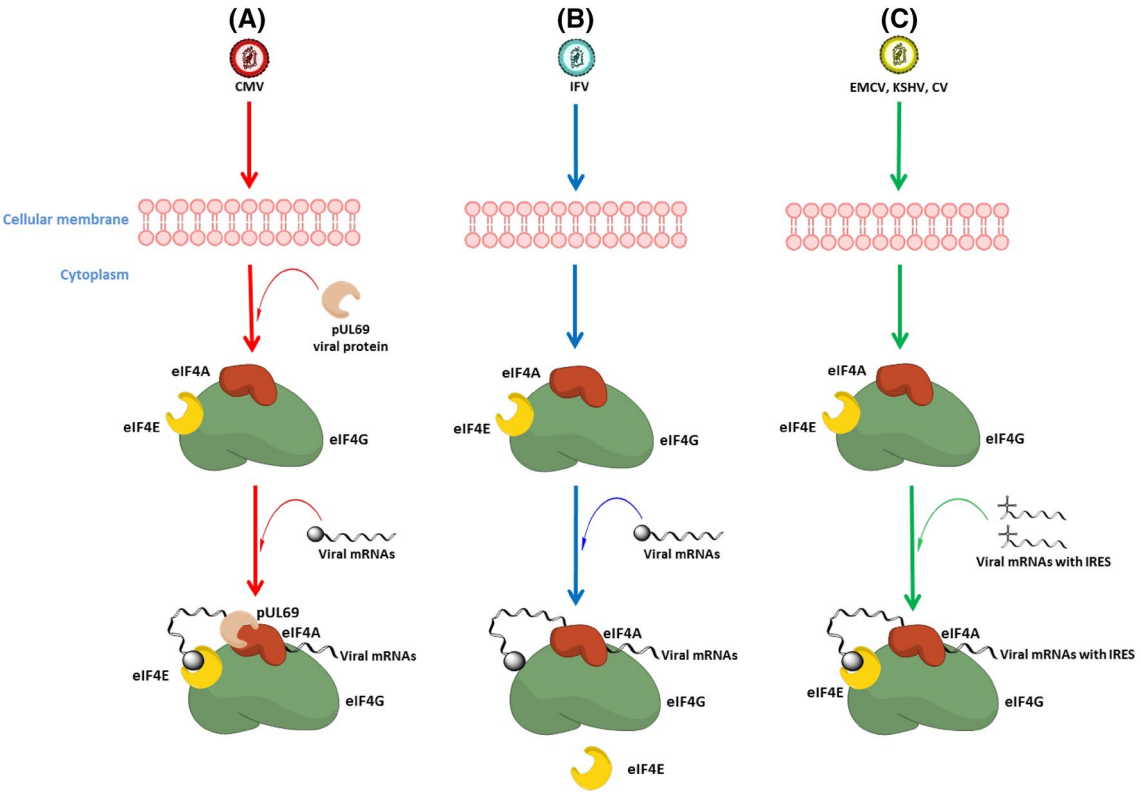

Fig. 2 Translational mechanisms of viral mRNAs that require eIF4A. **a** Cytomegalovirus protein pUL69 (CMV) ensures the recruitment of eIF4A into the eIF4F complex, making it more stable. **b** Influenza virus (IFV) employs a mechanism for the translation of its mRNAs that depends on eIF4A activity and the presence of eIF4G but not on the presence of eIF4E. **c** IRES in mRNAs of encephalomyocarditis virus (EMCV), Kaposi's sarcoma-associated herpesvirus (KSHV), and calicivirus (CV) are all dependent on eIF4A

ribosomal units are recruited. This function of the helicase is crucial not only during cap-dependent translation as part of the eIF4F complex but also during the cap-independent translation of some viral mRNAs via IRES. Consistently, the encephalomyocarditis virus IRES has been found to use an initiation mechanism that depends on this structure in which conformational changes are required in the downstream region of the initial codon while being mediated by eIF4A (Fig. 2c) [42].

Evidence of the participation of eIF4A in the translation of other viral IRES mRNAs has established that, in some occasions, an association between eIF4A and other factors of the eIF4F complex is necessary, such as in the IRES of Kaposi's sarcoma-associated herpesvirus [43] and calicivirus mRNAs (Fig. 2c) [44]. Although the importance of eIF4A binding to other translation factors is not fully understood, it is clear that such interactions increase translation efficiency [43, 44].

eIF4A may not be required during protein synthesis by some viruses

Each virus has evolved differently. As previously mentioned, some viruses employ the classic cap-dependent translational mechanism in which one or more canonical factors are manipulated. There is a case of viral mRNAs, namely, those of hantavirus, in which translation takes place via a cap-dependent mechanism, but the function of eIF4A is substituted by a viral protein named N [45]. What makes this protein even more interesting is the fact that it also plays the roles of eIF4G and eIF4E. The advantage of the N function is not only the substitution of the eIF4F function; it is also able to differentiate between a viral and cellular mRNA, favoring viral mRNA, and consequently, the formation of new viral particles (Fig. 3a) [45]. This case shows the great diversity and multiple functions of viral proteins.

The *Cotesia plutellae* bracovirus (CpBV), a DNA virus (family: Polydnaviridae, genus: *Bracovirus*), inhibits cellular mRNA translation in infected cells through viral proteins that target eIF4A. It has been found that a viral protein termed CpBV15β is synthesized during the late phase of infection. This protein has a region homologous to that of

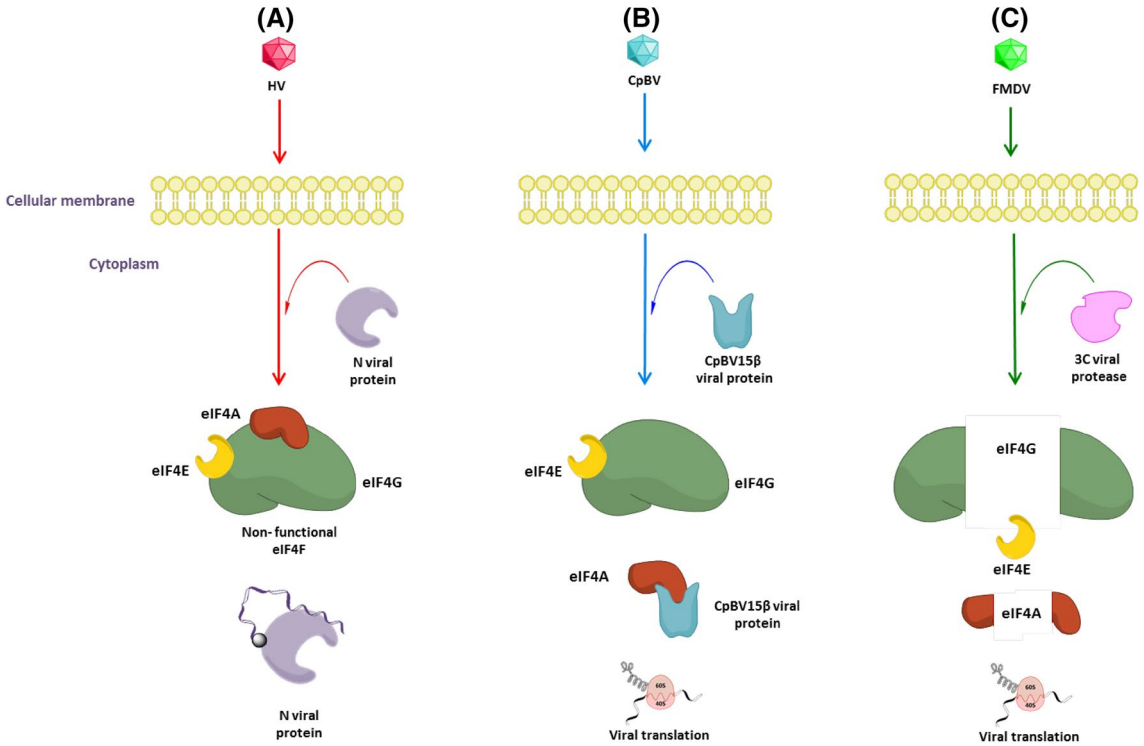

Fig. 3 The eIF4A factor may not be necessary in some viral translation mechanisms. **a** Hantavirus codes for the N protein, which substitutes the function of the eIF4F complex. **b** Protein CpBV15β of *Cotesia plutellae* bracovirus (CpBV) has the task of sequestering eIF4A and thus inhibiting the formation of eIF4F. **c** Protease 3C, coded by the foot and mouth disease virus (FMDV), cuts eIF4A and eIF4G, which increases viral protein synthesis

eIF4G. CpBV15β has the characteristic of binding to eIF4A and sequestering it, thus avoiding the formation of eIF4F (Fig. 3b) [46]. In this late phase of infection, the mRNAs that can be translated contain secondary structures in their 5′ UTR that would only be present in viral mRNAs, resulting in their selection over cellular mRNAs [47].

Cellular initiation factors, such as eIF4G and PABP, have been reported as targets for coded proteases by some viruses [48–51]. There is evidence that eIF4A is a target for these viral proteases, such is the case of protease 3C, coded by foot and mouth disease virus. This protease also cuts eIF4G, making it capable of generating a synergic effect due the cuts of both factors, which results in a decrease of cellular protein synthesis via a cap-dependent mechanism, whereas viral protein synthesis takes place via a cap-independent mechanism (Fig. 3c) [52].

Research addressing the role of the trans-dominant eIF4A mutant and that of hippuristanol, a specific eIF4A inhibitor that prevents eIF4A from binding to mRNA, has confirmed that mRNAs with IRES in some viruses are resistant to these conditions, which suggests the independence of eIF4A from these translation processes. Such is the case for hepatitis C virus, classic swine fever virus [53], porcine teschovirus type 1 [54], and cricket paralysis viruses [55].

Viruses that modulate their requirement of eIF4A according to the context in which they are found

There are interesting examples of the versatility of viral mRNA concerning its translation requirements. Messenger RNA can alternate among different translational mechanisms depending on its current context. Sindbis virus is one of these examples; in infected cells and in cells transfected with replicons of the virus, viral protein synthesis is independent of eIF4A. However, when genomic and subgenomic mRNAs were transfected to cells via a vector, their expression was completely dependent on eIF4A. The presence of any viral protein that could be supplanting eIF4A function during infection has been experimentally discarded [56]; the results of this study suggest that Sindbis virus mRNAs are capable of adapting to different conditions depending on the availability of translation initiation factors.

The genomic mRNA of human immunodeficiency virus type 1 (HIV) has two AUG start codons that allow the synthesis of two isoforms of the Gag protein: codon 1 generates the p55 isoform, and it is translated via a cap-dependent mechanism that uses eIF4A and can switch to the cap-independent mechanism when an IRES structure is present in the 5′ UTR and Codon 2, which generates the p40 isoform, is only translated via cap-independent mechanism through an IRES found in the Gag's ORF [57, 58]. This alternating behavior between cap-dependent and cap-independent translations of codon 1 suggests that some viral mRNAs have to be translated according to intracellular conditions and the availability of initiation factors in order to secure viral protein synthesis.

The eIF4A inhibitors

There are some compounds that have the characteristic of inhibiting eIF4A: silvestrol [59], hippuristanol [60], elisabatin and allolaurintenol [61], rocaglamide [62], and pateamine A and some of its derivatives [30]. These compounds are emerging as a new antiviral therapeutic strategy whose mechanism of action is the inhibition of eIF4A. Consistent with this, silvestrol has shown antiviral activity in vitro against RNA viruses: Ebola virus, hepatitis E, coronavirus, rhinovirus, and poliovirus [59, 63–65]. Hippuristanol has been tested in preclinical studies for possible use in patients with HTLV-1 [31]. Therefore, the use of compounds that inhibit the activity of eIF4A holds great interest in virology as antiviral agents.

Conclusions

Despite the important role of eIF4A in intracellular events, available information on how this protein participates during viral infection is scarce. The eIF4A protein participates in cap-dependent translation as part of the eIF4F complex; paradoxically, it also participates in cap-independent translation via IRES during some viral infections [66]. The fact that eIF4A participates in the replicative cycles of some viruses makes it useful for controlling infections. To date, there are compounds known to have a specific effect on eIF4A. Experimental use of these compounds has shown interesting results in animal study models [31]. Related preclinical studies serve as a foundation for the use of hippuristanol as a therapeutic treatment that could be used against some viral infections in which eIF4A is of high importance to viral replication.

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Author contributions All authors contributed to writing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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