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Review

Targeting RNA helicases in cancer: The translation trap

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ABSTRACT

Cancer cells are reliant on the cellular translational machinery for both global elevation of protein synthesis and the translation of specific mRNAs that promote tumor cell survival. Targeting translational control in cancer is therefore increasingly recognized as a promising therapeutic strategy. In this regard, DEAD/H box RNA helicases are a very interesting group of proteins, with several family members regulating mRNA translation in cancer cells. In this review, we delineate the mechanisms by which DEAD/H box proteins modulate oncogenic translation and how inhibition of these RNA helicases can be exploited for anti-cancer therapeutics.

1. Introduction

The crux of anti-cancer drug development is walking the fine line between efficacy in cancer cells and normal cell toxicity. In the current era of targeted therapy a common approach is to try to develop inhibitors for oncogenes that are driving a specific cancer, but are absent, (temporarily) redundant or compensated for in normal cells. Although this approach is logical and specific, it has the inherent problem that few driver mutations are actually targetable. In addition, in the last decade large-scale sequencing studies have shown that there are only a handful of oncogenes frequently mutated, whereas cancers are mostly driven by their own unique set of low-frequency genetic alterations [1], limiting the use of potential inhibitors to a small subset of patients. An alternative approach is not to target the genetic factors directly driving oncogenesis, but the vulnerabilities that arise as a result of stress phenotypes that allow cancers to thrive. Cancer cells are dependent on specific cellular pathways for execution of oncogenic functions and simultaneous maintenance of cellular homeostasis. Since these pathways are often shared among tumors with different genetic alterations, these so-called non-oncogene addiction factors could be the Achilles' heel of cancer and potentially provide more widely applicable targets for therapeutic development.

Specific stressors in cancer cells cause non-oncogene addiction to different potentially targetable cellular pathways. A well-known example is the dependence of certain cancer types on DNA damage repair pathways as a result of genomic instability. Another example of non-oncogene addiction is the reliance on translation factors. Cancer cells are dependent on the translational machinery for both global elevation of protein synthesis, as well as the translation of specific mRNAs that promote tumor survival [2]. The first observation indicating that regulators of mRNA translation are key facilitators of cancer cells is more than a century old, when prominent nucleoli, reflecting increased ribosome production to meet enhanced protein synthesis demands, were recognized as a morphological hallmark of cancer [3]. Energetically translation is the most demanding and rate-limiting step of the gene expression process [4]. In addition, we now know that variation in protein abundance is only partially (~40%) determined by transcript abundance, and instead was found to be predominantly controlled at the mRNA translation level [5]. It is therefore not surprising that translation is a prime target of several signaling pathways driving oncogenesis (e.g., mTORC1, MYC and MAPK signaling) [6]. In addition, both enhanced expression or activity of proteins involved in translation [7] and uncoupling of translation inhibition from tumor cell stressors (e.g., hypoxia, nutrient deprivation) are commonly observed in cancer [8]. In the past years, we have gained a vast body of knowledge on what specific changes occur in the translational machinery in cancer cells [7] and, although still in its infancy, the field of targeting translational control beholds great promise for anti-cancer drug development [2].

DEAD/H box RNA helicases are an interesting group of proteins serving as potential translational targets in cancer. These proteins belong to superfamily 2, the largest group of eukaryotic RNA helicases, are named after a conserved amino sequence (Asp-Glu-Ala-Asp/His) and have the ability to unwind and restructure RNA molecules with complex secondary structures in an ATPase dependent fashion. They remodel complex RNA structures like hairpins and mRNP complexes [9] and have been reported to play a pivotal role in virtually all steps of mRNA processing and translation. Interestingly, cancer cells seem to rely heavily on RNA helicases to meet not only the increased general

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protein synthesis demand, but also for translation of specific pro-oncogenic mRNAs to enhance survival [2]. In this review, our main objective is to evaluate DEAD/H box RNA helicases as potential targets in cancer translation. We will focus specifically on the mechanisms by which DEAD/H box proteins modulate translation of oncogenes and how inhibition of these RNA helicases can be exploited for anti-cancer therapeutics.

2. Role of DEAD/H box proteins in translating the cancer genome

Human cells have multiple mechanisms to translate mRNAs into proteins. The most abundant translation mechanism in eukaryotes is cap-dependent translation. However, under stressed conditions, translation initiation can also occur in a cap-independent fashion, where the ribosomes are directly recruited to the start codon by binding a so-called internal ribosomal entry site (IRES). In addition, mitochondria have their own genome and independent translational machinery. In the following paragraphs we will explain how these three translational mechanisms are reliant on DEAD/H box RNA helicase activity, and how these processes are specifically important for translating the cancer genome.

2.1. DEAD/H box RNA helicases mediate cap-dependent translation initiation of oncogenic mRNAs with a complex 5′UTR structure

In contrast to bacteria, where ribosomes are directly recruited to the initiation codon by binding the Shine-Dalgarno mRNA sequence, cap-dependent translation in eukaryotes is a more intricate process [10] (Fig. 1A). The translation initation complex eIF4F recruits the 40S ribosomal unit to the 5′ m^7G-cap structure of the mRNA. eIF4F consists of three subunits: (1) eIF4E binds the complex to the m^7G-cap, (2) eIF4A is a DEAD box RNA helicase that unwinds local RNA structures, and (3) eIF4G has scaffolding function and recruits the complex to mRNA through interaction with eIF3 [10]. Oncogenic PI3K/Akt/mTOR signaling influences eIF4F formation in several ways. eIF4E is sequestered from the eIF4F complex by eIF4E binding proteins (4E-BPs). mTOR signaling results in 4E-BP phosphorylation and inactivation, hereby liberating eIF4E [11]. In addition, it stimulates its downstream target S6K1, which phosphorylates and hereby causes degradation of PDCD4, an inhibitor of eIF4A [11]. A complex of translation initiation factors, among which eIF4F, eIF3, the initiator tRNA (Met-tRNA) and the 40S ribosomal unit together form the 43S ribosomal pre-initiation complex, which starts scanning the mRNA sequence in a 5′ to 3′ direction until it encounters the start codon. After base pairing of the Met-tRNA and the start codon, the 48S ribosomal complex is formed. Subsequently the 60S ribosomal unit gets recruited and after release of the initiation factors, the 48S and 60S complexes together form the mature 80S ribosomal complex that is competent for translation elongation [10]. Secondary structures, high GC content and bound proteins in the 5′UTR area impede ribosomal scanning for initiation sites and binding of the translation initiation machinery [12]. Several DEAD/H box proteins facilitate translation initiation in the presence of a complex 5′UTR, which can be resolved by their helicase activity. Interestingly, among the proteins that have mRNAs with structured or long 5′UTRs are many (proto) oncogenes [13]. Systematic searches of bacterial and human genomes identified 5′ UTR mRNA regions containing secondary structures called G-quadruplexes to be enriched for genes involved in processes such as replication, cell cycle control and cell motility [14,15]. In line with this observation the potential for G-quadruplex formation at 5′ UTRs was found to be significantly higher among oncogene than tumor suppressor gene [16]. It is therefore intuitive that several oncogenes require RNA helicase activity to be expressed to their fullest extent. Below we will describe several ways in which DEAD/H box RNA helicases modulate cap-dependent translation of oncogenes with a complex 5′UTR.

2.2. eIF4A and DHX29 are general unwinders of moderately complex 5′UTR oncogenes

The most extensive evidence for requirement of RNA helicase activity for complex 5′UTR unwinding exists in the case of elongation initiation factor 4A (eIF4A). There are three human eIF4A isoforms that are encoded by separate genes. eIF4AI (DDX2A) and eIF4AII (DDX2B) have a 91% sequence identity and although some differences with regard to their function in translation have been reported [17], most

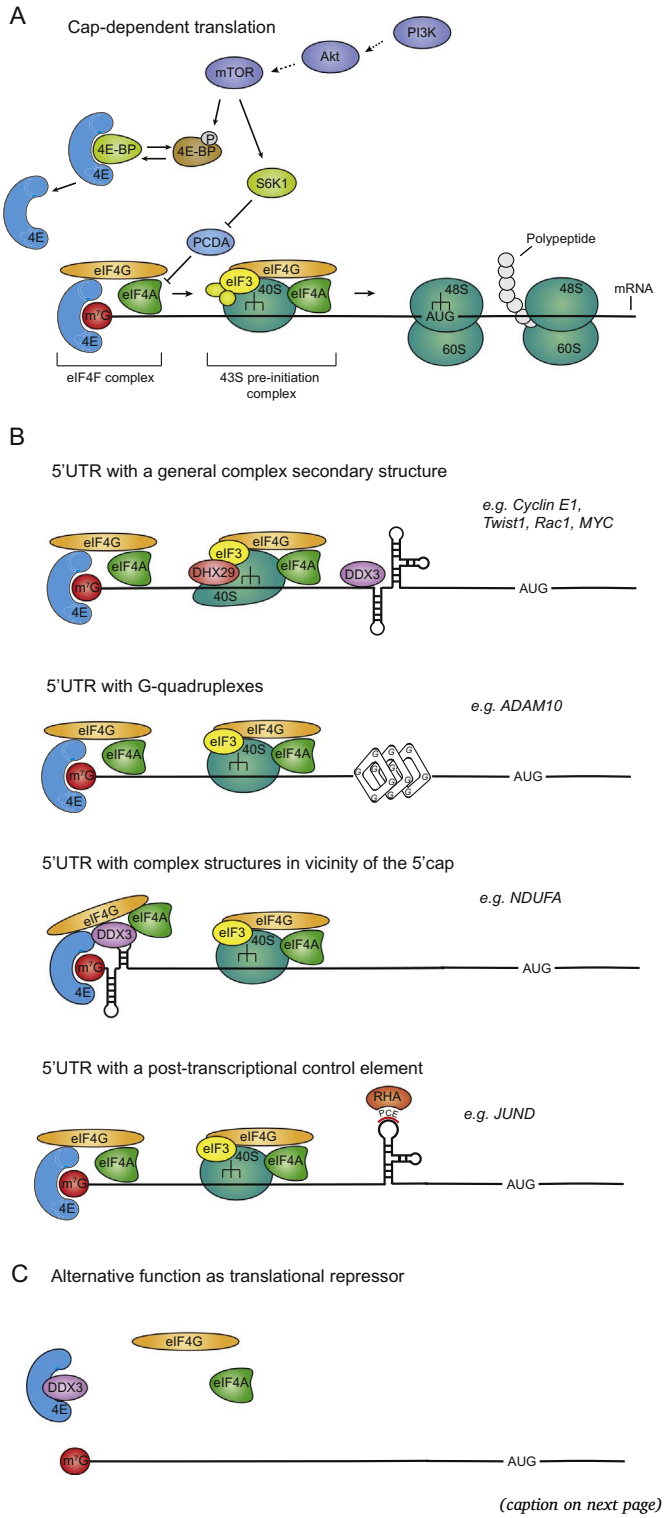

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Fig. 1. DEAD/H box RNA helicases mediate cap-dependent translation initiation of oncogenic mRNAs with a complex 5′UTR structure.
A. Schematic representation of cap-dependent translation. The three subunits of the eIF4F translation initiation complex recruit the 40S ribosomal unit to the 5′ m^7G-cap mRNA structure and together with several initiation factors and the initiator tRNA form the 43S pre-initiation complex, which scans the 5′UTR until it encounters the AUG start codon. Subsequently, the 60S ribosomal unit is recruited and together with the now 48S small subunit forms the mature 80S ribosomal complex that is competent for translation elongation. Cap-dependent translation is stimulated by oncogenic PI3K/Akt/mTOR signaling through phosphorylation and hereby inactivation of eIF4E-binding protein (4E-BP), which sequesters eIF4E from eIF4F, and via activation of S6K1, which inactivates PCDA, an eIF4A inhibitor.
B. Schematic representations of how RNA helicases facilitate cap-dependent translation of mRNAs with a complex 5′UTR region. eIF4A (DDX2) unwinds secondary structures in the 5′UTR and is essential for translation of mRNAs with G-quadruplexes [21,22]. DHX29 modifies the 40S ribosomal subunit and hereby enhances its processing activity [25]. DDX3 was found to facilitate both translation of general complex secondary structures [32,33], as well as mRNAs with secondary structure in immediate vicinity to their m^7GTP cap [31]. RHA (DHX9) promotes translation of mRNAs with a specific RNA sequence containing two stemloop structures known as the post-transcriptional control element (PCE) in their 5′ UTR [50].
C. Alternative roles for DDX3 as a translational repressor through binding and sequestration of eIF4E have also been reported [29].

studies do not differentiate between the two. We will refer to both isoforms by eIF4A, unless one isoform is specifically indicated. eIF4III (DDX48) has distinct functions as a translational repressor [18]. eIF4A is the prototype DEAD box RNA helicase consisting only of a helicase core, while lacking the prominent N- and C-terminal domain present in most other family members. The activity of eIF4A is highest when it is incorporated into the eIF4F complex and is stimulated by its interacting partners eIF4B and eIF4H. For a more detailed description of the interactions between several RNA helicases and other translation initiation factors we refer to an excellent recent review [9]. Although general translation initiation is impaired after eIF4A inhibition [9,19], the requirement for eIF4A for translation initiation was found to be directly proportion to the complexity of the mRNA 5′UTR region [20] (Fig. 1B). Polysome profiling and ribosome footprinting experiments confirmed that the eIF4AI dependent translatome is enriched for mRNAs with a complex 5′UTR [21], in particular those characterized by long length, GGC repeats and the presence of G-quadruplexes [22] (Fig. 1B). Among the genes reliant on eIF4AI for efficient translation is a long list of oncogenes (e.g. MYC, NOTCH1, MYB, CDK6, MDM2, CCND3, BCL2, ETS1, ADAM10, LEF1, BCL10, MALT1, ARF6, CCND1, ROCK1) [22,23].

Another DEAD/H box family member involved in translation initiation in general and especially of mRNAs with a complex 5′UTR is DHX29. DEAH proteins seem to have more RNP remodeling than continuous RNA unwinding activity and unlike eIF4A, DHX29 does not seem to directly unwind secondary mRNA structures, but instead most likely modifies the 40S ribosomal unit to facilitate mRNA entry [24] and enhance its processing activity [25] (Fig. 1B). Thus, DHX29 ensures correct mRNA position in the 43S ribosome and stimulates assembly of the 80S ribosomal complex [26], especially on mRNAs with a complex 5′UTR.

2.3. A specific role for DDX3 in unwinding very long and complex 5′UTRs in close vicinity to the 5′ cap structure?

Although eIF4A has the ability to resolve most 5′UTR regions with secondary RNA structures, it has also been reported that very long 5′UTRs with multiple stem loops are resistant to eIF4A and that additional RNA helicases are needed to support cap-dependent translation [27]. Ded1, the yeast homologue of DDX3, was found to have more potent unwinding activity [28]. Whether DDX3, like Ded1, is essential for general translation initiation in human cells is an ongoing investigation [29,30], with most studies inferring that DDX3 inhibition does not result in major changes in general protein synthesis [24,31,32]. However, there is evidence that DDX3 plays a role in translation initiation of mRNAs with specific 5′ UTR features. DDX3 facilitates local strand separation to allow loading of the pre-initiation complex and is required for translation initiation of mRNAs with a long 5′ UTR [32,33] or high GC content [33] and mRNAs with complex structures (e.g. stem loops) in immediate vicinity to their m^7GTP cap, which inhibit binding of the eIF4F complex [31] (Fig. 1B). DDX3 was implied to allow RNA binding of the eIF4F complex by direct interaction with eIF4G [31] and eIF4A [32]. In addition, binding with the translation initiation promoting factor eIF3 was reported [30]. Contradictory reports however found DDX3 to bind and sequester eIF4E, disabling proper formation of the eIF4F initiation complex [29] (Fig. 1C). In addition, it was reported that human recombinant DDX3 has no effect on 48S formation in the presence of stem loops [24] and even that DDX3 inhibits translation of a reporter with a stem loop containing 5′UTR [34]. Potential explanations for these discrepancies are differences in cell lines or reporter types used, or the fact that an inhibitory role was mainly observed after overexpression of recombinant DDX3 [29,32]. Expression of RNA helicases has been suggested to maintain a ‘Goldilocks zone’ like equilibrium, where too little is harmful, but very high expression can have a disturbing effect on cellular functions as well [35]. In addition, production of full length human recombinant DDX3 for in vitro studies has been proven problematic [36] and studies on its enzymatic function are hampered by it being a constituent of several multiprotein complexes and having a dynamic nature with multiple conformations [9]. In support of a translation initiation promoting role for DDX3, it was found to be required for translation of several oncogenes with a complex or long 5′UTR, among which are cell cycle regulators like cyclin E1 [33] and Rac1 [37]. The combined evidence from literature is more supportive for a stimulatory role of DDX3 on translation initiation, but the exact role of DDX3 on cap-dependent translation initiation remains ambiguous and deserves further investigation.

DDX3 mutations were identified in several cancer types [38], among which medulloblastomas [39], head and neck squamous cell carcinomas (HNSCC) [40], and hematological malignancies [41–43]. In medulloblastomas, 50% of the Wnt subtype and 11% of the SHH subgroup tumors have a DDX3 mutation. All mutations in medulloblastomas are non-synonymous missense mutations in the helicase core domain. The mutations were primarily thought to be gain-of-function, since a stimulatory effect on oncogenic Wnt-signaling has been reported [39]. However, more recent reports have found that the mutations have inhibitory effects on mRNA translation. Specific mutations occurring in medulloblastoma were found to result in reduced RNA unwinding activity [44], defects in RNA-stimulated ATP hydrolysis [45] and hyper-assembly of RNA stress granules, which have a general inhibitory effect on translation [46]. It was proposed that inhibition of translation potentially provides a survival advantage to medulloblastoma cells during progression. Unlike medulloblastoma, where all mutations where single nucleotide variations, deleterious frameshift mutations were detected in HNSCC [40] and cancers of hematological origin [41–43]. Whether the functionality of these mutations is similar to those occurring in medulloblastoma remains to be evaluated. Genetic alterations in *DDX3X* are in stark contrast with the reports on overexpression of DDX3 in several cancers as compared to the normal tissue of origin [47]. High DDX3 expression correlated with high grade and worse overall survival in breast [48] and lung cancer [49]. DDX3 mutations were not frequently detected in genome wide mutation analyses in these cancer types. It is unclear why some cancers appear to benefit from low DDX3 activity, whereas others benefit from high DDX3 expression levels.

2.4. RNA helicase A and YTHDC2 facilitate translation by binding specific RNA sequences

Another example of a DEAD/H box family member that is not involved in general translation, but has a role in translation of specific mRNAs with a complex 5′UTR is the DEAH box protein, RNA Helicase A

(RHA/DHX9). RHA was found to promote translation initiation of retroviral RNAs by interaction of its N-terminal double strand RNA binding motives (dsRBD) with a specific RNA sequence containing two stemloop structures known as the post-transcriptional control element (PCE) in their 5′ UTR [50] (Fig. 1B). Interestingly there are also mammalian mRNAs with 5′UTR containing a similar sequence, such as the oncogene *JUND* [50].

YTHDC2 is another DEAH box RNA helicase with a conserved domain binding specific RNA sequences. The YTH domain binds to N6 methylated adenosines (m^6A), a post-transcriptional RNA modification enriched in stop codons and the 3′UTR, which has been associated with modulation of translation efficiency through recruitment of translation initiation factors [51]. However, YTHDC2 has recently also been associated with translation initiation in the presence of a complex 5′UTR. Knockdown of YTHDC2 resulted in accumulation of several mRNAs in the 40S ribosomal fraction, indicating translation was stalled at the initiation phase. Overall this group of mRNAs was not characterized by long or complex mRNAs. However, reporter assays indicated YTHDC2 was required for translation of the proto-oncogenes *TWIST1* and *HIF1α* that both do have long a particularly long and structured 5′UTR [52]. Further studies are required to better characterize the YTHDC2 and RHA translatome.

It is interesting to note that some DEAD/H box family members are also involved in repression of mRNA translation through interaction with the 3′UTR. YBX1 and eIF4E recruit the general translation repressor DDX6 (RCK/p54) to the 3′UTR of mRNAs involved with self-renewal (e.g. CDK1, EZH2) and destabilizes them in a miRNA dependent manner [53]. DDX6 also interacts with A-rich elements (ARE) in the 3′UTR to negatively regulate translation [54]. Although interesting, negative regulation of translation by RNA helicases through miRNA involvement is beyond the scope of this review.

2.5. Specific DEAD/H box proteins are required for IRES-dependent translation due to oncogenic stress

Cellular stress conditions, like growth arrest, nutrient starvation, hypoxia, DNA damage, mitosis and apoptosis, occur frequently in cancer cells. In response to these stressors, cap-dependent translation is downregulated in order to preserve nutrients and energy [55]. Many genes that are upregulated by cells to cope with stress conditions are translated in an IRES dependent fashion [56], which does not require a 5′ cap structure, the cap-binding protein eIF4E or a free 5′ end. Cellular IRES often have a strong secondary structure that recruits the 40S ribosomes to the translation initiation site, either by binding directly to the ribosome or indirectly by binding canonical translation initiation factors like eIF3 and eIF4G or specific IRES transacting factors (ITAFs) [56](Fig. 2). Because tumor cells are dependent on factors to maintain cellular homeostasis and survive under stressed conditions, IRES mediated translation has been put forward as a therapeutic target in cancer [56]. Among the IRES mediated proteins are anti-apoptotic proteins like BCL-2 [27], c-IAP1 [57] and XIAP [55], growth promoting proteins like MYC [58], EGFR [59] and c-jun [60], cell cycle regulator CDK1 [27] and regulators of angiogenesis like HIF-1A [61] and VEGF [62]. However, several IRES mediated transcripts have opposing functions and not all promote oncogenesis (e.g., p53 [63]). In addition, not all cellular mRNA's that contain IRES elements function as such, and there is need for proper functional validation [2].

Different IRES require different auxiliary translation initiation factors to facilitate ribosomal recruitment and translation onset [9,19]. DEAD/H box family members have been found to facilitate IRES dependent translation of certain oncogenic mRNAs. Inhibition of eIF4A was found to block IRES dependent translation of EGFR [59] and c-MYC [58] under hypoxia and IRES dependent translation of the transcription factor LEF1 [64] (Fig. 2). DDX3 was found to have a stimulatory role on translation of the Hepatitis C Virus IRES [29,30], potentially through its interaction with eIF4E. However, it remains to be seen whether DDX3 also mediates IRES dependent translation of cellular mRNAs.

Not all effects of DEAD/H box family members on IRES dependent translation are stimulatory or pro-oncogenic. The conformational changes imposed by DHX29 on the 40S ribosome, impede ribosomal binding to certain IRES [25]. In addition, DHX9 (RHA) mediates IRES dependent translation of p53 under genotoxic stress [63] and through this mechanism has more of a tumor suppressive role. Furthermore, DDX6 reduces IRES translation of VEGF in hypoxic cells [65].

2.6. Involvement of RNA helicases in mitochondrial translation

Mitochondria function as the ATP-generators of eukaryotic cells and most likely are derived from an incorporated bacterial ancestor. Although most of its genes have been transferred to the nuclear genome, mitochondria still have their own circular genome encoding 13 proteins, 2 rRNAs and 22 tRNAs [66]. These 13 genes all translate into subunits of four out of the five oxidative phosphorylation (OXPHOS) complexes (Fig. 3). The remainder of the proteins in these complexes is encoded on the nuclear genome, translated in the cytoplasm and imported into the mitochondria. Together the OXPHOS complexes are responsible for generating an H^+-gradient over the mitochondrial inner membrane that fuels ATP-synthase (complex V). Mitochondria have maintained their own (nuclear encoded) transcriptional and translational machinery, which is uniquely different from general protein synthesis in both eukaryotes and bacteria. Excellent reviews that explain what is known about mitochondrial translation are already published [67]. Briefly, the mitochondrial genome yields two poly-cistronic mtDNA transcripts that get cleaved into 9 mono-cistronic and 2 bi-cistronic mt-mRNAs. Mammalian mt-mRNAs lack a significant 5′UTR (Fig. 3). The mitoribosome consists out of a 28S small subunit and a 39S large subunit, which with the help of the mitochondrial initiation factors mtIF2 and mtIF3 bind directly to the start codon of the mt-mRNA, hereby initiating translation. The large subunit is anchored to the inner mitochondrial membrane and is believed to facilitate incorporation of the newly synthesized OXPHOS proteins [67].

Cancer metabolism is an area of renewed attention. One of the best known metabolic alterations in cancer cells is the upregulation of glycolysis in the presence of oxygen, the so-called Warburg effect. This aerobic glycolysis phenomenon is often erroneously interpreted as a sign of impaired OXPHOS in cancer. In fact, increasing evidence indicates that cancer cells are reliant on mitochondria for their bioenergetic machinery and macromolecule synthesis function [68], especially when encountering cellular stressors, like chemotherapy [69], radiation therapy [70] or during metastasis [71]. It is therefore not surprising that mitochondrial respiration is being recognized as viable target for cancer therapy [68]. Given the involvement of mitochondrial translation products in OXPHOS, targeting mitochondrial translation is an approach to selectively inhibit mitochondrial translation functions and has been identified as a therapeutic target in the treatment of acute myeloid leukemia [72].

Although mt-mRNA seems to lack a complex 5′UTR in need of unwinding, there is evidence for the (indirect) involvement of DEAD/H box RNA helicases in mitochondrial translation. The RNA helicases DDX28 [73] and DHX30 [74] facilitate mitoribosome assembly in the an area that serves as the mitochondrial equivalent of the nucleolus, called mitochondriolus [73] or processing body (Fig. 3). DDX28 interacts mainly with the 16S rRNA and large mitoribosomal unit, and DHX30 was identified in all mitoribosomal fractions [74]. The mitoribosome assembly process has only recently started being uncovered, and it is likely that other RNA helicases are involved in this process as well. Interestingly, DDX3, DDX5 and RHA were detected by mass spectrometry in the immunoprecipitate of mitochondriolus' proteins GRSF1 and DDX28 after crosslinking [73,74]. DDX3 does localize to the mitochondria [48] and inhibition of DDX3 with the small molecule inhibitor RK-33 resulted in decreased mitochondrial translation, and hereby decreased synthesis of OXPHOS complexes. As a result,

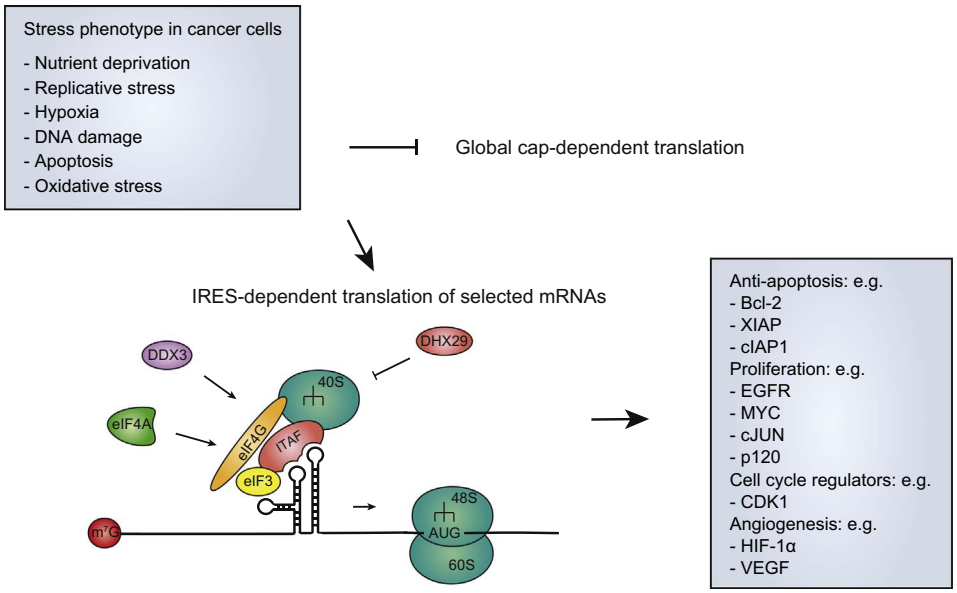

Fig. 2. Specific DEAD/H box proteins are required for IRES-dependent translation due to oncogenic stress.
Schematic representation of how cellular stress conditions that occur frequently in cancer cells inhibit global cap-dependent translation and activate IRES-dependent of selected mRNAs. 40S ribosomes are recruited to the secondary structure of the IRES, either directly or by binding canonical translation initiation factors like eIF3 and eIF4G or specific IRES transacting factors (ITAFs) [25]. Both eIF4A and DDX3 facilitate IRES dependent translation of specific mRNAs [29,58,59], whereas the conformational changes imposed by DHX29 on the 40S ribosome, impede ribosomal binding to certain IRES [25].

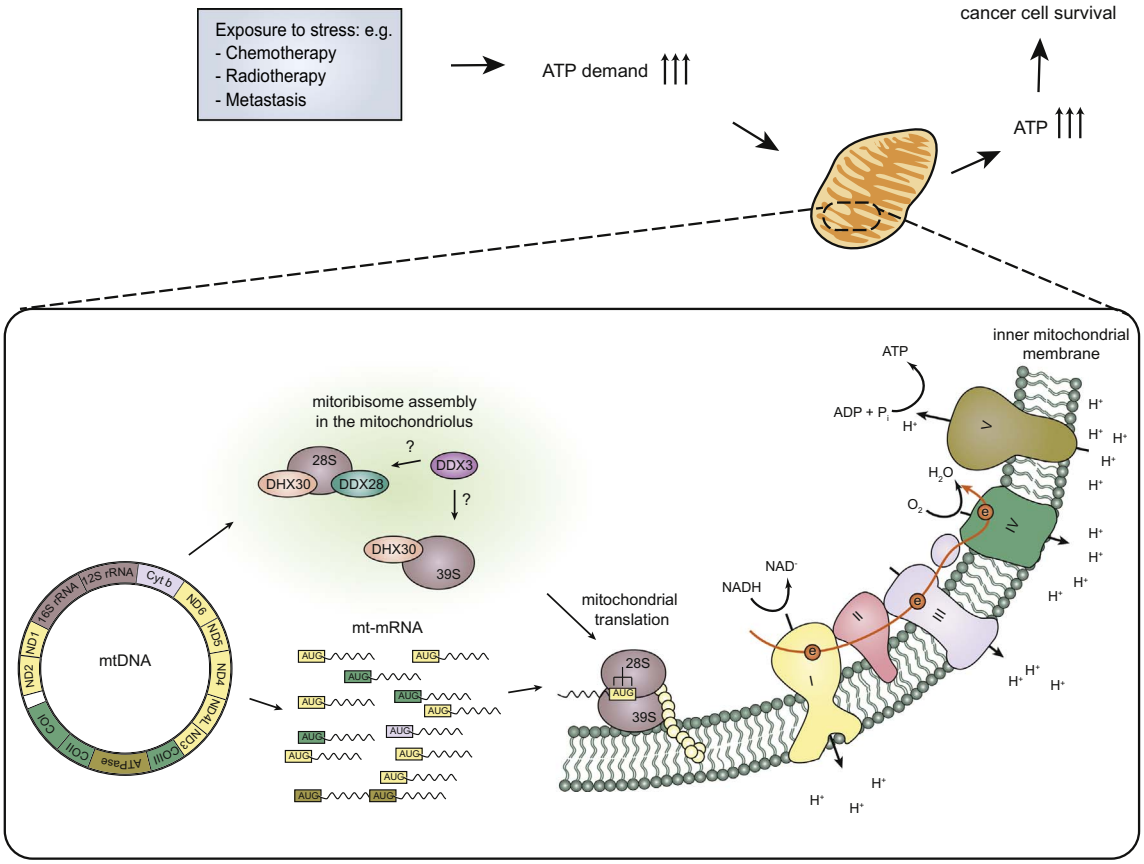

Fig. 3. The involvement of RNA helicases in mitochondrial translation promotes cancer through synthesis of OXPHOS proteins.
Schematic representation of how exposure to stressors in the cancer cell environment (e.g., radiotherapy) can cause a sudden increase in the need for ATP, which is met by mitochondrial upregulation of oxidative phosphorylation, hereby supporting cancer cell survival. Oxidative phosphorylation (OXPHOS) occurs on the inner mitochondrial membrane. Complexes I-IV of the electron transport chain create a H^+-gradient that fuels ATP-synthase (complex V), which converts ADP into ATP. The mitochondrial genome (mtDNA) contains genes encoding 13 proteins that are all part of OXPHOS complexes. Mitochondrial mRNAs (mt-mRNA) are translated by the mitochondrial translation complex called the mitoribosome. Assembly of the 28S small and 39S large mitoribosome subunits occurs in a distinct mitochondrial area called the mitochondriolus [73], and is facilitated by DDX28 [73], DHX30 [74] and possibly DDX3 [48].

decreased OXPHOS capacity and increased ROS production were observed, culminating in bioenergetic catastrophe in cancer cells [48]. Future studies are needed to further evaluate the specific role of DDX3 in mitochondrial translation facilitation.

2.7. DEAD/H box RNA helicases mediate oncogenesis through other cellular processes

DEAD/H box RNA helicase family members are involved in almost

all steps of RNA metabolism and our knowledge of their involvement in oncogenesis remains growing. How RNA helicases mediate oncogenesis by other means than regulating translation lies beyond the scope of this review. However, it is worth mentioning that RNA helicases have additional roles in cancer biology through regulation of transcription and alternative splicing (e.g., DDX5, DDX17, RHA and DDX53), ribosomal biogenesis (e.g., DDX5, DDX21, DDX43 and DHX33), mRNA export (e.g., DDX5, DDX3), miRNA regulation (e.g., DDX3, DDX5, DDX6, DDX17, DDX23) and apoptosis (e.g., DDX3, RHA), among other processes. For a more elaborate and systematic overview of the additional roles of DEAD/H box RNA helicases in cancer, we refer to several more general recent reviews [75].

3. Targeting oncogenic translation with DEAD/H box RNA helicase inhibitors

3.1. Development of eIF4A inhibitors

Knockdown experiments of eIF4A reduced proliferation and induced cell death in cancer cell lines [17,76]. In addition, in murine models overexpression of eIF4A accelerated leukemia development [22]. Several eIF4A inhibitors are currently under development and are thought to exert their effect by translational inhibition of key oncogenes (e.g., *c-MYC*) [21–23,76] (Table 1).

The polyoxugenated steroid Hippurastinol was isolated from the coral *Isis hippuris* and identified in a screen to inhibit protein synthesis [77]. Hippurastinol binds to the c-terminal domain of eIF4A and was found to specifically inhibit its ATPase, helicase and mRNA binding activity [19] (Fig. 4). Translation initiation could be rescued with recombinant eIF4A after Hippuristanol treatment, showing that Hippuristanol specifically mediates it effect through eIF4A inhibition [19]. mRNAs with a long or complex 5′UTR are most affected by Hippurastinol treatment [78].

The natural product Pateamine A (PatA) was derived from the marine sponge *Mycale* sp. and stimulates RNA binding activity of free eIF4A (eIF4A$_F$) [79]. Inhibition of eIF4A$_F$ was found to inhibit cap-dependent translation, most likely by a conformational change increasing the RNA affinity, hereby sequestering it and perturbing the interactions of eIF4A$_F$ with other translation initiation factors [80] (Fig. 4). Surprisingly, PatA also increases the Helicase and ATPase activity of eIF4A [81]. Both PatA and the PatA analogue des-methyl desamino Pateamine A (DMDA-PatA) affect DNA and RNA synthesis, as well [81,82] and PatA does not inhibit eIF4A incorporated in eIF4F (eIF4A$_c$), which has about 20-fold higher enzymatic activity [79]. Whether PatA analogues are directly exerting their working mechanism through eIF4A inhibition requires further evaluation.

Derivatives of the *Aglaia foveolata* plant (rocaglates/flavaglines), which are characterized by a common cyclopenta[*b*]benzofuran skeleton, were also found to inhibit protein synthesis through increasing the mRNA affinity of eIF4A [77], but unlike PatA affect both eIF4A$_f$ and eIF4$_C$ [23,83]. The specificity of Rocaglates for inhibition of eIF4AI was confirmed by genetic complementation and crispr/cas9 gene editing, using an eIF4A mutant with impaired rocaglate binding, while retaining its functionality [84]. Silvestrol, one of the most studied rocaglates, reduces translation initiation, especially of mRNAs with a complex 5′UTR [22], and was originally thought to sequester eIF4A from the eIF4F complex by its increased RNA affinity [23,83]. However, the sensitivity of translation of specific mRNAs to Silvestrol could only partially be explained by complex features in the 5′UTR [21], and a recent study by Iwasaki et al. indicated that in contrast to Hippurastinol, a complex 5′UTR was only a minor determinant of Rocaglamide A (RocA) efficacy. Instead they found RocA to clamp eIF4A on mRNAs that have short polypurine sequences in their 5′UTR, hereby putting up a roadblock for ribosomal scanning [78] (Fig. 4). Unfortunately, RocA was not compared directly to Silvestrol in this study, and it remains to be determined whether the specificity for polypurine mRNA sequences

Table 1
Inhibitors currently under development for RNA helicases involved in regulation of translation.

Target	Compound	Mechanism	Developmental status	Results
eIF4A	Hippurastinol	Inhibits eIF4A RNA binding and helicase activity	Preclinical animal studies	Anticancer activity in several hematological cancer mouse models [89,94]
eIF4A	(DMDA)Pateamine A	Increase RNA binding affinity of eIF4A$_F$	Preclinical animal studies	Potent anticancer activity in multiple human cancer xenograft models [82] and activity against cachexia-induced muscle wasting in mice [91]
eIF4A	Rocaglates/Flavaglines (Silvestrol, episilvestrol, FL-3, Rocaglamide, CR-1-31-B, (−)-SDS−/− 021)	Increase RNA binding affinity of eIF4A	Preclinical animal studies	Potent anticancer activity in mouse models of both solid and hematoligical malignancies [22,23,83,86,92,93]
eIF4A	RNA aptamers against eIF4A	Inhibit ATP hydrolysis activity of eIF4A	Tissue culture	Anti-cancer activity not tested [88]
DDX3	REN analogs (NZ51)	Target ATP-binding domain of DDX3	Tissue culture	Reduces cancer cell viability and motility [96]
DDX3	RK-33 (PLGA [120]-RK-33)	Targets ATP-binding domain of DDX3	Preclinical animal studies	Causes radiosensitization in several mouse models [49,97] and has single agent activity in a Ewing Sarcoma mouse model [107]
DDX3	NSC305787	Inhibitor of the DDX3-Ezrin interaction	Tissue culture	Anti-cancer activity not tested [34]
DDX3	Ketorolac salt (ZINC00011012)	Targets ATP-binding domain of DDX3	Preclinical animal studies	Anticancer activity in a mouse oral squamous cell carcinoma model [108]
DDX3	Rhodanine and Triazine derivatives	Target DDX3 ATP-binding domain	Tissue culture	In vitro anti-viral activity, anti-cancer efficacy not tested [109]
DDX3	16d	Inhibitor of RNA helicase activity	Tissue culture	in vitro anti-viral activity, anti-cancer efficacy not tested [110]
RHA	YK-4-279	Inhibitor of the EWS-FLI interaction with RHA	Preclinical animal studies	Efficacy in several murine Ewing sarcoma models [112]

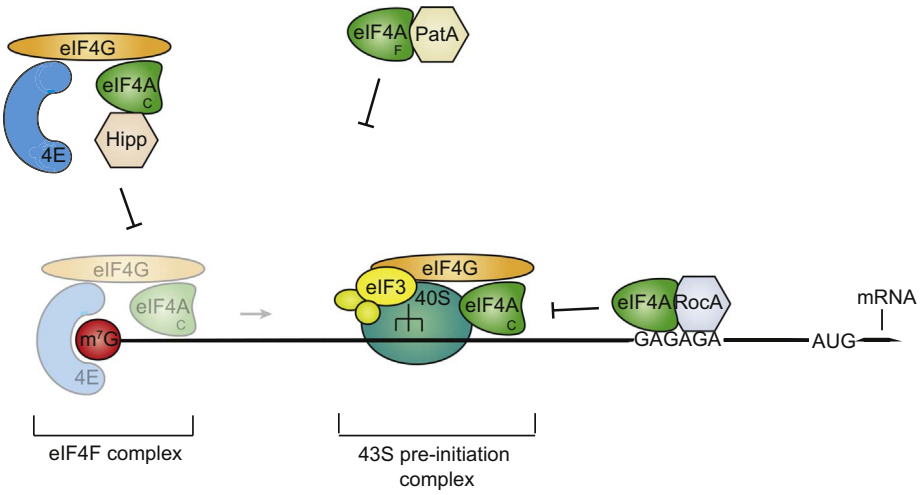

Fig. 4. Working mechanism of eIF4A inhibitors.
Schematic representation of how eIF4A inhibitors affect cap-dependent translation of mRNAs with specific 5′UTR features. Hippurastinol (Hipp) binds to the c-terminal domain of eIF4A and was found to specifically inhibit its ATPase, helicase and mRNA binding activity [19]. Pateamine A (PatA) stimulates RNA binding activity of free eIF4A ($eIF4A_F$) [79], most likely hereby sequestering it and perturbing the interactions with other translation initiation factors [81]. Of the family of Rocaglates, Rocaglamide A (RocA) clamps eIF4A on mRNAs that have short polypurine sequences in their 5′UTR, hereby putting up a roadblock for ribosomal scanning [78]. Silvestrol, one of the most studied rocaglates is thought to sequester eIF4A from the eIF4F complex by its increased RNA affinity [23,83], whether it also has a polypurine specificity remains to be determined.

is a feature of all rocaglates. Silvestrol was found to have suboptimal pharmacokinetic properties and to be sensitive to P-glycoprotein multidrug resistance transporters [85]. Synthetic rocaglates with potent in vivo activity and reduced sensitivity to multidrug resistance were developed, of which FL-3 [86] and (-)-SDS-/-021 [87] are promising candidates. In addition to natural products, RNA aptamers selectively binding eIF4A and interfering with cap-dependent translation by inhibiting its ATPase activity have also been developed [88].

3.2. Efficacy of eIF4A inhibitors in preclinical studies

Single agent activity has been identified in human xenograft models of hematological and solid malignancies for several eIF4A inhibitors. Hippurastinol was found to be effective in a human xenograft mouse model of primary effusion lymphoma caused by Kaposi's sarcoma-associated herpesvirus [89], and adult T cel leukemia [90]. DMDA-PatA inhibited growth in human xenograft mouse models of multiple solid cancers, and even induced tumor regression in the LOX and MDA-MB-435 melanoma models [82]. Interestingly DMDA-PatA was found to have a potential role in prevention of cachexia as well, as it was found to prevent muscle wasting by the cytokines, interferon γ and tumor necrosis factor α [91]. The rocaglates Silvestrol and CR-31-B reduced tumor growth and increased the percentage of leukemia free mice in a T-ALL mouse model without affecting body weight [22]. In addition, Silvestrol inhibited growth in a breast cancer model [23], among models of other solid malignancies. The flavagline FL3 was found to be able to overcome multi-drug resistance and reduced tumor growth in a melanoma human xenograft model [86]. eIF4A inhibitors are also promising candidates for combination regimens. For instance, resistance to the BRAF-V600E inhibitor vemurafenib is mediated through upregulation of the MAPK and PI3K/AKT/mTOR signaling pathways, both of which induce translation initiation through eIF4F. Vemurafenib resistant melanoma cells had increased eIF4F formation. In line with these observations, the Silvestrol analogues CR-1-31-B and FL-3 synergize with vemurafenib in melanoma xenografts [86]. In addition, Silvestrol was found to synergize with doxorubicin [83], daunarubicin [92], rapamycin [93] and dexamethason [76]. In a similar way, Hippurastinol overcomes resistance in PI3K/Akt/mTOR driven tumors and synergizes with the Bcl-2 family inhibitor ABT-373 and resensitizes Eμ-Myc lymphomas to DNA damaging agents [94].

3.3. The effect of DDX3 knockdown on oncogenic properties of cancer cells

DDX3 was found to have anti-apoptotic properties and knockdown reduces in vitro cancer cell proliferation [49,95–97], cell cycle progression [49,95], invasion, motility [37,98] and survival under stressed conditions [99]. In addition, DDX3 knockdown resulted in reduced outgrowth and metastases in human xenograft models [95,121]. However, similar to the controversy that exists on the role of DDX3 in translation initiation, there are also contradictory reports that argue that DDX3 has a tumor suppressing role. The group of YH Lee found that DDX3 reduces cell cycle progression via the p53-DDX3-p21 axis [100] [101]. A potential explanation for the opposite roles of DDX3 described by this group is the fact that they mainly use DDX3 overexpression models, which can be problematic as explained earlier, and HPV, HBV or HCV driven cancer models. DDX3 is known to play a role in the anti-viral immune response [102]. It is plausible that virally transformed cells benefit from lowering DDX3 levels, whereas cancers with different carcinogenetic backgrounds (e.g. cigarette smoke [98,103]) are dependent on high DDX3 expression.

3.4. Development and efficacy of DDX3 inhibitors

Several DDX3 inhibitors have been developed (Table 1). Ring expanded nucleoside (REN) analogues structurally mimic adenosine nucleosides and can be rationally designed to specifically target the ATP-binding cleft of DDX3, hereby inhibiting its helicase activity [104]. NZ-51 is a REN analogue that was found to inhibit in vitro viability and motility of breast cancer cells, but did not show any in vivo activity [96]. By using the X-ray crystallographic structure of the core domains of DDX3 [36], REN analogues were structurally modified into a series of tricyclic 5:7:5-fused diimidazo[4,5-d:4′,5′-f] [1,3]diazepine analogues [105]. Of these, RK-33 is the lead compound and the most studied DDX3 inhibitor in the cancer field. Biotin pull down experiments showed that RK-33 specifically binds DDX3 and not the closely related DEAD box RNA helicases DDX5 and DDX17 and reduces the helicase activity of the Ded1p, the yeast homologue of DDX3 [49]. Interestingly, RK-33 has potent in vivo radiosensitizing activity in several forms of cancer where radiation is frequently used. RK-33 was a stronger radiosensitizer than carboplatin, which is the most frequently used radiosensitizer in lung cancer [49]. In addition, RK-33 was found to work as a radiosensitizer in a human xenograft model of prostate cancer [97]. RK-33 most likely specifically sensitizes cancer cells to radiation therapy by inhibiting double strand break repair [49] via blockage of the required increase in OXPHOS by inhibiting mitochondrial translation [48]. RK-33 also sensitized breast cancer cells to PARP inhibitors [106]. In addition, single agent activity was observed against Ewing sarcoma human xenografts with high DDX3 expression [107]. No normal tissue toxicity was observed after RK-33 treatment in mice [49].

Although less studied in the cancer field, there are several other DDX3 inhibitors under development. In silico screening of DDX3 inhibitors led to identification of Ketorolac salt as a potential DDX3

inhibitor. Ketorolac salt inhibited ATPase activity and tumor growth in a 4-NQO induced tongue oral squamous cell carcinoma mouse model [108]. In addition, due to the role of DDX3 in viral mRNA translation, an effort has been made to develop DDX3 inhibitors for anti-viral (e.g., HCV, HIV-1, West-Nile virus and dengue virus) therapy as well [104,109]. Rhodanine analogues and triazine derivatives were identified from databases of commercially available compounds to bind the ATP-binding site of DDX3 [109]. The small molecule inhibitor 16d was recently designed to bind the RNA-binding site of DDX3. 16D inhibited helicase activity of DDX3 and showed broad-spectrum anti-viral activity in vitro [110]. It will be interesting to see further in vivo evaluation of these DDX3 inhibitors as potential anti-cancer drugs.

3.5. Other DDX/DHX family members as targets for cancer therapy

Besides eIF4A and DDX3, several other DEAD box RNA helicases have been designated as potential targets for anti-cancer therapy. EWS-FLI is a fusion oncogene occurring in Ewing sarcoma. RHA was found to augment the effect of EWS-FLI in modulating oncogenesis [111] and genetic knockdown of RHA reduced cell viability in Ewing sarcoma cell lines. YK-4-279 is a small molecule inhibitor of the EWS-FLI RHA interaction and was found to inhibit tumor growth in several murine Ewing sarcoma models [112]. The oncogenic effect of EWS-FLI and RHA in these models seemed to be mediated through regulation of alternative splicing [113] and so far no studies indicated an effect on translation of mRNAs with a complex 5′UTR containing PCEs. A recent study shows that RHA knockdown also reduces oncogenesis in the absence of the EWS-FLI translocation, without causing normal tissue toxicity [114]. Whether this effect is mediated through regulation of translation initiation of specific target mRNAs or through other functions of RHA remains to be determined.

Knockdown of DHX29 was found to reduce in vitro proliferation, anchorage independent growth and colony forming ability of cancer cells and resulted in outgrowth of HeLa cells in nude mice through regulation of translation initiation [26]. Furthermore, knockdown of YTHDC2, another DEAD/H box family member that functions as a translation initiation regulator, reduced proliferation and motility in liver and colorectal cancer cell lines and reduced liver metastases after splenic injection of colorectal cancer cells [52]. Both DHX29 and YTHDC2 are potential candidates for targeting oncogenic translation as a therapeutic strategy.

3.6. Therapeutic window of DEAD/H box protein inhibitors

Since translation is a process occurring not only in fast proliferating cancer cells, but also in normal tissues, there are concerns about normal cell toxicity of translation inhibitors. The question is whether the dependence of cancer cells on translation initiation of oncogenic mRNAs is large enough to facilitate a therapeutic window. None of the DEAD/H box inhibitors currently under development have reached the stage of clinical assessment of toxicity in a human phase I trial. However, preclinical studies indicated that rocaglate inhibitors of eIF4A, like Silvestrol [23] and the DDX3 inhibitor RK-33 [49] does not cause toxicity in mice at effective dose levels. Interestingly, inhibition of eIF4A with rocaglates has even been reported to have a chemoprotective role in normal cells, while simultaneously blocking proliferation in cancer cells [115]. In addition, there are other inhibitors of translation initiation that have been clinically evaluated. Haploinsufficiency of eIF4E, and therefore the eIF4F complex, did not affect normal development, but did impair cellular transformation, indicating a differential requirement for eIF4E in normal and cancer cells [116]. Phase 1 trials with antisense oligo of eIF4E (4E-ASOs) found few adverse effects, but unfortunately also no significant anti-tumor response with single agent treatment [117]. Phase II trials with the combination of 4E-ASOs and chemotherapeutics are currently ongoing [NCT1234038; NCT0124025]. Furthermore, several drugs currently used in clinic were found to inhibit translation initiation. The anti-viral guanosine analogue ribavirin was found to inhibit eIF4E binding to the 7-methyl guanosine 5′UTR mRNA cap and for this reason has been clinically evaluated as a potential treatment for acute myeloid leukemia [118]. In addition, PI3K/Akt/mTOR signaling is an upstream regulator of translation initiation and mTOR inhibitors result in reduced translation of oncogenic mRNAs [119]. These examples show proof of principle that translation inhibitors can be used to selectively target cancer cells, without unacceptable normal cell toxicity. However, clinical trials in humans will need to determine whether there is a sufficient therapeutic window for the use of specific DEAD/H box inhibitors as anti-cancer drugs.

4. Concluding remarks

Overall there is strong evidence for the non-oncogene addiction of cancer cells to DEAD/H box RNA helicases due to their role in facilitation of translation initiation of mRNAs with specific 5′UTR features. DEAD/H box dependent translation facilitates both primary oncogenic signaling and resistance to several therapies. However, more research is needed to further define the role in both translation initiation and oncogenesis of DDX3 and other RNA helicases. Efficacy has been shown for both eIF4A and DDX3 inhibitors in pre-clinical models, especially as an adjuvans to chemo- or radiotherapy, warranting the evaluation of this novel class of drugs in clinical trials.

Conflict of interest

Venu Raman has received a patent for the use of RK-33 as a radiosensitizer (US8,518,901).Venu, Raman and Paul van Diest have received a patent for the use of DDX3 as a cancer biomarker (US9,322,831). Paul van Diest and Venu Raman are on the advisory board of Natsar Pharmaceuticals.

Transparency document

The Transparency document associated with this article can be found, in online version.

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