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REVIEW

Hippuristanol - A potent steroid inhibitor of eukaryotic initiation factor 4A

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ABSTRACT
Protein synthesis and its regulatory signaling pathways play essential roles in the initiation and maintenance of the cancer phenotype. Insight obtained over the last 3 decades on the mechanisms regulating translation in normal and transformed cells have revealed that perturbed control in cancer cells may offer an Achilles' heel for the development of novel anti-neoplastic agents. Several small molecule inhibitors have been identified and characterized that target translation initiation – more specifically, the rate-limiting step where ribosomes are recruited to mRNA templates. Among these, hippuristanol, a polyhydroxysteroid from the gorgonian *Isis hippuris* has been found to inhibit translation initiation by blocking the activity of eukaryotic initiation factor (eIF) 4A, an essential RNA helicase involved in this process. Herein, we highlight the biological properties of this compound, its potential development as an anti-cancer agent, and its use to validate eIF4A as an anti-neoplastic target.

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Introduction

Perturbed translational control has been implicated in the initiation and maintenance of the cancer phenotype, supporting angiogenesis, and modulating drug response.[1-3] The energetically demanding process of translation is highly regulated predominantly at the level of initiation, with control exerted by 2 factors – eukaryotic initiation factor (eIF) 2 and eIF4F.[4,5] The role of eIF2 in translation initiation under normal physiological or stress conditions has been extensively reviewed[4,5] and regulation imposed at this step profoundly inhibits translation of a majority of mRNAs.[4,5] Since perturbation of eIF2 activity in cancer biology is less characterized and understood than the role of eIF4F, this review will focus solely on the latter.

The eIF4F complex consists of 3 subunits that function to recruit ribosomes to mRNAs (Fig. 1A). The eIF4E subunit recognizes 5′ cap structures (m^7GpppN, where N is any nucleotide), eIF4A is an RNA helicase required to remodel secondary structure proximal to the cap structure, and eIF4G provides a platform for subunit association, participates in RNA binding, and recruits the 40S ribosome (with associated factors) through bridging interactions with ribosome-bound eIF3.[6-8] The eIF4F complex does not bind all mRNAs equally, but rather appears to favor templates with an accessible cap structure[9-12] and reduced cap-proximal secondary structure.[12-16] Assembly of the eIF4F complex is regulated by mTOR via phosphorylation of eIF4E-Binding Proteins (4E-BPs – of which there are 3 genes with 4E-BP1 being the best characterized). Stimulation of mTOR signaling results in phosphorylation of 4E-BPs, dissociating 4E-BP:eIF4E complexes and enabling eIF4E to associate with eIF4G.[17]

eIF4E appears to be the least abundant of all the initiation factors (0.2–0.3 molcules/ribosome)[18,19] implying that mRNAs must compete for the limiting amounts of eIF4F during translation initiation with the outcome dictated, in part, by structural elements in the 5′ untranslated region (UTR). This point has been challenged since reductions in eIF4E levels in $eIF4E^{+/-}$ mice show little effect on global translation (at least in MEFs) and has been interpreted to indicate that eIF4E is not rate-limiting *in vivo*.[20] However, similar observations had been previously documented in cells treated with anti-sense oligonucleotides[21] or shRNAs[22,23] targeting eIF4E. eIF4E is

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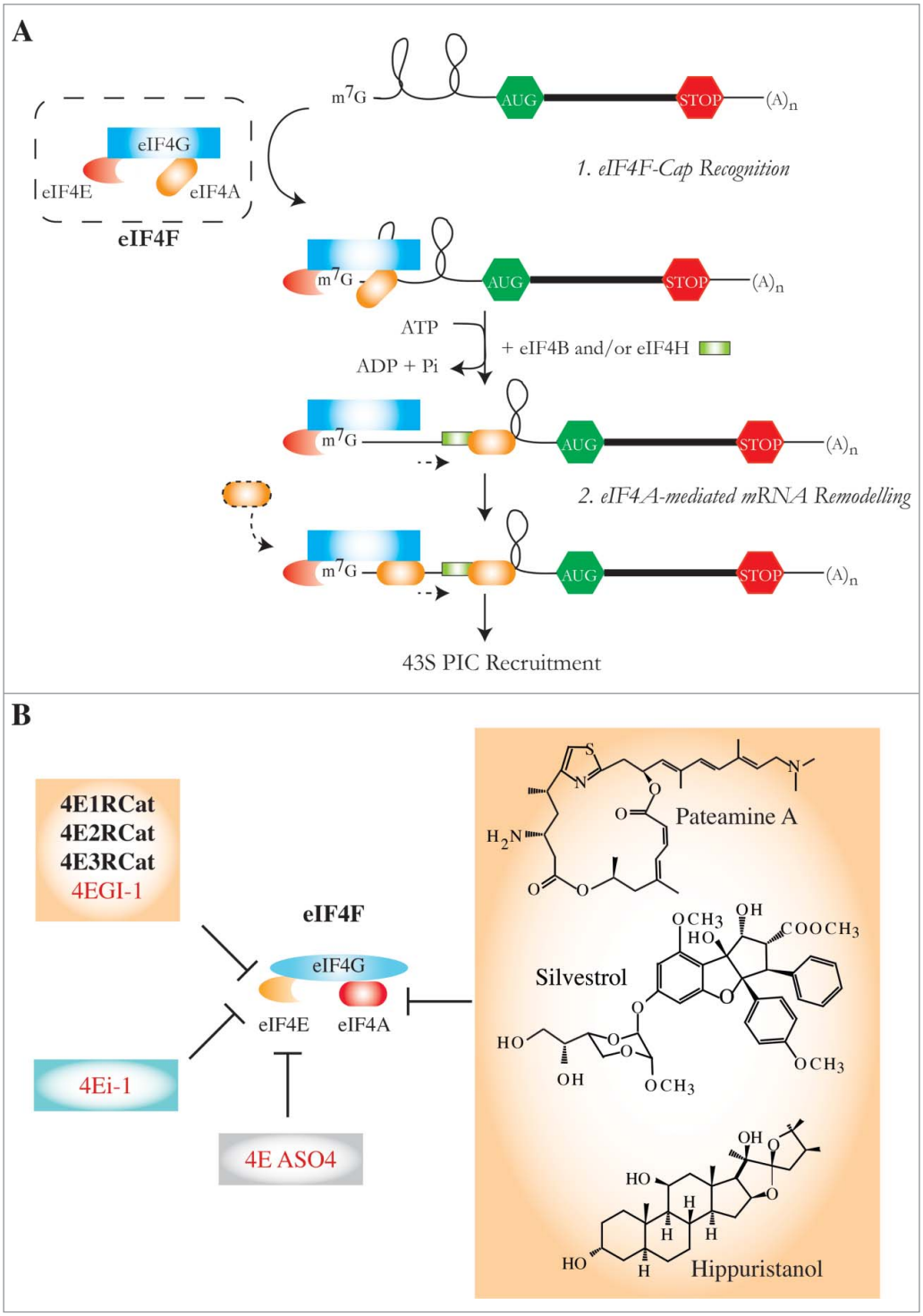

Figure 1. A. Simplified model of eIF4F-dependent initiation displaying cap recognition and subsequent destabilization of local secondary structure. eIF4H and eIF4B share a common binding site on eIF4A and these interactions are mutually exclusive.[111] Not shown is mRNA circularization mediated through poly(A) tail:poly(A)-binding protein (PABP) and eIF4G. B. Schematic diagram illustrating targets of various small molecules and anti-sense oligonucleotides (ASO) that target eIF4E-cap interaction (4Ei-1), prevent synthesis of the eIF4E subunit (4E ASO), inhibit eIF4E:eIF4G interaction (4E1RCat, 4E2RCat, 4E3RCat (unpublished data), 4EGI-1), and interfere with eIF4A helicase activity (silvestrol, hippuristanol, pateamine A). (Note that although ribavirin has been claimed to inhibit eIF4E-cap interaction,[112] this has been questioned.)[113,114]

under homeostatic control via regulation of 4E-BP levels and reductions in eIF4E levels leads to increased degradation of 4E-BP1, buffering against changes in eIF4F levels.[24]

Changes in eIF4F activity is not expected to impact all mRNAs equally but rather cause a small change in global translation with a disproportionate, selective alteration in translation of a subset of mRNAs.[1-3] As it turns out, several of these eIF4F-dependent mRNAs fuel tumorigenesis and thus one way to impact on tumor maintenance is to block eIF4F activity.[1-3] There has therefore been intense interest in identifying small molecule inhibitors of eIF4F. Several HTS assays and directed synthetic efforts have identified compounds that target eIF4E-cap interaction,[25] prevent synthesis of the eIF4E subunit,[21,26] inhibit eIF4E:eIF4G interaction,[27-29] and interfere with eIF4A helicase activity[30-32] (Fig. 1B). Although these have been reviewed,[1-3] here we update the current development status of hippuristanol, a polyhydroxysteroid first isolated from the coral *Isis hippuris*,[33] and for which until recently, biological characterization was delayed due to limitations in supply.

eIF4A and translation initiation

eIF4A is a prototypical member of the DEAD-box family of RNA helicases and one of the more abundant translation factors (approximately 3 copies/ribosome).[34,35] Given that eIF4E levels are approximately 10-fold lower,[34,35] the majority (approximately 90%) of eIF4A exists as free form while only a small fraction is present in the eIF4F subunit.[36-38] The higher abundance of eIF4A, relative to eIF4F, as well as the ability to crosslink (in a cap-dependent manner) eIF4A to sites located 52 nucleotides downstream of the cap structure, has lead to models invoking recycling of eIF4A through the eIF4F complex during translation initiation (Fig. 1A). [39,40] Mammals have 2 eIF4A proteins (eIF4AI [DDX2A] and eIF4AII [DDX2B]) which share approximately 90% sequence identity at the amino acid level.[41] Although eIF4AI and eIF4AII are functionally interchangeable *in vitro*,[42] they do not appear to be equivalent *in vivo*. eIF4AI, but not eIF4AII, is required for cell viability[19,43] and eIF4AII is not capable of rescuing the inhibition of translation that ensues following suppression of eIF4AI.[19] In general, eIF4AI is the more abundant protein[41,44,45] and the majority of biochemical studies assessing eIF4A activity have been performed with eIF4AI. eIF4AI and eIF4AII possess both RNA-stimulated ATPase and ATP-stimulated RNA-binding activity. The eIF4A helicase and ATPase activities are strongly stimulated when eIF4A is part of the eIF4F complex or is associated with either of 2 RNA binding proteins, eIF4B or eIF4H[46 47] (Fig. 1A).

Dominant-negative (dn) mutants of eIF4A have highlighted the critical role that this factor plays in translation.[48,49] One such mutant is capable of assembling into the eIF4F complex and prevents cap recognition.[49] Supplementing translation extracts with dn eIF4A mutants has revealed that translation inhibition is directly related to the degree of 5′ UTR secondary structure. Analysis of transcripts sensitive to eIF4A inhibition by silvestrol (another eIF4A inhibitor) is consistent with the concept that structural barriers within the 5′ UTR are a key determinant of eIF4A dependency.[50-52]

The activity of eIF4A can be negatively regulated by PDCD4, a tumor suppressor gene product.[53-55] PDCD4 associates with eIF4A, displacing eIF4G and RNA,[54] and resulting in preferential suppression of translation of mRNAs with structured 5′ UTRs.[53,56] The association between PDCD4 and eIF4A is regulated by the PI3K/mTOR signaling pathway through the downstream S6K branch.[57] Phosphorylation of PDCD4 by S6K1 leads to its ubiquitin-mediated degradation, freeing eIF4A for assembly into the eIF4F complex.[57]

Data implicating a direct role for dysregulated eIF4A levels contributing to tumor initiation or maintenance is sparse. This might be expected for an abundant protein, if its critical functional role is one mediated through a rate-limiting complex. On the other hand, there is a significant body of work indicating that eIF4F activity or eIF4E levels will drive tumor initiation, support tumor cell maintenance, and contribute to chemoresistance.[1-3] *Ex vivo* experiments have shown the efficacy of targeting eIF4A using ASOs[58] or ectopic PDCD4 expression to block transformation[59] and delay tumor onset and progression in a chemically-induced skin tumor model.[60] As well, another eIF4A inhibitor, silvestrol, has shown activity in a variety of pre-clinical cancer models.[31,50,51,61-63] Presumably, these physiological responses are due to inhibition of eIF4F activity. Given the difficulty in "translating" biologicals such as proteins and ASOs into therapeutics, there was

excitement when hippuristanol emerged from a high throughput screen aimed at identifying novel inhibitors of cap-dependent translation.[32,64]

Hippuristanol – A selective inhibitor of eIF4A

Hippuristanol is a member of one of 4 classes of polyoxygenated steroids. These include (i) the hippurin or hippuristanol type containing a spiroketal ring, (ii) the gorgosterol type containing a cyclopropane residue; (iii) the hippuristerone type possessing a 3-keto functionality, and (iv) the hippuristerol type (Fig. 2A). Although a large number of compounds from the various groups have been isolated and characterized, those belonging to the hippurin or hippuristanol class exhibit the most potent cytotoxic activity *ex vivo* against tumor cell lines, underscoring the importance of the spiroketal group for activity.[32,33,65-67] Some members of the gorgosterol class exhibit moderate cytotoxicity[68,69] (IC_{50} approximately 2 μM against NBT-T2 rat bladder epithelial cells and approximately 15 μM [for presumably a 4 day exposure period[70]]) and have shown activity against human epidermoid carcinoma KB drug-resistant cells expressing the drug transporter, ABCB1/P-glycoprotein (approximately 6–10 greater activity than against cells not expressing ABCB1), but less so against cells expressing multidrug resistance protein-1 (MRP1).[68] Tumor cell cytotoxicity has been reported for compounds of the hippuristerone family[66] but these are far less potent than hippurin or hippuristanol-like compounds. There is also one report describing moderate activity of a hippuristerone against human cytomegalovirus (HCMV) (EC_{50} approximately 10 μM), while (together with 4 other hippuristerones) the same compound showed no activity against P-388 mouse lymphocytic leukemia, HT-29 human colon carcinoma, or human embryonic lung cells.[71] Acknowledging the fact that not all gorgosterols, hippuristerones, and hippuristanols isolated to date have been tested for cytotoxicity,[72-75] in general it is the hippurin/hippuristanol class of compounds that exhibit the highest level of activity against tumor cells in culture (e.g. IC_{50} approximately 700 nM against HeLa cells for a 24 hrs exposure[32]).

Hippuristanol's mechanism of action differs significantly from that of 2 other eIF4A inhibitors, pateamine A and rocaglates. Whereas pateamine A and rocaglates appear to act as chemical inducers of dimerization by stimulating eIF4A:RNA binding, hippuristanol prevents both free eIF4A and eIF4F-bound eIF4A from interacting with RNA.[32] Hippuristanol does not inhibit ATP binding.[32] Single molecule FRET experiments have shown that hippuristanol locks eIF4AI in a closed conformation preventing its transition from a closed to an open state, an event essential to eIF4AI's helicase activity.[76] Since eIF4A does not normally sample the closed state (transition to the closed conformation is eIF4G- and eIF4B-stimulated) and the eIF4A closed conformation is normally RNA bound,[77] hippuristanol may be locking eIF4A in an aberrant closed complex that can no longer participate in initiation.

NMR and site-directed mutagenesis studies have revealed that hippuristanol interacts with the C-terminal domain of eIF4A in a pocket involving amino acids within and spanning conserved motifs V and VI (Fig. 2B).[32,78] These studies provided valuable insight into some of the key residues involved in the interaction of eIF4A with hippuristanol.[32,78] Hippuristanol is thought to make direct contacts with mouse eIF4AI residues $G_{335}I_{336}$, V_{338}, $L_{343}V_{344}$, as well as K_{369} - V_{371} whereas residues T_{328} - N_{346} and R_{368} - I_{373} lie within 5Å of hippuristanol (Fig. 2B). Residues making direct contacts with hippuristanol are conserved among eIF4AI, eIF4AII, as well as the yeast TIF1 and TIF 2 homologues (Fig. 2B).[78] These results have been validated by mutagenesis studies of the hippuristanol binding site which led to altered sensitivity (RNA binding and helicase activity of recombinant proteins) to hippuristanol *in vitro*.[78] Hippuristanol-resistant eIF4A alleles were able to rescue *in vitro* inhibition of translation by hippuristanol, consistent with the effects of this small molecule on translation being mediated through eIF4A inhibition.[78] Hippuristanol inhibits the RNA-stimulated ATPase activity of both eIF4AI and eIF4AII to similar extents.[78]

Among all members of the DEAD-box helicase family, eIF4AIII [DDX48]) [implicated in nonsense-mediated decay (NMD)[79-82]] has the most related hippuristanol binding site - differing by 6 amino acids compared to the eIF4AI site (Figs. 2B and 3). Consequently ten times more hippuristanol is required to inhibit the ATPase activity of eIF4AIII compared to eIF4AI or eIF4AII.[78] Increased sensitivity to hippuristanol has been engineered into eIF4AIII by grafting the eIF4AI hippuristanol binding site into eIF4AIII.[78] Other members

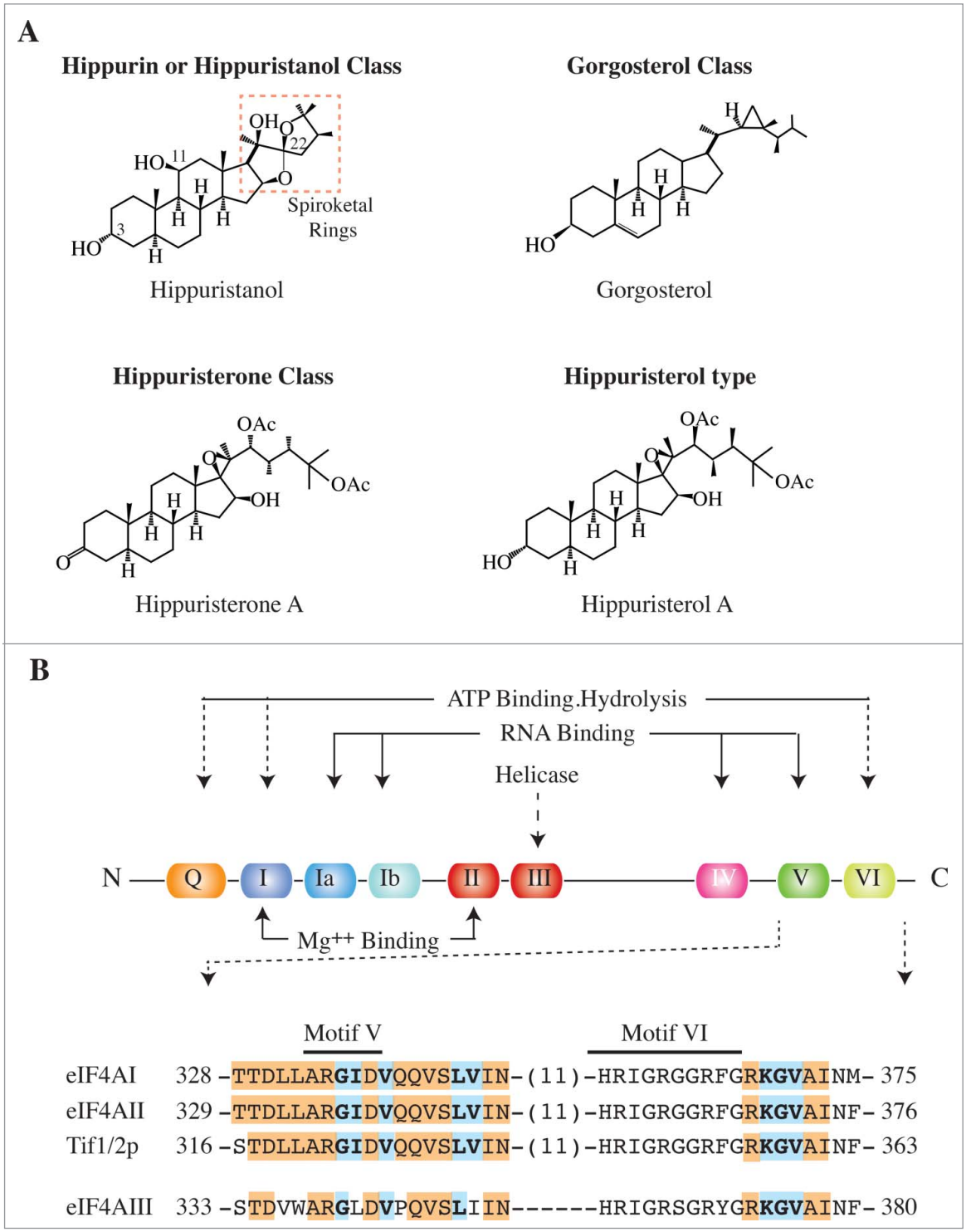

Figure 2. A. Structure of representative molecules from the 4 polyoxygenated steroid classes. B. Schematic diagram illustrating characteristic domains that comprise DEAD-box RNA helicases with functions of the motifs indicated. Primary amino acid sequence of conserved motifs V and VI (indicated by overline) and neighboring amino acids of the indicated helicases. Direct protein-hippuristanol NOEs are highlighted in bold and light blue and those within ~5Å are in orange shading.

of the DEAD-box helicase family display higher degeneracy within the hippuristanol-binding site (Fig. 3) and are thus not expected to be as sensitive to hippuristanol as eIF4AI or eIF4AII. Indeed, to date none have been found to be responsive to hippuristanol concentrations as high as 50 μM.[78] Whether hippuristanol targets other cellular proteins is unknown.

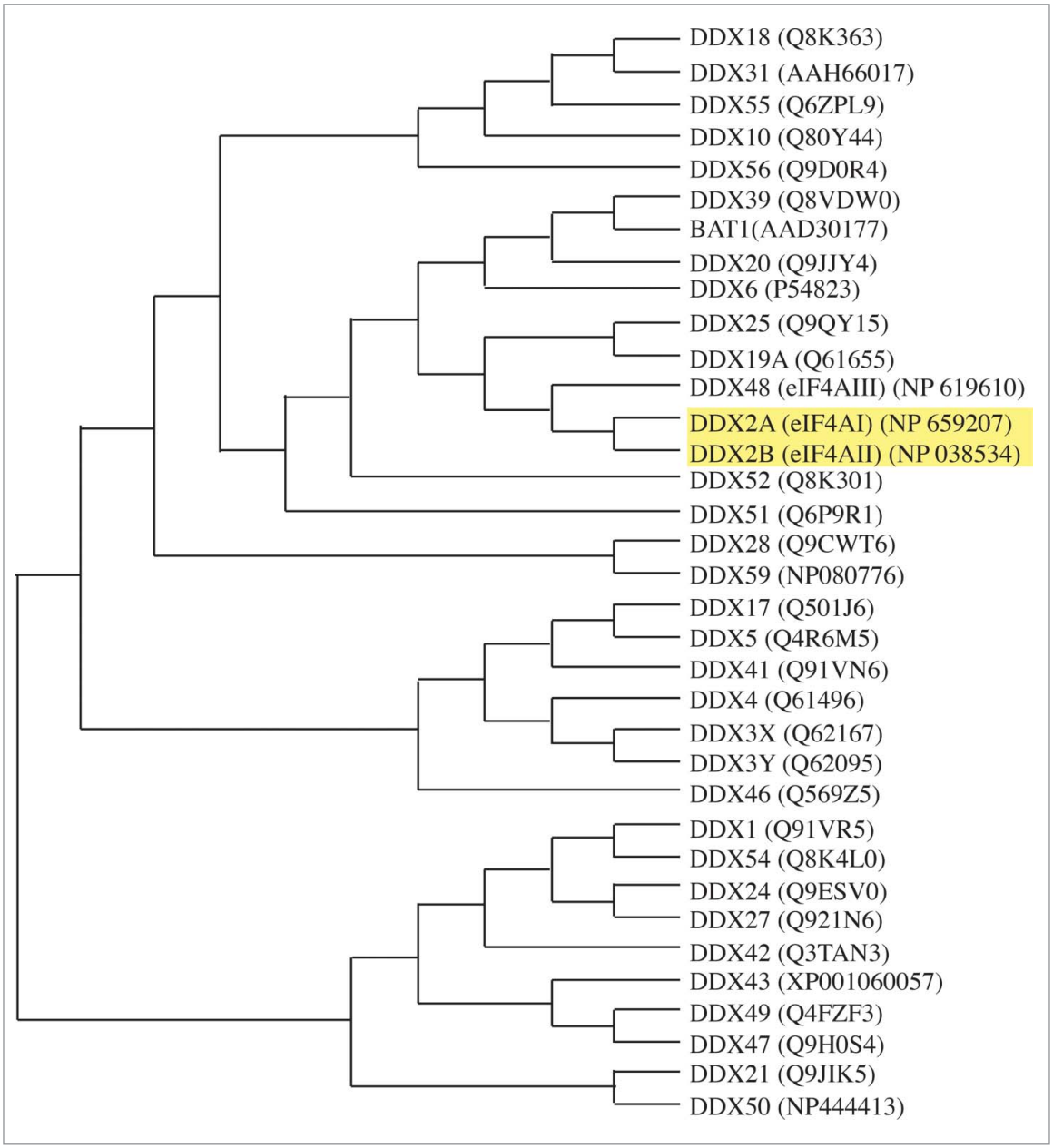

Figure 3. Cladogram displaying the multiple sequence alignment obtained with murine DEAD-box RNA helicase family members using Clustal Omega (http://www.ebi.ac.uk/clustalw/). Alignments were performed with sequences spanning and immediately flanking conserved motifs V and VI only. For example, this would correspond to 328-TTDLLARGIDVQQVSLVIN—-HRIGRGGRFGRKGVAINM-375 for eIF4AI. A complete list of sequences compared can be found in Figure S2 of Ref.[78] The Entrez Protein IDs are in parenthesis. eIF4AI and eIF4AII are highlighted in yellow for easy reference.

The selectivity of hippuristanol for eIF4A has provided a powerful tool by which to probe for eIF4A-dependent processes. Hippuristanol has been used to characterize viral and cellular IRESes *in vitro* and *in vivo*[32,83-86] and to probe the eIF4A-dependency of cellular mRNAs.[87-91] As well, it has been used to investigate the effects of Herpes Simplex Virus 1 (HSV 1) virion host shutoff (vhs) protein on cell type specific translation of viral late RNAs,[92] the effect of HSV 1 host translation shutoff on nuclear envelope-derived autophagy,[93] and the dependency of Influenza virus A polymerase on eIF4F.[94] As might be expected, hippuristanol exhibits anti-viral activity,[29] but whether it can be used as an anti-viral therapeutic remains untested. Hippuristanol has also been used to characterize the eIF4A dependency of translational events required for long-term synaptic plasticity and potentiation.[95,96]

Anti-neoplastic activity of hippuristanol

Hippuristanol as a single agent has shown promising anti-neoplastic activity. In 1981, Higa et al.[33] reported that hippuristanol inhibited the growth of DBA/MC fibrosarcoma cells and exhibited *in vivo* activity against lymphocytic leukemia P-388 tumors in mice. More recently, hippuristanol has shown activity against human adult T-cell leukemia (ATL) *in vitro* and *in vivo* in a xenograft model.[97] Additionally, hippuristanol is active against primary effusion lymphoma (PEL), causing cell cycle arrest and caspase activation followed by apoptosis.[98] What is currently required is a comprehensive understanding of the pharmacokinetic/pharmacodynamics properties of hippuristanol so that an optimal dosing schedule and route of administration can be determined for testing in a larger number of xenograft and genetically engineered mouse models (GEMMs) of cancer.

Elevated eIF4E levels and eIF4F activity have also been linked to acquired resistance of PI3K and MAPK pathway targeted therapies (reviewed in Refs.[1-3]). Increased eIF4E levels are associated with resistance to PI3K/mTOR targeted therapies in cell based models,[99,100] as well as doxorubicin[101] and rapamycin[102] resistance in the Eμ-Myc lymphoma model.[101] In addition, elevated eIF4F levels have been associated with resistance to anti-BRAF and anti-MEK therapies[103] and targeting eIF4F synergizes with anti-BRAF therapy.[103] Targeting eIF4A has also been shown to be a viable approach for overcoming some of this acquired resistance. More specifically, in a Myc-driven lymphoma model (the Eμ-Myc mouse) hippuristanol is capable of resensitizing tumor cells to DNA damaging agents (doxorubicin).[104] As well, hippuristanol is capable of synergizing with the Bcl-2 family inhibitor, ABT-737, to induce a potent synergistic response that triggers cell death in mouse and human lymphoma and leukemia cells.[104] Multiple myeloma cells are sensitive to hippuristanol (IC_{50} approximately 50 nM for a 48 h exposure)[105] and hippuristanol synergizes with dexamethasone *ex vivo*, a frontline glucocorticoid used in the management of this disease.[105] These studies demonstrate a role for eIF4F in contributing to drug resistance and proof-of-concept for overcoming this with eIF4A inhibitors.

Structure-activity relationships of hippuristanol

Hippuristanol is a rare natural product and it was critical to develop synthetic routes to obtain sufficient material for biological studies as well as undertaking structure-activity relationship (SAR) studies. Four synthetic routes to hippuristanol have been published and used as starting material either hydrocortisone or hecogenin acetate/11-ketotigigenin[106-109] (Fig. 4A). These routes were employed to generate a number of analogs that have been tested for translation inhibition activity[106,109] and inhibition of cell proliferation against HeLa cells.[106] Taken together with data assessing the activity of several naturally occurring hippuristanol congeners in translation and eIF4A helicase activity,[32] we have a fairly good understanding of the essential features required for optimal hippuristanol activity (Fig. 4B). The R stereochemistry at C22 is essential for activity[32] as are the *gem*-dimethyl substitutions on the F ring.[110] Appending functionalities onto R1 results in a 3-fold decrease in activity, whereas altering the R_2 OH leads to a 25-fold decrease in activity.[32,109] Converting the R_4 OH to a ketone or acetate diminishes activity approximately 25- and >2000 -fold, respectively.[32] Eliminating the R_5 CH_3 group decreases activity approximately 5–8 fold, whereas increasing the bulkiness at R_5 decreases activity >15-fold.[109] The rank order of inhibition obtained in *in vitro* translation assays was similar to when several of the same congeners were assessed for direct inhibition of eIF4A RNA helicase activity[32] - consistent with eIF4A being the target through which hippuristanol exerts its inhibitory effects on protein synthesis. These results demonstrate that a large surface area of hippuristanol likely participates in binding to eIF4A.

Future perspectives

There are several issues that will need to be resolved as hippuristanol is developed for clinical assessment. A detailed assessment of the pharmacological properties is urgently needed. In the past this information could not be obtained due to limitations in compound availability, but this has recently been overcome by synthetic routes allowing access to sufficient quantities of material for pharmacological

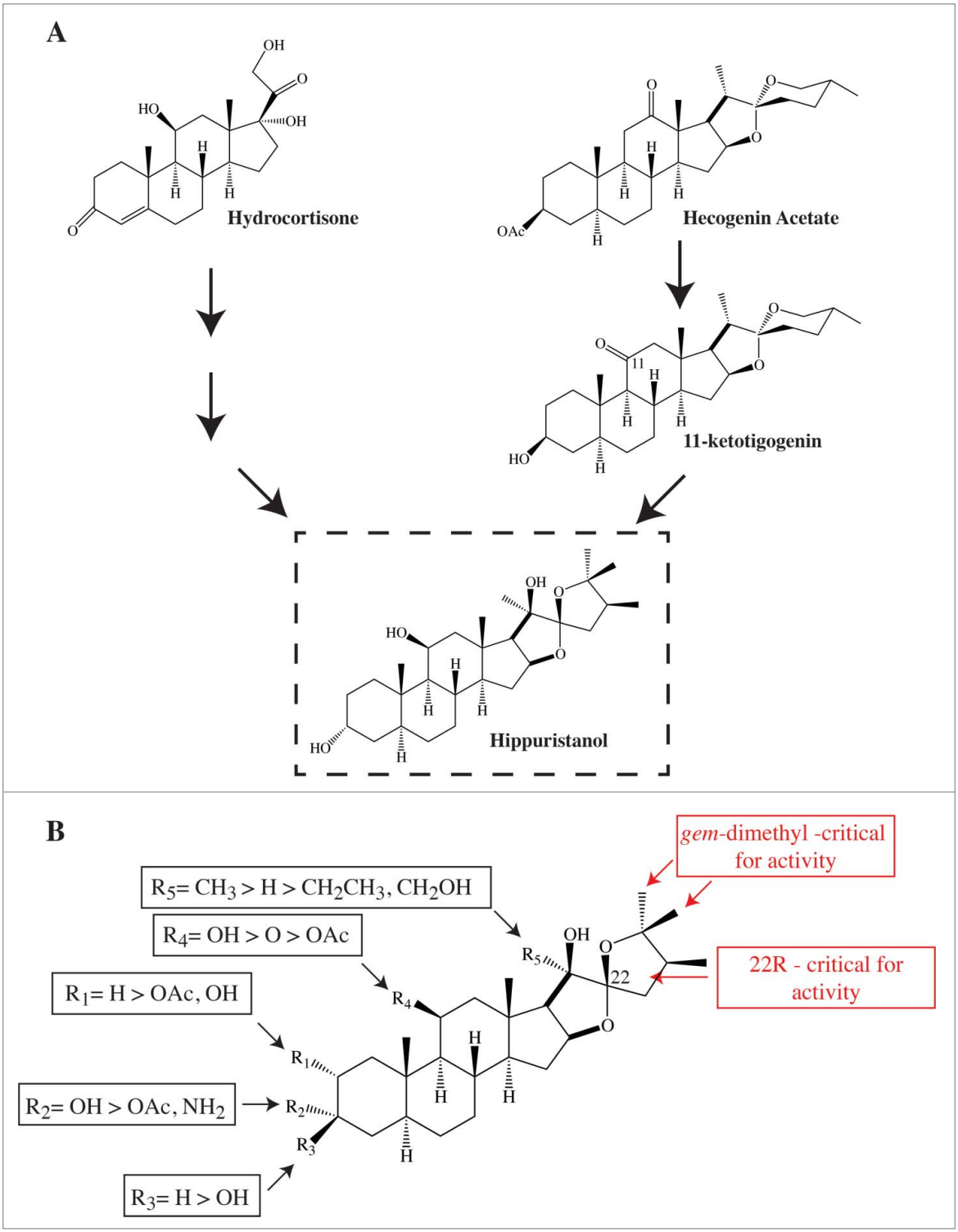

Figure 4. A. Several synthetic routes to hippuristanol have been elaborated, involving hydrocortisone,[106,109] hecogenin acetate,[108] or 11-ketotigogenin[107] as starting material. B. Structure-activity relationship for hippuristanol. See text for details.

studies. A better understanding of the types of tumor cells that are most likely to respond to eIF4A inhibition is required. The identification of surrogate biomarkers that can report on eIF4A/eIF4F inhibition will also be important to ensure that target inhibition is maintained *in vivo*. As challenging as these are, they are essential to optimizing the chances of success for eIF4A inhibitors as they

move forward from being powerful tools used in the laboratory to potential drugs for blocking eIF4A/eIF4F function in tumor cells. We look forward helping extend the paradigm of targeting eIF4F for the treatment of cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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