Targeting PI3K/mTOR Signaling with Potent, Selective and Orally-Available Small Molecule Inhibitors of eIF4E

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Abstract

Ablation protein translation plays a role in the pathogenesis of multiple solid tumors and hematological malignancies. The translation initiation factor eIF4E is essential for the translation of m7G-capped mRNA and is a key point of convergence for several signaling pathways, such as PI3K/mTOR and MAPK, which are intimately involved in tumor cell growth and survival. As such, eIF4E has generated intense interest as a target for anti-cancer drug discovery. We have designed a series of potent, selective and orally-available m7G-cap-competitive inhibitors of eIF4E (eFT-4Ei) with favorable drug-like properties. These inhibitors bind free eIF4E, eIF4E-4EBP and eIF4E-eIF4F complexes within tumor cells. Ribosome profiling of eIF4E inhibitor-treated tumor cells has identified a subset of translationally regulated target genes that overlap with mTORC1/2 regulated genes, but also include a larger set of unique translationally regulated target mRNAs that are enriched for 5'-TOP, PEST and CERT sequence elements in their 5'-untranslated regions. eIF4E inhibition results in potent anti-proliferative activity and induction of apoptosis in a subset of tumor cell lines. Consistent with this observation, our eIF4E inhibitors show some similarities, yet several important differences from existing mTORC1 or mTORC1/2 dual inhibitors. eIF4E inhibition is differentiated from mTORC1/2 inhibition (lack of feedback activation of AKT and MNK1/2 or hyperglycemia) and has shown efficacy in xenograft-bearing animals (n=10/arm) with differences in tumor xenografts between patients. Ablation of eIF4E in vivo using a novel anti-eIF4E monoclonal antibody demonstrated that m7G-cap binding but does not inhibit eIF4E binding to the 4E-BP1/mTORC1 pathway. Aberrant protein translation plays a role in the pathogenesis of multiple solid tumors and hematological malignancies. The translation initiation factor eIF4E is a key downstream effector of the PI3K/mTORC1 pathway. eIF4E is required for the translation of m7G-capped mRNA. eIF4E is part of the eIF4F translation initiation complex, which is comprised of eIF4E, eIF4A, and eIF4G. eIF4E is required for the translation of m7G-capped mRNA. eIF4E is a key downstream effector of the PI3K/mTORC1 pathway.

Introduction

Results

Conclusions

- eFFECTOR Therapeutics has designed a series of potent, selective small molecule inhibitors of eIF4E targeting the mG-cap binding site.
- Ribosome profiling with eIF4E inhibitors highlights the regulation of a subset of genes involved in mTOR signaling (mRNA translation, ribosome biogenesis, metabolism) as well as unique signaling pathways.
- eIF4E inhibition is differentiated from mTORC2/1 inhibition (lack of feedback inhibition of AKT and MNK1/2 or hyperglycemia).
- eIF4E inhibitors demonstrate differential anti-proliferative activity in vitro with enrichment of apoptosis in BRAFV600E mutant cell lines.
- eIF4E inhibitors show significant anti-tumor efficacy on a daily or intermittent dosing schedule in vivo.