

The potential function of alternative translation initiation of Argonaute 1 in cancer

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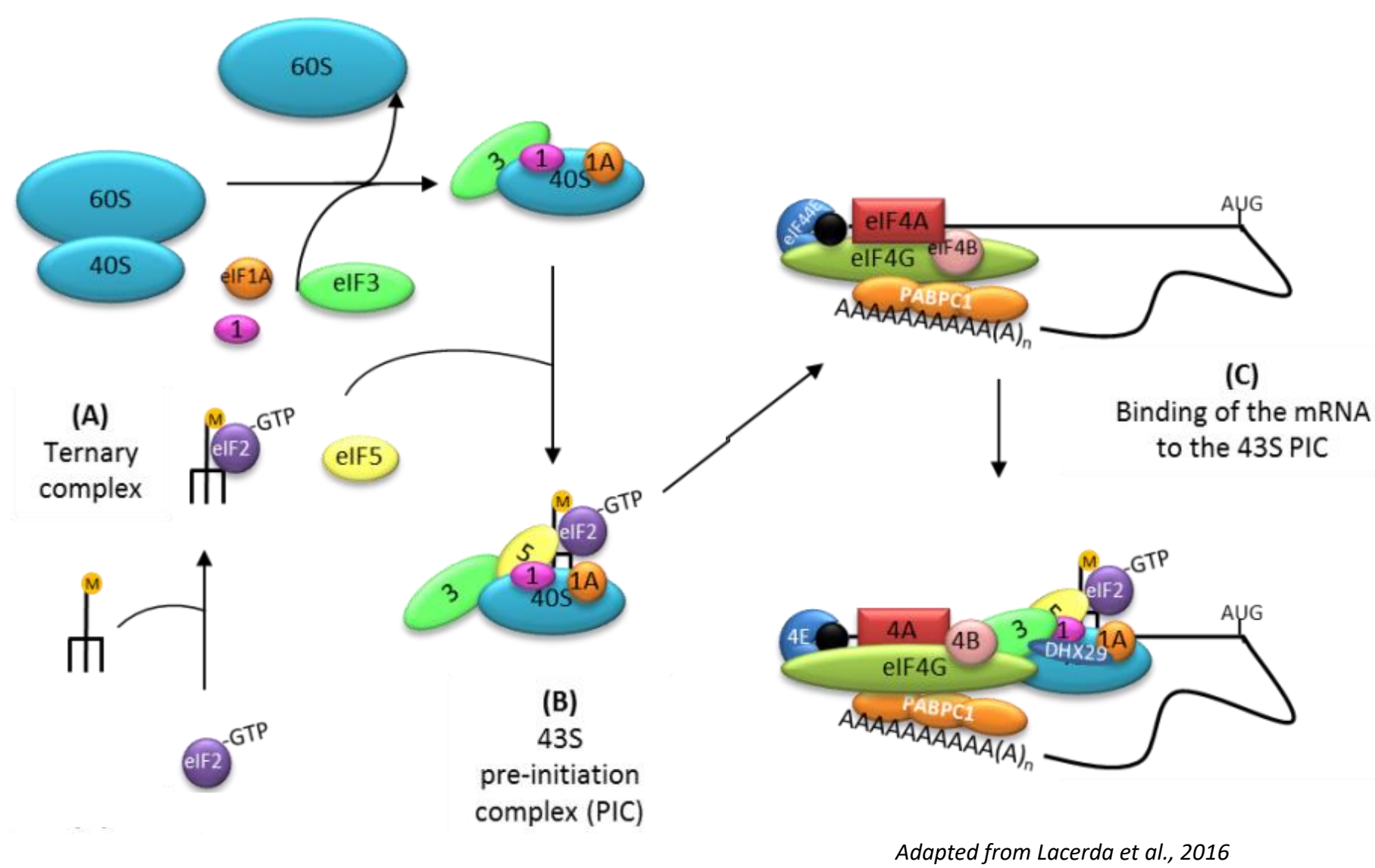
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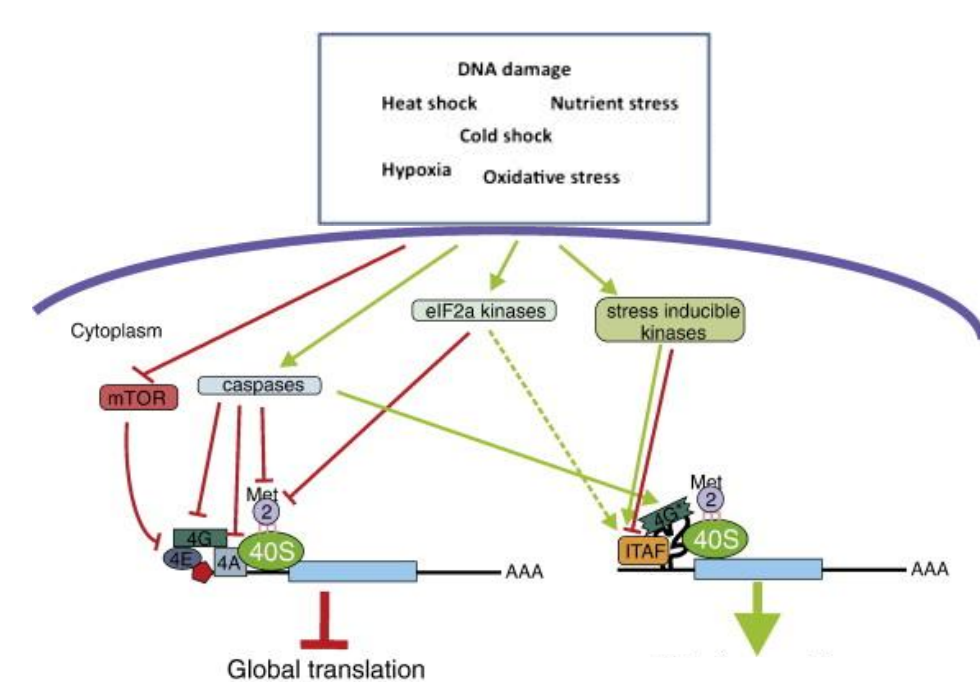
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Introduction

The canonical model of translation initiation



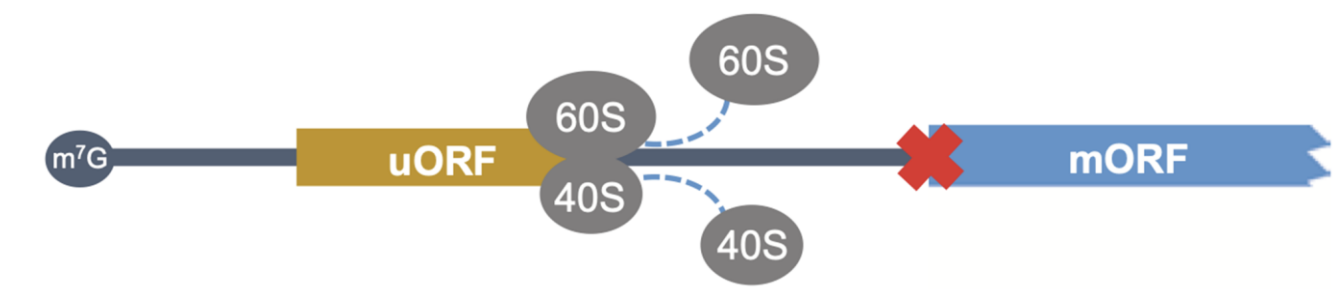
Canonical translation initiation is inhibited under stress



Adapted from Faye & Holcik, 2015

Selective translation of proteins that are vital for cell survival and stress recovery

uORF-mediated translation initiation



- Upstream open reading frames (uORF) are *cis*-regulatory elements in the 5' untranslated region (UTR), initiated by a start codon in frame with a stop codon, located upstream or overlapping the main ORF (mORF)
- Can repress or, in some cases, activate translation of the mORF
- Can trigger mRNA degradation

Silva J et al, 2019

Several proteins are able to maintain their expression via non-canonical mechanisms of translation initiation that can occur under stress conditions

Role of AGO1 in the cell:

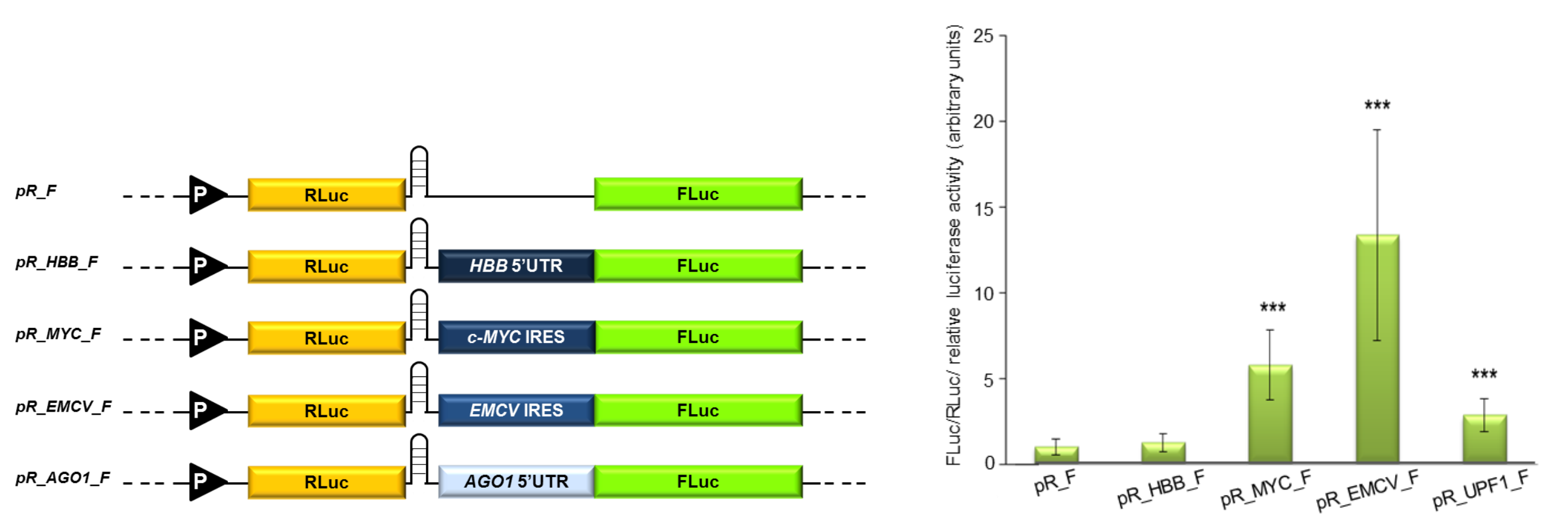
- Essential effector in RNA-mediated gene silencing pathways
- Involved in developmental control
- Involved in stem cell maintenance
- Related to tumorigenesis

Carmell et al., 2002
Ender and Meister, 2010

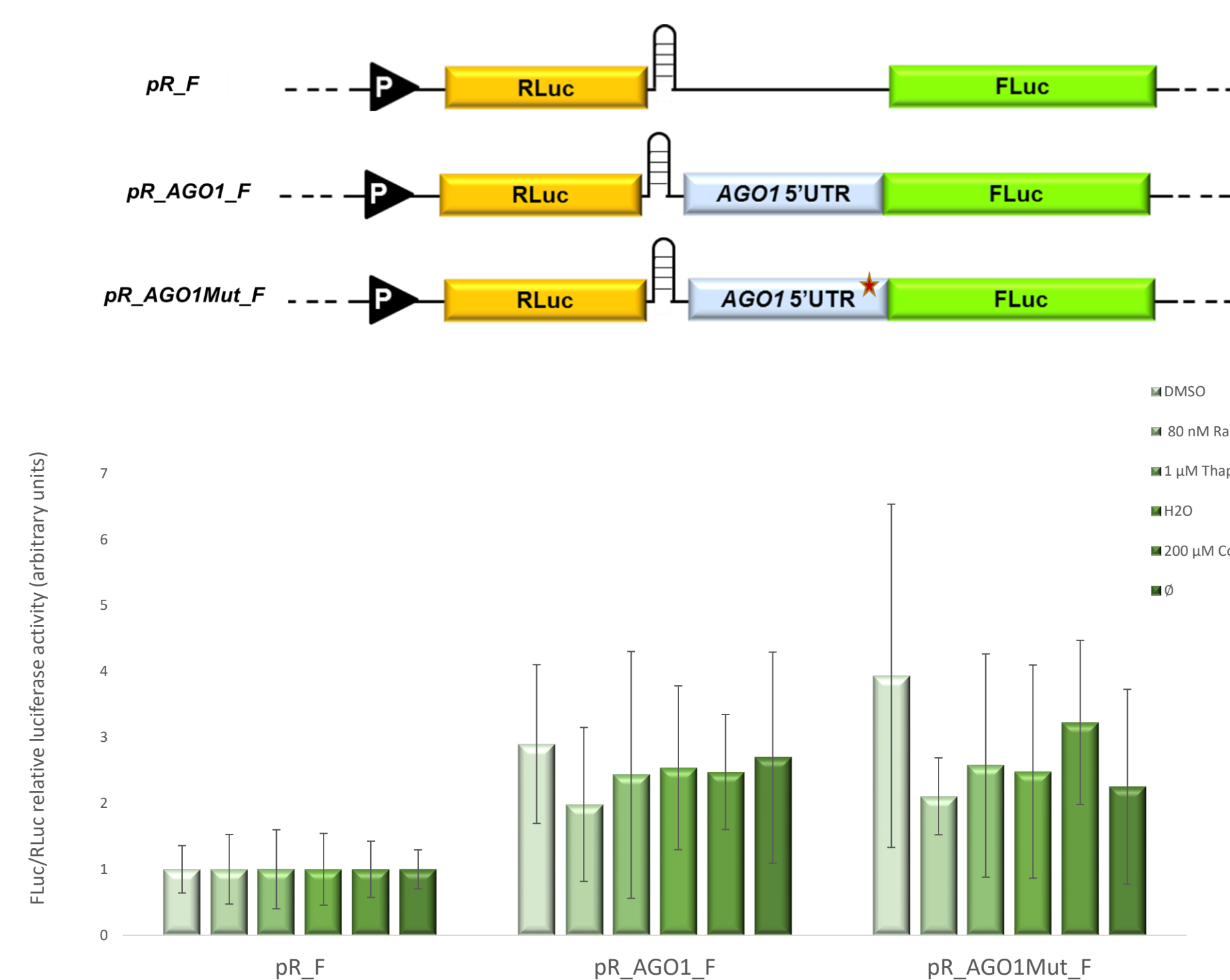
Hypothesis

How does AGO1 5'UTR regulate non-canonical translation initiation of the corresponding protein ?

AGO1 5'UTR drives FLuc expression in a bicistronic context

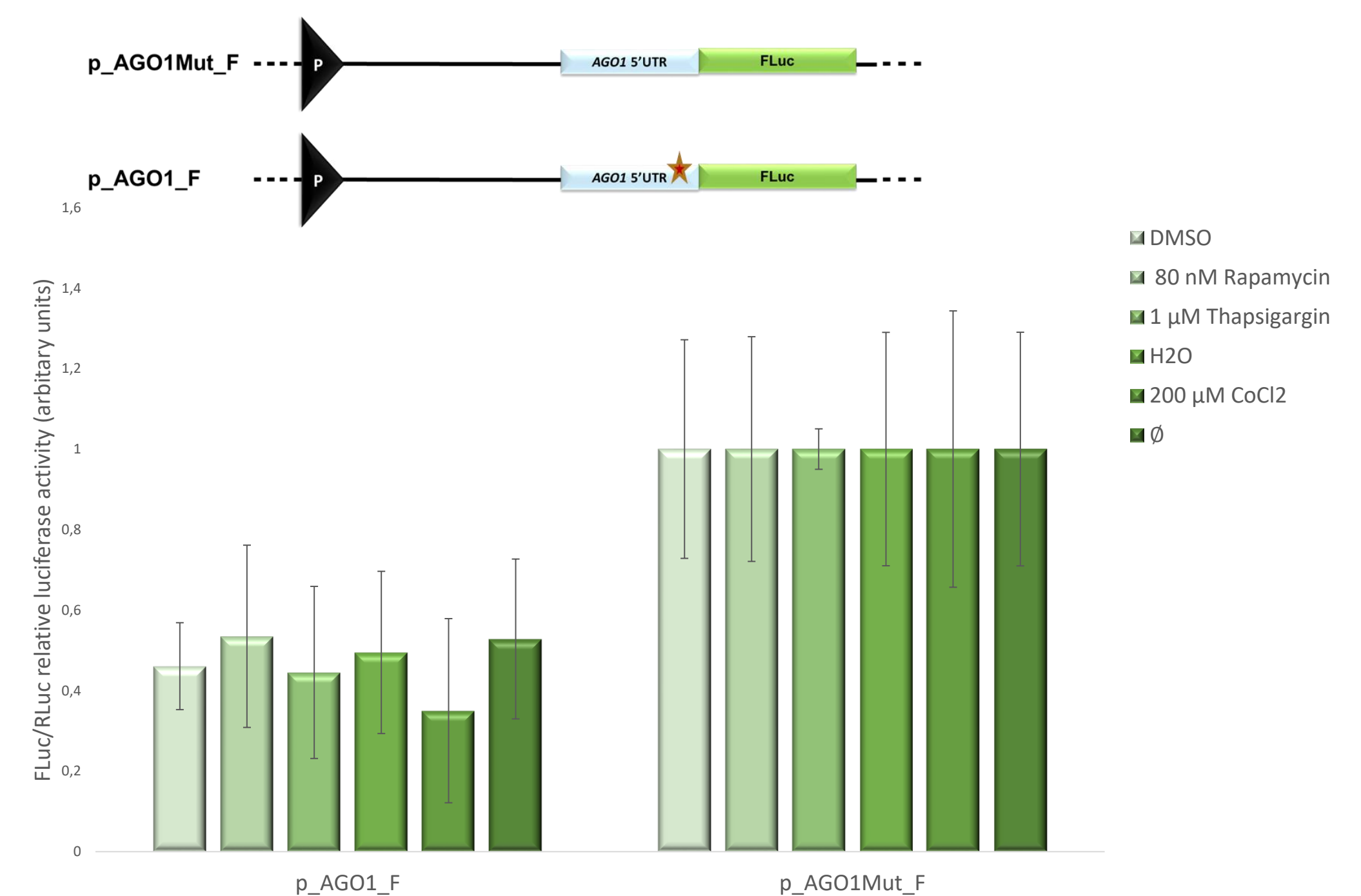


AGO1 5'UTR contains a uORF drives cap-independent translation initiation

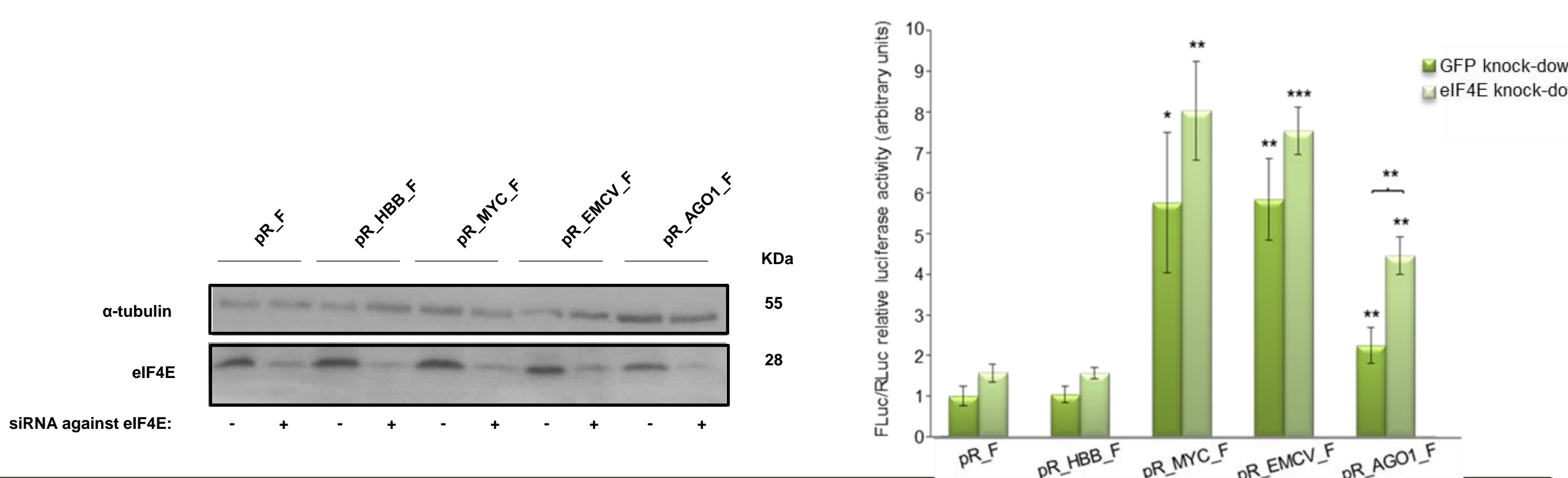


uORF role in AGO1 5'UTR is not detected in a bicistronic context and under stress conditions

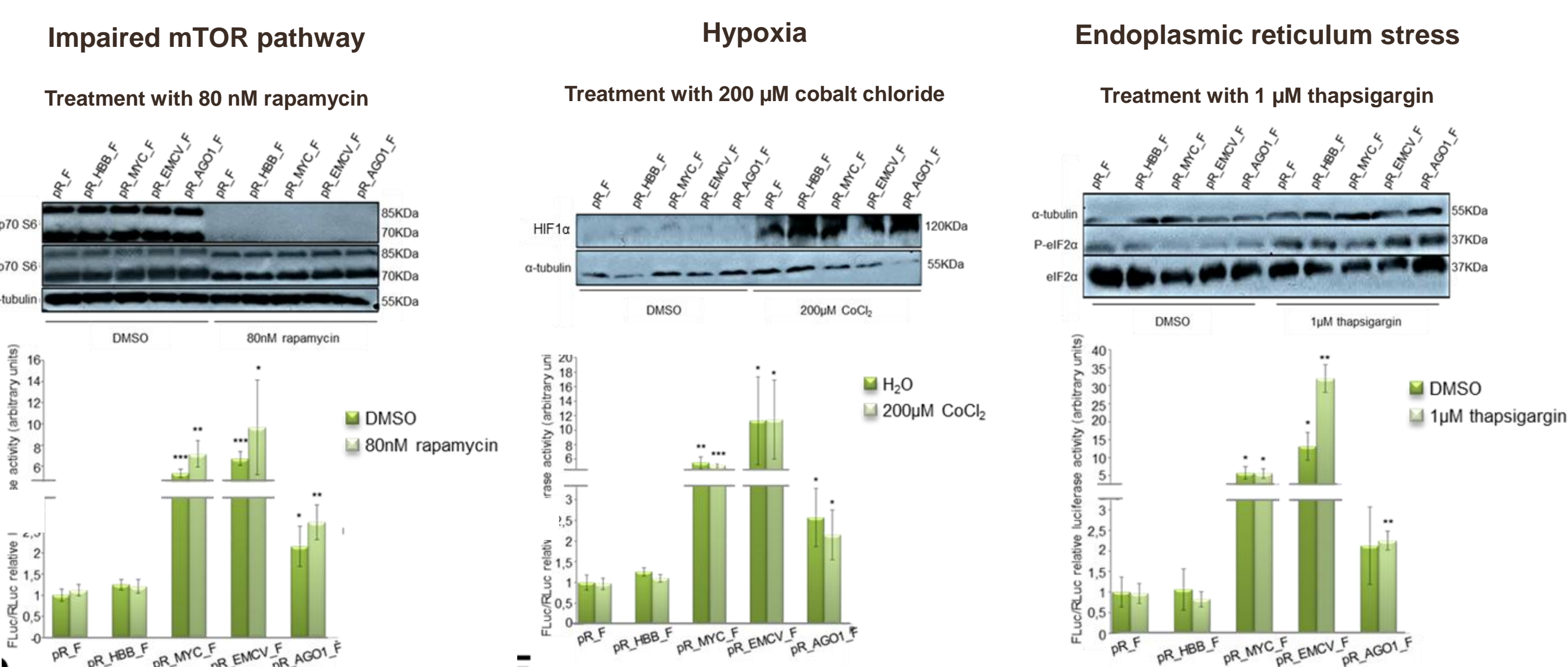
uORF in AGO1 5'UTR represses FLuc expression in a monocistronic context regardless of the stress conditions



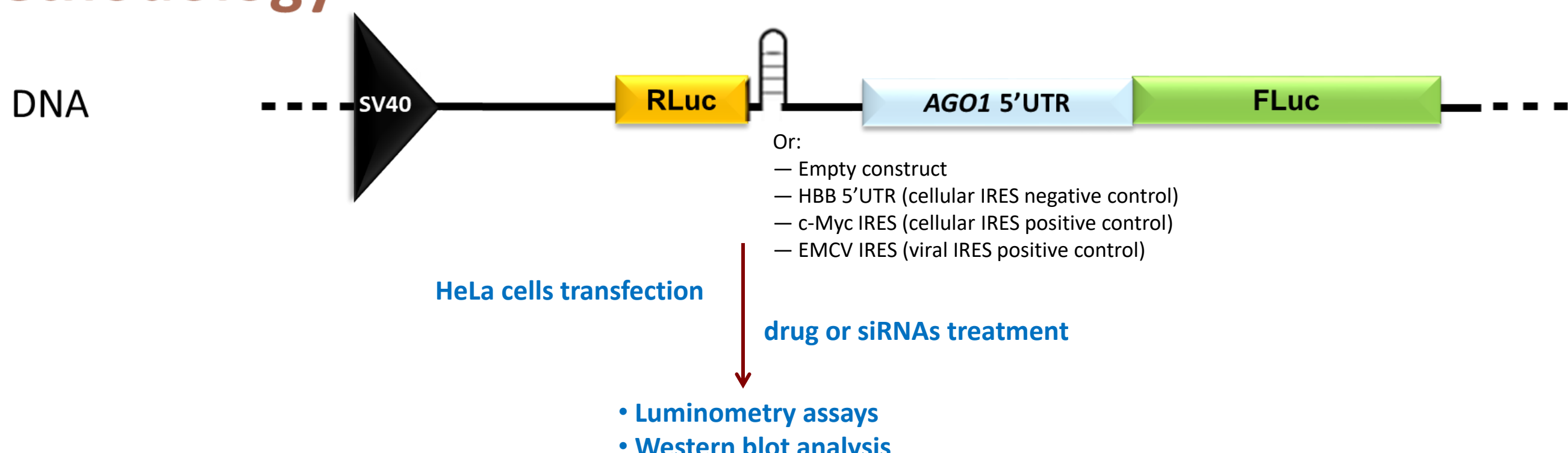
AGO1 5'UTR enhances translation of FLuc in HeLa cells under eIF4E knock-down conditions



AGO1 5'UTR-mediated cap-independent translation is maintained under stress conditions



Methodology



Acknowledgements

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Conclusions

AGO1 5'UTR mediates cap-independent translation initiation in normal conditions and under stress. eIF4E seems to inhibit AGO1 cap-independent translation initiation. The AGO1 uORF represses translation initiation of the main ORF in all tested conditions.

The uORF and the cap-independent mechanism of translation initiation may act together to regulate the expression levels of AGO1.