A Tale of Two Cities: eIF4G1 and eIF4G2's Mechanisms in Translation Initiation

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Translation initiation in human embryonic stem cells (hESCs) is governed by a delicate balance among canonical, cap-dependent and alternative pathways. This study dissects the roles of eIF4G1/2 by combining in vitro luciferase assays on 48 putative transcripts with computational analysis. Challenging eIF4G1's essential role as a scaffold, its knockdown led to increased translation in >95% of eIF4G1 putative transcripts (and >2-fold change in 14/24 transcripts), suggesting compensatory non-canonical mechanisms. eIF4G2 depletion resulted in varied transcript activity. ~58% of transcripts showed upregulation. Variation in how eIF4G2 knockdown affects translation indicates that specific features in the 5' UTR use different translation initiation methods, possibly leaky scanning or IRES-dependent pathways. Notably, the partial restoration of translation by the addition of Nat1 protein emphasizes its role in modulating alternative initiation pathways under stress. Comprehensive motif discovery revealed a highly conserved GC-rich 16-nucleotide sequence consistent with RNA G-quadruplex structures and enriched binding sites for YY1/YY2 transcription factors. Evolutionary analyses flagged critical IRES elements (oncogenic drivers like c-MYC, HIF1a) as conserved across vertebrates, linking the results to translational dysregulation in colorectal cancer and renal cell carcinoma. RBPMap analysis indicated that eIF4G2 may regulate translation of specific cellular processes (ion transport and protein ubiquitination) rather than acting as a general translation factor. Together, these results redefine the roles of eIF4G isoforms as context-dependent regulators of translational plasticity, with far-reaching implications for both stem cell biology and therapeutic targeting in oncology.

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