The expression of UPF1 is regulated by a cap-independent translation initiation mechanism and a cryptic promoter within its 5' untranslated region

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Regulation of gene expression occurs at several steps, including translation initiation. Under normal circumstances, translation initiation is mainly cap-dependent; however, several proteins can initiate translation in a cap-independent way, allowing the maintenance of these proteins under conditions that reduce global protein synthesis.
hUPF1(human up-frameshift 1) plays important roles in several key cellular processes such as nonsense-mediated decay, telomere replication and homeostasis, and cell cycle progression, suggesting its expression must be tightly regulated to prevent abnormal cell proliferation. This protein is essential in the G2/M transition, a step known by a reduced overall protein synthesis. Taking these data into account, we hypothesized that UPF1 might initiate translation in a cap-independent way, allowing the cell to maintain its levels under conditions that impair cap-dependent translation initiation.
To test this hypothesis, we cloned the h*UPF1* 5'UTR in a dicistronic vector and transfected CC and CRC cell lines with either this construct or the control counterparts. We observed a 15- to 25-fold increase in relative luciferase activity of the *UPF1* 5'UTR-containing construct compared to the levels obtained from the empty counterpart in all tested cell lines, suggesting a cap-independent translation initiation. To control whether luciferase activity levels are due to a cryptic promoter within *UPF1* 5'UTR, we transfected cells with promoterless plasmids and observed the same result, demonstrating that *UPF1* 5'UTR contains a cryptic promoter. Transfecting cells with *in vitro* transcribed mRNAs resulted in a 2-fold increase in protein levels, suggesting that translation can occur in a cap-independent way. This is maintained under conditions of global protein synthesis inhibition. Deletional analysis of *UPF1* 5'UTR revealed that the first 50 nucleotides are essential for cryptic promoter and cap-independent activities.
These results provide new insights on the mechanisms that govern UPF1 expression.