The main goal of the present project was to analyze the potential oxygen-dependent functional role of HELZ. The hypoxia–inducible transcription factor (HIF) is a key component of the cellular adaptation mechanisms to hypoxic conditions. HIFα subunits are degraded by prolyl-4-hydroxylase domain (PHD) enzyme-dependent prolyl-4-hydroxylation of two LxxLAP motifs that confer oxygen-dependent proteolytic degradation. Interestingly, a comprehensive *in silico* screen revealed only three non-HIFα proteins contain two phylogenetically conserved LxxLAP motifs, including the putative RNA helicase with a zinc finger domain HELZ, besides the CCR4-NOT transcription complex (CNOT1) and the faciogenital dysplasia protein (FGD1). However, HELZ proteolytic regulation was found to be oxygen-independent, supporting the notion that a LxxLAP sequence motif alone is not sufficient for oxygen-dependent protein destruction. Since biochemical pathways involving RNA often require RNA helicases to modulate RNA structure and activity, we used luciferase reporter gene constructs and metabolic labeling to demonstrate that HELZ overexpression activates global protein translation whereas RNA-interference mediated HELZ suppression had the opposite effect. Although HELZ interacted with the poly(A)-binding protein (PABP) via its PAM2 motif, PABP was dispensable for HELZ function in protein translation. Importantly, downregulation of HELZ reduced translational initiation, resulting in the disassembly of polysomes, in a reduction of cell proliferation and hypophosphorylation of ribosomal protein S6.