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Interplay between PDCD4 and eIF4G in Translation Termination: Insights into Protein Synthesis Regulation

Научный руководитель – Алкалаева Елена Зиновьевна

Al Sheikh W.[1], *Shuvalova E.Y.*[2]

1 - Московский физико-технический институт, Москва, Россия, *E-mail: walaa.samer.alsheikh95@gmail.com*; 2 - Институт молекулярной биологии им. В.А.Энгельгардта РАН, Москва, Россия, *E-mail: Hritova_Katia@mail.ru*

Programmed Cell Death 4 (PDCD4) protein serves as a tumor suppressor, impacting various cellular functions, including transcription, translation, apoptosis, and modulation of signal transduction pathways. Downregulation in its expression is frequently noticed in various cancers pointing to its potential role in inhibiting tumor promotion, invasion/metastasis, and proliferation. Additionally, it is involved into protein translation regulation. PDCD4 inhibits its binding partner, eIF4A, hindering proper mRNA unwinding and impeding translation initiation. Furthermore, it may directly bind to mRNA, disrupting the translation process [1,2]. Recent study revealed that PDCD4 stimulates translation termination by influencing peptidyl-tRNA hydrolysis induced by eukaryotic release factors, eRF1-eRF3 [3]. This stimulation is independent from its another binding partner PolyA Binding Protein (PABP) which is also activates translation termination [4].

Interestingly, PDCD4 contains two domains structurally similar to domains of eukaryotic Initiation Factor 4G (eIF4G). As eIF4G is involved in translation initiation and mRNA closed-loop structure formation interacting with PABP, we proposed that PDCD4 may suppress its activity in these two processes. To test this hypothesis, we compared translation termination efficiency of the pre-termination complexes (preTCs) preincubated with PDCD4 and preTCs where PDCD4 was added after release factors. We observed a significant decrease in peptide release of preincubated with PDCD4 preTCs compared to complexes without preincubation. This inhibitory effect aligns with PDCD4's known role in inhibition of translation, highlighting its role in protein synthesis regulation. Then additional experiments were performed to explore the interplay of PDCD4 and eIF4G in translation termination.

Exploration of the intricate interactions between PDCD4, release factors, eIF4G and ribosomes contributes to fine-tuning protein synthesis regulation. Further investigations into specific molecular mechanisms will improve understanding of PDCD4's role in cellular processes, which may have potential implications for targeted therapeutic interventions.

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