Impact of Cell-Free Synthetic Biology and Translation Biology through Lyophilization

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Citation: Paternotte A (2023) Impact of Cell-Free Synthetic Biology and Translation Biology through Lyophilization. Electronic J Biol, 19(5):1-2

Received date: September 07, 2023, Manuscript No. IPEJBIO-23-18164; **Editor assigned date:** September 11, 2023, PreQC No. IPEJBIO-23-18164 (PQ); **Reviewed date:** September 25, 2023, QC No. IPEJBIO-23-18164; **Revised date:** October 02, 2023, Manuscript No. IPEJBIO-23-18164 (R); **Published date:** October 09, 2023, DOI: 10.36648/1860-3122.19.5.096

Description

Cell free synthetic biology is an exciting and new branch in the field of synthetic biology. This has brought new and perhaps even unexpected advantages. Chief among these is the ability to operate genetically encoded tools in a sterile and abiotic format. Recent work has extended this advantage by freeze-drying these cell-free systems into dried pellets or embedded paper-based reactions. Taken together, these new ideas have solved the longstanding challenge of how to deploy poised synthetic gene networks in a bio safe mode outside of the laboratory. There is significant excitement in the potential of this newfound venue and the community has begun to extend proof-of-concept demonstrations in important and creative ways.

The field of cell-free synthetic biology has undergone tremendous growth in the past few years and is on track to become an important domain of application-based synthetic biology. This, along with the work of others, has introduced the exciting possibility of deploying poised synthetic gene networks outside of the laboratory in a bio-safe mode. These Freeze-Dried Cell-Free (FD-CF) reactions also have the important advantage of allowing for distribution and storage at room temperature, and thus avoid the need for a cold chain. In the time since these ideas were first reported, work from us and from across the community has extended this concept to other exciting applications, and there is a growing interest in using FD-CF reactions for the delivery of synthetic biology and biotechnology to new environments.

Internal Ribosome Entry Sites

Eukaryotic mRNAs were historically thought to rely exclusively on recognition and binding of their 5′ cap by initiation factors to effect protein translation. While Internal Ribosome Entry Sites (IRESs) are well accepted as necessary for the cap-independent translation of many viral genomes, there is now recognition that eukaryotic mRNAs also undergo non-canonical modes of translation initiation. Recently, high-throughput assays have identified thousands of mammalian transcripts with translation initiation occurring at non-canonical start codons, upstream of and within protein coding regions.

In addition to IRES-mediated events, regulatory mechanisms of translation initiation have been described involving alternate 5′ cap recognition, mRNA sequence elements, and ribosome selection. These mechanisms ensure translation of specific mRNAs under conditions where cap-dependent translation is shut down and contribute to pathological states including cardiac hypertrophy and cancer. Such global and gene-specific dynamic regulation of translation presents us with an increasing number of novel therapeutic targets. While these newly discovered modes of translation initiation have been largely studied in isolation, it is likely that several acts on the same mRNA and exquisite coordination is necessary to maintain ‘normal’ translation. In this short review, we summarize the current state of knowledge of these alternative mechanisms of eukaryotic protein translation, their contribution to normal and pathological cell biology, and the potential of targeting translation initiation therapeutically in human disease.

Upstream Open Reading Frames

Translation of Upstream Open Reading Frames (UORFs), non-AUG (RAN), and other models of alternative translation activated during pathological states have been the subjects of recent reviews, to which we refer readers. Modifying the translational program allows a rapid response to extracellular signals, effecting changes in protein expression from translation of existing mRNAs. Translation initiation is a point where many mechanisms of regulation converge to determine if an mRNA will be translated, and a canonical model of translation initiation central to our understanding of this process has arisen. Alternative mechanisms of translation initiation are characterized by distinct modes of initiation complex recruitment to the mRNA to facilitate translation initiation.

These include 5′ cap-dependent and independent models with diverse molecular mechanisms such as alternate cap recognition and mRNA methylation capable of allowing the formation of elongation competent ribosomes. There is also growing evidence to support a critical role of the ribosome

itself in regulating translation. This brief review will discuss several models of alternative translation initiation and the evidence for their occurrence in eukaryotic cells, and provide examples of mRNAs for which alternative translation is necessary to maintain normal cellular function. Yeast have served as a powerful tool to gain mechanistic insight in studies of translation initiation, however for this review we focus on studies conducted in mammalian model systems. Given the high cellular energy demand of protein translation, it is unsurprising that distinct mechanisms that exquisitely regulate this process occur. Canonical, cap-dependent translation initiation proceeds with greater efficiency than many alternative mechanisms of translation initiation and remains responsible for a large portion of protein output during cellular homeostasis.