Molecular mechanisms of translational control

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Ribosome dysregulation is the underlying cause for multiple disease states and is the primary mechanism by which many bacterial antibiotics function. My laboratory currently studies three aspects of translation regulation: mRNA frame maintenance and fidelity of protein synthesis, cell stress and toxin-mediated mRNA decay, and antibiotic resistance mediated by RNA modifications. Since the ribosome is one of the critical cellular macromolecular complexes and numerous disease states are attributed to mutations in translation factors, tRNAs or mRNAs, understanding the mechanisms of ribosome function is central to human health. Here, I will describe our studies aimed at determining how the ribosome maintains the universal mRNA three-nucleotide code (or “reading frame”) critical for correct protein expression. The absolute requirement for the precise correlation between the mRNA frame and the correct protein sequence expressed underlies an important, fundamental but unanswered question in molecular biology: what regulates the mRNA reading frame? To address this question, we study two examples of defined biological mechanisms that *subvert* the three-nucleotide mRNA reading frame and undergo high levels of frameshifting. Next, I will discuss how bacteria alter their metabolic rates during periods of stress, such as antibiotic exposure, by the specific regulation of protein synthesis. Specifically, the action of so-called toxin enzymes inhibit translation by cleaving mRNAs bound to the ribosome and, as a result, reduce expression to survive the particular stress. Our studies reveal that toxins recognize ribosome-bound RNA in novel ways that allow us to rationalize observed codon specificity of different toxins. Analysis of mRNA transcripts that escape degradation by different toxins suggests a mechanism by which bacteria have tuned their expression profiles to allow survival.