Regulation of protein synthesis is one mechanism by which bacteria alter their metabolic rates during times of stress. The ‘stringent response’ where deacylated tRNAs accumulate and stall the ribosome is one signal that initiates a cascade of events ultimately resulting in the activation of toxin proteins. Type II toxin proteins halt translation by cleaving mRNAs bound to the ribosome and as a result, reduce expression to survive the particular stress. Here, we use biochemical and structural approaches to characterize different toxin proteins and their specificity of select mRNAs. Our studies reveal that toxins recognize ribosome-bound RNA in novel ways that rationalizes codon specificity by different toxins. Furthermore, analysis of mRNA transcripts allowed to escape degradation by different toxins suggests a mechanism by which bacteria have tuned their expression profiles to allow survival.