Reconfiguring Ribosomes During and After Assembly

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Ribosomes produce protein in all cells. In doing so, they must faithfully translate the mRNA sequence into protein *and* interpret other instructions in the mRNA to maintain protein homeostasis via differential translation initiation rates, and by modulating elongation and termination efficiencies. Failure to accurately interpret the instructions that specify protein sequence or levels leads to pathologies, including cancer. Our work has shown that "specialized" ribosomes, lacking individual ribosomal proteins, accumulate both under physiological as well as pathological cellular situations. These ribosomes divert the normal translational program, which can modulate the stress response. Using the information from high throughput sequencing and luciferase reporter assays, we can re-program entire cellular pathways to make them responsive to stress-induced changes in ribosome composition. Excitingly, computational analysis of natural yeast isolates demonstrates that these changes also occur during adaptation, suggesting that specialized ribosomes provide a facile route for evolution. Finally, we provide a mechanism by which cancer cells disrupt mechanisms that ensure stoichiometric assembly of ribosomal proteins into the small subunit head in normal cells, to produce heterogeneous ribosomes, which endow the cells with stress resistance, but also unique vulnerabilities.