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Title: Rewriting Natural Decoding Rules by \textit{de novo} Genome Synthesis

Abstract:

Unnatural amino acids could be incorporated to expand the chemical, physical and biological properties of proteins to expand the function of life itself. There are two conceptual possibilities to achieve this goal: i). creation of orthogonal decoding rules running independently to the wildtype decoding rules to incorporate unnatural amino acids; and ii). \textit{de novo} synthesis of a new genome with artificially redefined synthetic decoding rules to expand natural decoding capacities to include unnatural amino acids.

To explore the first possibility, the orthogonal ribosome and multiple tRNAs were co-evolved to efficiently decode cognate quadruplet codons on an orthogonal mRNA for incorporation of multiple distinct unnatural amino acids. This established the possibility to enhance the efficiency of unnatural amino acid incorporation in response to a synthetic orthogonal quadruplet codes, creating maximally $4^4=256$ new quadruplet codons for unnatural amino acid incorporation.

The second possibility requires the \textit{de novo} construction of a synthetic genome with re-programmed synthetic decoding rules to re-build a synthetic life that fundamentally go beyond the limits of the 20 natural amino acid side chains. To pave the foundation to reach for this goal, an efficient, specific, and iterative method in \textit{E. coli} to replace defined genomic fragment with synthetic sequence (replicon excision enhanced recombination, REXER) has been developed; together with a feasible, modular, and scalable route for \textit{de novo} genome synthesis (genome stepwise interchange synthesis, GENESIS), which allows the replacement of the entire 4.6-mb \textit{E. coli} genome with synthetic DNA in around 15 or less iterated REXER steps.