Generation of an arginine-tRNA-adapted *Saccharomyces cerevisiae* strain for effective heterologous protein expression.

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Abstract

The tRNA population reflects the codon bias of the organism and affects the translation of heterologous target mRNA molecules. In this study, *Saccharomyces cerevisiae* strains with modified levels of rare tRNA were engineered, that allowed efficient generation of recombinant proteins with unfavorable codon usage. We established a novel synthetic tRNA expression cassette and verified functional nonsense suppressor tRNAGlnSCUA generation in a stop codon read-through assay with a modified β-galactosidase reporter gene. Correlation between altered tRNA and protein level was shown by survival of copper sensitive *S. cerevisiae* cells in the presence of copper ions by an increased transcription of tRNAArgCCG molecules, recognizing rare codons in a modified CUP1 gene. Genome integration of tRNA expression cassette led to the

generation of arginine-tRNA-adapted *S. cerevisiae* strains, which showed elevated tRNA levels (tRNAArgCCG, tRNAArgGCG and tRNAArgUCG) pairing to rare codons. The modified strain MNY3 revealed a considerably improved monitoring of protein-protein interaction from *Aspergillus fumigatus* bait and prey sequences in yeast two-hybrid experiments. In future, this principle to overcome limited recombinant protein expression by tRNA adaption of expression strains instead of codon adaption might provide new designer yeast cells for an efficient protein production and for improved genome-wide protein-protein interaction analyses.

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