Synthetic addiction extends the productive life time of engineered Escherichia coli populations - DTU Orbit (16/08/2019)

**Synthetic addiction extends the productive life time of engineered Escherichia coli populations**

Bio-production of chemicals is an important driver of the societal transition toward sustainability. However, fermentations with heavily engineered production organisms can be challenging to scale to industrial volumes. Such fermentations are subject to evolutionary pressures that select for a wide range of genetic variants that disrupt the biosynthetic capacity of the engineered organism. Synthetic product addiction that couples high-yield production of a desired metabolite to expression of nonconditionally essential genes could offer a solution to this problem by selectively favoring cells with biosynthetic capacity in the population without constraining the medium. We constructed such synthetic product addiction by controlling the expression of two nonconditionally essential genes with a mevalonic acid biosensor. The product-addicted production organism retained high-yield mevalonic acid production through 95 generations of cultivation, corresponding to the number of cell generations required for >200-m3 industrial-scale production, at which time the nonaddicted strain completely abolished production. Using deep DNA sequencing, we find that the product-addicted populations do not accumulate genetic variants that compromise biosynthetic capacity, highlighting how synthetic networks can be designed to control genetic population heterogeneity. Such synthetic redesign of evolutionary forces with endogenous processes may be a promising concept for realizing complex cellular designs required for sustainable bio-manufacturing.

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