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Harnessing Photoenzymatic Reactions for Unnatural Biosynthesis in Microorganisms

Background/Objective

Photoenzymatic catalysis combines enzymatic selectivity and light energy to enable biotransformations beyond traditional biosynthetic capabilities. However, its scalability is hindered by high enzyme loading, reliance on costly cofactors, and instability under radical-generating conditions. Integrating new-to-nature biosynthetic reactions would enable more precise and efficient assembly of complex molecules. Here, we report the integration of light-driven photoenzymatic reactions into the cellular metabolism of *Escherichia coli*, bridging flavin-based photobiocatalysis with biosynthesis.

Approach

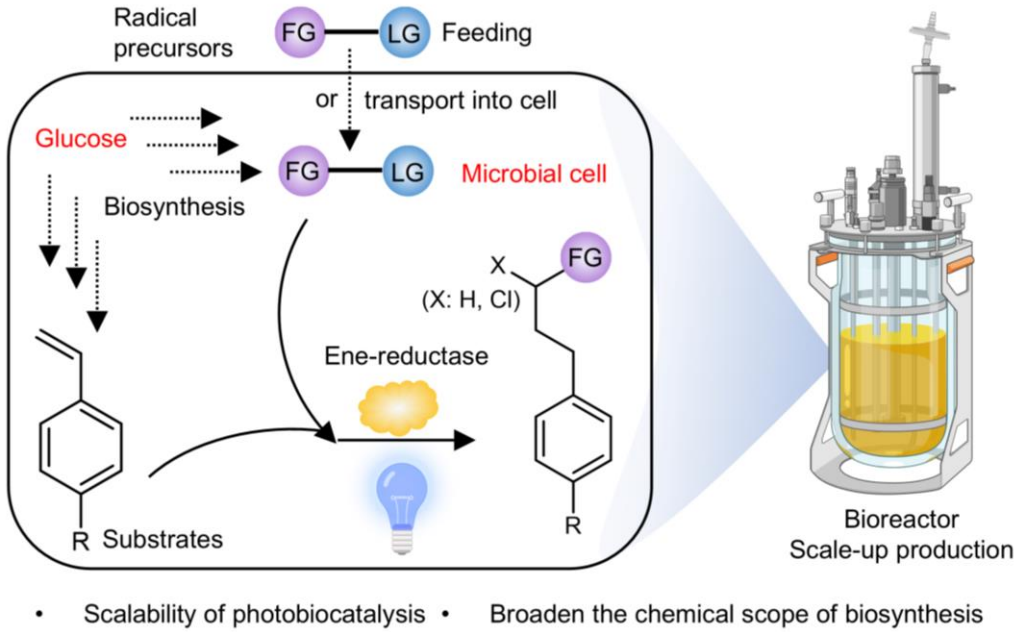
Using synthetic biology strategies, we engineered microbial cells to continuously produce olefin substrates and ene-reductase photoenzyme while regenerating cofactors directly from glucose. By externally supplying radical precursors or by introducing synthetic pathways for their *in situ* production, we enabled fermentation-based microbial photobiosynthesis, achieving high titers and demonstrating its feasibility for scale-up in bioreactor.

Results

We successfully integrated photoenzymatic reactions into *E. coli* and validated microbial production of diverse unnatural compounds including phenol-indole analogue (DIEP) at 0.62 g/L titers under fed-batched conditions.

Significance/Impacts

This work establishes a programmable and scalable platform for *ab initio* biosynthetic design, demonstrating a new method for biomanufacturing.



Overview of photoenzymatic catalysis.
FG: function group; LG: leaving group

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