Multi-level rebalancing of the naringenin pathway with artificial riboswitch-based biosensors

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Recombinant microbes have emerged as promising alternatives to natural sources of naringenin—a key molecular scaffold for flavonoids. Expression levels of the pathway genes should be optimized at both transcription and the translation stages to precisely allocate cellular resources and maximize metabolite production. However, the expression optimization of naringenin generally relies on evaluating a small number of variants from libraries constructed by varying transcription efficiency only. In this study, we introduce a systematic strategy for the multi-level optimization of biosynthetic pathways. Furthermore, we identified improved strains through high-throughput screening based on a synthetic naringenin riboswitch. The most-optimized strain obtained using this approach exhibited a 3-fold increase in naringenin production, compared with the parental strain in which only the transcription efficiency was modulated. Notably, the optimized strain produced 260.2 mg/L naringenin, which is the highest concentration reported to date for glycerol-based production. Collectively, this work provides an efficient strategy for the expression optimization of the biosynthetic pathways.