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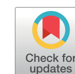
Research Highlights

Boosting polyketides production in cell factories
Shared target-pathway for pharmaceutical polyketides engineering



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Polyketides (PKSs) are secondary metabolites produced by microorganisms with important pharmaceutical applications [1]. However, the production yield of these bioactive metabolites is often low in native hosts, largely because their biosynthetic gene clusters (BGCs) are mostly silent, or their starting substrates limited. To improve the production yield of PKSs, multiple strategies have been developed, including metabolic engineering the native hosts or heterologously overexpressing their BGCs in a different host [2,3].

Acetyl-CoA is one of the starting substrates for PKS biosynthesis. It is reasonable to speculate that directing the carbon flux towards acetyl-CoA synthesis will boost PKS production titer. TAGs (lipids) are converted into acetyl-CoA via fatty acids (FAs) by the way of β-oxidation. Both studies highlighted in this issue focus on this shared pathway to boost polyketides production titer but using different strategies. In one study, Wang et al. [4] revealed that intracellular triacylglycerols (TAGs) degradation during the stationary phase of *Streptomyces* facilitates PKS biosynthesis and devised a 'dynamic degradation of TAG' (ddTAG) strategy to mobilize the TAG pool and increase PKS production titer. In another, Palmer et al. [5] set up a heterologous platform in *Yarrowia lipolytica* for producing 4-coumaroyl-CoA derived polyketides by mediating its endogenous lipid β-oxidation.

Wang et al. reported an innovative approach to promote *Streptomyces* PKS production via modulating its intracellular TAG pool. Using a metabolomics approach, they first found that the accumulating TAG pool is an intracellular carbon source for polyketide biosynthesis during the stationary phase. Next, they proposed that enhancing the cellular TAG degradation will lead to an increased production of acetyl-CoA (PKS starting material) and PKS production during stationary phase. Indeed, they discovered that production yields of multiple PKSs, including actinorhodin, jadomycin B, oxytetracycline and avermectin B_{1a}, are elevated after mobilizing TAG pool. To dynamically modulate cellular TAG pool, they identified one key acyl-CoA synthetase (ACS) gene *sco6196* that is responsible for TAG degradation and by temporally mediating the expression of *sco6196* to mobilize the TAG pool. This strategy, named 'dynamic degradation of TAG' (ddTAG), proven to work very well in various *Streptomyces* PKS producers. Application of ddTAG in *S. venezuelae* and *S. rimosus* significantly boosted the production of jadomycin B and oxytetracycline, respectively. Moreover, they were able to increase the titer of avermectin B_{1a} (an anti-pesticide drug) by 50% to 9.31 g l^{-1} in a 180-m^3 industrial-scale fermentation. This is the highest titer ever reported in the literature. In summary, this study demonstrated the potential of regulating cellular TAG pool to boost multiple PKSs in various *Streptomyces* isolates.

A previous study [6] enabled the high-titer production of a simple polyketide triacetic acid lactone in a nonconventional yeast *Y. lipolytica* via overexpressing the peroxisome biogenesis factor gene *PEX10* responsible for converting acyl-CoA to acetyl-CoA. In this work, Palmer et al. engineered *Y. lipolytica* to biosynthesize more complex polyketides like naringenin, resveratrol, and bisdemethoxycurcumin. The biosynthetic machinery of these 4-coumaroyl-CoA-derived PKSs utilize both 4-coumaric acid and acetyl-CoA as starting substrates. To boost their production titer, they heterologously expressed pathways for 4-coumaric acid production (via 4-coumaroyl-CoA) and employed a β-oxidation related strategy to increase acetyl-CoA accumulation. This combination allows the strain to produce several phenylpropanoid-derived polyketides including naringenin, resveratrol, and bisdemethoxycurcumin et al. by feeding *Y. lipolytica* with 4-coumaric acid, and achieved the highest titer of naringenin ever reported. In conclusion, these results revealed that the metabolically engineered yeast *Y. lipolytica* is an optimal host for the high-level production of complex, phenylpropanoid-derived PKSs.

Both studies utilize metabolic engineering strategies targeting the degradation of TAGs (lipids) towards acetyl-CoA to improve PKS production titer in the host. The PKS substrates, like acetyl-CoA and malonyl-CoA, could derive from various carbon sources and it will be very interesting to systematically explore the genes and pathways that could shunt the carbon flux toward acetyl-CoA and malonyl-CoA, and presumably increase PKS titer in a native host. Moving forward, it will be interesting to test if this strategy will boost the production titer of other characterized PKSs in different bacterial or even fungal hosts. It will also be more exciting to explore if this strategy will elicit the production of some cryptic or silent PKSs, because in general, the total number of PKS biosynthetic gene clusters still outnumbered the number of PKSs that have been reported in the literature.

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