Synthetic biology and metabolic engineering of actinomycetes for natural product discovery

Actinomycetes are one of the most valuable sources of natural products with industrial and medicinal importance. After more than half a century of exploitation, it has become increasingly challenging to find novel natural products with useful properties as the same known compounds are often repeatedly re-discovered when using traditional approaches. Modern genome mining approaches have led to the discovery of new biosynthetic gene clusters, thus indicating that actinomycetes still harbor a huge unexploited potential to produce novel natural products. In recent years, innovative synthetic biology and metabolic engineering tools have greatly accelerated the discovery of new natural products and the engineering of actinomycetes. In the first part of this review, we outline the successful application of metabolic engineering to optimize natural product production, focusing on the use of multi-omics data, genome-scale metabolic models, rational approaches to balance precursor pools, and the engineering of regulatory genes and regulatory elements. In the second part, we summarize the recent advances of synthetic biology for actinomycetal metabolic engineering including cluster assembly, cloning and expression, CRISPR/Cas9 technologies, and chassis strain development for natural product overproduction and discovery. Finally, we describe new advances in reprogramming biosynthetic pathways through polyketide synthase and non-ribosomal peptide synthetase engineering. These new developments are expected to revitalize discovery and development of new natural products with medicinal and other industrial applications.