Towards systems metabolic engineering of streptomycetes for secondary metabolites production

Streptomycetes are known for their inherent ability to produce pharmaceutically relevant secondary metabolites. Discovery of medically useful, yet novel compounds has become a great challenge due to frequent rediscovery of known compounds and a consequent decline in the number of relevant clinical trials in the last decades. A paradigm shift took place when the first whole genome sequences of streptomycetes became available, from which silent or "cryptic" biosynthetic gene clusters (BGCs) were discovered. Cryptic BGCs reveal a so far untapped potential of the microorganisms for the production of novel compounds, which has spurred new efforts in understanding the complex regulation between primary and secondary metabolism. This new trend has been accompanied with development of new computational resources (genome and compound mining tools), generation of various high-quality omics data, establishment of molecular tools and other strain engineering strategies. They all come together to enable systems metabolic engineering of streptomycetes, allowing more systematic and efficient strain development. In this review, we present recent progresses within systems metabolic engineering of streptomycetes for uncovering their hidden potential to produce novel compounds and for the improved production of secondary metabolites.