Exploring the Capacity of Microorganisms for Natural Product Biosynthesis

Full Abstract

A wide variety of compounds from various sources have been historically used in the treatment and prevention of diseases. Natural products as a major source of new drugs are extensively explored due to their huge structural diversity and promising biological activities, such as antimicrobial, anticancer, antifungal, antiviral and antioxidant properties. For instance, penicillin as an early-discovered antimicrobial agent has saved millions of lives, indicating the historical importance of natural products. However, the alarming rise in the prevalence of drug resistance is a serious threat to public health and it has coincided with the decreasing supply of new antibiotics. Bacteria with a tremendous undiscovered potential has still been one of the richest sources of pharmaceutically-important compounds to tackle the growing threat of antibiotic-resistant pathogens. Nevertheless, the production level of those important compounds is often quite low, and sometimes it is so low that we can not detect with current analytical techniques. The main goal of my doctoral dissertation research is to engineer natural product biosynthetic pathways for the generation of novel compounds and to improve the production of known medicinally important compounds. Firstly, I heterologously expressed some of the biosynthetic genes from the sch biosynthetic gene cluster found in Streptomyces sp. SCC-2136, leading to the production of a novel glycosylated derivative of angucyclines. I was also able to generate another glycosylated new derivative of angucycline through gene disruption of tailoring enzymes. Secondly, I engineered the regulatory elements in Streptomyces sp. SCC-2136 through overexpression and targeted gene disruption approaches for enhanced production of a pharmaceutically important angucycline Sch47554. Lastly, I isolated a new carotenoid-producing endophytic bacterium from a tree leaf and will optimize the fermentation conditions for an improved yield of zeaxanthin diglucoside.