Journal Club No.681 January 27, 2015

Jun-Pil JANG

The chemical diversity encoded by natural microbial communities has been significantly underexplored due to limitations associated with the inability to culture the majority of environmental bacteria and the silencing of biosynthetic pathways under laboratory conditions. Soils are predicted to contain thousands of unique bacterial species, which potentially harbor tens of thousands of functionally unexplored natural product biosynthetic gene clusters. With the development of metagenomic cloning methods, it is now possible to use DNA extracted directly from soil (environmental DNA, eDNA) to construct libraries that capture the enormous biosynthetic diversity present in soil environments. These libraries provide a means of functionally examining unexplored soil biosynthetic gene clusters and are therefore, appealing resources for sequence guided natural product discovery programs. Based on the magnitude of the biosynthetic diversity captured in saturating soil eDNA libraries, we believed that it would be possible to use these libraries to identify novel members of clinically relevant natural product families with potentially improved biological activities. To this end, we used a natural product sequence-tag driven approach to guide the discovery of an anthracycline-based aromatic polyketide that shows improved *in vitro* antiproliferative activity compared to the natural product anthracyclines that are currently in clinical use. In heterologous expression experiments the eDNA-derived *arm* cluster was found to encode for arimetamycin A, an anthracycline that is more potent than clinically used natural anthracyclines and retains activity against multidrug-resistant (MDR) cancer cells..

紹介論文

Angew. Chem. Int. Ed. 2013, 52, 11063 –11067

Arimetamycin A: improving clinically relevant families of naturalproducts through sequence guided screening of soil metagenomes

Dr. Hahk-Soo Kang and Prof. Sean F. Brady

Abstract

Sequence-tag-guided screening of soil environmental DNA libraries can be used to guide the discovery of new compounds with improved properties. In heterologous expression experiments the eDNA-derived *arm* cluster encodes arimetamycin A (see picture), an anthracycline that is more potent than clinically used natural anthracyclines and retains activity against multidrug-resistant (MDR) cancer cells.