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Bioprospecting novel natural products for potential anti-infective drugs

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Natural products occupy tremendous chemical structural space unmatched by any other small molecule families. One of the major limiting factors in natural products drug discovery industry is that pharmaceuticals have been traditionally designed to target individual factors in a disease system, but diseases are complex in nature and vulnerable at multiple attacks. Therefore, a systematic novel synergistic drug screening approach based on a multifactorial principle is urgently needed. Many drugs could be more effective at a reduced dosage if low dosages of other synergistic compounds are introduced simultaneously. To rapidly discover new antifungal agents especially for drug-resistant pathogens, we developed a high-throughput synergy screening (HTSS) strategy for novel microbial natural products. Here we also report an unexpected consequence of MDR1 upregulation: It confers enhanced sensitivity to the natural product berberine. We show that berberine is indeed highly efficacious in inhibiting the growth of azole-resistant clinical *C. albicans* isolates, with upregulated MDR1, from HIV infected patients. This effect is at least in part due to enhanced accumulation of berberine inside cells and a number of berberine structural analogues exhibited similar MDR1-dependent antifungal activity. Our study reveals a novel function of MDR1 in increasing sensitivity of drug-resistant fungal pathogens to selected natural products. The production of secondary metabolites will be increased by synthetic biology approaches.

Biography

Lixin Zhang is a Deputy Director of CAS Key Laboratory of Pathogenic Microbiology & Immunology, Institute of Microbiology, Chinese Academy of Sciences (IMCAS). Before joining IMCAS in 2006, he worked in 3 pharmaceutical companies in USA: SynerZ, Cetek and Microbia, Inc. He received his Ph.D. degree in Institute of Applied Ecology, CAS and did his postdoc at Emory University, USA. He has published seven books, more than 100 papers and holds eleven PCT patents. He co-edited a book with Prof. Arnold Demain on natural products in 2005 by Humana Press. He served as an Executive Board Member of International Symposium on the Biology of Actinomycetes (ISBA) and The International Chemical Biology Society (ICBS). He was recognized as an Honorary lifetime member, Sino-American Pharmaceutical Professional Association (SAPA). He has been appointed as an associate Editor-in-Chief for “Applied Microbiology and Biotechnology” and on the editorial board of 6 other peer-reviewed journals. The long-term goal of his research is to discover and develop synergistic medicines from marine microbial natural products. His research is focused on: Diversifying marine microbial natural product library; screening for synergistic medicines in a high throughput manner; increasing the production of drugable secondary metabolites from microbial producers by synthetic biology (serve as a chief PI for a 973 program). His Avermectin project won Award for "Excellence to improve science and technologies” and the paper was published in PNAS. He was recognized as an Awardee for National Distinguished Young Scholar Program, China.

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