Cyanobacteria: microbial factories for drug discovery

Cyanobacteria, the only prokaryotes that perform the oxygen-producing photosynthesis, are ancient organisms that shaped the atmosphere of our planet. In colonizing most waters and soils, where they face various environmental challenges and competition with many biological organisms, cyanobacteria have developed as widely diverse organisms that produce a wealth of biologically active compounds from solar energy, water and minerals. Many of these cyanobacterial products influence human health (antioxidants, vitamins, antibacterial, antifungal, antiviral, toxins). Thus, they can lead to the discovery of novel drugs and their targets. Altogether, it has been estimated that about 20% of the natural products approved by the American "food and drugs administration" are originating from cyanobacteria.

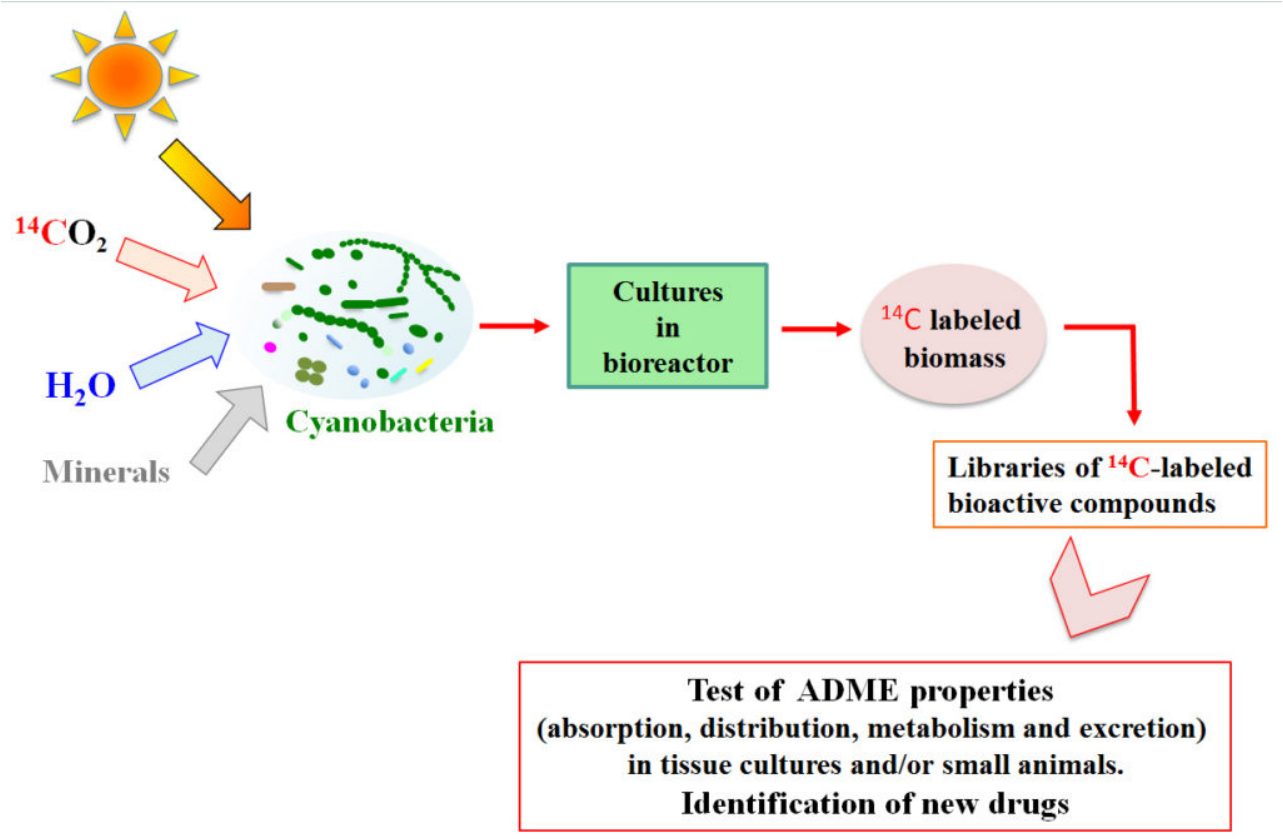

Fig. 1 Exploring the biodiversity of cyanobacteria for drug discovery.

Many cyanobacterial products are peptides synthesized by ribosomes and post-translationally modified, such as the microviridins (serine protease inhibitors). However, the majority of cyanobacterial products are either non-ribosomal peptides (such as lyngbyatoxin), polyketides (for

example anatoxin A) or hybrid peptide–polyketide compounds (such as apratoxin, curacin A and microcystin). The corresponding cascades of synthesis and modification enzymes generate a large array of products, some of which occurring in multiple variants (there are 100 variants of microcystin). Furthermore, recent genome sequencing and mining studies have revealed that cyanobacteria have the capacity to synthesize many more products than what have been characterized so far. Moreover, the vast panoply of the corresponding enzymes (polyketide synthases and non-ribosomal peptide synthases) can still be increased through gene manipulations with the tools available for a few model strains.

Together with the metabolic diversity of cyanobacteria, their powerful photosynthesis and radiation resistance, which allow them to grow efficiently on pure $^{14}CO_2$ as the sole carbon source, can be exploited for the cheap production of a vast array of compounds uniformly labeled with ^{14}C (Figure. Though the specific activity of ^{14}C-tracers is lower than those labeled with short-lived nuclides, this limitation can be partly counterbalanced by employing tracers that contain multiple ^{14}C atoms per molecule. Furthermore, powerful (last generation) radio-imagers can be used for digital autoradiography detection in animal tissue sections of weakly-labeled and very-low-abundant (few femtomoles) compounds. Hence the cyanobacterial libraries of ^{14}C-uniformly-labeled bioactive products are useful tools to screen for new drugs and analyze their ADME properties (absorption, distribution, metabolism and excretion) in tissue cultures and/or small animals.

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