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Chemical biotechnology: microbial solutions to global change

Editorial overview

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Microorganisms make up the majority of the living biomass on Earth and as such play crucial roles in global change, often as silent partners in human activities. These roles range from producing and consuming atmospheric gases that affect climate to mobilizing toxic elements such as mercury, arsenic, and selenium to causing infectious diseases. The complex interactions among humans, microorganisms, and the rest of the biosphere have created some of our most challenging global problems in the human history such as global warming, energy security, severe pollutions and environmental degradation, and emergence or re-emergence of old and new epidemics and diseases. Thus, there is an urgent need for new technologies to tackle these challenging global problems. This issue of *Current Opinion in Chemical Biotechnology* contains eight articles that describe various microbial solutions to three key global problems including energy security, environmental challenges, and infectious diseases. To a large extent, all these solutions were arisen from the fundamental understanding of the microbial physiology, genetics, diversity, and ecology.

Understanding the microbial world

Microorganisms have been widely exploited for medical, agricultural, food, and industrial applications. For example, a large fraction of small-molecule drugs such as penicillin and vancomycin were derived from microorganisms. Most of the industrial enzymes were also isolated from microorganisms. In addition, microorganisms were used as whole-cell catalysts for a variety of important chemical transformations. As an alternative, microorganisms were engineered to produce recombinant proteins and chemicals such as drugs, biofuels, and amino acids. Yet, the majority of microorganisms on Earth have not been characterized. In the review by Cardenas and Tiedje, several new tools that enable the rapid discovery and characterization of new microbes were discussed, including massive sequencing technologies based on pyrosequencing or single molecule sequencing, new isolation techniques, microfluidics, metagenomics, metatranscriptomics, and metaproteomics. These tools allow researchers to study microbial communities in their natural habitats and with higher resolutions, which may lead to new insights about their genetic potential and functional diversity.

An important feature in microbial communities concerns cell–cell communication. One of the ways by which microbes are able to communicate with each other is through quorum sensing in which microbes can regulate gene expression through the production, release, and detection of signaling molecules in a cell-density-dependent manner. Hooshang and Bentley reviewed the recent advances in understanding the mechanisms and regulation of quorum sensing at the molecular level, with emphasis on the formation of biofilms. In addition, they outlined some of the potential applications of quorum sensing in the chemical biotechnology area. Notable examples include creating a synthetic multi-cellular pulse generator, programming cell death in *Escherichia coli* and implanting a predator–prey ecosystem model. Such studies, albeit being primitive, represent first steps in creating more complex phenotypes and should help better understand the complexity and dynamics of microbial communities.

Microbial solutions to energy security

According to the new Energy Policy Act, billion gallons of renewable fuel must be produced by 2012 with most of that produced as biofuels using renewable biomass. Currently, the ethanol and biodiesel are the most widely used biofuels generated from renewable resources. However, neither of these biofuels is ideal as alternative transportation fuel because of their lower energy content. Efforts have recently begun in designing microbes for the production of transportation fuels from renewable lignocellulosic biomass. An excellent summary on the recent advances in this area was provided by the Keasling group. Several examples on the use of engineered microbes for the production of isobutanol, isopropanol, and high carbon content fatty acids or alkanes as biodiesels were discussed. The use of metabolic models and synthetic biology tools to complement experiment design was highlighted.

In addition to conventional liquid biofuels, the use of microbes for bioelectricity generation has received considerable attention because of the possibility of extracting current from a wide range of biomass and wastes. One major limitation with existing microbial fuel cell technology is the relatively low current density. Some emerging advances in this area were summarized by Lovely. An improved understanding in the direct electron transfer from microorganisms to the anodes is a key in improving the efficiency. A systems biology approach to evolve microbial interactions with the electrodes appears to be the key in addressing this issue.

Microbial solutions to environmental challenges

Over the past few decades enormous quantities of industrial pollutants have been released into the environment. Efforts have been made in recent years toward the use of bioremediation as an environmentally friendly cleanup approach. However, the recalcitrant nature of these pollutants has prompted the use of metabolic engineering or synthetic biology approaches toward the goal of a designer microbe for their effective cleanup. An excellent overview in these efforts was provided by Wood. Most noticeable is the use of advanced metabolic engineering and protein engineering tools for complex pathway engineering for the remediation of both organic and inorganic pollutants. In particular, it was suggested that the use of both transcriptome and proteome profiling may further improve the effectiveness in the practical use of bioremediation.

Although the idea of using designer microbes is very attractive, their practical realization is still constrained by the interaction with the local microbial population and the ability to retain activity. This increasing complexity makes it ideal for the use of systems biology tools to decipher the desirable characteristics as described by de Lorenzo. Recently, a systematic analysis was attempted to connect all known reactions from the University of Minnesota Biocatalysis/Biodegradation Database (UMBBD, http://www.umbbd.msi.umn.edu), resulting in connectivities of metabolic networks never seen in any single organisms. This type of system approach is an excellent example suggesting the potential to design complex metabolic pathways necessary for successful bioremediation.

Microbial solutions to infectious diseases

Despite significant advances in medical science, combating infectious diseases remains a global challenge. It was believed that most new infections are not caused by truly new pathogens but are microorganisms that find a new way to enter a susceptible host [1]. The incidence of microbial diseases such as plaque, cholera, and Lyme disease are all linked to global change. Thus, there is an urgent need for new drugs to combat infectious diseases. Fortunately, microorganisms have evolved to produce a myriad array of complex molecules known as secondary metabolites. Secondary metabolites – natural products – are a prolific source for pharmaceutical drugs. Recent advances in molecular biology and genomics have revolutionized our ability to discover and engineer the biosynthetic pathways that synthesize natural products. One of the most effective approaches to manipulate the biosynthetic pathways is combinatorial biosynthesis. Tang and co-workers reviewed the recent advances in combinatorial biosynthesis of several major classes of natural products derived from microorganisms, such as cyclic lipopeptides and macrolides. In addition, they showed that some of individual enzymes and extracted domains from the biosynthetic pathways can be used as biocatalysts for the synthesis of important pharmaceutical compounds. Examples include the terminal thioesterase domain from non-ribosomal peptide synthetase, glycotransferases, and acyltransferases.

Similar to microorganisms, plants produce an amazing array of natural products, many of which have biological activities. However, since plants and microorganisms that produce interesting natural products are often poorly characterized or even uncultivable, the ability to manipulate their biosynthetic pathways is rather limited. In addition, many of the natural product-based drugs are produced in minute amounts in their native hosts, making the drugs very expensive. On the contrary, total chemical synthesis of natural products with complex structures is typically non-viable commercially. Thus, reconstruction of biosynthetic pathways in platform organisms such as *E. coli* and *Sacchromyces cerevisiae* represents a desirable strategy complementary to organic synthesis. Tang and co-workers briefly discussed this strategy in their review, while Chemler and Koffas offered extensive overview of the recent efforts in producing plant derived natural products in microorganisms. One most prominent example is the engineering of *E. coli* and *S. cerevisiae* to produce the antimalarial drug artemisinin. The corresponding bioprocess was recently commercialized. Because that 'malaria is an old disease with the potential of re-emerging as a new disease, especially in association with climate change' [1], this particular example truly highlights the effectiveness of microbial solutions to global change. Other examples include the microbial synthesis of lycopene, flavonoids, stilbenes, and alkaloids. Both Tang and co-workers and Chemler and Koffas emphasized the importance of engineering approaches in discovering and producing new drugs or drug leads in their reviews.

Conclusions

Some of the leaders in Chemical Biotechnology provided reviews in this issue to highlight the potential of using different genetic and genomic tools to address key problems related to energy security, environmental challenges, and infectious diseases. Increasingly, our ability to address these key global issues are no longer restricted by the available tools but on the ability to incorporate large-scale system and synthetic approaches to tackle these complex issues. Continuous investment in this area is important to maintain the initial momentum toward a biotechnology solution to high quality of life globally.

References

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