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Review

Synthetic biology era: Improving antibiotic's world

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ABSTRACT

The emergence of antibiotic-resistant pathogen microorganisms is problematic in the context of the current spectrum of available medication. The poor specificity and the high toxicity of some available molecules have made imperative the search for new strategies to improve the specificity and to pursue the discovery of novel compounds with increased bioactivity. Using living cells as platforms, synthetic biology has counteracted this problem by offering novel pathways to create synthetic systems with improved and desired functions. Among many other biotechnological approaches, the advances in synthetic biology have made it possible to design and construct novel biological systems in order to look for new drugs with increased bioactivity. Advancements have also been made in the redesigning of RNA and DNA molecules in order to engineer antibiotic clusters for antibiotic overexpression. As for the production of these antibacterial compounds, yeasts and filamentous fungi as well as gene therapy are utilized to enhance protein solubility. Specific delivery is achieved by creating chimeras using plant genes into bacterial hosts. Some of these synthetic systems are currently in clinical trials, proving the proficiency of synthetic biology in terms of both pharmacological activities as well as an increase in the biosafety of treatments. It is possible that we may just be seeing the tip of the iceberg, and synthetic biology applications will overpass expectations beyond our present knowledge.

Contents

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1. Introduction

Large scale antibiotic use is widespread not only in human therapy, but also for farm animals and for aquaculture. As result of their wide applications, antibiotic related ecological pressure led to the arise of multi-resistant pathogenic bacteria. Therefore, new and more effective antibiotics are continuously required to fight antibiotic-resistant bacteria and pathogenic yeast. Antibiotic resistance progressively limits the efficiency of the current antimicrobial drugs. The incidence of resistant bacteria is highly increased in hospitals [1] and the infections caused by them kill many people around the world. In addition to antibiotic resistance, the appearance of an increasing number of multidrug-resistant pathogens makes the panorama more difficult to resolve [2]. Among them, *Staphylococcus aureus* causes half of the hospital-acquired infections and causes deaths of many people around the world [1]. In addition to the antibiotic resistance, new antibiotics are required to face new diseases caused by evolving pathogens. From 1980 to 1995 at least 30 new diseases were detected which are growing in prevalence. The picture is worst considering reemerging diseases such as the novel varieties of influenza and hepatitis B. The costs of combating such diseases are more than $120 billion per year.

Many pharmaceutical companies moved away from natural product research programs [3], especially from antibiotics. This was reflected in the number of natural drug approvals by FDA, which dropped from 36 in 2004 to 7 between 2003 and 2012. Nevertheless, the antimicrobial pharmaceuticals still amount for a significant percent of the drug market and the search for new active molecules is continuing, in both academia and industry. According to Baltz [4], we can no longer depend on the pharmaceutical companies alone to isolate and produce new antibiotics. The effort will need to come from medical research by the academia in collaboration with the biotechnology and pharmaceutical companies.

Finding new leads is clearly a priority. Traditionally, the new drugs have been obtained from natural microbial products, but with the increase in the knowledge from microbial physiology and with the technological developments, new avenues are opening. For example, new screening approaches, including the search for novel targets [5] and the exploration of non-conventional places as sources of the producer microorganisms are being implemented. In this regard, plant endophytes [6], springs/geysers [7] and caves [8], have been successfully explored. Most of the clinically used antibiotics have been derived from the bacterial small molecules produced by dedicated biosynthetic gene clusters, 90% of which remain unexplored. Therefore, the modern metagenomic and genome-mining that have recently been introduced show a strong potential for the discovery of new antibiotics [9,10]. As a discipline meant to design and construct organisms with desired properties, synthetic biology has generated rapid progresses in the last decade. This review will cover the strategies for synthetic biology applications, and some examples of pharmaceutical active compounds discovered by this modern discipline.

1.1. Introduction to the concept of synthetic biology

Finding an accurate definition of synthetic biology has been challenging. However, one plausible option is to understand synthetic biology as an engineering approach to improve or completely create systems and organisms with specific or desirable functions. This field of science incorporates different knowledge areas such as biology, chemistry, biotechnology, engineering, genetics and informatics to better comprehended living cells as working factories capable to evolve into anything imaginable [11–13]. According to the Presidential Commission of the USA [14], there are two main types of synthetic biology research, bottom-up and top-down. The first one creates new systems from nothing but complex organic chemicals. The second one uses living organisms as models, but rearranges their enzymes, genes and chemical molecules in a new puzzle. Despite its inherently challenging and complex nature, synthetic biology has allowed scientists to develop new strategies to exert control over the cellular behavior through this large library of building blocks.

Origins of synthetic biology have been differently reported. Some reports refer to the discovery and the study of the *lac* operon as the breakthrough in molecular biology, which allowed scientists to learn how regulatory circuits are controlled by specific conditions. This milestone discovery leads to the understanding of regulation and of gene expression of the cellular components [15,16].

Some of the most impressive highlights achieved thanks to synthetic biology could be consulted in other reviews [7,17–19]. One of the finest examples is the engineering of an *Escherichia coli* strain able to respond as a biological film, projecting different patterns of light to create a chemical image [20]. This goal was achieved by creating a chimera in which a synthetic sensor kinase from a cyanobacterial photoreceptor was fused to an *E. coli* intracellular histidine kinase domain. This experiment required the creation of a genetic circuit never reported before, using iGEM building blocks [21], thus attesting for the possibilities of synthetic biology. Another outstanding example involves the creation of the first self-replicating synthetic genome in bacteria by scientists at the J. Craig Venter Institute [22].

Synthetic biology has accelerated research in many scientific areas. Metabolic and microbial engineering has been one of the most benefited fields, since every metabolic capability (including cellular metabolism and gene regulatory and signaling networks) may be increased, for example by directing the metabolic fluxes to produce novel compounds with a specific biological activity [23]. In this review we will focus on the advances of the antibiotic drug discovery generated by synthetic biology. These advances have led to the discovery of novel and safer medicines. Among others, some examples include the development of genetic circuits, the enhancement of metabolite production, the awakening of silent clusters and the use of bacteria as drug delivery agents.

Synthetic biology brings many benefits meant to improve the clean energy, agriculture, food and medicine industries. Therefore, the applications are beyond our present knowledge, and they will most probably change the biological sciences as we know them.

2. Synthetic biology for drug research

In the following pages, we will review examples of how synthetic biology has improved the development of drugs, especially antibiotics.

The aforementioned new emerging pathogens and the prevalence of antibiotic-resistant strains have become an unresolved health problem of global dimensions. Despite many efforts, the