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Chasing New Drugs against Infectious Diseases: A Herculean Task

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Abstract

Infectious diseases are global health related disorder caused by pathogenic microorganisms such as bacteria, viruses, fungi or parasites. Infectious diseases today are the leading cause of death worldwide, will probably never be completely eradicated. In recent years, the antibiotics or vaccines available to treat infectious diseases have proven to be effective in most cases, yet the growing problem of drug resistance by pathogenic microbes has cornered infectious disease as global public health threat.

Keywords: Infectious diseases; Antibiotics; Vaccines; Bug-killing drugs

Commentary

Infectious diseases are the leading cause of deaths worldwide and will probably never be completely eradicated. During recent years, antibiotics recommended for standard infection control measures become ineffective due to marked increase in proportion of antibiotic resistant strains [1]. Microbes such as bacteria, viruses and fungi successively evolved resistance to almost every class of antibiotics and their rapid spread from infected to healthy individuals poses a rising threat to global public health security [2]. Nearly 50% of antibiotics prescribed by doctors are not optimal and given an incorrect medication dosage, frequency or duration, which constitutes an important source of antimicrobial resistance across the world [3]. Further, the ongoing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains have worsened medical procedures leading to long term financial and health implications for patients. In 2009, antibiotic market has generated sales of US$ 42 billion globally representing 46% of total sales of anti-infective agents [4]. In recent past, pharmaceutical industries have slashed investment in antibiotics due to poor sales of existing drugs, whose overuse has spurred the spread of resistance. Industries claim that "bug-killing drugs" are severely undervalued, if it fails to fight against infections [5-7]. Thus, the global health impact of antimicrobial resistance together with rapid depletion of antibiotic arsenal has revived interest in the discovery and development of new therapeutic drugs.

Peptide-based antimicrobial agent receives greater attention in recent years due to technological advancement in peptide engineering, solid-phase peptide synthesis and potential to select peptides as efficient drug with acceptable toxicity profiles [8]. Antimicrobial peptides (AMPs) are at the forefront of cutting edge research initiatives meeting the need to substitute conventional antibiotics and get rid of garbage antibiotics. AMPs are small bioactive molecules produced naturally by wide variety of organisms as a part of their first line of defense and demonstrate a broad range of antibacterial, antiviral and antifungal activities. AMPs can be considered as a promising and potential drug candidate in near future for combating infections and microbial drug resistance, due to their broad range of activity, lesser toxicity and projected slow emergence of resistance development by microbes. Further, their ability to overcome most antibiotic resistance by MDR/XDR strains has also gained considerable attention and clinical interest [9]. Besides antimicrobial functions, AMPs also has ability to act as multifunctional effector molecules such as signaling molecule, immune modulators, mitogen, antitumor, and contraceptive agent that added benefits to explore every aspect of their structural and biological properties for prophylactic and therapeutic applications [10]. Furthermore, the availability of new technological pipelines employing high-throughput omics technologies and flow cytometry greatly accelerate antimicrobial drug discovery and development processes for treatment of infectious diseases [11,12].

Among several AMPs listed in antimicrobial peptide databases (i.e. APD, CAMP, LAMP, DRAMP) with antimicrobial activity, only a small fraction has been extensively studied and tested. Despite their evolutionary success as essential component of host defense system in most species, AMPs research is still at the premature stage to conclude their apparent clinical role as potential therapeutic agent. Unfortunately, certain conditions such as proteolytic degradation of AMPs, loss of antimicrobial activity due to serum binding or physiological salt concentration and toxicity to host cells hindered translation of AMPs from bench to clinics [13]. These unique challenges will need to be overcome by custom peptide design and imaginative formulation of AMPs. Since, AMPs formed by L-amino acids are highly susceptible to degradation by proteases and clearance of serum components, which can be overcome by amino acid substitution including replacement of L-amino acids with D-amino acids. These substitutions may promote alteration in AMP properties without altering its antimicrobial activity, besides leaving AMPs more stable to proteolytic attack and serum binding [14]. Rational design of AMPs based on modification of peptide composition, structural (α-helix, β-sheet), physicochemical determinants (isoelectric point, hydrophobicity, net charge, amphipathicity) and aggregation propensities of existing AMPs (antibacterial or antiviral or antifungal) would benefit testing of modified derivatives for greater stability, specificity and antimicrobial efficacy to combat infections and microbial resistance [15]. Machine learning methods are instrumental in prediction and rational design of AMPs that would benefit identification prior to synthesis of novel analogues [16]. Moreover, intensive research is warranted to determine whether unlike other natural AMPs, synthetic AMPs also would potentially show low resistance in microbes.

In recent years, metagenomic approaches are being developed to access untapped reservoir of chemical diversity and for discovery of novel resistance determinants in clinical and natural environments [6]. As an alternative, metagenomics can be used as reliable approach

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to explore prospective reservoir of natural AMPs from unexplored environments, which might be the potential source of therapeutic peptides in near future. Thus, the development of novel AMPs has tremendous potential to reduce overall infection and infection-related deaths. Further, the emerging problem of antibiotic resistance can also be tackled by improving awareness and understanding of antimicrobial resistance among public, strengthening surveillance and antimicrobial research, reducing incidence of infection, optimizing use of antimicrobial drugs and ensure sustainable investment in fighting antimicrobial resistance. It should be highly acknowledged and despite extensive effort should be made in promoting AMPs research to prevent the burden of infectious diseases.

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