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Opinion Open Access

Perspectives to Combat Microbial Resistance

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Abstract

Microbial infectious diseases continue to be one of the greatest health problems worldwide, afflicting millions of people annually. Due to the diminutive arsenal of efficient antimicrobial agents and the frequent appearance of resistance to the drugs in current use, which consequently reduce the means to treat infected patients, there is a very urgent and continuous need to develop new chemotherapeutic drugs. This paper presents a personal opinion on this theme and some beneficial examples obtained and published by my research group along the last five years.

Keywords: Microbial resistance; Alternative chemotherapy; Antimicrobial drugs; Microbial targets; New antimicrobial strategies.

Opinion

A major global concern is the emergence and spread of systemic life-threatening microbial infections, particularly in critically ill patients [1-7]. Furthermore, the resistance to antimicrobial drugs has become a topical and alarming problem that culminates in longer period of hospitalization, increases in the financial cost and severe morbimortality outcomes, which constitute a real socioeconomic issue all over the world [8-10]. The development of new potent antimicrobial drugs is becoming more challenging every day since current drugs either have too many side-effects or they tend to lose effectiveness due to the emergence of resistant microbial strains [11-13]. In view of this alarming scenario, a number of different strategies have emerged, including (i) detection of new microbial targets, (ii) synthesis of bioactive compounds presenting new mechanisms of action, (iii) search for new compounds from different environmental sources, (iv) drug repurposing, and (v) combined therapy with synergistic effect [14-23].

Microbial proteases have emerged as potential targets for the development of novel antimicrobial chemotherapeutics, since this class of hydrolytic enzymes is directly implicated in several facets of basic biological processes as well as in numerous events of interaction between microorganisms and host structures [24-26]. In this way, our research group showed that aspartic protease inhibitors commonly used in the anti-human immunodeficiency virus therapy were able to (i) inhibit the hydrolytic activity of aspartic-type proteases, (ii) arrest crucial physiological events (e.g., nutrition, proliferation, growth and differentiation), (iii) induce morphological and ultrastructural alterations, and (iv) block the expression of virulence attributes linked to the infective process in distinct classes of microorganisms, such as yeasts (e.g., *Candida albicans, Candida parapsilosis* and *Cryptococcus neoformans*), filamentous fungi (e.g., *Fonsecaea pedrosoi*) and protozoa (e.g., *Leishmania amazonensis* and *Trypanosoma cruzi*), which culminated in the blockage of adhesion to both abiotic (e.g., plastic and glass) and biotic (e.g., mammalian cells) surfaces as well as in the increased susceptibility to killing by phagocytic cells [27-43].

Metal-based chemotherapeutic drugs are widely documented as powerful antimicrobial agents [44-46]. Corroborating this statement, a few metal-based drugs are already available in clinical arena, and others are currently being developed [47-49]. In this context, our group in collaboration to Irish researchers leaded by Dr. Malachy McCann (Chemistry Department, National University of Ireland), Michael Devereux (The Inorganic Pharmaceutical and Biomimetic Research Centre, Focas Research Institute, Dublin Institute of Technology) and Andrew Kellett (School of Chemical Sciences and the National Institute for Cellular Biotechnology, Dublin City University) have demonstrated that the coordination of 1,10-phenanthroline-5,6-dione (phendione), an heteroaromatic derivative of phenanthrene, to silver (Ag^{+}) or copper (Cu^{2+}) ions represents a new promising group of anti-infective agents, which revealed a potent anti-*Pseudomonas aeruginosa* action against both planktonic- and biofilm-growing cells [50].

The high morbidity and mortality associated with microbial infections is compounded by the limited therapeutic options and the emergence of drug-resistant strains. In parallel, the pharmaceutical companies are losing interest in new antimicrobial development. In this context, the researchers around the world will have a central and crucial mission to overcome this eminent dilemma, for example, helping in the proposition of novel practice and cheap solutions to solve this public concern.

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