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Antimicrobial molecular nanocarrier–drug conjugates

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Abstract

Many antimicrobial drugs are poorly active against pathogenic microbes causing intracellular infections, such as *Mycobacterium tuberculosis* or *Plasmodium falciparum*. On the other hand, several known antimicrobial agents are not effective enough because of their limited cellular penetration. A common feature of both challenges is the inability of an active agent to cross the biological membrane(s). One of the possible approaches facing these challenges is conjugation of an active substance with a molecular organic nanocarrier. The conjugate thus formed should be able to penetrate the membrane(s) and, once internalized, the active component could reach its intracellular target, either after release from the conjugate or in an intact form. Several molecular nanocarriers have been proposed: oligopeptides, including cell penetrating peptides, carbon nanotubes, siderophores, dendrimers, terpenoids and molecular umbrellas. A comprehensive review of the current status of molecular organic nanocarrier–drug conjugates and the future perspectives of their application as novel antimicrobials is presented.

Key words: Peptides; Siderophores; Terpenoids; Carbon nanotubes; Dendrimers; Molecular umbrellas

For many years, antimicrobial drugs have been used to inhibit or kill bacteria and other microbes. Unfortunately, overconsumption and inappropriate use of these drugs have created major environmental pressures for microbial pathogens to evolve towards resistance. In consequence, resistance to antimicrobial drugs has become increasingly widespread and this has resulted in a significant threat to public health and a substantial challenge for antimicrobial chemotherapy.[1] There are numerous mechanisms of microbial resistance but the most challenging is that of the multi-drug type, resulting from disturbance of drug transport across the microbial membranes, including an impaired uptake and/or active efflux of antimicrobials. Moreover, some of the antimicrobial chemotherapeutics also exhibit strongly reduced activity against biofilm-forming micro-organisms. These pathogens are often able to synthesize and secrete a matrix consisting of an extracellular polymeric substance (EPS) which accumulates and eventually surrounds the population of microbial cells. The EPS matrix is a barrier to diffusion of intact antibiotic molecules and, in consequence, microbes in biofilms are up to 1000 times more resistant to antibiotics than the planktonic ones.[2]

Another challenge for contemporary chemotherapy is the treatment of intracellular microbial pathogens. Several human pathogenic micro-organisms, including *Staphylococcus aureus*, *Salmonella enterica* serovar Typhimurium, *Mycobacterium tuberculosis*, *Plasmodium falciparum* and *Cryptococcus neoformans*, have developed the ability to persist in mammalian cells, making the infection latent or recurrent. The intracellular location provides a particular shelter for microbial pathogens because they are protected not only from host defenses but also from antimicrobial therapy. Indeed, among the antibiotic families, some of them, such as, β-lactams and aminoglycosides, exhibit restricted cellular penetration owing to their high hydrophilicity and, some others, like fluoroquinolones and macrolides, display low intracellular retention. Therefore, intracellular active concentration of these agents is often subtherapeutic, resulting in the emergence of resistance that cannot be managed by high doses of antibiotics, generating many side effects and toxicity.[3]

Abbreviations: AmB, amphotericin B; CNT, carbon nanotube; CPP, cell penetrating peptide; DFO, desferrioxamine B; MDR, multidrug resistance; MIC, minimal inhibitory concentration; MWCNT, multiwalled CNT; PAMAM, poly(amidoamine); PEG, polyethylene glycol; PPI, poly(propyleneimine); SWCNT, single-walled CNT.

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