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Historical perspective

Membrane interactions and antimicrobial effects of inorganic nanoparticles

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ABSTRACT

Interactions between nanoparticles and biological membranes are attracting increasing attention in current nanomedicine, and play a key role both for nanotoxicology and for utilizing nanomaterials in diagnostics, drug delivery, functional biomaterials, as well as combinations of these, e.g., in theranostics. In addition, there is considerable current interest in the use of nanomaterials as antimicrobial agents, motivated by increasing resistance development against conventional antibiotics. Here, various nanomaterials offer opportunities for triggered functionalites to combat challenging infections. Although the performance in these diverse applications is governed by a complex interplay between the nanomaterial, the properties of included drugs (if any), and the biological system, nanoparticle-membrane interactions constitute a key initial step and play a key role for the subsequent biological response. In the present overview, the current understanding of inorganic nanomaterials as antimicrobial agents is outlined, with special focus on the interplay between antimicrobial effects and membrane interactions, and how membrane interactions and antimicrobial effects of such materials depend on nanoparticle properties, membrane composition, and external (e.g., light and magnetic) fields.

Contents

Abbreviations: DMPA, dimyristoylphosphatidic acid; DMPC, dimyrostoylphosphatidylcholine; DMPG, dimyristoylphosphatidylglycerol; DMPS, dimyrostoylphosphatidylserine; DOCP, dioleoylphosphatidylcholine with reversed polar headgroup; DOPC, dioleoylphosphatidylcholine; DOPG, dioleoylphosphatidylglycerol; DOTAP, dioleoyltrimethylammoniumpropane; DPPC, dipalmitoylphosphatidylcholine; DPPG, dipalmitoylphosphatidylglycerol; DSPC, distearoylphosphatidylcholine; DTPC, ditridecanoylphosphatidylcholine; PC, phosphatidylcholine; PG, phosphatidylglycerol; POPC, palmitoyloleoylphosphatidylcholine; TMCL, dimyristoylglycerophosphoglycerol.

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1. Introduction

Motivated both by advances in material science, and challenges to reach efficacy and safety for challenging for novel therapeutics, drug delivery research has undergone considerable broadening during the last decade in particular, from more traditional drug delivery systems, such as lipids, surfactants, and polymers, which still dominate drug delivery research, particularly in relation to industrial development, to include also a wide range of nanomaterials [1–3]. Analogously, nanoparticles are generating considerable interest as novel antimicrobial agents [4–6], notably due to increasing resistance development against convential antibiotics, such as tetracycline, β-lactam, aminoglycoside, macrolide, and quinolone antibiotics [7]. Apart from scalability and versatility, such materials offer advantages related to presently undeveloped bacterial resistance, as well as possibilities of responsiveness of antimicrobial and other effects, controlled by a range of triggering factors. Antimicrobial nanomaterials may therefore provide an alternative to both low molecular weight and biomacromolecular antimicrobial agents in a range of contexts.

Nanoparticles may display antimicrobial action through widely different modes of action, including not only direct membrane disruption, but also i) damage to oxidation-sensitive lipids and proteins by generation of reactive oxygen species (ROS), iii) DNA damage, iii) damage to the functionality of cellular proteins/enzymes, iv) triggering of inflammation, and iv) damage to mitochondrial function [4–6,8]. Contrary to cell membrane disruption, all of the latter may be obtained also from the molecular, atomic, or ionic species constituting the nanoparticles, thus not solely relying on the nanoparticle nature of the material. For example, ROS generation of metal oxide nanoparticles frequently does not necessarily require the material to be present as nanoparticles [4]. Analogously, dissolved silver ions have been demonstrated as a key factor for the antimicrobial effect displayed by silver nanoparticles [9]. Although focus in the rest of the discussion will be placed on membrane-nanoparticle interactions, it should be kept in mind that generally, several of these pathways operate in concert.

It should be noted that nanoparticles rarely, if ever, retain their properties once introduced into a biological system. For example, numerous serum proteins adsorb readily at nanoparticles introduced to the bloodstream, whereby surface-bound serum proteins ('opsonins') effectively tag the particles as non-edogenous, facilitating their uptake in macrophages and other defense cells [10]. Through this, nanoparticles are frequently cleared rapidly from bloodstream circulation, and accumulated in macrophage-rich tissues through the so-called reticuloendothelial system (RES). The opsonization process has been recognized as central for parenteral drug delivery for decades, and laid the foundation for poly(ethylene glycol)-modified (PEGylated) liposomes and related drug delivery systems [10]. More recently, it has attracted interest in relation to the toxicity of, and drug delivery/theranostic uses of, novel nanomaterials [11]. From this, there is growing knowledge that a corona is formed not only by serum proteins, but also by other compounds such as polar lipids, amino acids, and sugars, and that both composition and dynamics differ between different regions of the nanoparticle corona [12,13]. Irrespectively of detailed composition and dynamics variations, corona formation at the surface of nanoparticles in biological solutions, as such, needs to be taken into account in the design of nanoparticles for antimicrobial and other functionality.

In efforts to clarify the interplay between membrane destabilization and antimicrobial effect, model systems are valuable since they facilitate mechanistic studies of membrane destabilization. At the same time, model lipid membranes differ in several key respects from real bacteria and human cells, e.g., relating to more complex lipid compositions of the latter, presence of considerable amounts of non-lipid components (e.g., lipopolysaccharide in Gram-negative bacteria, lipoteichoic acid in Gram-positive bacteria, and peptidoglycan in both of these). Correlation between results obtained with model membranes and those obtained for real bacteria or cells can therefore not be taken for granted, and model experiments should therefore always be run in parallel to bacteria and cell experiments. Having said that, there is considerable support from the related field of antimicrobial peptides that model membrane experiments correlate very well with antimicrobial effects of such peptides, provided that model lipid systems are chosen with care [14].

Finally, we note that there are many different ways to group different types of nanoparticles, e.g., depending on key physical properties (e.g. polarizability), chemical composition, or areas of applications. In the present overview, however, nanoparticles are grouped according to chemical composition and primary functionality in order to clearly demonstrate main effects involved, also for biologists and other non-nanotechnologists.

2. Metal nanoparticles

2.1. Membrane interactions

Metal nanoparticles offer interesting opportunities for drug delivery, also in the context of infections. For example, both low molecular weight and biomacromolecular drugs can be readily adsorbed at the surface of these nanoparticles, allowing large drug loads due to their large specific surface area. Drug release can be achieved, e.g., through simple desorption induced by a change in pH or ionic strength, by light exposure for drugs covalently bound to the nanoparticles through photolabile linking groups, or through reduction of thiol links used for drug chemisorption [2]. In addition, metal nanoparticles (notably Ag, but also Au and Cu) are interesting as antimicrobial agents. The latter effects originate from several mechanisms, including direct membrane rupture, binding to sulfhydryl groups of metabolic enzymes, binding to microbial DNA, and generation of reactive oxygen species, in turn causing bacterial enzyme and lipid oxidation [4,5].

A key factor influencing membrane interactions of metal nanoparticles is that of their surface properties. Exemplifying this, Xiao et al. investigated binding of carboxylated Au nanoparticles at POPC/DOTAP and DSPC/DOTAP bilayers as a function of cationic DOTAP content, as well as effects thereof on membrane destabilization. While nanoparticle