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Antibacterial and membrane-damaging activities of mannosylated bovine serum albumin

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ABSTRACT

The aim of this study was to test whether mannosylated BSA (Man-BSA) exerts antibacterial activity on *Escherichia coli* (gram-negative bacteria) and *Staphylococcus aureus* (gram-positive bacteria) via its membrane-damaging effect. Man-BSA caused inhibition of growth of *E. coli* and *S. aureus*. Moreover, bactericidal action of Man-BSA on *E. coli* and *S. aureus* positively correlated with the increase in membrane permeability of the bacterial cells. Morphological examination showed that Man-BSA disrupted bacterial membrane integrity. Destabilization of the lipopolysaccharide (LPS) layer and inhibition of lipoteichoic acid (LTA) biosynthesis in the cell wall increased the bactericidal effect of Man-BSA on *E. coli* and *S. aureus*. Man-BSA also induced leakage and fusion of membrane-mimicking liposomes in *E. coli* and *S. aureus*. Man-BSA showed similar binding affinity for LPS and LTA. LPS and LTA strongly suppressed the membrane-damaging activity of Man-BSA, whereas an increase in the Man-BSA concentration attenuated the inhibitory action of LPS and LTA. Taken together, our data indicate that Man-BSA's bactericidal activity depends strongly on its ability to induce membrane permeability. Moreover, the bactericidal action of Man-BSA proven in this study suggests that Man-BSA may serve as a prototype for the development of anti-infective agents targeting *E. coli* and *S. aureus*.

Introduction

The development of resistance of bacteria to antibiotics is a global problem that underscores the need for new therapeutic agents. Antimicrobial peptides and proteins are currently under consideration as a potential alternative to conventional antibiotics, on account of their widespread occurrence in nature [1,2]. Antimicrobial peptides and proteins display a broad spectrum of activities against a wide range of pathogens including bacteria, fungi and enveloped viruses. A common feature of most of these peptides and proteins is that they are cationic and have amphipathic properties. Because the bacterial membrane consists of abundant negatively charged phospholipids, it is believed that most of the antimicrobial peptides and proteins interact with anionic phospholipids and kill microorganisms by permeabilizing the bacterial membrane, by thinning the membrane or by destabilizing the membrane structure [3]. Nevertheless, antimicrobial peptides and proteins may kill bacteria by inhibiting macromolecular biosynthesis and/or by interacting with specific vital components inside the bacterial cells [3].

Given that membrane composition of bacteria includes abundantly anionic phospholipids, an increase in the positive charge of the antibiotic proteins via blocking of negatively charged carboxylate groups may enhance the interaction of such proteins with the bacterial membrane and thus enhance the potency of the antibacterial effect. Several studies revealed that bovine α-lactoglobulin and bovine lactoferrin have antibacterial properties [4–6]. Pan et al. [7–9] found that amidation of bovine α-lactoglobulin and bovine lactoferrin increases the net positive charge of these proteins, sharply increasing their bactericidal activity. Nevertheless, there are no studies exploring the possibility that novel antimicrobial proteins could be prepared from nonbactericidal proteins after modification of carboxyl groups. Because antimicrobial proteins usually exert their activity by damaging the bacterial membrane, proteins that preferably interact with phospholipids but do not

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