The role of outer membrane proteins and lipopolysaccharides for the sensitivity of escherichia coli to antimicrobial peptides

Bacterial resistance to classical antibiotics is emerging worldwide. The number of infections caused by multidrug resistant bacteria is increasing and becoming a serious threat for human health globally. In particular, Gram-negative pathogens including multidrug resistant Escherichia coli are of serious concern being resistant to the currently available antibiotics. All Gram-negative bacteria are enclosed by an outer membrane which acts as an additional protection barrier preventing the entry of toxic compounds including antibiotics and antimicrobial peptides (AMPs). In this study we report that the outer membrane component lipopolysaccharide (LPS) plays a crucial role for the antimicrobial susceptibility of E. coli BW25113 against the cationic AMPs Cap18, Cap11, Cap11-1-18m2, melittin, indolicidin, cecropin P1, cecropin B, and the polypeptide antibiotic colistin, whereas the outer membrane protease OmpT and the lipoprotein Lpp only play a minor role for the susceptibility against cationic AMPs. Increased susceptibility toward cationic AMPs was found for LPS deficient mutants of E. coli BW25113 harboring deletions in any of the genes required for the inner part of core-oligosaccharide of the LPS, waaC, waaE, waaF, yaaG, and gmhA. In addition, our study demonstrates that the antimicrobial activity of Cap18, Cap11, Cap11-1-18m2, cecropin B, and cecropin P1 is not only dependent on the inner part of the core oligosaccharide, but also on the outer part and its sugar composition. Finally, we demonstrated that the antimicrobial activity of selected Cap18 derivatives harboring amino acid substitutions in the hydrophobic interface, are non-active against wild-type E. coli ATCC29522. By deleting waaC, waaE, waaF, or waaG the antimicrobial activity of the non-active derivatives can be partially or fully restored, suggesting a very close interplay between the LPS core oligosaccharide and the specific Cap18 derivative. Summarizing, this study implicates that the nature of the outer membrane component LPS has a big impact on the antimicrobial activity of cationic AMPs against E. coli. In particular, the inner as well as the outer part of the core oligosaccharide are important elements determining the antimicrobial susceptibility of E. coli against cationic AMPs.