Delivery of cytotoxic peptides – Granulysin & Granzyme-B by lipid nanocarriers as targeted therapeutic systems

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Infectious diseases are the leading cause of death worldwide. Aside from new infectious diseases emerging regularly, the increasing prevalence of antibiotic resistant strains present a global health crisis. There is an urgent need to develop new alternatives to the conventional antibiotics. The immune response by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells against various bacterial pathogens involves release of cytotoxic proteins, in particular of the antimicrobial effector protein granulysin and group of homologous serine proteases, the granzymes. These candidates for the targeted immunotherapy with lipid nanocarriers might help to overcome their limited applications due to the chemical instability in biological environments, low aqueous solubility, and host toxicity when employed at high concentrations. The design and characterization of effective self-assembled nanocarriers with pH-enabled antimicrobial activity has potential to provide targeted delivery of such antimicrobial peptides. Biological *in vitro* assays against *Escherichia coli* showed high antimicrobial activity of the positively charged oleic acid (OA) and granulysin aggregates at pH 5.0, while negligible antimicrobial activity was observed at pH 7.0 for the negatively charged cylindrical micelles. The nanocarrier's ability to switch its biological activity "on" and "off" in response to changes in pH has potential to focus the antimicrobial peptides' action to areas of specific pH in the body. This study presents a promising strategy against antibiotic resistant bacteria while protecting the beneficial microbiome in the body and eliminating adverse effects.

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