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Exploring endolysin-loaded liposomes for a transtympanic treatment of *S. pneumoniae* otitis media

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Otitis media, the main reason antibiotics are prescribed in childhood, is often caused by Streptococcus pneumoniae. The exogenous use of recombinantly produced endolysins, peptidoglycan hydrolases encoded by bacteriophages at the end of their lytic cycle, has shown effectiveness against this pathogen. The endolysins' bioavailability could be increased if they could be directly applied to the ear. This would also reduce the probability of recurrent or chronic middle ear infection. However, the endolysins need to be encapsulated into delivery systems with permeation enhancing characteristics that can surpass the barrier provided by the tympanic membrane. Therefore, this work aimed to develop a novel endolysins delivery system for a transtympanic treatment of pneumococcal otitis media.

The MSlys endolysin was encapsulated into deformable liposomes composed of L-alpha-lecithin and sodium cholate (L:SC:MSlys) or PEG2000 PE (L:PEG:MSlys) with an efficiency of approximately 35% on average, being released in a controlled manner. Liposomes loaded with MSlys showed no cytotoxicity against keratinocyte and fibroblast cell lines. Moreover, MSlys-loaded liposomes interacted with S. pneumoniae cells, significantly reducing planktonic and biofilm cells. Transtympanic permeation studies demonstrated that PEGylated liposomes significantly enhanced the transport of MSlys through human tympanic membranes in an ex vivo model, showing antipneumococcal effect after 2 hours. Nevertheless, degradation of MSlys occurred during extended incubation at 37 ºC, which affected its effectiveness.

In conclusion, endolysin-loaded liposomes are promising for transtympanic treatment of otitis media caused by S. pneumoniae. Nevertheless, further optimization is required in order to increase effectiveness.