Antimicrobial activity of gentamicin carried by niosomes against uropathogenic *Escherichia coli* strains

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Abstract

Urinary tract infections (UTI) are the most frequent bacterial community infections, and the leading case of hospital-acquired infection, of which 80% of cases occur following catheterization [1]. Uropathogenic Escherichia coli (UPEC) is the major causative agent of UTI [2]. UPEC initially colonize the human host adhering to the bladder epithelium. Adhesion is followed by bacterial invasion of urothelial epithelial cells where they can replicate to form intracellular bacterial communities (IBCs), compact aggregates of intracellular bacteria with biofilm-like properties. UPEC strains may persist within epithelial urothelial cells thus acting as quiescent intracellular bacterial reservoirs (QIRs). It has been proposed that host cell invasion may facilitate both the establishment and persistence of UPEC within the human urinary tract. UPEC strains are equipped with a variety of virulence factors including fimbrial adhesins, toxins, invasins, iron-acquisition systems which cooperate to the establishment of long lasting infections UTIs and hence recurrent episodes [3]. Considering the spread of antibiotic-multi resistance, new strategies for the treatment of UTI are a priority. To improve the therapeutic drug efficacy and overcome the issue, the use of nanotecnology received particular attention [4]. Gentamicin (GM), a broad-spectrum antibiotic, exhibits a concentration-dependent activity and a post-antibiotic effect, the bioactivity of GM is hampered by its poor penetration into cells and, moreover, the molecule accumulates mainly in lysosomes, where its activity is low. In addition, GM oral administration is not effective, so repeated high parenteral doses are usually required, inducing systemic side effects (such as nephrotoxicity and ototoxicity) [5]. This work aims to evaluate the ability of delivery systems, such as niosomes, to improve the delivery and intracellular concentration of GM, and the effect against persistent intracellular UPEC strains isolated from a patient with recurrent UTI. The activity of gentamicin loaded niosomes on intracellular, invasive and persistent UPEC in T-24 bladder cells has also been evaluated. In this work the niosomes prepared and characterized were suitable for the investigation, showing nanometric dimensions, a good stability profile and an efficient drug entrapment efficiency. Moreover, due to the particular structure of niosomes it is possible to obtain the co-loading of GM (in the aqueous core) and Nile Red (in the lipophilic bilayer). The internalization of these samples occurred in T-24 monolayers already after 7 hours of contact. Cytotoxicity studies, conducted by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and antibacterial activity performed by micro dilution in broth, have shown a significant inhibiting effect on both cells and bacteria viability after treatment with GM loaded niosomes. To evaluate a potential anti invasive activity, non-cytotoxic and non-bactericidal concentrations of GM loaded niosomes were finally tested during the infection phase. The decrease in invasion rates leads us to hypothesize a release of the antibiotic inside the cell. In conclusion, we can speculate that the delivery of antibiotic by niosomes may be very promising but at the same time has aspects that still need to be elucidated for a potential application in the therapeutic field.

Keywords

Antibiotic resistance; Infectious diseases; Uropathogenic *Escherichia coli*; Nanotechnologies; Gentamicin.

References

[1] E. Serretiello, V. Folliero, B. Santella et al., Int J Microbiol 2021 (2021) 1-10.
[2] A.L.F. Flores Mireles, J.N. Walker, M. Caparon, S.J. Hultgren, Nat. Rev. Microbiol. 13 (2015) 269-284.
[3] A. Kim, J. Ahn, W.S. Choi et al. Int Neuroulog J 25 (2021) 192–201.
[4] C. Marianecci, L. Di Marzio, F. Rinaldi et al., Adv Colloid Interface Sci 205 (2014) 187–206.
[5] A. Pietropaolo, P. Jones, M. Moors, B. Birch, B.K. Somani, Curr Urol Rep 19 (2018) 78.