Journal of Controlled Release 290 (2018) 180

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Inherent antimicrobial activity by bacteria-derived vesicles

Bacterial infections with difficult-to-treat pathogens are becoming an increasingly important matter. It is estimated that up to 25,000 patients are killed every year by these infections in Europe, with about the same number of patients in the United States, and these numbers will only rise in the next decade. Indeed, the World Health Organization (WHO) has declared resistant bacteria as one of the top three threats to humanity. Increasing scientific effort has been focused on the discovery of new antimicrobial compounds, such as natural products or target-based molecules. The clinical development of such compounds also requires their formulation into a delivery system that can efficiently and selectively transport its cargo to the site of infection. Targeting of antibiotics is essential for reducing unwanted side effects and dose-limiting tissue toxicity, e.g., nephrotoxicity of aminoglycosides. Encapsulation of common antibiotics into traditional delivery systems has shown to improve tissue distribution and reduce acute undesired side-effects to a certain extent, but the current delivery systems are still far from achieving targeted delivery.

In this issue, Dr. Gregor Fuhrmann and his team characterized a type of naturally occurring membrane vesicles derived from non-pathogenic bacteria that possess inherent antimicrobial activity [1]. These outer membrane vesicles (OMVs) are a class of extracellular vesicles (EVs) shed by soil-living myxobacteria. In recent years, EVs have attracted scientific interest for their known property of natural conveyers of cell-to-cell communication. They have shown reduced immunogenicity, making them interesting drug delivery vehicles not only in the field of infection treatment [2,3]. Such a potential, however, comes with various challenges, such as difficulties in large scale production and in efficient drug loading, not to mention safety to humans. The Fuhrmann team has demonstrated that OMVs derived from myxobacteria may be a valid alternative to overcome these issues. Myxobacteria show predatory activity on other bacteria without being pathogenic to humans which make them optimal sources for OMVs. Two representative strains of myxobacteria, namely *Cystobacter velatus* (Cbv34) and an unclassified Sorangiineae strain (SBSr073), were used for OMV isolation by ultracentrifugation followed by size-exclusion purification. OMVs had an average size of < 200 nm and they showed promising storage stability under different conditions including –80 °C, –20 °C and also lyophilization. When incubating OMVs with epithelial A549 cells and activated THP-1 macrophages, they did not induce any changes in cell viability and there was no underlying cytotoxicity detectable; even at ratios of 50,000 OMVs/cell. Moreover, the vesicles did not show a higher endotoxin concentration compared with negative controls. These promising results point to a good biocompatibility, but it needs to be verified in more complex tissue culture models, and of course in humans. Uptake studies of OMVs with *E. coli* as Gram-negative model bacteria showed co-localization of OMVs with bacteria in a similar manner than standard liposomes. OMVs showed a dose-dependent inhibition of *E. coli* which was elicited by cystobactamid 919-1 – a novel inhibitor of bacterial topoisomerase [4]. This drug is naturally loaded into OMVs, thus equipping them with the ability to kill competing bacteria.

The Fuhrmann team's finding is unique in that bacteria-derived OMVs themselves possess an inherent antimicrobial effect. Obtaining the bulk quantities of OMVs may not be a limiting step in developing clinical formulations, since the production of OMVs can easily be scaled up by culturing bacteria in large fermenters. For successful translation into clinical applications, a more fundamental understanding is required. Further studies are necessary to find out whether OMVs are fusing with bacterial membranes or whether they only stick to their surface to maximize the efficacy. It is also necessary to study the OMVs' impact on other pathogenic and Gram-positive bacteria, ideally in complex co-culture models with mammalian epithelial cells, and in suitable in vivo models. Moreover, it will be relevant to investigate whether varying the bacterial culture conditions has an impact on cystobactamid loading into OMVs. Such fundamental studies will undoubtedly allow fine-tuning of these natural carriers for the maximum antibiotic efficacy of existing and future antibiotics. The work by the Fuhrmann team provides an essential link to the therapeutic use of EVs in an infection setting using a simple and accessible method.

References

[1] E. Schulz, A. Goes, R. Garcia, F. Panter, M. Koch, R. Müller, K. Fuhrmann, G. Fuhrmann, Biocompatible bacteria-derived vesicles show inherent antimicrobial activity, J. Control Release 290 (2018) 46–55.

[2] A. Pinheiro, A.M. Silva, J.H. Teixeira, R.M. Gonçalves, M.I. Almeida, M.A. Barbosa, S.G. Santos, Extracellular vesicles: intelligent delivery strategies for therapeutic applications, J. Control Release 289 (2018) 56–69.

[3] A. Goes, G. Fuhrmann, Biogenic and biomimetic carriers as versatile transporters to treat infections, ACS Infect. Dis. 4 (2018) 881–892.

[4] S. Baumann, J. Herrmann, R. Raju, H. Steinmetz, K.I. Mohr, S. Hüttel, K. Harmrolfs, M. Stadler, R. Müller, Cystobactamids: myxobacterial topoisomerase inhibitors exhibiting potent antibacterial activity, Angew. Chem. Int. Ed. 53 (2014) 14605–14609.

Kinam Park
Purdue University
Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu.

https://doi.org/10.1016/j.jconrel.2018.10.031