DESIGN OF GLYCOLIPID-FUNCTIONALIZED EXTRACELLULAR VESICLES FOR THEIR SELECTIVE TARGETING TO DENDRITIC CELLS

Jordi Guixeras[a], Antoni Planas[b], Chiara Pizzichetti[d], Santiago F. González[d], Cristina Fornaguera[c], Magda Faijes[b]

[a] Grup d'Enginyeria de Materials (Gemat) and Laboratory of Biochemistry, Institut Químic de Sarrià (IQS), Universitat Ramon Llull (URL), Via Augusta 390, 08017 Barcelona, Spain
jordiguixerasc@iqs.url.edu
[b] Laboratory of Biochemistry, Institut Químic de Sarrià (IQS), Universitat Ramon Llull (URL), Via Augusta 390, 08017 Barcelona, Spain
[c] Grup d'Enginyeria de Materials (Gemat), Institut Químic de Sarrià (IQS), Universitat Ramon Llull (URL), Via Augusta 390, 08017 Barcelona, Spain
[d] Istituto di Ricerca in Biomedicina (IRB), Università della Svizzera, Universitat Ramon Llull (URL), Via Francesco Chiesa 5, 6500 Bellinzona, Switzarland

Despite progress in cancer treatment, many new drugs developed through conventional approaches still cause significant side effects and are limited by tumour resistance to chemotherapy [1]. As a result, immunotherapy has gained attention as an alternative strategy that works by activating the immune system to recognise and attack cancer cells. Among the different types of immunotherapies, therapeutic vaccines aim to stimulate the patient's immune response by delivering tumour antigens after the disease has developed. This is intended to activate cytotoxic lymphocytes, which are responsible for killing cancer cells [2]. Using nucleic acids to encode antigens has several advantages, including their ability to act as natural adjuvants and the flexibility to modify the enconded antigens without major changes to the formulation. However, nucleic acids are unstable and do not easily enter cells, so they need to be delivered by a carrier that can both protect them and target antigen-presenting cells specifically. Thus, the aim of the present work is to develop new nano-vectors based on lipid systems that encapsulate the antigenic genetic material and are selectively vectorised towards the antigen presenting cells.

Among the various existing vectors, extracellular vesicles (EVs), nanosystems naturally released by all human cells that already contain genetic material and have intercellular communication functions through gene material and proteins transference, have been chosen [3]. It has been designed a new type of vectorization of EVs, using glycolipids, which are expected to integrate into their lipid membrane and expose the sugar moiety on the surface, enabling selectively targeted to antigen presenting cells. Five different compounds have been developed, which differ in the presence, length or absence of a linker between the lipid and sugar units, monosaccharide or disaccharide and the inclusion of a peptide moiety for comparison. The method of incorporation of these glycolipids into the vesicles has been established and their integration has been confirmed by confocal microscopy and flow cytometry. Furthermore, preliminary results were also obtained from in vitro and in vivo assays. In conclusion, this study demonstrates the successful functionalization of EVs, resulting in altered biodistribution to lymph nodes and modified uptake patterns by immune cells—supporting their potential as a promising platform for nucleic acid-based therapeutic vaccines.

Acknowledgements: This work was supported by MINECO/FEDER (grants, SAF2015-64927-C2-2-R; RTI2018-094734-B-C22 and PID2019-104350RB-100).

References:

1. C.-Y. Huang, D.-T. Ju, C.-F. Chang, P. M. Reddy, and B. K. Velmurugan, BioMedicine, vol. 7, no. 4, 2017, doi: 10.1051/BMDCN/2017070423.
2. J. Schlom et al., "Therapeutic cancer vaccines," in Advances in Cancer Research, vol. 121, Academic Press Inc., 2014, pp. 67–124.
3. C. Giacobino, M. Canta, C. Fornaguera, S. Borrós, and V. Cauda, Cancers, vol. 13, no. 9. Multidisciplinary Digital Publishing Institute (MDPI), May 01, 2021, doi: 10.3390/cancers13092280.