RNA Horizons 2024
Therapeutics Symposium
Unlocking the RNA's Potential in Medicine
September 25-27, 2024
Alfandega Congress Centre, Porto, Portugal

Targeted polymeric nanoparticles for personalized mRNA-based immunotherapy of cancer

Binder Amanda, Espinós I Longa Ignasi, Torres Coll Antoni, Bremm Franziska, Reinhard Voll, Carola Berking, Salvador Borrós, Cristina Fornaguera, Schaft Niels, **Jan Dörrie**

Universitatsklinikum Erlangen, Germany

Background: To date, therapeutic cancer vaccination using tumor-associated antigens (TAA) yielded limited clinical success. Nanoparticles (NPs) that shuttle TAA-encoding mRNA directly to antigen presenting cells (APCs) in vivo may increase the therapeutic efficiency. The encoded protein is translated intracellularly and mainly presented on MHC I by the APCs to induce CD8+ cytotoxic anti- tumoral T-cells. Furthermore, in addition to vaccination antigens, mRNA can encode functional proteins to reprogram immune cells in situ to overcome immunosuppression and support immune activation.

Methods: In this project, poly(β-amino ester) NPs were used to encapsulate mRNA, encoding GFP, the TAA MAGE-A3, or a constitutively active mutant of the IKKβ that activates the NF-kappaB pathway. Their ability to transfect and reprogram different types of human ex-vivo-generated APCs such as dendritic cells (DCs) and macrophages was tested and antigen presentation as well as phenotypic polarization were examined. In addition, the NPs' ability to transfect tumor cells was addressed. Electroporation of pure mRNA was used in parallel for comparison.

Results: The NPs were able to transfect DCs and macrophages with intermediate efficiency while various tumor cells were transfected very efficiently. The transfection of DCs and macrophages resulted in MHC I-restricted antigen presentation, as shown by activation of autologous specific CD8+ T cells. Expression of IKKβ in macrophages resulted in a phenotypic shift from M2 towards M1 and increased their T-cell stimulation capacity.

Conclusion: mRNA-encapsulating poly(β-amino ester) NPs represent a possible approach to target different cell types during immunotherapeutic treatment. They can mediate antigen presentation and functional reprogramming of APCs and potentially tumor cells. While the former can be rendered more immunogenic, the latter may be turned into functional APCs as well, for example by equipping them with costimulatory molecules or pro-inflammatory cytokines.