New polymeric nanocomplexes against glioblastoma initiating cells

Carla Garcia-Mazas, Marcos García Fuentes, Noemi Csaba

Center for Research in Molecular Medicine and Chronic Diseases, Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Santiago de Compostela, Santiago de Compostela, Spain

Gene therapy emerged as an alternative to small drugs and proteins in the treatment of a large variety of diseases. However, the administration of nucleic acids still remains a challenge due to the biological barriers that need to be overcome before reaching the target cells. Indeed, polynucleotides are very sensitive to degradation and cannot cross cell membranes. To overcome these obstacles, nucleic acids are often included in viral, lipid or polymeric particles. Polymeric gene nanocarriers offer chemical flexibility and good protection for the therapeutic genes, but the materials used still need to be optimized to achieve improved efficiency in the gene delivery process.

Considering this background, the objective of this work has been the development of new prototypes of polymeric nanoparticles for their use in gene therapy and to test their potential for the treatment of glioblastoma. For this, a variety of synthetic cationic polymers have been combined with plasmid DNA or with both plasmid and an endosomolytic polymer. The nanoparticles were characterized for their physicochemical properties, for their toxicity and transfection efficiency in cell cultures. The polymer having primary amines and hydrophobic side groups, combined with the endosomolytic polymer provided some of the best results regarding their transfection/toxicity ratio. This advanced prototype was used with a therapeutic plasmid encoding Bone Morphogenic Protein-4 as a potential treatment against glioblastoma. These therapeutic nanoparticles showed the capacity to suppress glioblastoma growth in a murine xenograft model when combined with Temozolomide, due to the synergistic effect between those two treatments administered together.

Supervisors: Marcos García Fuentes, Noemi Csaba