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Cyclodextrin as enhancer of targeting ability of folate-decorated polyethylenglycol-polycaprolactone nanoparticles to solid tumors

C Conte[1], **I Fotticchia**[1], **F Moret**[2], **C Giancola**[1], **E Reddi**[2], **F Ungaro**[1] and **F Quaglia**[1]
[1]University of Naples, Italy
[2]University of Padova, Italy

Introduction: In the field of innovative anticancer therapies, PEGylated nanoncologicals have attracted significant attention in recent years, due to their ability to deliver selectively one or more drugs directly to solid tumors through passively targeting mechanisms. However, the most common approach to improve their selectivity remains surface decoration with different targeting motifs over-expressed in cancer cells or blood vessels, including antibodies, peptides and small molecules, thus building an actively-targeted nano-medicine. Amid them, folate (Fol) receptor (Fr) is one of the most extensively employed target to enhance nano-carrier accumulation in cancer cells since it is overexpressed on the vast majority of cancer tissues (epithelial, ovarian, cervical, breast, lung, kidney, colorectal, brain). Unfortunately, the extent of targeting ligand presentation at nanoparticle (NP) surface, including Fol-targeted nano-carriers, can be much lower than theoretical, which can result in poor benefits of the targeting approach.

Aim: On these premises, in this study we propose a novel strategy to promote Fol exposition on core shell NPs based on amphiphilic block copolymers of poly(caprolactone) (PCL) and polyethylenglycol (PEG), through the aid of (2-hydroxypropyl)-cyclodextrin (HPβCD), due to its ability to form very stable complex with Fol.

Methods: Non-targeted NPs (nt-NPs) and targeted NPs (t-NPs) with and without HPβCD were prepared by a slightly modified melting/sonication procedure from PCL-PEG and PCL-PEG/PCL-PEG-Fol mixtures, respectively. NPs were characterized for size, morphology, charge, fixed aqueous layer thickness (FALT) and HPβCD content. Interaction of NPs with a specific antibody against folate (mAb-antiFol) was monitored by isothermal titration calorimetry (ITC). Uptake in FR (+) (KB) and FR (-) (A549) cell lines was finally assessed.

Results: All the formulations showed very similar properties in term of size (60-70 nm), poly-dispersity index and zeta potential (slightly negative). tNPs showed the lowest shell thickness (1.3 nm) followed by ntNPs (2.0 nm). Shell thickness increased to 4.1 and 3.3 nm respectively for HPβCD-modified nt-NPs and tNPs. The reduction of shell thickness in the case of tNPs could be related to a more compact arrangement of PEG fringe due to affinity of Fol for PEG chains. In fact, the hydrophobic nature of Fol moieties probably induces their folding in the PEG coating, thus quashing the possible interaction of Fol-decorated NPs with the target receptor. Conversely, the presence of HPβCD increases the PEG shell, presumably due to its ability to interact with both PEG chains and Fol, finally promoting targeting ligand exposition on the surface. Surface exposure of Fol on NPs was then evaluated through the binding of mAb-antiFol. Results confirmed that HPβCD drives the assembling process of PCL-PEG-Fol promoting an extensive exposition of Fol molecules on the surface. Finally, cell studies indicated that the saturation of FR through free Fol significantly inhibited the uptake only of HPβCD-tNPs and only in FR (+) KB cells. FR was involved in the specific uptake of a fraction of HPβCD-tNPs while a large amount of NPs was taken up via receptor-independent mechanisms.

Conclusions: We have demonstrated that the use of HPβCD can be a suitable strategy to modify shell properties of PEGylated NPs, thus enhancing the targeting ability of Fol-decorated PCL-PEG NPs, designed for the treatment of solid tumors

claudia.conte@unina.it

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