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| Title | Photochemical internalization of targeted nanoparticles for the intracellular delivery of a cytotoxic protein. |
| Keywords (up to 5) | Targeting, nanoparticles, protein, photosensitizer, nanobody |
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| Abstract | <p>Cytotoxic proteins have been proposed as anti-cancer agents due to their specificity and potency. Proteins can be encapsulated in polymeric nanoparticles (NPs) to increase their physicochemical stability and to prolong their circulation time. Additionally, their retention and uptake in diseased tissues can be enhanced by functionalizing the NPs with targeting ligands. Cell uptake of NPs occurs by endocytosis and endosomal escape is necessary to prevent their eventual degradation in the lysosomes. Endosomal escape can be achieved by photochemical internalization (PCI), which relies on the presence of a photosensitizer in the membrane of endosomes in which a nanocarrier is entrapped. Upon light exposure, the photosensitizer damages the endosomal membrane, resulting in the release of its content to the cytosol [1].</p> <p>In this study, NPs were prepared using PEGylated poly(lactic-co-glycolic-hydroxymethyl glycolic acid) (PLGHMGA) and loaded with saporin, a cytotoxic protein. The NPs were functionalized with the nanobody 11A4 which binds with high affinity to the HER-2 receptor [2], overexpressed in 20-30% of invasive breast cancers [3]. Confocal microscopy on SkBr3 cells (HER-2 positive) confirmed that the cellular uptake of 11A4-NPs occurs faster and to a greater extent than for non targeted NPs. Decrease in cell viability in SkBr3 cells was only observed when the saporin loaded NPs were co-administered with PCI treatment. This decrease was achieved at lower concentrations for 11A4-NPs in comparison to NPs without targeting ligand.</p> <p>Functionalization of saporin loaded PEG-PLGHMGA NPs with 11A4 results in fast, enhanced, internalization of this nanocarrier by HER-2 positive cancer cells, while PCI is successfully used to overcome endosomal entrapment and increase the cytotoxicity of the NPs. By combining the use of a targeting ligand and local light exposure during the PCI treatment, the system under study would allow for the localized delivery of therapeutic agents, thereby minimizing side effects in other tissues.</p> |
| References | <ol style="list-style-type: none"> 1. P.K. Selbo, A. Weyergang, A. Hogset, O.J. Norum, M. Brandal Berstad, M. Vikdal and K. Berg. <i>Journal of Controlled Release</i>, 2010, 148, 2-12. 2. M. Kijanka, F.J. Warnders, M. El Khattabi, M. Lub-de Hooge, G.M. van Dam, V. Ntziachristos, L. de Vries, S. Oliveira, P.M. van Bergen en Henegouwen. <i>European Journal of Nuclear Medicine and Molecular Imaging</i>, 2013, 40, 1718-1729. 3. S.A. Hurvitz, Y. Hu, N. O'Brien, R.S. Finn. <i>Cancer Treatment Reviews</i>, 2013, 39, 219-229. |