Photo-Targeted Nanoparticles

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Targeting of drugs and drug delivery systems to diseased cells and tissues using nanoparticles has emerged as a central focus in drug delivery research, as it can minimize nonspecific toxicity and/or enhance the efficiency of therapy. Targeting of systemically-administered nanoparticles can be passive or active. Passive targeting depends on the physical properties of the particles and/or the target tissue to encourage relatively selective uptake. Example of this include the selective uptake of microparticles by phagocytic cells, and the size-dependent accretion of nanoparticles within the relatively leaky vasculature of tumors. However, since the majority of clinical conditions do not provide means of passive targeting, active targeting becomes necessary, in which the nanoparticles are delivered to their targets by specific ligands. Such ligands include antibodies, peptides or aptamers, which bind specific receptors, channels or other molecules on the cell membrane. Recent studies have demonstrated selective targeting of engineered nanoparticles to tumors and clinical feasibility of such systems has been demonstrated. Unfortunately, that approach is limited by the relative paucity of known specific cell-surface ligands. This research addresses the urgent need for additional methods of targeting nanoparticles.

Here we describe the use of light to target nanoparticle binding (as compared to single release events) in specific illuminated areas. The basic design (Figure 1) is a drug-loaded nanoparticle whose surface is covalently modified with a targeting moiety consisting of an avid but non-specific ligand that is rendered biologically non-functional (“caged”) and prevented from binding by chemical modification with a photo-removable protecting group. The caging group is removed at the desired site by illumination.

Methods: Synthesis of the caged particles. Ten milligrams of fluorescent polystyrene carboxylated nanoparticle suspension were incubated with 100 mg of EDC and 200 mg of sulfo-NHS for 2.5 hours at room temperature with stirring. The resulting NHS-activated particles were covalently linked to 5 mg - GGGGYY(DMNB)IGSR-NH2 peptide overnight at room temperature with gentle stirring. The resulting NHS-activated particles were covalently linked to 5 mg - GGGGYY(DMNB)IGSR-NH2 peptide overnight at room temperature with gentle stirring. The C-terminally amidated peptide GGGGYY(DMNB)IGSR-NH2 was chosen in order to maximize the interaction with integrin β1. The C-terminally amidated peptide GGGGYY(DMNB)IGSR-NH2 was chosen in order to maximize the interaction with integrin β1. The C-terminally amidated peptide GGGGYYIGSR-NH2 and the peptide NH2-GGGGFHPDYRVI-NH2 which is not known to be an adhering peptide, were conjugated in a similar fashion and served as control targeters. The nanoparticles had 445 μeq/g carboxylic groups and introduction of the targeter in excess theoretically leads to the conjugation of ~5000 targeter molecules on each particle.

Results: In both HUVECs and MSCs cultures, the percentage of attachment of caged nanoparticles was significantly higher after 1 minute of illumination than in non-illuminated cultures. Furthermore, cell binding of illuminated caged nanoparticles was similar to that of particles conjugated to un-caged peptides; p = 0.67 and 0.53 in HUVECs and MSCs, respectively. Binding of the non-illuminated caged nanoparticles cells was similar to that of nanoparticles whose surfaces were modified in the same manner with a non-adhering peptide (FHPDYRVI), confirming that the caging group inactivated the YIGSR (at least to the extent that it was as poor a ligand as the non-adhering sequence).

Conclusions: we report what is to our knowledge the first example of a targeting system capable of binding nanoparticles to cells selectively upon illumination. In contrast to other reports where nanoparticles have been triggered to produce a single drug release event by light our approach results in the deposition of a sustained release system at the desired site.

References:

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