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Cover story

Ligand Affinity: Multivalency counterbalances PEGylation

In the drug delivery area, PEGylation has been used mainly to minimize protein adsorption to nanoparticle surfaces to extend plasma circulation half-lives. It has been understood that PEGylation reduces the drug bioefficacy, but the longer blood circulation results in an overall increase in the drug activity. Receptor ligands are frequently conjugated to the distal ends of PEG chains for targeting cell recognition and for controlling the particle fate such as receptor-mediated cell uptake [1]. Although this strategy is frequently used in the field of nanomedicine [2], it is often overlooked that the attachment of a ligand to a polymer strand can severely affect its affinity to the receptor's binding pocket. This phenomenon, which is widely known from many macromolecular drugs [3], has often been neglected for ligands that are attached to PEGylated nanoparticles.

In this issue, Professor Goepferich and his team investigated the extent to which PEGylation altered a ligand's affinity and to what degree the multivalency of nanoparticles compensated for the affinity loss [4]. A small non-peptide antagonist for the angiotensin II receptor type 1 (AT_1), a receptor recently investigated for targeted drug delivery [5], was conjugated to a linear PEG molecule or PEGylated nanoparticles. PEGylation of the ligand led to a 600-fold affinity decrease. Conversely, when the ligand was bound to the surface of PEGylated nanoparticles its high nanomolar affinity was regained. Because ligands grafted on nanoparticles can undergo multiple binding to several cell surface receptors simultaneously, the nanoparticle counterbalanced the affinity loss caused by PEGylation. Because of nanoparticle's multivalency, a very large amount of free ligand was needed to displace the nanoparticles from the cell surface.

The findings by the Goepferich team have two major implications for active nanoparticle targeting: First, targeting ligands should be selected from a library of PEGylated ligands, and the selected ligand should have the lowest affinity loss upon PEGylation. This way, the affinity loss that results from the attachment to the nanoparticle PEG corona can be minimized. Second, if a ligand suffers from loss of affinity due to the attachment to the PEG strand, high nanoparticle avidity is absolutely necessary to establish strong interactions to the target cell. In the study by the Goepferich team, the surface grafting of PEGylated ligands were able to regain the high affinity, but this may not happen for other systems. In fact, different ligands at different surface density, and different PEG length may have different outcomes. Overall, a more in-depth characterization of nanomaterials seems mandatory to understand the intricate molecular interactions at the nano-bio interface. The effect of PEGylation has never been straightforward, and further advances in the PEGylation technology can be made only through better understanding of the impacts of PEGylation in each case.

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Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

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