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Bioorthogonal click chemistry on living cell membranes: the frontiers of metabolic glycoengineering and the functionalization of magnetic nanoparticles

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The heating properties of magnetic nanoparticles (MNPs) in the presence of an alternating magnetic field (AMF) have traditionally been studied for cancer treatment applications focused on the internalization of MNPs in target cells. Herein, we propose an innovative approach to apply localized heating onto living cell membranes based on the covalent immobilization of MNPs via bioorthogonal click chemistry. Our hypothesis is that with this particular localization, controlled changes of membrane biophysics would be obtained without compromising cell viability. We therefore anticipate that our approach could be adapted to a wide variety of therapeutic applications.

Preliminary results concerning immobilization of MNPs on living cell membranes are reported and the two main challenges for the standardization of a universal method of "click" attachment are going to be discussed: 1) the installation of suitable chemical reporters on cell membranes; 2) the functionalization of MNPs for a selective interaction with cells.

We propose the strain-promoted "click" [3 + 2] azide-alkyne cycloaddition (SPAAC) for the immobilization of the MNPs on the membrane. The expression of azide reporters on MCF7 cells surface has been optimized by using metabolic glycoengineering. By incubating cells with an azide-modified sugar derivative they can metabolize it and incorporate it onto the membrane glycoproteins in a dose-dependent manner and with a half-life time of around 8 h. However, studies developed in other cell lines (A549, B16 or Vero) pointed out differences in terms of metabolism rate of the sugar derivative and their subsequent limitation for the development of a universal protocol.

Regarding the functionalization, 12-nm water-soluble MNPs have been functionalized with strained alkynes and with polyethyleneglycol (PEG) to increase colloidal stability and biocompatibility. Results obtained using fluorescence microscopy techniques revealed that is possible to control the cell-MNP interactions depending on the size and density of the PEG coating. In addition, we have recently demonstrated the importance of having a very fine control of the amount of MNPs per cell in order to enhance click specificity and avoid unspecific interactions or internalization. Our ongoing work is focused on two main challenges: 1) the analysis of the subcellular localization of low concentrations of MNPs, which is not trivial and 2) the evaluation of the heating effect induced by these MNPs on the membrane biophysics.

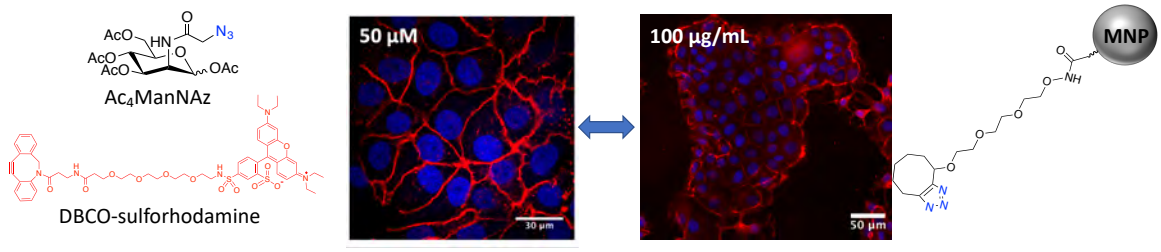

Figure 1. *From metabolic glycoengineering to click immobilization of MNPs.*