Development of nanoparticle complexes as breast cancer imaging and therapy agent

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Scientific Thrust Area:

Among various forms of cancer that afflict women, breast cancer is the most prevalent. One of key prognostic and therapeutic markers for breast cancers is over expressed estrogen receptors (ERs). Although ERs are general considered to be nucleus transcription factor, they have recently been found to exist on cell membrane as well. However, the detailed functions of ERs in the cytoplasm and membrane remain unclear. The development of better fluorophores that have a higher binding specificity for ERs, with higher fluorescence quantum yield and lower photo-bleaching behavior, could help to elucidate the diverse ER functions in breast cancer and ultimately lead to a cure for breast cancer.

Research Achievement:

Utilizing resources at the Center for Nanoscale Materials, we have made several major breakthroughs in utilizing nanoparticles for breast cancer imaging.

(i) We have synthesized the first bio-conjugated CdSe/ZnS core-shell quantum dot system that contains estradiol (E2) moiety.

(ii) By pretreatment of cancer cells with a different size of QDs without E2 ligand, we are able to eliminate nonspecific binding sites and demonstrate E2-conjugated QDs bind only specifically to ERs. Figure 1a shows the coexistence of both types of QDs on the cell surface, namely the nonspecific binding of QDs without E2 (emits at 525 nm) and the E2-conjugatecd QDs (emits at 605 nm). The yellow color comes from overlap of the emission from both types of QDs. The predominant and slightly punctuate yellow color indicates that nonspecific binding sites are more or less evenly distributed on the cell surface, whereas the ER specific binding sites

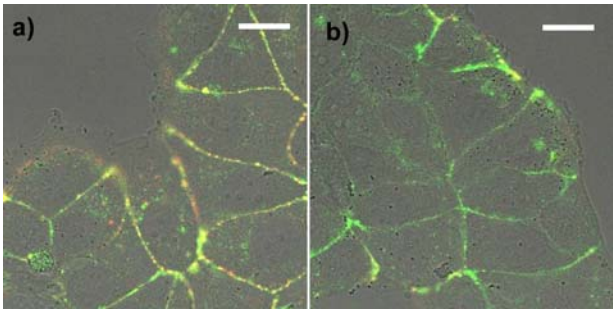

Figure 1 a) Fluorescence signals from both nonspecific-binding QDs (green) and specific binding QDs (red) in a cross section of MCF-7 K1 cells obtained by a confocal scanning optical microscope. b) shows non-specific binding QDs only.

are much more localized. Figure 1b shows the result of a control experiment performed with diethylstilbestrol (DES), a substance known to block ES binding sites. As a result, very little specific binding occurred, which is evident from a predominant green fluorescence from QDs without E2.

(iii) By measuring the amount of ligand conjugated on the QDs and the free ligand remained in solution, we are able to elucidate the effect of both parameters on nanoparticle cell binding process, as shown in Figure 2. These E2-conjugated QDs could be used as an optical marker to elucidate the functions of membrane associated ERs, help to deliver drugs locally to carcinoma cells, which could inhibit the molecular pathways that are critical for cell growth.

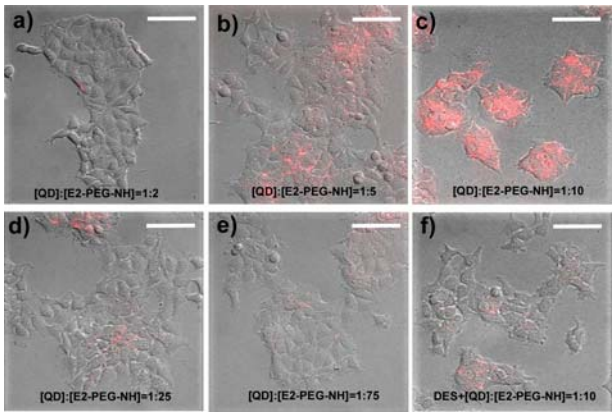

Figure 2. Fluorescence signals from E2-conjugated QDs or K1 cells. (a)-(e) are from different batches of conjugated Q solution, obtained by reacting 1μM of QD605 with varying of E2-PEG-NH ligand. In panel (f), DES was added prior t incubation the cell with E2-conjugated QDs.

Future work:

Our experiments also showed that the stability of the polymeric ligand shell on commercial QDs is still not robust enough for carrying out many experiments in physiological environment. We will further improve its stability. This could help us to carry out experiments to track bioconjugated QDs in cellular environment over an extended period of time, without concerns about the possible detachment of target ligand motifs from the QD surface. Besides targeting cancer cells, we will study various drug delivers strategies using conjugated nanoparticles as a platform.

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