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Development of a bifunctional PEGylated transferrin-conjugated liposome with gene delivery and tumor targeting properties *in vivo*

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T argeted gene delivery systems that combine imaging and therapeutic modalities in a single macromolecular construct may offer advantages in the development and application of nanomedicines *in vivo*. Here, we describe the synthesis, biophysical characterization, tumor cell-selective internalization, and targeted gene delivery system of PEGylated transferrin-conjugated liposomes (PTf-Ls). An improved protocol for DNA encapsulation in interstitial space, based on ethanol/calcium-mediated DNA condensation was developed. The nanoparticles obviously accumulated in tumor cells, exhibited high transfection efficiency, which were resistant to serum, and relatively low cell cytotoxicity. In a Balb/c nude mice breast cancer cells MDA-MB-231-Luc (containing luciferase gene) xenograft model, systemic administration of fluorescence dye (Koadak X-sight 670 Large Stokes Shift Dye) labeled PTf-Ls, which effectively eliminated the nonspecific binding, significantly prolonged circulation, and selectively and efficiently internalized in tumor cells, demonstrated a gradual increase of fluorescence in tumor over time up to 26 hrs, specific tumor imaging at 32 h and lasting for more than 58 hrs. Furthermore, we assessed the utility of this system in cancer gene therapy using Interferon (IFN)- γ inducible protein-10(IP-10) corded plasmid DNA. It dramatically suppressed tumor growth. Therefore, this new bifunctional PTf-Ls system has the potential for gene delivery and targeted tumor imaging *in vivo*.

HER2 and β-catenin protein location: Importance in the prognosis of breast cancer patients and their correlation when breast cancer cells suffer stressful situations

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In human breast cancer, β -catenin localization has been related with disease prognosis. Since HER2-positive patients are an important subgroup and that in breast cancer cells a direct interaction of β -catenin/HER2 has been reported, in the present study we have explored whether β -catenin location is related with the disease survival. The study was performed in a tumor bank from patients (n=140) that did not receive specific anti-HER2 therapy. The proteins were detected by immunohistochemistry in serial sections, 47 (33.5%) patients were HER2-positive with a long follow-up. HER2-positive patients that displayed β -catenin at the plasma membrane (completely surrounding the tumour cells) showed a significant better disease-free survival and overall survival than the patients showing the protein on other locations. Then we explored the dynamics of the co-expression of β -catenin and HER2 in human MCF-7 and SKBR3 cells exposed to different stressful situations. In untreated conditions MCF-7 and SKBR3 cells showed very different β -catenin localization. In MCF-7 cells, cadmium administration caused a striking change in β -catenin localization driving it from plasma membrane to cytoplasmic and perinuclear areas and HER2 showed a similar localization patterns. The changes induced by cadmium were compared with heat shock, H2O2 and tamoxifen treatments. In conclusion, this study shows the dynamical associations of HER2 and β -catenin and their changes in subcellular localizations driven by stressful situations. In addition, we report for the first time the correlation between plasma membrane associated β -catenin in HER2-positive breast cancer and survival outcome, and the importance of the protein localization in breast cancer samples.