

S015 Receptor-mediated internalization of chelator-PNA-peptide hybridization probes for radioimaging or magnetic resonance imaging of oncogene mRNAs in tumors
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Early external detection of cancer gene activity might enable early treatment of cancer and might reduce cancer mortality. We hypothesized that oncogene mRNA overexpressed at thousands of copies per malignant cell in a zone of transformed cells could be imaged externally by scintigraphic imaging, positron emission tomography (PET), or magnetic resonance imaging (MRI) with peptide nucleic acid (PNA) hybridization probes that include chelators for metal cations and a cyclized peptide analog of insulin-like growth factor 1 (IGF1), Δ (CSKC), to mediate internalization by IGF1 receptor overexpressed on cancer cells. We observed that human MCF7 breast cancer cells that overexpress IGF1R efficiently internalized fluorescein-chelator-PNA- Δ (CSKC) to the cytoplasm, but not with Δ (CAAC). Scintigraphic imaging of MCF7 xenografts in immunocompromised mice revealed that CCND1 and MYC [^{99m}Tc]chelator-PNA- Δ (CSKC) probes yielded xenograft. PET imaging with [⁶⁴Cu]chelator-PNA- Δ (CSKC) yielded stronger signals. Scintigraphic imaging of human AsPC1 pancreas cancer xenografts with [^{99m}Tc]chelator-KRAS PNA- Δ (CSKC) yielded strong xenograft signals. Stronger xenograft image intensities were obtained by PET imaging of [⁶⁴Cu]chelator-KRAS PNA- Δ (CSKC). MRI required extension of chelator-polydiamidopropanoate dendrimers from the N-termini of the PNA probes to increase the number of contrast paramagnetic gadolinium (III) cations per probe. These results constitute a proof-of-principle for detection of oncogene activity in tissues from outside the body by hybridization with metal-chelator-PNA-peptides that are selectively internalized by cancer cells. Supported by DOE/BER ER63055 and NIH/NCI CO27175 (E. W.), and by NIH HL59769 and CA109231 (M. L. T.)