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Validation of Neurotensin tetra-branched peptides as tumor targeting agents in pancreas, colon and bladder carcinoma

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The identification of new tumor targeting agents, which might allow either cancer cell tracing or therapy, is a crucial issue in cancer research. Membrane receptors for endogenous peptides such as neurotensin, somatostatin, bombesin and many others are over-expressed in different human cancers and could therefore be targeted as tumor-specific antigens. In the meantime the extremely short half-life of peptides impeded their development for effective peptide-based tumor targeting strategies.
We synthesized tetra-branched neurotensin peptides (NT4), which ensure extremely long half-life maintaining peptide specificity and increasing avidity through multimeric binding. Moreover this bio-synthetical strategy allows a considerable modularity of peptides through the conjugation of different functional unit, such as fluorophore, radioactive moieties or chemotherapeutic drugs.
Aim of our studies is to validate NT4 for cancer cell tracing in different human tumors. In this view we use fluorophore-conjugated NT4 to discriminate between tumor and healthy tissue obtained by surgical samples from pancreas, colon and bladder carcinoma. Peptide binding on tumor and healthy biopsies was measured in each patient by quantitative analysis of confocal microscopy images. These results show a considerable difference in fluorescence emission between healthy and tumor samples in colon, pancreas and bladder cancer, opening the way to the development of NT4 as selective diagnostic tools for these pathologies. Moreover our peptides can be conjugated with different chemotherapeutic moieties in order to allow the selective killing of tumor cells.

Tumor selective drug delivery by Neurotensin branched peptides

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Detection of new tumor-selective targets, which allow either cancer cell tracing or therapy, is a crucial issue in cancer research. Membrane receptors for endogenous peptides such as Neurotensin are over-expressed in many human cancers and could therefore be used as tumor-specific antigen, while peptide ligands might act as targeting agents.
The development of peptides as drug has always been limited by their short half-life, due to degradation by peptidases and proteases. Chemical modification, which can stabilize the molecules, may modify peptide affinity or specificity. Moreover, coupling of peptides to effector units for imaging or therapy, may interfere with biological activity. We demonstrated that peptide sequences, when synthesized in an oligo-branched form, become resistant to proteolysis and thank to their multimericity are more efficient than corresponding monomers in binding cellular antigens1. Moreover, the branched core allow coupling of effector units without affecting peptide activity. Drug-armed tetra-branched neurotensin peptides (NT4) were synthesized with different conjugation methods, resulting either in uncleavable adducts or drug-releasing molecules2-4. Recently we developed DOPC liposomes filled with the cytotoxic drug Doxorubicin (Doxo) and functionalized with NT4. Armed DOPC liposomes showed a clear advantage with respect to nude liposomes in drug internalization and their cytotoxicity is fourfold increased with respect to the same nude liposomes.
Conjugation to NT4 switches drug internalization to a peptide-receptor mediated mechanism, which greatly increases drug selectivity and also might allow by-passing drug cell resistance. In vitro and in vivo results indicated that branched NT peptides are valuable tools for tumor selective targeting.