Design, Synthesis, and Characterization of a Paclitaxel Formulation Activated by Extracellular MMP9

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The concept of triggered drug release offers a possibility to overcome the toxic side effects of chemotherapeutics in cancer treatment by reducing systemic exposure to the active drug. In the present work, the concept foresees the use of the extracellular enzyme MMP9 as an enzymatic trigger for drug release in the proximity of tumor cells.; A paclitaxel-hemisuccinate-peptide conjugate as a building block for self-assembling nanoparticles was synthesized using standard conjugation approaches. The building block was purified via preparative HPLC and analyzed by LC-MS. Nanoparticles were formed using the nanoprecipitation method and characterized. For selection of a suitable in vitro model system, common bioanalytical methods were used to determine mRNA expression, enzyme amount, and activity of MMP9.; The MMP9-labile prodrug was synthesized and characterized. Nanoparticles were formed out of MMP9-labile conjugate-building blocks. The nanoparticle's diameter averaged at around 120 nm and presented a spherical shape. LN-18 cells, a glioblastoma multiforme derived cell line, were chosen as an in vitro model based on findings in cancer tissue and cell line characterization. The prodrug showed cytotoxicity in LN-18 cells, which was reduced by addition of an MMP9 inhibitor.; taken together, we confirmed increased MMP9 in several cancer tissues (cervical, esophageal, lung, and brain) compared to healthy tissue and showed the effectiveness of MMP9-labile prodrug in in vitro tests.
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