Design, synthesis and characterization of folate-cyclodextrin bioconjugate for active drug delivery: results from combined computational and experimental efforts

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Recent advances in tumor therapy demonstrate that successful anticancer strategies can be developed by employing proper carrier systems able to deliver probes, drugs, or genes to tumor targets. Many efforts are in progress to develop active drug targeting systems, which on one hand allow for specific drug delivery into the disease site and, on the other, limit the toxicological drawbacks due to the broad and nonspecific disposition of the therapeutic agents. Folic acid is a vitamin required for one-carbon transfer reactions in several metabolic pathways. Because folic acid is essential for the biosynthesis of nucleotide bases, the vitamin is consumed in elevated quantities by proliferating cells. Normal cells transport physiological folates across the plasma membrane using either of two-membrane associated proteins, the reduced folate carrier or the folate receptor (FR). While low concentration of the reduced folate carrier are probably sufficient to supply the folate requirement of most normal cells, FR is frequently overexpressed on cancer cells, perhaps enabling the malignant cell to compete successfully for the vitamin when supplies are limited. While overexpression of FR on many cancer cells obviously identifies the receptor as a potential target for a variety of ligand- and antibody-directed cancer therapeutics, FR may be further qualified as a tumor-specific target, since it generally becomes accessible to intravenous drugs only after a malignant transformation. By virtue of its ability to be taken up by folate receptor overexpressing tumor cells, folic acid has thus been widely investigated as targeting molecule for active anticancer drug delivery, and proper synthesis procedures have been pointed out to link folic acid to drug carriers to produce effective targeting drug delivery systems. Although successful results have been published, the therapeutic application of the folate conjugates is often limited by their large size. Indeed, it was established that, even though large molecules undergo passive accumulation into solid tumors by enhanced permeation and retention effect (EPR), the intratumor overpressure limits their penetration into the neoplastic mass. Therefore, it seems rational to produce low molecular weight conjugates, which can easily reach the tumor site and be taken up actively by the tumor cells where the drug can be released.

Cyclodextrins are carbohydrate macrocycles which, by virtue of their ability to form molecular inclusion complexes with a wide range of hydrophobic molecules, are interesting for exploitation as a new class of conjugates for drug delivery. Actually, cyclodextrins have been investigated to optimize the solubility, stability, and bioavailability of many drugs. Nevertheless, the parenteral administration of natural cyclodextrins, namely beta-cyclodextrins, causes undesirable toxic effects such as hemolysis. To overcome these problems, semisynthetic cyclodextrins obtained by hydroxyl substitution with methyl, hydroxy-alkyl or sulfo-alkyl functions have been prepared and investigated for systemic administration. Recently, cyclodextrins have been modified by conjugation of water-soluble polymers to obtain derivatives with peculiar biopharmaceutical properties.

Aimed at exploiting cyclodextrin bioconjugates for active drug targeting, this paper report the results of combined experimental and modeling efforts for the design, synthesis and characterization of new derivatives, where beta-cyclodextrin is linked to folic acid through a bipartate hydrocarbon-poly(ethylene glycol) spacer arms. The relevant inclusion complexes with some anticancer drugs will also be modeled and discussed.