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Evaluation of the Cytotoxicity and Cellular Uptake of a Cyclodextrin-Based Drug Delivery System for Cancer Therapy

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Abstract : Drug delivery systems are proposed for use in cancer treatment to specifically target cancer cells and deliver a therapeutic dose without affecting normal cells. For that purpose, the use of folate receptors (FR) can be considered a key strategy, since they are commonly over-expressed in cancer cells. In this study, cyclodextrins (CD) have being used as vehicles to target FR and deliver the chemotherapeutic drug, methotrexate (MTX). CDs have the ability to form inclusion complexes, in which molecules of suitable dimensions are included within their cavities. Here, β-CD has been modified using folic acid so as to specifically target the FR. Thus, this drug delivery system consists of β-CD, folic acid and MTX (CDEnFA:MTX). Cellular uptake of folic acid is mediated with high affinity by folate receptors while the cellular uptake of antifolates, such as MTX, is mediated with high affinity by the reduced folate carriers (RFCs). This study addresses the gene (mRNA) and protein expression levels of FRs and RFCs in the cancer cell lines CaCo-2, SKOV-3, HeLa, MCF-7, A549 and the normal cell line BEAS-2B, quantified by real-time polymerase chain reaction (real-time PCR) and flow cytometry, respectively. From that, four cell lines with different levels of FRs, were chosen for cytotoxicity assays of MTX and CDEnFA:MTX using the MTT assay. Real-time PCR and flow cytometry data demonstrated that all cell lines ubiquitously express moderate levels of RFC. These experiments have also shown that levels of FR protein in CaCo-2 cells are high, while levels in SKOV-3, HeLa and MCF-7 cells are moderate. A549 and BEAS-2B cells express low levels of FR protein. FRs are highly expressed in all the cancer cell lines analysed when compared to the normal cell line BEAS-2B. The cell lines CaCo-2, MCF-7, A549 and BEAS-2B were used in the cell viability assays. 48 hours treatment with the free drug and the complex resulted in IC50 values of 93.9 μM ± 15.2 and 56.0 μM ± 4.0 for CaCo-2 for free MTX and CDEnFA:MTX respectively, 118.2 μM ± 16.8 and 97.8 μM ± 12.3 for MCF-7, 36.4 μM ± 6.9 and 75.0 μM ± 10.5 for A549 and 132.6 μM ± 16.1 and 288.1 μM ± 26.3 for BEAS-2B. These results demonstrate that free MTX is more toxic towards cell lines expressing low levels of FR, such as the BEAS-2B. More importantly, these results demonstrate that the inclusion complex CDEnFA:MTX showed greater cytotoxicity than the free drug towards the high FR expressing CaCo-2 cells, indicating that it has potential to target this receptor, enhancing the specificity and the efficiency of the drug. The use of cell imaging by confocal microscopy has allowed visualisation of FR targeting in cancer cells, as well as the identification of the interlisation pathway of the drug. Hence, the cellular uptake and internalisation process of this drug delivery system is being addressed.

Keywords : cancer treatment, cyclodextrins, drug delivery, folate receptors, reduced folate carriers
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