Treatment of colorectal cancer cells with nanocarrier encap-sulated camptothecin reveals histone modifier genes in the Wnt signaling pathway as important molecular cues for cancer targeting

ABSTRACT

Cancer cells are able to proliferate in an unregulated manner. There are several mechanisms involved that propel such neoplastic transformations. One of these processes involves bypassing cell death through changes in gene expression and, consequently, cell growth. This involves a complex epigenetic interaction within the cell, which drives it towards oncogenic transformations. These epigenetic events augment cellular growth by potentially altering chromatin structures and influencing key gene expressions. Therapeutic mechanisms have been developed to combat this by taking advantage of the underlying oncogenic mechanisms through chemical modulation. Camptothecin (CPT) is an example of this type of drug. It is a selective topoisomerase I inhibitor that is effective against many cancers, such as colorectal cancer. Previously, we successfully formulated a magnetic nanocarrier-conjugated CPT with β-cyclodextrin and iron NPs (Fe3O4) cross-linked using EDTA (CPT-CEF). Compared to CPT alone, it boasts higher efficacy due to its selective targeting and increased solubility. In this study, we treated HT29 colon cancer cells with CPT-CEF and attempted to investigate the cytotoxic effects of the formulation through an epigenetic perspective. By using RNA-Seq, several differentially expressed genes were obtained ($p < 0.05$). Enrichr was then used for the over-representation analysis, and the genes were compared to the epigenetic roadmap and histone modification database. The results showed that the DEGs had a high correlation with epigenetic modifications involving histone H3 acetylation. Furthermore, a subset of these genes was shown to be associated with the Wnt/β-catenin signaling pathway, which is highly upregulated in a large number of cancer cells. These genes could be investigated as downstream therapeutic targets against the uncontrolled proliferation of cancer cells. Further interaction analysis of the identified genes with the key genes of the Wnt/β-catenin signaling pathway in colorectal cancer identified the direct interactors and a few transcription regulators. Further analysis in cBioPortal confirmed their genetic alterations and their distribution across patient samples. Thus, the findings of this study reveal that colorectal cancer could be reversed by treatment with the CPT-CEF nanoparticle-conjugated nanocarrier through an epigenetic mechanism.

Keyword: Camptothecin; Colorectal cancer; Wnt signaling pathway; Bioinformatics; Natural product