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Dissertation

Title *Development of a Therapeutic Model of Early Liver Cancer Using Crocin-Coated Magnetite Nano-particles*

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Abstract

Hepatocellular carcinoma is one of the most common health problems that is difficult to treat. As a result of the side effects frequently experienced with conventional cancer treatments, there has been a growing interest to develop controlled drug delivery system that can reduce the mortality rate of liver cancer pa-tients and un-harm healthy tissues. Magnetite nanoparticles are potentially important in hepatocellular carcinoma treatment, since they can be used as delivery system. Pure and coated magnetite nanoparticles were synthesized via modified co-precipitation method in air at low temperature. Various reaction param-eters and coating materials have been investigated and characterized. Among these parameters and coat-ing materials, 1.0 % of dextran was selected as an optimum coating for nanoparticles using a slow feeding rate for the Fe2+/Fe3+ reactants, maintaining the stirring and soaking temperatures at 60°C. After that dex-tran-coated magnetite nanoparticles were bound to crocin, a pharmacologically active component of saf-fron, via cross-linker. Crocin alone has shown anti-cancer activity in different in vitro and in vivo settings by several studies. The aim of this study was to synthesize dextran-coated magnetite nanoparticles con-taining crocin with a higher therapeutic index for hepatocellular carcinoma treatment. The nanoparticles with crocin were tested in vitro and in vivo for their anti-cancer effects as compared to free crocin. HepG2 cells treated with crocin-dextran-coated magnetite nanoparticles showed a decrease in cell proliferation compared to control (non-treated cells) or to those treated with free crocin or dextran-coated nanoparti-cles. The anti-cancer activity of crocin-dextran-coated nanoparticles was also evaluated in Balb/c mice. These mice were injected with carcinogenic agent, diethylnitrosamine. Histological examination revealed several precancerous changes. The immunohistochemical analysis using antibodies indication of cell pro-liferation (Ki-67), apoptosis (M30-Cytodeath and Bcl-2), inflammation (cyclooxygenase-2) and angiogen-esis (vascular endothelial growth factor), indicated that magnetite nanoparticles conjugated with dextran plus crocin does indeed improve its anti-tumorigenic activity over free crocin. These results provide the basis for designing new modalities for treatment of liver cancer which could hopefully reduce its high mortality rate.

Research Relevance and Potential Impact

Liver cancer is among the leading causes of cancer-related death at UAE and worldwide. As diagnosis and therapy continue to rep-resent major challenges, in this thesis we encapsulated a major bioactive principal (crocin) of the commonly used spice "saffron" in magnetite nanoparticles. Those crocin-loaded nanoparticles inhibited cell division of liver cells of cancer-induced mice and in human liver cancer cell line. They also unregulated cell death and reduced inflammation and angiogenesis more efficiently than crocin alone. Thus, our engineered crocin-nanoparticles is expected to have a potential clinical impact against liver cancer.