Extended Abstract

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# Sulforaphane Inhibits Liver Cancer Cell Growth an Angiogenesis

Dr. Moriya K

## Abstract:

Sulforaphane (SFN) exhibits inhibitory effects in different types of cancers. However, its inhibitory effect on liver cancer remains unknown. This study aimed to determine the therapeutic potential of SFN for the treatment of liver cancer and explore the functional mechanisms underlying the inhibitory effects of SFN. Water-Soluble Tetrazolium salt (WST-1) assay was performed to assess the in vitro effect of SFN on cell proliferation in the human liver cancer cell lines, HepG2 and Huh-7. The mRNA levels of Nrf2 target genes and cell cycle-related genes were determined using quantitative RT-PCR. For assessing the inhibitory effect of SFN in vivo, we injected immortalized liver cancer cells into BALB/c nude mice as a xenograft model. SFN was orally administrated daily after tumor inoculation and continued for thirty-five days until their sacrifices. Nrf2 activation, induced by SFN, was confirmed by mRNA upregulation of HO-1, MRP2, and NQO1 in both the cell lines. Significant inhibition of liver cancer cell proliferation by SFN was shown in vitro in a dose-dependent manner by the downregulation of CCND1, CCNB1, CDK1 and CDK2. In in vivo studies, the administration of SFN significantly reduced the subcutaneous tumor burdens at the end of experiments by suppressing tumor cell proliferation, confirmed by Ki67 immunohistochemically analysis. The mRNA levels of CCND1, CCNB1, CDK1 and CDK2 were also decreased in these SFN- treated xenograft tumors. Moreover, CD34 immunostaining elucidated that the intratumoral neovascularization was markedly attenuated in the SFN-treated xenograft tumors. SFN exerts inhibitory effect on human liver cancer cells with antiangiogenic activity. The earlier version of this study was presented at the meeting of AASLD Liver Learning on Oct 2017.

**Keywords**: Sulforaphane; Nrf2; Liver cancer; Angiogenesis

## Introduction:

Hepatocellular carcinoma (HCC) is a highly aggressive form of solid malignancy and is the third cause of cancer-related deaths [1]. The incidence of HCC is rising globally at an accelerated rate [2], making it the fifth most common cancer in men and the seventh most common cancer in women [1,3]. HCC can be treated curatively via surgical resection or liver transplantation if diagnosed during the early stage; however, majority of the HCC patients are diagnosed during the advanced stage; therefore, their median survival times are generally lower than one year, resulting in poor prognosis. A primary reason for poor prognosis in HCC patients is the absence of effective therapies, particularly for the advanced stages. Sorafenib, a multi-kinase inhibitor, is the first agent that has demonstrated survival benefits in patients with unresectable advanced HCC [4]. Sorafenib has showed overall survival benefit; however, the response rate is not acceptable in clinical practice because given the several adverse effects of this drug, only few patients were able to continue it. In patients with conditions, such as hand-foot syndrome, severe hypertension, and acute liver injury, more effective therapies are required to improve the prognosis of advanced HCC patients. In addition to a molecular targeted therapy, the potent antitumor activity exerted by certain natural product-derived drugs has been reported for several types of cancers [5,6].

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## Results:

SFN suppresses HepG2 cell growth by causing cell cycle arrest In order to explore the inhibitory effect of SFN on the human liver cancer cell lines, WST assay was performed. The WST assay examined the effect of SFN on cell proliferation of the HepG2 cells. SFN significantly inhibited cell proliferation of the HepG2 cells in a dose- dependent manner (Figure 1A). Thereafter, we evaluated the gene expression of HMO1, ABCC2, and NQO1 in the HepG2 cells to determine whether Nrf2 partly mediated the inhibiting effect of SFN, a known Nrf2 agonist. All these were Nrf2 target genes and were significantly upregulated in the SFN-treated group (Figure 1B). Given that growth inhibition of cancer cells is usually associated with cell cycle arrest, we investigated the effect of SFN on the expression of the cell cycle-related genes, CCND1,CCNB1, CDK1, CDK2, and CDKN1A in the HepG2 cell. Compared with those of the controls, the mRNA expression levels of CCND1, CCNB1, CDK1 and CDK2 in the HepG2 cells were distinctly lower in the SFN-treated group (Figure 2).

## Discussion and Conclusion:

SFN, a dietary isothiocyanate that is present in broccoli and cauliflower, has been widely used for treating inflammatory diseases, and recent studies have demonstrated its inhibitory activities in tumor cell lines and animals models [11,12,25-27]. Moreover, SFN from broccoli sprouts has already been evaluated in a phase I clinical trial that demonstrated a good safety profile of SFN [28], a phase II clinical trial that aims to treat patients with recurrent prostate cancer is currently ongoing (ClinicalTrials.gov, NCT01228084). These reports indicate that SFN is a potential inhibitory agent for treating cancer. Actually, several studies have been reported for the efficacy of SFN as an inhibitory agent against the HepG2 cell line [29-31]. However, these reports evaluated the effect of SFN in the “ex vivo” or “in vitro” study. Our study assessed the inhibitory effect of SFN in the “in vivo” study using the xenograft model which was simple and would reflect the clinical treatment.