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Impact of sulforaphane on FOLFOX induced toxicity to human colon cancer cells

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Colorectal cancer is a major health problem. Liver is the most common site of CRC metastases, which extremely worsen the prognoses of patients. When possible, surgical resection is the standard of care for liver metastases, however the majority of metastases are initially non-resectable or never likely to be resectable. At least 50% of all CRC patients receive chemotherapy in the attempt to palliate unresectable disease or downstage lesions making patients eligible for surgery and reduce the risk of recurrence after surgery. FOLFOX is widely used established standard chemotherapy for advanced CRC. However, unwanted side effects, namely hematologic, neurologic, digestive, general toxicity, as well as relapses and metastases after the treatment, limit successful therapeutic outcome of FOLFOX based regimens. It is therefore important to investigate new drug combinations to obtain higher efficacy and reduce side effects of chemotherapy. Phytochemical sulforaphane is a promising candidate for combination therapy due to its chemopreventive properties and cytotoxicity to different cancer types. Pharmacokinetic studies of SF in animal and human show good dietary absorption and distribution in the body reaching therapeutic concentration in target tissues. Clinical studies confirm that SF is safe and well tolerated by patients with advanced solid malignancies. However, final conclusions can not be made about the toxicity of SF due to the lack of strong evidence. Previous and experiments from the present work show that SF is nontoxic to nonmalignant cells and animals. Therefore, we investigated a combination therapy of FOLFOX and SF using colon cancer cells CX-1 and SW948. In the present work we show for the first time that SF has at least additive effect to FOLFOX against colon cancer cells CX-1 and SW948 by decreasing viability in two-dimensional cell culture. The result is obtained partly due to FOLFOX induced and SF enhanced apoptosis. Moreover, we demonstrate that SF additively to FOLFOX inhibits sphere formation in a more realistic three-dimensional model, relevant to micrometastases formation in vivo. Furthermore, we investigated cell properties,

recently described as CSC features and found that some CX-1 and SW948 cell populations formed primary, secondary, tertiary spheroids, were positive for ALDH1 and CD44/EpCAM. Treatment with SF targeted ALDH1 positive cells. Our data suggest that SF-rich compounds overall increases the effectiveness of FOLFOX against colon cancer cells, thus lower doses of FOLFOX may be used. Consequently, clinicians may add SF to the chemotherapy aiming to reduce adverse events and improve clinical outcomes, especially for resistant cancer. The clinical trial with FOLFOX and SF treatment in advanced CRC patients could be conducted.