CHAPTER I

INTRODUCTION

Introduction

The well-known broad-spectrum anti-bacterial agent triclosan (2,4,4'–trichloro-2'-hydroxydiphenyl ether; TCS) has been commercially used in a variety of products to inhibit the growth of bacteria, fungi, and mildew (1, 2). TCS has been used under the regulation of the Food and Drug Administration (i.e. cosmetics, deodorant, hand soaps, toothpaste) as well as the Environmental Protection Agency (i.e. materials preservative incorporated into household plastics and textiles) (2, 3). The concentrations used of TCS in different products may vary; however, its levels in most personal care products are ranging from 0.1-2% (1, 3). Significant levels of TCS are detectable in the plasma of TCS-exposed human, approximately at the concentrations ranging from 0.02 and 20 μg/ml (0.069 and 69 μM) (4). The concentration of unconjugated form of TCS in human plasma was about 30-35% of total level of TCS for the first 6 h after oral administration (5). These results lead to the possible conception that this agent may possible impact human physiology (4).

Focusing on cancer, up-to-date information has pointed out that TCS has insignificant effects on carcinogenesis and direct gene mutation (2, 6, 7). However, considering TCS usage is life-long, it is important to fully understand the possible effects of this agent not only on carcinogenesis but also the possible impact on cancer cell behaviors. Recent studies have indicated that the transition of cellular phenotype form epithelial to mesenchymal named epithelial-to-mesenchymal transition (EMT) is a critical factor for facilitating metastasis of many cancers (8-10). EMT has received

considerable attention in cancer-related researches and EMT has been recognized as a hallmark of cancer stemness as well as aggressiveness (11). EMT process results in the alteration of cell behaviors which, in most cases, enhances ability to metastases, including potentiates migration of the cells from its primary tumor and increases resistance to apoptosis. Importantly, EMT has been reported to induce stem-like characteristics of cancer cells such as tumor forming potential or tumorigenicity of cells (12-15).

Most evidence has suggested that the sub population of cancer cells that exhibiting anoikis resistant property is the majority of cells undergo successful metastasis (16-20). Anoikis resistant cells are also known as circulating tumor cells (CTCs) (21). In clinical practice, CTCs have been considered to be a potential biomarker that reflects cancer aggressiveness of many types of cancer such as breast, prostate, colorectal, bladder, gastric, liver and lung cancers (22-26). Importantly, EMT has been considered as a critical mechanism to promote metastatic potential, anoikis resistance and invasive ability of CTCs (16, 22).

The chemical existing in the blood of cancer patients is likely to have possible impact on cancer cell behaviors. Together with the fact that effects of TCS on CTC lung cancer cell behaviors in relation to EMT is not yet clarified, the present study aimed to investigate the effect as well as the possible effect of this compound on the aggressive population of lung cancer cells. Better understandings obtained from this study may benefit the safety use of TCS and suggest the new assessment approach for cancer-related toxicity.

Research Questions

1. Can TCS induce anoikis resistance in human lung cancer H460 cells?
2. Can TCS induce EMT phenotype in anoikis resistant H460 cells?
3. Can TCS-induced EMT promote tumorigenicity as well as migratory and invasive ability in anoikis resistant H460 cells?
4. What are the underlying molecular mechanisms that TCS induce EMT phenotype as well as migration and invasion in anoikis resistant H460 cells?

Objectives

1. To investigate the effect of TCS on anoikis of human lung cancer H460 cells
2. To investigate the EMT-inducing effect of TCS on anoikis resistant H460 cells
3. To investigate the effect of TCS-induced EMT on tumorigenicity as well as migration and invasion in anoikis resistant H460 cells
4. To study molecular mechanisms that TCS induce EMT phenotype as well as migratory and invasive ability in anoikis resistant H460 cells

Hypothesis

TCS was able to induce anoikis resistance in lung cancer H460 cells. Also, TCS was able to promote EMT process resulting in enhanced tumorigenicity as well as migratory and invasive ability of anoikis resistant H460 cells .

Expected benefits from the study

This research provided the new toxicological information of TCS that has been widely used in health care products. The aspect of information is about EMT which is a key indicator of cancer aggressive behaviors. In addition, this new information would encourage the awareness of triclosn use in cancer patients.