Inhibitory Effect of Snake Venom Toxin on Colorectal Cancer HCT116 Cells Growth through Induction of Intrinsic or Extrinsic Apoptosis

Kyung Tae Kim and Ho Sueb Song

Department of Acupuncture & Moxibustion Medicine, College of Oriental Medicine, Gachon University

[Abstract]

I investigated whether snake venom toxin (SVT) from Vipera lebetina turanica enhances the apoptosis ability of tumor necrosis factor (TNF)-related apoptosis–inducing ligand (TRAIL) in cancer cells. TRAIL inhibited HCT116 cell growth in a dose-dependent manner. Consistent with cell growth inhibition, the expression of TRAIL receptors: DR4 and DR5 was significantly increased as well as apoptosis related proteins such as cleaved caspase–3, 8, 9 and Bax. However, the expression of survival proteins (e.g., cFLIP, survivin, XIAP and Bcl2) was suppressed by the combination treatment of SVT and TRAIL. Pretreatment with the reactive oxygen species (ROS) scavenger N-acetylcysteine reduced the SVT and TRAIL-induced upregulation of DR4 and DR5 expression and expression of the apoptosis related protein such as caspase–3 and–9 as well as cell growth inhibitory effects. The collective results suggest that SVT facilitates TRAIL–induced apoptosis in human colorectal cancer HCT116 cells through up-regulation of the TRAIL receptors; DR4 and DR5 via ROS pathway signals.

Key words: SVT; TRAIL; DR4; DR5; ROS


This research was supported by the Gachon University Research Fund in 2012 (GCU–2012–R270)

Corresponding author: Department of Acupuncture and Moxibustion Medicine, Gil Oriental Medicine Hospital of Gachon University, 1200–1, Guwol-dong, Namdong-gu, Incheon, 405–760, Republic of Korea
Tel: +82–70–7120–5012  E–mail: hssong70@gachon.ac.kr

This is an Open–Access article distributed under the terms of the Creative Commons Attribution Non–Commercial License (http://creativecommons.org/licenses/by–nc/3.0) which permits unrestricted non–commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2013 KAMMS. Korean Acupuncture & Moxibustion Medicine Society. All rights reserved.
I. Introduction

Colorectal cancer is one of the most prevailed human malignancies which affects both sex equally and accounts for approximately 9.4 % in a worldwide cumulative incidence rate as a second leading cause of cancer deaths. It usually develops in the cecum, colon and rectum and mostly recovered by enucleation of tumoral tissue in the local lesions confined within the intestinal wall. However, To cope with the advanced metastasized stage, effective chemotherapy should be essentially accompanied by surgical options. Although pathogenesis and chemoprevention is under intense investigation, current development of standard anti-cancer drug for colorectal cancer such as 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin has the limitation due to the existence of relatively rare, highly chemo-resistance and its quiescent or slow proliferating cancer stem cells. Thus, a novel therapeutic strategy for this cancer is urgently needed to resolve the tough challenge and to discover a new agent on the basis of better understanding of the molecular mechanisms of apoptosis.

Selective and specific induction of death receptor signaling apoptosis involving intrinsic or extrinsic apoptotic pathway has been more and more recognized as a promising therapeutic approach for many cancers, including colorectal cancer. Tumor necrosis factor (TNF)-α–related apoptosis–inducing ligand (TRAIL), a member of the TNF ligand super family, can representatively induce selective and specific apoptosis in vitro and in vivo with no harm on normal cells. This is why TRAIL has increasingly attracted attention and it can be a potential target in cancer therapy and the discovery of agents. In spite of its usefulness, another challenge remains to be overcome, which is the resistance of death receptor 4 (DR4) and death receptor 5 (DR5) to TRAIL because of decreased or mutated DR4 and DR5 or damaged distal signaling cascades. For these reasons, it is recommended not to use TRAIL alone but to use it together with other chemotherapeutic agents that can upregulate TRAIL receptors. That is, Sensitizing cancer cells by subtoxic concentrations of chemotherapeutic drugs is helpful for TRAIL to restore its sensitivity through increase of DR4 and DR5 expressions. Several recent studies have reported that the DR4 and DR5 TRAIL receptors are up-regulated by different mechanisms, such as ROS generation by agents such as ursolic acid, Gossypol, curcumin, baicalein and 15-deoxy-delta-prostaglandin J2 in cancer cells.

In the extrinsic apoptotic pathway, DR4 and DR5 exists on the cell surface of Tumors and they becomes activated or oligomerized upon binding to its ligand TRAIL or overexpression as soon as receiving ROS stimuli and subsequently signals apoptosis through caspase-8–mediated rapid activation of caspase cascades. They also initiated a mitochondrial regulated apoptotic pathway simultaneously by translocation of a truncated form of Bid(tBid) into mitochondria, inducing enhanced mitochondrial outer membrane permeability following increased Bax/Bcl-2, cytochrome C release, consecutively activated caspase cascade system. Many previous studies demonstrated that natural toxins sensitize cancer cells to TRAIL–mediated apoptotic cell death, and researchers believe that natural snake venom toxin (SVT) is helpful as a biological resource due to several pharmacologically active factors with potential therapeutic value regardless of apprehension about its safety. Recently there have been a lot of studies substantiating the above such as antihypertensive drug, anticoagulant drug, and drugs of hepatic–induced thrombocytopenia and stroke. In particular, SVT from Vipera lebetina turanica was previously demonstrated as a possible chemotherapeutic agent against the growth of human prostate cancer cell and neuroblastoma cell through induction of apoptotic cell death that is mediated by the modulated expression of apoptosis regulatory proteins. Previously, we found that SVT increases DRs expression in colon cancer cells. Therefore, In this study, I confirmed cancer cell response toward SVT from Vipera lebetina turanica combined with TRAIL in TRAIL sensitive colorectal cancer HCT.