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Original Article

Costunolide specifically binds and inhibits thioredoxin reductase 1 to induce apoptosis in colon cancer

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ABSTRACT

Colon cancer is one of the leading causes of cancer-related deaths. A natural sesquiterpene lactone, costunolide (CTD), showed inhibition of cancer development. However, the underlying mechanisms are not known. Here, we have examined the therapeutic activity and novel mechanisms of the anti-cancer activities of CTD in colon cancer cells. Using SPR analysis and enzyme activity assay on recombinant TrxR1 protein, our results show that CTD directly binds and inhibits the activity of TrxR1, which caused enhanced generation of ROS and led to ROS-dependent endoplasmic reticulum stress and cell apoptosis in colon cancer cells. Overexpression of TrxR1 in HCT116 cells reversed CTD-induced cell apoptosis and ROS increase. CTD treatment of mice implanted with colon cancer cells showed tumor growth inhibition and reduced TrxR1 activity and ROS level. In addition, it was observed that TrxR1 was significantly up-regulated in existing colon cancer gene database and clinically obtained colon cancer tissues. Our studies have uncovered the mechanism underlying the biological activity of CTD in colon cancer and suggest that targeting TrxR1 may prove to be beneficial as a treatment option.

Introduction

Colon cancer is a leading cause of cancer-related deaths. Currently, colon cancer is managed through surgery and chemotherapy [1]. The overall survival of patients with advanced colon cancer has improved over the past few decades. Response to current systemic chemotherapies can reach up to 50%. However, resistance develops in nearly all patients with colon cancer and limits the therapeutic efficacies of many anti-cancer agents [2]. These developments eventually lead to chemotherapy failure. Studies to date have identified a number of molecular derangements which serve as biomarkers. These include microsatellite instability, CpG island methylator phenotype, chromosomal instability, and *BRAF* and *KRAS* mutations [3,4]. Using these biomarkers and subtyping colon cancer can lead to marked differences in survival [5]. However, drug resistance remains an obstacle to successful chemotherapy [6]. Therefore, a novel approach to combatting colon cancer is needed.

The use of various natural and synthetic drugs for colon cancer is gaining attention in recent years. We know that up to seventy percent of all cancers correlate with diet and almost 90% of colon cancer may be preventable through modifying diet [7]. One such natural compound that shows remarkable anti-cancer activities in a host of human cancers is costunolide (CTD). CTD is a naturally

Abbreviations: ER, endoplasmic reticulum; TrxR1, thioredoxin/thioredoxin reductase 1; EIF2, eukaryotic initiation factor 2; ATF-4, activating transcription factor 4; CHOP, CAAT/enhancer-binding protein homologous protein; PI, propidium iodide; DCFH-DA, 20,70-dichlorodihydrofluorescein diacetate; MDM-2, murine double minute 2; Cdc2, cyclin-dependent kinase 1 cell division cycle protein 2; PARP, poly ADP-ribose polymerase; NAC, N-acetyl cysteine; MTT, 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Ki-67, nuclear protein associated with cell proliferation; MDA, malondialdehyde.

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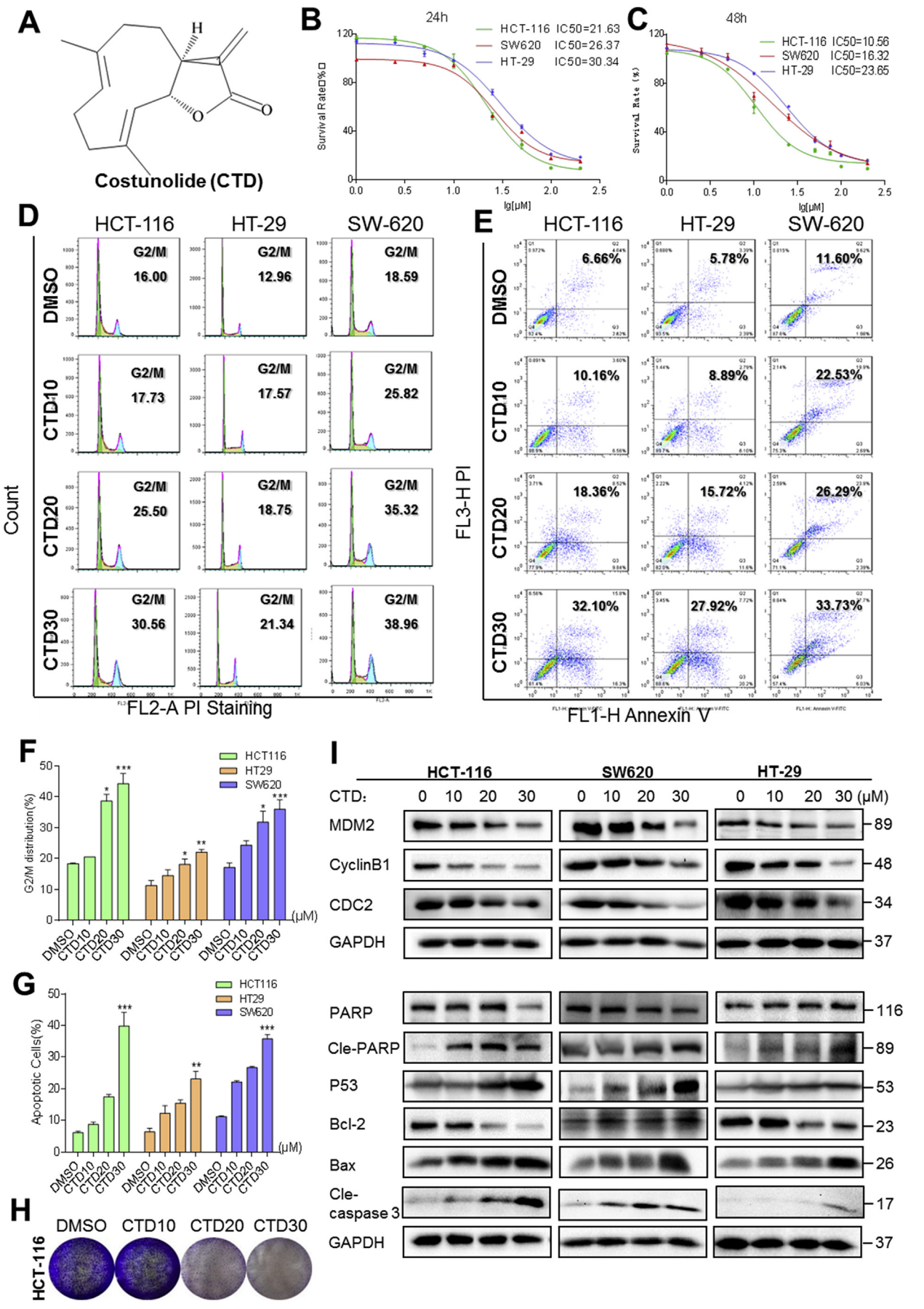

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