香港浸會大學
HONG KONG BAPTIST UNIVERSITY

HKBU Scholars

DOCTORAL THESIS

Study of the anti-cancer effect and mechanism of compound 9: a novel derivative of the PPD-type ginsenoside

Dong, Hang

Date of Award:
2012

Link to publication

General rights
Copyright and intellectual property rights for the publications made accessible in HKBU Scholars are retained by the authors and/or other copyright owners. In addition to the restrictions prescribed by the Copyright Ordinance of Hong Kong, all users and readers must also observe the following terms of use:

- Users may download and print one copy of any publication from HKBU Scholars for the purpose of private study or research
- Users cannot further distribute the material or use it for any profit-making activity or commercial gain
- To share publications in HKBU Scholars with others, users are welcome to freely distribute the permanent URL assigned to the publication

Download date: 27 Jan, 2023

Study of The Anti-cancer Effect and Mechanism of Compound 9, a Novel Derivative of the PPD-type Ginsenoside

DONG Hang

A thesis submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Principal Supervisor: Dr. Yu Zhiling

Hong Kong Baptist University

March 2012

ABSTRACT

In the research of drug discovery it shows promise from natural sources. However, the ideal therapeutics for cancer treatment remains still in highly demanding. In the past decades, much attention has been paid on screening ideal anti-cancer agents from ginseng radix et rhizoma (ginseng) as it has been popularly used as a healthful medicinal herb in Asian countries for prevention and treatment of various illnesses including cancers. Previous reports showed the extracts of ginseng to be effective of inhibiting cancers in humans and animals. Also, the total ginsenosides and a number of purified single ginsenosides with anti-cancer potency have been isolated from the plant. Nevertheless, the specific cytotoxic effect of ginsenosides on cancer cells but not on normal cells has not yet been identified.

In the current studies, Compound **9**, a novel derivative from ginsenoside 20(*R*)-Rh2 with structure modification, exhibited specific cytotoxic effect to a panel of cancer cells but not to the normal human lung fibroblasts *in vitro*. At the same time, it could significantly suppress tumor growth in LLC-1 xenograft-bearing mice, but without significant negative impairments to the general condition and immune organs of the animals. *In vitro* studies showed that Compound **9** treatment induced a significant cell cycle arrest in S phase concomitant with down-regulation of Cdks and Cyclins alongside up-regulation of p21 and p27 expression. And, the complex formation between Cdk2/Cyclin E and Cdk4/Cyclin D1 were decreased, while the recruitments of p21 or p27 to Cyclin E/Cdk2 complex increased. In addition, the

Compound **9**-induced cell death and S phase arrest could be significantly attenuated by knockdown of p21 or p27 protein. Compound **9** could also activate MAPK and p53 pathways, leading to subsequent activation of p27/p21 and suppression of Cyclin/Cdk complex activity. However, only the inhibitor of ERK (U0126) could suppress Compound **9**-induced cytotoxicity and up-regulation of p53/p27 or /p21 and egr-1/p27 or /p21 expression.

The F-box protein s-phase kinase-associated protein 2 (skp2), which acts as an oncogene through targeting p27 for degradation, is overexpressed in many different human cancers. With treatment of Compound **9**, the skp2 autoinduction loop was shut off via blocking the expression of skp2 and then resulted in inhibition of p27 degradation, activation of Cyclin E/Cdk 2, phosphorylation of Rb, and E2F release. And, the Compound **9**-induced cytotoxicity and S phase cell cycle arrest in cancer cells could be attenuated by over-expression of skp2 gene, indicating an important role being paid by skp2 in Compound **9**-mediated *in vitro* tumor suppression.

DNA damage occurs in all phases of a cell cycle of cancer cells, especially when the cells pass through S phase during which DNA get synthesized. In our experiments, Compound **9** treatment could induce activation of ATM and increase phosphorylation of Chk1/Cdc25C/H2A.X, which eventually resulted in lack of the activated Cyclin B1/Cdk1 and thereafter led to unable movement of the cells through the mitotic phase.

Moreover, Compound **9** could significantly and dose-dependently inhibit the invasive ability of cancer cells *in vitro*, while this anti-invasive action could be partially associated with suppression of VEGF, COX-2 and MMP-9 which are usually

over-expressed in tumor cells.

In conclusion, a novel anti-cancer derivative of ginsenoside 20(*R*)-Rh2 has been at the first time identified in current studies, which showed effectively in suppression of tumor growth in LLC-1 bearing mice but without significant negative impairment to the general condition and immune organs of the animals. Mechanistic studies on the anti-cancer effect of Compound **9** showed closely association with induction of S phase arrest of the cancer cell cycle via up-regulation of p21 and p27, suppression of Cyclin/Cdk complex activity and VEGF, COX-2 and MMP-9 expression. Interestingly, Compound **9** had no cytotoxic effect to the normal human lung fibroblasts. Taken together, Compound **9** has potentials as a novel candidate anti-cancer agent for further investigation.

TABLES OF CONTENTS