Oncogene (2005) **24,** 6256–6268. doi:10.1038/sj.onc.1208759; published online 23 May 2005

Diallyl trisulfide-induced G_2–M phase cell cycle arrest in human prostate cancer cells is caused by reactive oxygen species-dependent destruction and hyperphosphorylation of Cdc25C

Dong Xiao[1,2], Anna Herman-Antosiewicz[1,2], Jedrzej Antosiewicz[1], Hui Xiao[1], Marni Brisson[1], John S Lazo[1] and Shivendra V Singh[1]

[1]Department of Pharmacology and University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Correspondence: SV Singh, 2.32A Hillman Cancer Center Research Pavilion, 5117 Centre Avenue, Pittsburgh, PA 15213, USA. E-mail: singhs@upmc.edu

[2]These authors contributed equally to this work

Received 2 February 2005; Revised 12 April 2005; Accepted 12 April 2005; Published online 23 May 2005.

Top of page

Abstract

Molecular mechanism of cell cycle arrest caused by diallyl trisulfide (DATS), a garlic-derived cancer chemopreventive agent, has been investigated using PC-3 and DU145 human prostate cancer cells as a model. Treatment of PC-3 and DU145 cells, but not a normal prostate epithelial cell line (PrEC), with growth suppressive concentrations of DATS caused enrichment of the G_2–M fraction. The DATS-induced cell cycle arrest in PC-3 cells was associated with increased Tyr^{15} phosphorylation of cyclin-dependent kinase 1 (Cdk1) and inhibition of Cdk1/cyclinB1 kinase activity. The DATS-treated PC-3 and DU145 cells also exhibited a decrease in the protein level of Cdc25C and an increase in its Ser^{216} phosphorylation. The DATS-mediated decrease in protein level and Ser^{216} phosphorylation of Cdc25C as well as G_2–M phase cell cycle arrest were significantly attenuated in the presence of *N*-acetylcysteine implicating reactive oxygen species (ROS) in cell cycle arrest caused by DATS. ROS generation was observed in DATS-treated PC-3 and DU145 cells. DATS treatment also caused an increase in the protein level of Cdk inhibitor p21, but DATS-induced G_2–M phase arrest was not affected by antisense-mediated suppression of

p21 protein level. In conclusion, the results of the present study indicate that DATS-induced G_2–M phase cell cycle arrest in human prostate cancer cells is caused by ROS-mediated destruction and hyperphosphorylation of Cdc25C.

Keywords:

diallyl trisulfide, ROS, Cdc25C, cell cycle arrest, prostate cancer, chemoprevention

Otra referencia con relación al dialil trisulfuro.

Garlic Constituent Diallyl Trisulfide Prevents Development of Poorly Differentiated Prostate Cancer and Pulmonary Metastasis Multiplicity in TRAMP Mice

1. Shivendra V. Singh1,2,
2. Anna A. Powolny1,
3. Silvia D. Stan1,
4. Dong Xiao1,
5. Julie A. Arlotti2,
6. Renaud Warin1,
7. Eun-Ryeong Hahm1,
8. Stanley W. Marynowski2,
9. Ajay Bommareddy1,
10. Douglas M. Potter3, and
11. Rajiv Dhir2

+ Author Affiliations

1. *[1]Department of Pharmacology and Chemical Biology, and [2]University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, and [3]Biostatistics Department, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania*

1. **Requests for reprints:**
Shivendra V. Singh, 2.32A Hillman Cancer Center Research Pavilion, 5117 Centre Avenue, Pittsburgh, PA 15213. Phone: 412-623-3263; Fax: 412-623-7828; E-mail: singhs@upmc.edu.

Abstract

Identification of agents that are nontoxic but can delay onset and/or progression of prostate cancer, which is the second leading cause of cancer-related deaths among men in the United States, is highly desirable. We now show that p.o. gavage of garlic constituent diallyl trisulfide (DATS; 1 and 2 mg/day, thrice/week for 13 weeks beginning at age 8 weeks) significantly inhibits progression to poorly differentiated prostate carcinoma and pulmonary metastasis multiplicity in transgenic adenocarcinoma of mouse prostate (TRAMP) mice without any side effects. There was a trend of a decrease in average wet weights of the urogenital tract and prostate gland in 1 and 2 mg DATS–treated mice compared with controls (~25–46% decrease in DATS-treated mice compared with controls). The incidence and the area of the dorsolateral prostate occupied by the poorly differentiated carcinoma were significantly lower in both 1 and 2 mg DATS–treated mice compared with control mice. In addition, DATS administration resulted in a statistically significant decrease in pulmonary metastasis multiplicity compared with controls (P = 0.002). The dorsolateral prostate from DATS-treated TRAMP mice exhibited decreased cellular proliferation in association with induction of cyclinB1 and securin protein levels, and suppression of the expression of neuroendocrine marker synaptophysin. However, DATS administration did not have any appreciable effect on apoptosis induction, angiogenesis, or natural killer and dendritic cell function. In conclusion, the results of the present study show, for the first time, that DATS administration prevents progression to invasive carcinoma and lung metastasis in TRAMP mice. [Cancer Res 2008;68(22):9503–11]