Inhibition of Stat3 activation by sanguinarine suppresses prostate cancer cell growth and invasion.


Source


Department of Urology, University of California at Davis, Sacramento, California; Graduate Program of Pharmacology and Toxicology and Cancer Center, University of California at Davis, Sacramento, California.

Abstract

BACKGROUND:

Signal transducer and activator of transcription 3 (Stat3) is an oncogenic transcriptional factor that plays a critical role in carcinogenesis and cancer progression and is a potential therapeutic target. Sanguinarine, a benzophenanthridine alkaloid derived primarily from the bloodroot plant, was identified previously as a novel inhibitor of survivin that selectively kills prostate cancer cells over "normal" prostate epithelial cells.

METHODS:

DU145, C4-2B, and LNCaP cells were treated with sanguinarine. The phosphorylation status of Stat3 and related proteins were measured with Western blots. Activation of transcription by Stat3 was measured with luciferase reporter assay. The effect of sanguinarine on anchorage-independent growth was examined with soft agar assay, and on cell migration and invasion of DU145 cells were measured with scratch assay and invasion assay, respectively.

RESULTS:
In this study, we identified sanguinarine as a potent inhibitor of Stat3 activation which was able to suppress prostate cancer growth, migration, and invasion. Sanguinarine inhibits constitutive as well as IL6-induced phosphorylation of Stat3 at both Tyr705 and Ser727 in prostate cancer cells. The inhibition of Stat3 phosphorylation by sanguinarine correlates with reduction of Janus-activated Kinase 2 (Jak2) and Src phosphorylation. Sanguinarine downregulates the expression of Stat3-mediated genes such as c-myc and survivin and inhibits the Stat3 responsive element luciferase reporter activity. Sanguinarine inhibits the anchorage-independent growth of DU145 and LN-S17 cells expressing constitutively activated Stat3. Migration and invasion abilities of DU145 cells were also inhibited by sanguinarine in a manner similar to the dominant negative form of Stat3.

CONCLUSIONS:

These data demonstrate that sanguinarine is a potent Stat3 inhibitor and it could be developed as a therapeutic agent for prostate cancer with constitutive activation of Stat3. Prostate © 2011 Wiley-Liss, Inc.

Copyright © 2011 Wiley-Liss, Inc.

PMID:

21538419