TITLE OF DISSERTATION
Molecular Mechanisms Regulating Simvastatin-mediated Inhibition of Prostate Cancer Cellular Functions in vitro and Tumor Growth in vivo

ABSTRACT
Prostate cancer is the second-leading cause of cancer-associated death among men in the United States. Statins are well known for their effects on cellular proliferation and inflammation, two key processes that also determine the rate of tumor growth. Hence, statins are believed to have potential therapeutic benefits for cancer. In the current study, we sought to investigate the effects of simvastatin on prostate cancer cell functions in vitro and tumor growth in vivo. Time- and dose-dependent effects of simvastatin on LNCaP (androgen-dependent) and PC3 (androgen-independent) cells indicated that as low as 25 μM simvastatin was sufficient to inhibit serum-stimulated Akt activity, migration, invasion, colony formation, and proliferation. Effects of simvastatin on PC3 cell colony formation were rescued by adenovirus-mediated expression of constitutively active Akt (my-Akt). A PC3 xenograft model performed in nude mice exhibited reduced tumor growth with simvastatin treatment associated with decreased Akt activity. Our biochemical and gene array analyses indicated that simvastatin inhibited intrinsic cell survival pathway in PC3 cells by enhancing phosphorylation of Bad, reducing the protein expression of Bcl-2, Bcl-xL and cleaved caspases 9/3. Simvastatin treatment also resulted in increased mRNA and protein expression of molecules such as TNF, Fas-L, Traf1 and cleaved caspase 8, major mediators of extrinsic apoptosis pathway and reduced protein levels of pro-survival genes Lhx4 and Nme5. Our study provides the first report that simvastatin simultaneously modulates intrinsic and extrinsic pathways in the regulation of prostate cancer cell apoptosis in vitro and in vivo. Finally, we tested the efficacy of simvastatin on the prevention of prostate cancer micrometastasis, an essential step prior to metastasis. Simvastatin treatment inhibited the ability of human PC3 cells for transendothelial migration in vitro. Simvastatin also modulated the expression of tumor-derived angiopoietins and VEGF-A at the mRNA and protein levels by the PC3 cells. Furthermore, simvastatin treatment directly activated endothelial cells resulting in enhanced endothelial-barrier resistance. Most importantly, simvastatin-mediated effect on PC3 micrometastasis was mediated through inhibition of integrin αvβ3 activity and suppression of interaction between prostate cancer cell integrin αvβ3 with endothelial ICAM-1. Altogether, our study demonstrates the therapeutic potential of simvastatin for prostate cancer, and render reasonable optimism that statins could become an attractive anti-cancer agent.
PERSONAL DATA

Birthplace: Kuwait, 1977

EDUCATION

B.S. Jordan University of Science and Technology, Jordan 1995-2000
M.S. Jordan University of Science and Technology, Jordan 2000-2002

HONORS

Pre-doctoral fellowship, Jordan University of Science and Technology, Jordan, 2008-2012

SOCIETIES

American College of Clinical Pharmacy (ACCP)
Hematology/Oncology Pharmacy Association (HOPA)
American Heart Association (AHA)

ABSTRACTS (Selected)

1. Southern Translational Education and Research (STAR) conference, September 6th-7th, Augusta, GA. Simvastatin inhibits micrometastasis of invasive prostate cancer cells via inhibition of integrin αvβ3 interactions with endothelial ICAM1, (Belal Al-Husein, Anna Goc, and Somanath P.R.)

PUBLICATIONS


PUBLICATIONS (COMMUNICATED/IN PREPARATION)