Geranylgeraniol suppresses the viability of human prostate cancer cells and HMG CoA reductase

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Researchers at Texas Woman's University have shown that a diterpene geranylgeraniol found in linseed oil, *Cedrela toona* wood oil, sucupira branca fruit oil and more recently, annatto seed oil, suppressed the viability of human DU145 prostate carcinoma cells via cell cycle arrest at the G1 phase and the initiation of apoptosis. This finding, reported in the November 2013 issue of *Experimental Biology and Medicine*, supplies recent evidence supporting the tumor-suppressive potential of dietary isoprenoids, a class of phytochemicals encompassing ~55,000 mevalonate-derived secondary metabolites.

"This line of work dates back to the 1980s when the University of Wisconsin groups led by Drs. Charles Elson and Michael Gould discovered the anti-tumor activity of monoterpenes and soon after, sesqui- and di-terpenes." said Dr. Huanbiao Mo, senior author and professor in the Department of Nutrition and Food Sciences. These compounds, widely present in fruits, vegetables and grains, were found to be much more effective in suppressing the growth of tumor cells than that of normal cells. A study by Mo's group in a 2011 issue of *Experimental Biology and Medicine* (236:604-613) showed that normal fibroblasts are 10-fold more resistant than murine B16 melanoma cells to geranylgeraniol-mediated growth suppression. This tumor-targeted action of isoprenoids was manifested in animal studies showing no toxicity of isoprenoids at tumor-suppressive doses (reviewed by Mo & Elson, *Exp Biol Med*, 2004, 229:567-85). Previous work also suggested

synergistic impact of isoprenoids on tumor growth, a finding remaining to be confirmed in prostate cancer.

In collaboration with the University of Texas Southwestern Medical Center (UTSW) in Dallas, the researchers found that the tumor-suppressive activity of geranylgeraniol was accompanied by down-regulation of HMG CoA reductase, a key enzyme in the mevalonate pathway that provides essential intermediates for the posttranslational modification of growth-related proteins such as Ras, nuclear lamins and insulin-like growth factor receptors. Isoprenoid-mediated suppression of HMG CoA reductase in tumors was previously correlated to growth arrest; the latter was attenuated by supplemental mevalonate. "This is the first time that geranylgeraniol was found to suppress HMG CoA reductase in prostate cancer cells," said Dr. Russell DeBose-Boyd, co-author and professor in the Department of Molecular Genetics and Howard Hughes Medical Institute at UTSW.

Other contributors are graduate students Nicolle Fernandes (now at Ball State University), Hoda Yeganehjoo, Rajasekhar Katuru (now at Baton Rouge General Medical Center), Lindsey Morris (UTSW), and Renee Michon and Dr. Zhi-Ling Yu of Hong Kong Baptist University.

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said "This study by Huanbiao Mo and colleagues at the Texas Woman's University and UT Southwestern Medical Center demonstrates that geranylgeraniol causes dose dependent apoptotic death of human prostate carcinoma cells. They further show that this diterpine downregulates HMG CoA reductase offering support to the concept that mevalonate deprivation causes cell cycle arrest at the G1 phase leading to apoptotic death of the prostate carcinoma cells. Importantly this article suggests that geranylgeraniol deserves further study as a potential therapy for human prostate cancer."