Tocopherol transfer protein sensitizes prostate cancer cells to vitamin E. S. Morley, V.Thakur, D. Danielpour, R. Parker, H. Arai, J. Atkinson, J. Barnholtz-Sloan, E. Klein, and D. Manor, *J. Biol. Chem*., **285**, 35578–35589 (2010).

Prostate cancer is a major cause of mortality in men in developed countries. It has been reported that the naturally occurring antioxidant α-tocopherol (vitamin E) attenuates prostate cancer cell proliferation in cultured cells and mouse models. We hypothesized that overexpression of the tocopherol transfer protein (TTP), a vitamin E-binding protein that regulates tocopherol status, will sensitize prostate cancer cells to the antiproliferative actions of the vitamin. To test this notion, we manipulated the expression levels of TTP in cultured prostate cells (LNCaP, PC3, DU145, and RWPE-1) using overexpression and knockdown approaches. Treatment of cells with tocopherol caused a time- and dose-dependent inhibition of cell proliferation. Overexpression of TTP dramatically sensitized the cells to the apoptotic effects of α-tocopherol, whereas reduction ("knockdown") of TTP expression resulted in resistance to the vitamin. TTP levels also augmented the inhibitory effects of vitamin E on proliferation in semi-solid medium. The sensitizing effects of TTP were paralleled by changes in the intracellular accumulation of a fluorescent analog of vitamin E and by a reduction in intracellular levels of reactive oxygen species and were not observed when a naturally occurring, ligand binding defective mutant of TTP was used. We conclude that TTP sensitizes prostate cancer cells to the anti-proliferative effects of vitamin E and that this activity stems from the ability of protein to increase the intracellular accumulation of the antioxidant. These observations support the notion that individual changes in the expression level or activity of TTP may determine the responsiveness of prostate cancer patients to intervention strategies that utilize vitamin E.