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### Anti-apoptotic and pro-angiogenic properties of thyroid hormone may oppose cancer chemotherapy

The principal secretory product of the thyroid gland, L-thyroxine ( $T_4$ ), is anti-apoptotic at physiological concentrations in a number of cancer cell lines. Among the mechanisms of anti-apoptosis activated by the hormone is interference with the Ser-15 phosphorylation (activation) of p53 and with TNF $\alpha$ /Fas-induced apoptosis. The hormone also decreases cellular abundance and activation of proteolytic caspases and of BAX and causes increased expression of X-linked inhibitor of apoptosis (XIAP). The anti-apoptotic effects of thyroid hormone largely are initiated at a cell surface thyroid hormone receptor on the extracellular domain of integrin  $\alpha\beta 3$  that is amply expressed and activated in cancer cells. Tetraiodothyroacetic acid (tetrac) is a  $T_4$  derivative that, in a model of resveratrol-induced p53-dependent apoptosis in glioma cells, blocks the anti-apoptotic action of thyroid hormone, permitting specific serine phosphorylation of p53 and apoptosis to proceed. In a nanoparticulate formulation limiting its action to  $\alpha\beta 3$ , tetrac modulates integrin-dependent effects on gene expression in human cancer cell lines that include stimulation of expression of a panel of pro-apoptotic genes and downregulated transcription of defensive anti-apoptotic XIAP and MCL1 genes. By a variety of mechanisms, thyroid hormone ( $T_4$ ) acts as an endogenous anti-apoptotic factor that may oppose chemotherapy-induced apoptosis in  $\alpha\beta 3$ -expressing cancer cells. It is possible to oppose this anti-apoptotic activity pharmacologically by reducing circulating levels of  $T_4$  or by blocking effects of  $T_4$  that are initiated at  $\alpha\beta 3$ .

### Biography

Davis is a graduate of Harvard Medical School and had his postgraduate medical training at Albert Einstein College of Medicine and the NIH. His academic positions have included Chair, Department of Medicine, Albany Medical College. He has served as President, American Thyroid Association, as a member of the Board of Directors of the American Board of Internal Medicine and he is Co-Head, Faculty of 1000 – Endocrinology. He serves on multiple Editorial Boards of His scientific interests include molecular mechanisms of actions of nonpeptide hormones, particularly, thyroid hormone. He and his colleagues described the cell surface receptor for thyroid hormone on integrin  $\alpha\beta 3$  that underlies the pro-angiogenic activity of the hormone and the proliferative action of the hormone on cancer cells. He has co-authored more than 200 original research articles and 30 textbook chapters and he has edited three medical textbooks.

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