

Cancer-Relevant Functions of the Plasma Membrane Receptor for Thyroid Hormone Analogues

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Integrin $\alpha\beta 3$ is a heterodimeric structural protein of the plasma membrane that contains a high affinity receptor for thyroid hormone. Functions of this receptor are wholly distinct from those of the classical nuclear receptor (TR) for thyroid hormone. The hormone receptor on $\alpha\beta 3$ enables L-thyroxine (T_4) and 3, 5, 3'-triiodo-L-thyronine (T_3) to stimulate cancer cell proliferation and angiogenesis. A deaminated derivative of T_4 , tetraiodothyroacetic acid (tetrac), blocks binding and proliferative actions of T_4 and T_3 at the $\alpha\beta 3$ receptor; tetrac also has anti-proliferative actions at the thyroid hormone receptor in the absence of T_4 and T_3 . Structure-activity relationships of hormone analogues at the receptor have been computer-modeled and indicate the receptor includes a site (S1) that binds T_3 and a site (S2) for which both T_4 and T_3 are ligands. Tetrac acts at both S1 and S2. Cell proliferation is modulated from the S2 site. Tetrac has been re-formulated as a nanoparticle (nanotetrac) that acts exclusively at the $\alpha\beta 3$ receptor and does not enter cells. Nanotetrac 1) disorders expression of genes in multiple cancer cell survival pathways 2) blocks human cancer cell proliferation *in vitro* and in tumor xenografts and 3) inhibits the pro-angiogenic actions *in vitro* of VEGF, bFGF and other growth factors. Nanotetrac radiosensitizes cancer cells by inhibiting repair of double-strand DNA breaks. Thus, the receptor described on integrin $\alpha\beta 3$ for T_4 and T_3 provides insight into tumor cell and vascular cell biology and tetrac formulations offer a novel, disabling effects on multiple cancer cell defense pathways.

Biography

Paul J. Davis obtained his M.D. at Harvard Medical School and his clinical training at Albert Einstein College of Medicine and the NIH. He is Senior Associate Dean for Clinical Research at Albany Medical College and a senior faculty at Albany College of Pharmacy and Health Sciences. He was a founder of Ordway Research Institute, a nonprofit translational biomedical research company. He is a basic science endocrinologist, is co-author of more than 200 original papers and 25 textbook chapters and is an Associate Editor of two medical journals.