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A cell surface receptor for thyroid hormone analogues on integrin $\alpha v\beta_3$ in tumor cells regulates expression of cancer cell genes relevant to the cell cycle apoptosis chemoresistance and angiogenesis

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Integrin $\alpha V\beta_3$ is a structural protein of the plasma membrane that is generously expressed by cancer cells and dividing endothelial cells; until recently, important functions of the integrin have been seen to relate to cell-cell and cell-extracellular matrix protein interactions. The extracellular domain of $\alpha v\beta_3$ is now appreciated to contain a small molecule receptor for thyroid hormone, primarily, L-thyroxine (T4). From this cell surface hormone receptor, the expression of a large panel of cancer-relevant genes is differentially regulated by thyroid hormone analogues. These genes include multiple cell division regulating cyclins and *HRAS* and *KRAS* genes linked to uncontrolled cell division; *KRAS* is also related to cancer stem cell (CSC) maintenance and to tumor recurrence. Transcription of these genes is downregulated by P-bi-TAT, consisting of a thyroid hormone analogue, tetraiodothyroacetic acid (tetrac), chemically coupled to polyethylene glycol (PEG). IDH2 is involved in tumor cell mitochondrial metabolism; P-bi-TAT decreases *IDH2* transcription, thus promoting apoptosis by the intrinsic (mitochondrial) pathway. Expression of *ERBB2* is important to tumor cell invasiveness and metastasis and is downregulated by P-bi-TAT. The ERBB family of proteins is also important to tumor cell chemoresistance. $\alpha v\beta_3$ regulates via the thyroid hormone receptor the transcription of *ABCB1*, whose gene product—the P-glycoprotein of the plasma membrane—exports a number of chemotherapeutic agents from tumor cells as a component of chemoresistance. Expression of pro-angiogenic *VEGFA*, *bFGF* and *PDGF* genes is also decreased by P-bi-TAT action at $\alpha v\beta_3$, as is the *EGFR* gene whose transcription is important to angiogenesis and tumor cell proliferation. Matrix metalloproteinase (MMP) gene expression is critical to cell migration/metastasis and to angiogenesis; P-bi-TAT induces a signal at the integrin to reduce MMP production. The EGFR protein is a tyrosine kinase and thus P-bi-TAT, by downregulating expression of *EGFR*, functions as a tumor cell-relevant tyrosine kinase inhibitor (TKI). Another TKI gene affected by P-bi-TAT is *KIT*. This complex set of actions of P-bi-TAT on gene expression implies that T4 may act on tumor cell $\alpha v\beta_3$ to support, rather than inhibit, the expression of these genes whose products are linked to tumor cell survival. We have

shown that T4 via $\alpha v\beta_3$ does stimulate expression of *VEGFA* and *bFGF*, of MMPs, *ABCB1* in tumor cells. Transduction of thyroid hormone and hormone analogue signals downstream of $\alpha v\beta_3$ is a function of MAPK/ERK1/2 and PI3K, the genes and enzyme activities of which are regulated by thyroid hormone. These observations indicate that the importance of αvβ3 to cancer cell function and survival also includes the actions of thyroid hormone analogues on the integrin.

Biography

Paul J Davis obtained the MD degree at Harvard Medical School and had his internal medicine clinical and endocrine research training, respectively, at Albert Einstein College of Medicine (NY) and the NIH. He has served in a number of senior administrative positions in academic institutions and in national societies. His research is focused on the molecular mechanisms of thyroid hormone actions. He has co-authored 275 research publications and 40 textbook chapters; he has co-edited four textbooks. He and colleague SA Mousa described the cell surface receptor for thyroid hormone on integrin $\alpha v\beta_3$. They also co-founded NanoPharmaceuticals LLC (Rensselaer, NY).

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