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Stem Cell Conference 2019_A cell surface receptor for thyroid hormone analogues on integrin αvβ3 in tumor cells regulates expression of cancer cell genes relevant to the cell cycle apoptosis chemoresistance and angiogenesis_ Paul J Davis_ Albany Medical College_ USA

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Integrin αvβ3 may be a structural protein of the cell wall that's generously expressed by cancer cells and dividing endothelial cells; until recently; important functions of the integrin are seen to relate to cell-cell and cell-extracellular matrix protein interactions. The extracellular domain of αvβ3 is now appreciated to contain alittle molecule receptor for hormone, primarily, L-thyroxine (T4). From this cell surface hormone receptor, the expression of an outsized panel of cancer-relevant genes is differentially regulated by 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 those genes is downregulated by P-bi-TAT, consisting of a 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 vital 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. αvβ3 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 αvβ3, 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 αvβ3 to support, rather than inhibit, the expression of these genes whose products are linked to tumor cell survival. We have shown that T4 via αvβ3 does stimulate expression of VEGFA and bFGF, of MMPs, ABCB1 in tumor cells. Transduction of thyroid hormone and hormone analogue signals downstream of αvβ3 is a function of MAPK/ ERK1/2 and PI3K, the genes and enzyme activities of which are regulated by thyroid hormone. Thyroxine (T4) is produced by the thyroid gland under regulation from the hypothalamus and pituitary gland. The feedback loop signals to the hypothalamus in to release thyrotropin-releasing hormone, which then stimulates the pituitary gland to release the thyroid stimulating hormone.These observations indicate that the importance of αvβ3 to neoplastic cell function and survival also includes the actions of hormone analogues on the integrin.

While the beneficial effects of thyroid hormones include weight loss, lowering serum cholesterol, and improving cardiac output, an excess of thyroid hormones is associated with an adverse effect on bones, skeletal muscles, and the heart. New thyroid hormone analogs that attempt to minimize these adverse effects are being developed as potential therapies for obesity, high cholesterol, and heart failure.

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.

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