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Modulation of angiogenesis and anti-angiogenesis at targets on integrin αvβ3

Plasma membrane integrin αvβ3 is extensively involved in angiogenesis. Generously expressed on dividing endothelial cells and tumor cells, αvβ3 mediates cell-cell interactions and interactions with angiogenesis-relevant extracellular matrix (ECM) proteins such as osteopontin, vitronectin and von Willebrand factor. αvβ3 also engages in crosstalk with adjacent vascular growth factor receptors. We have described small molecule ligands of the integrin, such as thyroid hormone, that exert extensive control over blood vessel formation. Acting at the integrin, L-thyroxine (T4) (< 10-10 M free hormone) and 3,3',5-triiodo-L-thyronine (T3) rapidly stimulate angiogenesis in the chick chorioallantoic membrane (CAM) model and Matrigel® microtubule formation system. Nanoparticulate T4 (agarose-T4) does not gain access to the cell interior and is equipotent angiogenically to unmodified T4. T4 is equipotent to VEGF and bFGF in the CAM model. The hormone receptor on αvβ3 mediates upregulation by T4 of a set of genes relevant to angiogenesis, including basic fibroblast growth factor (bFGF; FGF2) and several matrix metalloproteinases (MMPs). T4 also supports endothelial cell migration towards a vitronectin cue. Tetraiodothyroacetic acid (tetrac), a deaminated derivative of T4, inhibits binding of T4 and T3 to αvβ3 and, unmodified or reformulated as a poly(lactic-co-glycolic acid) nanoparticle (Nanotetrac; Nano-diamino-tetrac; NDAT), this agent antagonizes all of the pro-angiogenic actions of T4 and T3. Nanotetrac is anti-angiogenic by additional mechanisms unrelated to the binding of T4 and T3. These αvβ3-dependent actions include inhibition of the angiogenic actions of VEGF, bFGF and PDGF—reflecting, we propose, disruption of crosstalk between the integrin and nearby receptors for vascular growth factors—and stimulation of expression of the anti-angiogenic thrombospondin 1 (TSP1) gene in tumor cells. Also relevant to angiogenesis are the actions of Nanotetrac to decrease expression of VEGFA, EGFR, MMP-2, MMP-9 genes and miR-21 abundance. The microRNA increases cellular HIF-1α and VEGF content. Finally, resveratrol and testosterone are other small molecule ligands of αvβ3 that modulate angiogenesis. The pro-angiogenic action of resveratrol has been shown to be expressed via the αvβ3 receptor site for stilbenes, but the possibility that the dihydrotestosterone effect on HIF-1α is αvβ3-requiring has not yet been examined. In summary, integrin αvβ3 has small molecule ligands that regulate angiogenesis. A set of disparate thyroid hormone analogues is the best studied of such ligands and by multiple molecular mechanisms these analogues are pro- or anti-angiogenic.

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 avb3 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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