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Workshop

Exploiting integrins in cancer management and diagnosis

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Integrins are heterodimeric structural proteins of the plasma membrane that are critical to cell-cell and cell-extracellular matrix (ECM) protein interactions. The extracellular domains of 7 integrins contain an Arg-Gly-Asp (RGD) recognition site that enables the binding of multiple ECM proteins, including vitronectin, fibronectin and osteopontin. The small intracellular domain generates signals are transduced into cytoskeletal functions and expression of specific genes. This workshop is focused on integrin αvβ3, emphasizing structure-activity relationships (SARs). This integrin is generously expressed/activated by cancer cells and rapidly-dividing endothelial cells. αvβ3 engages in crosstalk with nearby vascular growth factor receptors. This set of features renders αvβ3 a cancer chemotherapeutic target and also a potential diagnostic imaging target in oncology. Vehicles by which αvβ3 may be targeted include antibodies to the integrin, snake venom disintegrins which contain the RGD sequence and RGD cyclic peptides. In addition, the extracellular domain of αvβ3 has been shown to contain a specific receptor for thyroid hormone and the thyroid hormone analogue, tetraiodothyroacetic acid (tetrac). This exracellular receptor has no homologies with the nuclear thyroid hormone receptor (TRs) and enables thyroid hormone (L-thyroxine, T4; 3,5,3'-triiodo-L-thyronine, T3) to be pro-angiogenic and to induce proliferation of solid tumor cells. Tetrac blocks binding of T4 and T3 to their receptor site αvβ3 on cancer cells and has a variety of anti-cancer effects beyond inhibiting binding of T4 and T3. Taken up by nonmalignant cells, however, tetrac is thyromimetic and has undesirable toxicology. Covalently bound to a biodegradable 200 nm PLGA nanoparticle, tetrac as a Nanotetrac formulation that acts exclusively at αvβ3 and is pro-apoptotic, disables anti-apoptotic and other cancer cell defense mechanisms and is anti-angiogenic. The latter effects are complex and involve VEGF, bFGF, PDGF and EGF and their receptors. All of these features make Nanotetrac a promising chemotherapeutic agent that has been shown to be effective in preclinical studies against a wide variety of human tumor cell xenografts. The thyroid hormone-tetrac site is distinct from, but geographically near, the RGD recognition site. Disintegrins of the RGD family are small proteins (45-84 amino acids) that offer another avenue—together with cRGD cyclic peptides—to the targeting of αvβ3 and several other integrins of some importance in cancers. The disintegrins may have anti-metastasis and anti-angiogenic properties. Insofar as imaging is concerned, the covalent binding of tetrac to liposomes as a radiolabeled product has been shown to have preclinical promise as a cancer imaging agent. The workshop reviews integrin selectivity and the designing of new ligands. We analyze the pattern of affinity/selectivity of the medium-sized K/RGD group of snake venom disintegrins and how to select the ligands that dock with αvβ3. The interaction of integrins and distintegrins will be explored from an SAR perspective, using molecular modeling tools that permit us to propose a model for designing new integrin ligands with different levels of specificity. In summary, the advantages and disadvantages of targeting αvβ3 for chemotherapy and for tumor or blood vessel imaging purposes are reviewed in this workshop, comparing the consequences of protein/antibody-binding to the integrin with small molecule (tetrac) targeting and the pharmacokinetics of Nanotetrac and K/RGD disintegrins.