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Nano-diamino-tetrac (NDAT; Nanotetrac) acts at its target on integrin $\alpha v\beta 3$ in human glioblastoma xenografts to induce necrosis via. anti-angiogenesis and apoptosis

Inical evidence in a limited number of patients supports the concept that glioblastoma multiforme (GBM) is a thyroid \checkmark hormone-dependent cancer. In vitro evidence indicates that L-thyroxine (T₄), the principal secretory product of the thyroid gland, at physiological concentrations stimulates proliferation of glioma/GBM cancer cells via a polyfunctional cell surface receptor for T_4 on the extracellular domain of cancer cell plasma membrane integrin $\alpha v\beta 3$. This action of T_4 is blocked by nanoparticulate tetraiodothyroacetic acid (Nanotetrac, Nano-diamino-tetrac, NDAT). Tetrac in this NDAT formulation is covalently bound via a diaminopropane linker to a poly(lactic-co-glycolic acid) (PLGA) nanoparticle. We have examined histopathologically the induction by NDAT of devascularization, of necrosis and apoptosis in U87MG human GBM cell xenografts in nude mice. Treatment regimen was 1 mg tetrac equivalent/kg body weight s.c. as NDAT daily X10 d, begun 2 d following tumor cell implantation when tumor volume estimates were 350 mm³. Xenografted control animals received void nanoparticulate PLGA. Xenograft weight in treated animals at sacrifice was reduced by 50% (P<0.01). Tumor area measured in histologic sections was reduced by 80% in treated animals compared to controls (P<0.001). Blinded analysis of changes in histologic slides from xenografts revealed essentially complete loss of tumor blood vessels with NDAT (P<0.001 vs. control xenografts). This finding was associated with no evidence of hemorrhage. Eighty percent of the cell population in grafts was either necrotic or apoptotic (P<0.001 vs. control) and cell density was reduced by 60% vs. control tumors (P<0.001 vs. control). Mitotic figures/field examined was reduced by 80%. In summary, NDAT, acting at the thyroid hormone-tetrac receptor on the extracellular domain of integrin $\alpha v\beta 3$, devascularized human GBM xenografts with resultant widespread necrosis. In the tumor cell population that was not necrotic, drug-induced apoptosis was documented. The thyroid hormone receptor on $\alpha\nu\beta\beta$ in U87MG cells is a single endocrine target with multiple downstream functions that are exploited by anticancer and antiangiogenic actions of NDAT.

Biography

Paul J Davis is a Professor of Medicine at Albany Medical College and Chief Scientific Officer at NanoPharmaceuticals LLC, Rensselaer, NY. He is former Chair at the Department of Medicine, Albany Medical College. As an Endocrine Researcher, he has co-authored 250 scientific publications and has co-edited two text books on Angiogenesis (Springer, 2013; Elsevier, 2016). He and Dr. Shaker Mousa described the thyroid hormone-tetrac receptor on integrin $\alpha v\beta 3$.

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