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Actions of L-thyroxine (T4) and Nano-diamino-tetrac (NDAT, Nanotetrac) on PD-L1 in cancer cells

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The PD-1 (programmed death-1)/PD-L1 (PD-ligand 1) checkpoint is a critical regulator of activated T cell-cancer cell interactions, serving to defend tumor cells against host immune destruction. Nano-diamino-tetrac (NDAT; Nanotetrac) is an anticancer/anti-angiogenic agent targeted to the thyroid hormone-tetrac receptor on the extracellular domain of integrin αvβ3. NDAT inhibits the cancer cell PI3-K and MAPK signal transduction pathways that are critical to PD-L1 gene expression. We examined actions *in vitro* of thyroid hormone (L-thyroxine, T4) and NDAT on PD-L1 mRNA abundance (qPCR) and PD-L1 protein content in human breast cancer (MDA-MB-231) cells and colon carcinoma (HCT116 and HT-29) cells. In MDA-MB-231 cells, a physiological concentration of T4 (10-7 M total; 10-10 M free hormone) stimulated PD-L1 gene expression by 38% and increased PD-L1 protein by 2.7-fold ($p<0.05$, all changes). NDAT (10-7 M) reduced PD-L1 in T4-exposed cells by 21% (mRNA) and 39% (protein) ($p<0.05$, all changes). In HCT116 cells, T4 enhanced PD-L1 gene expression by 17% and protein content by 24% ($p<0.05$). NDAT reduced basal PD-L1 mRNA by 35% and protein by 31% and in T4-treated cells lowered mRNA by 33% and protein by 66%. In HT-29 cells, T4 increased PD-L1 mRNA by 62% and protein by 27%. NDAT lowered basal and T4-stimulated responses in *PD-L1* mRNA and protein by 35-40% ($p<0.05$). Activation of ERK1/2 was involved in T4-induced PD-L1 accumulation. We propose that, by a nongenomic mechanism, endogenous T4 may clinically support activity of the defensive PD-1/PD-L1 checkpoint in tumor cells. NDAT non-immunologically suppresses basal and T4-induced PD-L1 gene expression in cancer cells.

Biography

Paul Davis is Professor of Medicine at Albany Medical College and former Chair of the Department of Medicine at that institution. He has co-authored 250 publications, most of which deal with thyroid hormone actions. Shaker Mousa is Executive Vice President and Chair, Pharmaceutical Research Institute of the Albany College of Pharmacy and Health Sciences. He was a Principal Research Scientist at DuPont. He has co-authored 600 publications. Hung-Yun Lin is Professor in the Graduate Institute of Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University. Drs. Mousa, Lin and Davis have collaborated in studies of nongenomic actions of thyroid hormone and tetraiodothyroacetic acid (tetrac) and NDAT.

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