Stimulation of tumour growth by thyroid hormone depends on integrin αvβ3 expression

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The thyroid hormones T3 and T4 are emerging as critical regulators of tumour growth and progression via a non-classical signalling pathway initiated at integrin αvβ3. To date, effects of thyroid hormones vs. tetrac, a specific inhibitor of thyroid hormone action at the integrin, on tumour growth have not been directly correlated with integrin αvβ3 expression. Therefore, we compared thyroid hormone effects on tumour growth in integrin αvβ3-positive vs. integrin αvβ3-negative tumours in vivo.

Integrin αvβ3-positive human anaplastic thyroid cancer cells SW1736 and integrin αvβ3-negative human hepatocellular carcinoma cells HuH7 were injected into the flanks of nude mice. Endogenous thyroid hormone production was blocked by MMI/perchlorate in the drinking water to establish identical treatment conditions. Mice were randomly assigned to treatment groups by daily injections of 20 ng/g body weight T4 (euthyroid) with or without 10 µg/g body weight tetrac, 100 ng/g body weight T4 (hyperthyroid) or saline (hypothyroid).

In SW1736 xenograft mice, hyperthyroidism led to a significantly increased tumour growth resulting in a median survival, defined by a tumour volume exceeding 1500 mm³, of 11 days. This was accompanied by an increased tumoural staining for proliferation marker Ki67 and a higher blood vessel density, as determined by CD31 staining, compared to euthyroid mice that showed a median survival of 16 days. Both in tetrac-treated and hypothyroid mice, in contrast, tumour growth and Ki67 staining were significantly reduced leading to median survivals of 23 and 25 days, respectively, though blood vessel densities were comparable to euthyroid mice. Preliminary results in integrin αvβ3-negative HuH7 tumour-bearing mice suggest no differences in tumour growth between the different thyroid hormone states.

Both the reduced tumour growth rate in tetrac-treated mice bearing integrin αvβ3-positive tumours and the fact that integrin αvβ3-negative tumours do not seem to react to thyroid hormone treatment, imply integrin αvβ3-dependency. These data have important clinical implications, showing significant regulation of tumor growth by thyroid hormones and tetrac in αvβ3-positive tumors, it may help identify those cancer patients that would profit from manipulation of their thyroid hormone levels.