HAVING A LOW CIRCULATING LEVEL OF ADIPONECTIN IS AN INDEPENDENT RISK FACTOR FOR PAPILLARY THYROID CANCER

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BACKGROUND

Although the mechanism is not clear, obesity increases the risk and worsens the prognosis of several cancers (1), and epidemiologic data suggest that this is also true for thyroid cancer. Adiponectin is the most abundant adipokine in the circulation, but its level is lower in obese patients, so they appear to receive less of its insulin-sensitizing, antiinflammatory, antiproliferative and vasoprotective effects. In contrast, the blood levels of cytokines such as interleukin-6 (IL-6), as well as leptin, insulin and insulin-like growth factor 1 (IGF-1), which can have mitogenic effects, are higher in obesity. In some disease models, increasing the adiponectin level can be protective, although the results may vary according to the particular form of adiponectin being studied. Low total adiponectin levels are associated with various clinical cancers: the current paper examined whether there was an association between adiponectin levels and thyroid cancer in patients from Northern Greece.

METHODS

Adiponectin (presumably the total level) was measured by radioimmunoassay (along with IGF-1, IGF binding protein 3, and leptin) in fasting sera from 175 patients with various thyroid cancers, and from 107 controls who had had thyroidectomies for Graves' disease, toxic or nontoxic multinodular goiter, or cold nodules but had no thyroid or other cancers. Ten percent of the cancer patients and 25% of controls were male (P<0.01). All subjects were on "appropriate" hormone replacement: the mean thyrotropin (TSH) level was significantly higher in the controls than in the cancer patients (1.39 vs. 0.56 mIU/L), as were the mean free triiodothyronine and free thyroxine levels (P<0.01 for each comparison). The protein levels of the two classical adiponectin receptors (adipoR1 and adipoR2) were assessed by immunohistochemistry on a commercial thyroid cancer tissue array. AdipoR1 and adipoR2 mRNAs were measured by real-time-polymerase-chainreaction assay on a commercial panel that included 32 papillary thyroid cancer (PTC) samples plus 4 normal thyroid tissue samples, and also on two thyroid cancer cell lines. These cell lines were also treated with an active proteolytic fragment of adiponectin, and several growth responses were assayed.

Clinical

THYROIDOLOGY

RESULTS

The mean adiponectin level was 13% higher in sera from controls than in that from patients with thyroid cancer (P<0.001). When the data from the patients with PTC and the controls were combined and divided into tertiles based on the adiponectin level, subjects in the highest tertile had significantly lower odds of being a patient with PTC, while the risk of PTC in the second and third tertiles was progressively greater, even after adjusting for confounders such as TSH, sex, age, body-mass index, diabetes, smoking and IGF-1 levels. Immunohistochemistry detected adipoR1 and adipoR2 in thyroid cancer samples, although the levels of adipoR1 and adipoR2 mRNA were significantly lower in PTC than in control thyroid samples, adjusted for age and gender. Incubating the thyroid cancer cell lines with globular adiponectin did not change their rates of proliferation or death.

CONCLUSIONS

Alow circulating level of adiponectin is an independent risk factor for PTC. The absence of a direct effect of adiponectin on the growth or death of two thyroid cancer cell lines suggests that the negative association of adiponectin levels with PTC reflects decreased peripheral effect(s) of adiponectin.

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Adiponectin can affect cells (directly or indirectly) through pathways regulated by adenosine monophosphate-activated protein kinase (AMPK), p38, nuclear factor kB, jun N-terminal kinase (JNK), signal transducer and activator of transcription 3 (Stat3), Akt, ceramidase, peroxisome proliferator-activated receptors (PPARs), and/or insulin receptor substrate (IRS2) (1-3). Adiponectin can also directly bind to certain growth factors, inhibiting their ability to interact with receptors. Drugs like salsalate as well as some thiazolidinediones and angiotensin-receptor II blockers can raise adiponectin levels, but

whether such agents might also affect cancer is not known. One should note that adiponectin levels can also be raised by extensive aerobic exercise or by a Mediterranean diet.

It is not clear why the results of the leptin assays performed in this study were not reported. Recent papers indicate that circulating leptin levels are not only increased in obesity, but are also associated with PTC; that leptin receptor levels are increased in PTCs; and that the levels of both leptin and its receptor are associated with more aggressive PTC behavior.

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