Tumor necrosis factor alpha induces three-dimensional cytomorphologic differentiation of human anaplastic thyroid carcinoma cells through activation of nuclear factor kappaB.

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摘要

Abstract

BACKGROUND: Anaplastic thyroid carcinoma is almost uniformly fatal. Microvilli are an important three-dimensional (3-D) cytomorphologic feature of thyrocyte differentiation, because fewer microvilli are seen in less differentiated tumors. Differentiation therapies, such as retinoic acid and somatostatin, have been tested previously in experimental models of differentiated thyroid carcinoma but not in anaplastic thyroid carcinoma. The objective of this study was to determine whether tumor necrosis factor alpha (TNF-alpha) is capable of inducing 3-D cytomorphologic differentiation of anaplastic thyroid carcinoma cells, and, if so, to investigate the mechanism involved. METHODS: Anaplastic thyroid carcinoma cells were treated with TNF-alpha and examined for evidence of cytomorphologic differentiation using electron microscopy. To study the mechanism of differentiation, immunoblotting was used to analyze inhibitory kappaB (I-kappaB) proteins and electrophoretic mobility shift assays to analyze nuclear factor kappaB (NF-kappaB) activation. The effect of NF-kappaB SN50, a NF-kappaB translocation inhibitor, on cytomorphologic changes induced in anaplastic thyroid carcinoma cells by TNF-alpha also was studied. In addition, levels of thyroglobulin and vascular endothelial growth factor (VEGF) secreted into the culture medium were measured. RESULTS: The results showed that TNF-alpha can induce activation of NF-kappaB and that the activation and translocation of NF-kappaB into the nucleus is responsible for promoting the 3-D cytomorphologic differentiation of anaplastic thyroid carcinoma cells, which was inhibited by the NF-kappaB translocation inhibitor, NF-kappaB SN50. TNF-alpha also induced increased thyroglobulin secretion andreduced VEGF secretion by anaplastic tumor cells.

CONCLUSIONS: The current data suggest that TNF-alpha can induce thyrocyte differentiation in anaplastic thyroid carcinoma cells through NF-kappaB and that it merits investigation as differentiation therapy for the treatment of patients with anaplastic thyroid carcinoma. The authors also found that microvilli were useful markers for studying thyrocyte differentiation in anaplastic thyroid carcinoma cells. Cancer 2002;95:1827-33..