Iodine-131 dose-dependent gene expression: alterations in both normal and tumor thyroid tissue of post-Chernobyl thyroid cancers

M. Abend[1], R. M. Pfeiffer[2], C. Ruf[1], M. Hatch[3], T. I. Bogdanova[4], M. D. Tronko[4], J. Hartmann[1], V. Meineke[1], K. Mabuchi[3], and A. V. Brenner[3]

[1]Bundeswehr Institute of Radiobiology, Neuherbergstr. 11, 80937 Munich, Germany
[2]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, NCI, 6120 Executive Plaza South, Bethesda, Maryland 20892-7238, USA
[3]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI, , 6120 Executive Plaza South, Bethesda, Maryland 20892-7238, USA
[4]State Institution "V.P.Komissarenko Institute of Endocrinology and Metabolism of Academy of Medical Sciences of Ukraine", 69 Vyshgorodskaya str., 254114 Kiev, Ukraine

Abstract

Background

A strong, consistent association between childhood irradiation and subsequent thyroid cancer provides an excellent model for studying radiation carcinogenesis.

Methods

We evaluated gene expression in 63 paired RNA specimens from frozen normal and tumor thyroid tissue with individual iodine-131 (I-131) doses (0.008-8.6 Gy, no unirradiated controls) received from Chernobyl fallout during childhood (Ukrainian-American cohort). Approximately half of these randomly selected samples (32 tumor/normal tissue RNA specimens) were hybridized on 64 whole genome microarrays (Agilent, 4x44K). Associations between I-131 dose and gene expression were assessed separately in normal and tumor tissue using Kruskal-Wallis and linear trend tests. Of 155 genes significantly associated with I-131 after Bonferroni correction and with ≥ 2 fold increase per dose category, we selected 95 genes. On the remaining 31 RNA samples these genes were used for validation purposes employing qRT-PCR.

Results

Expression of 8 genes (ABCC3, C1orf9, C6orf62, FGFR1OP2, HEY2, NDOR1, STAT3, UCP3) in normal tissue and 6 genes (ANKRD46, CD47, HNRNPH1, NDOR1, SCEL, SERPINA1) in tumor tissue was significantly associated with I-131. PANTHER/DAVID pathway analyses demonstrated significant overrepresentation of genes coding for nucleic acid binding in normal and tumor tissue and for p53, EGF, FGF signaling pathways in tumor tissue.

Conclusions

The multistep process of radiation carcinogenesis begins in histologically normal thyroid tissue and may involve dose-dependent gene expression changes.