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Short Communication

Thyroid non-Hodgkin's lymphoma expression pattern of nuclear retinoid and rexinoid receptor subtypes

Julius Brtko[1], Dana Macejova[1] and Stefan Galbavy[2,3]

[1] *Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia*
[2] *Institute of Laboratory Medicine, St. Elizabeth University of Health and Social Sciences and St. Elisabeth Institute of Oncology, Bratislava, Slovakia*
[3] *Institute of Forensic Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia*

Thyroid non-Hodgkin's lymphoma (TNHL) is an uncommon tumour, representing 2–8% of thyroid malignancies and approximately 1–2% of extranodal lymphomas. TNHL is a relative rare, and it occurs most frequently in elderly women and has been linked to Hashimoto's thyroiditis. The female preponderance is due to its origin from chronic lymphocytic thyroiditis, which tends to occur in elderly women (Evans et al. 1995; Harrington et al. 2005). A number of controversies exist regarding the roles of surgery, radiotherapy and chemotherapy in the management of this disease (Ha et al. 2001). Surgery occupied a pre-eminent place in management of TNHL, in recent years, the appreciation that TNHL is sensitive to radiotherapy and chemotherapy has resulted in a move towards limited number of surgical interventions (Harrington et al. 2005).

Retinoids, rexinoids and their biologically active derivatives are involved in a complex arrangement of physiological and developmental responses in many tissues of higher vertebrates. Both retinoids and rexinoids are either natural or synthetic compounds related to retinoic acids that act through interaction with two basic types of nuclear receptors belonging to the nuclear receptor superfamily: all-*trans* retinoic acid receptors, known as nuclear retinoid receptors (RARα, RARβ, and RARγ) and retinoid X receptors (RXRα, RXRβ and RXRγ) play a crucial role in both physiological and pathophysiological conditions as retinoid-inducible transcription factors (Brtko et al. 2009). Retinoids inhibit carcinogenesis, suppress premalignant epithelial lesions and tumour growth and invasion in a variety of tissues. Natural and synthetic retinoids exert important biological effects due to their antiproliferative and apoptosis-inducing effects. They are also known to cause redifferentiation or to prevent further dedifferentiation of various tumour tissues (Brtko and Thalhamer 2003; Brtko 2007). Acute promyelocytic leukemia (APL), characterized by its distinctive FAB-M3 morphology and its association with a bleeding coagulopathy, is known to be associated with at least four types of non-random reciprocal chromosomal translocation, but always involving the retinoic acid receptor α gene (RARα) on chromosome 17. The majority of APL patients with the promyelocytic gene-RARα fusion 21 and the rare cases of the nucleophosmin gene-RARα fusion 22 respond to retinoic acid-induced differentiation therapy; however, APL patients with the promyelocytic leukemia zinc finger gene-RARα fusion are unresponsive (So et al. 2000).

Here, we report the case of a 67-year-old woman in Slovakia who was admited to the Saint Elizabeth Institute of Oncology in Bratislava with a neck stiffness. Magnetic resonance demonstrated thyroid neoplasia with the size of 52 × 63 × 90 mm. The pathological examination after surgery confirmed TNHL of unspecified origin. The patient after tyreoidectomy underwent radiation therapy with the total dose of 60.0 Gy. TNHL tissue from this patient has been analyzed in order to get information about expression of all known subtypes of nuclear retinoid and nuclear retinoid X receptors mediating the effects of retinoic acids at the nuclear/cellular level. Determination of mRNA levels encoding all isoforms of nuclear retinoid receptors (RARα, RARβ, RARγ) and nuclear retinoid X receptors (RXRα, RXRβ, RXRγ) has been performed by the reverse transcription and subsequent PCR analyses by previously established protocols in this laboratory (Szabova et al. 2003). The band intensities were measured using the STS 6220I Documentation System (Ultralum, USA) and normalized to the band intensity of PCR product corresponding to the house keeper gene GAPDH (Fig. 1).

As shown in Fig. 1, the TNHL tissue excised from the patient thyroid expressed all isoforms of RARs or RXRs.

Correspondence to: Julius Brtko, Laboratory of Molecular Endocrinology, Institute of Experimental Endocrinology, Centre of Excellence Acknowledged by the European Commission, Slovak Academy of Sciences, Vlárska 3, 833 06 Bratislava, Slovakia
E-mail: julius.brtko@savba.sk

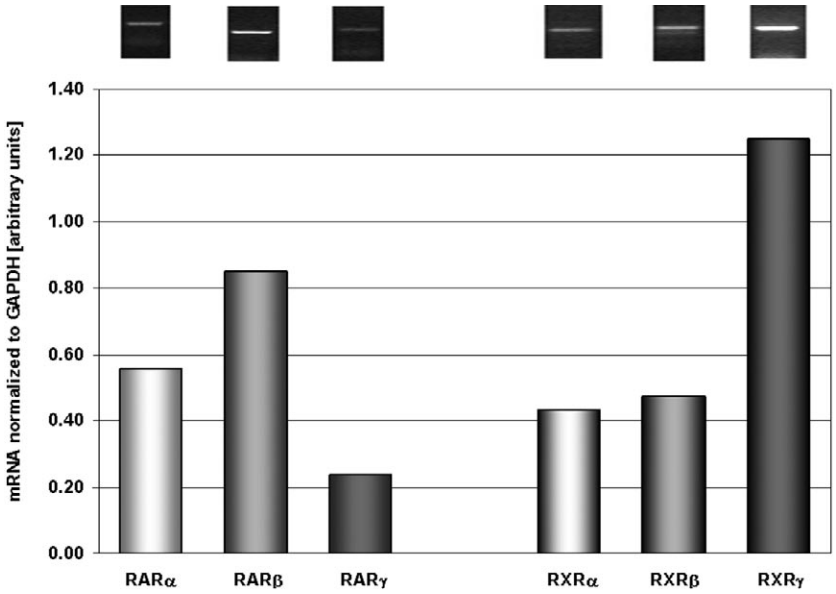

Figure 1. Expression of nuclear retinoid receptors (RARα, RARβ, RARγ) and nuclear retinoid X receptors (RXRα, RXRβ, RXRγ) in the unspecified thyroid non-Hodgkin's lymphoma.

The RXRγ isoform is not expressed in normal thyroid tissue but was found to be highly expressed in a subset of human thyroid carcinoma cell lines and tissues. Expression of RARβ and RXRγ in thyroid carcinomas seems to predict response to retinoids and/or rexinoids in tumour redifferention therapy (Haugen et al. 2004). Our data has shown that in the TNHL tissue from all-*trans* retinoic acid receptors, RARβ is the most expressed isoform of RARs. In contrast to normal thyroid tissue lacking to express RXRγ, TNHL tissue was found to highly express that isoform of RXRs. Since both nuclear retinoid and rexinoid receptors play a role as ligand-activated, DNA-binding, trans-acting, transcription-modulating proteins involved in a general molecular mechanism responsible for transcriptional responses in target genes, retinoids and/or rexinoids might probably thus represent a possible alternative to established treatments of TNHL.

Ethics approval: The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from the patient prior to sample collection for research with residual tumour tissue.

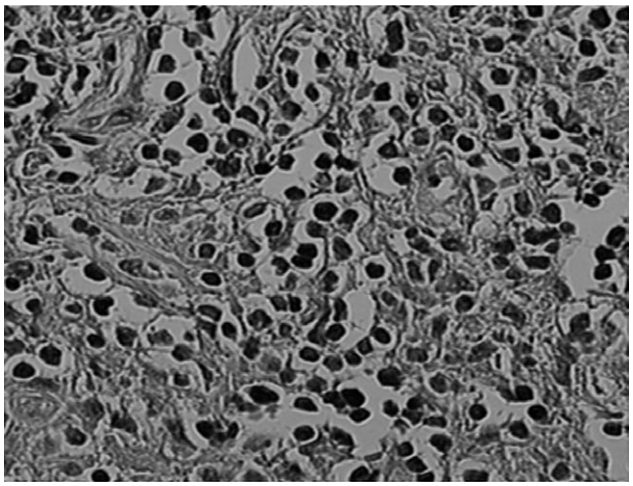

Figure 2. Histologic pattern of the unspecified thyroid non-Hodgkin's lymphoma. (H&E; magnification: ×200)

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References

Brtko J., Thalhamer J. (2003): Renaissance of the biologically active vitamin A derivatives: established and novel directed therapies for cancer and chemoprevention. Curr. Pharm. Des. **9,** 2067–2077; doi:10.2174/1381612033454144

Brtko J. (2007): Retinoids, rexinoids and their cognate nuclear receptors: character and their role in chemoprevention of selected malignant diseases. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc, Czech Repub. **151,** 187–194; PMid:18345250

Brtko J., Sejnová D., Ondková S., Macejová D. (2009): Malignant Triton tumour exhibits a complete expression pattern of nuclear retinoid and rexinoid receptor subtypes. Gen. Physiol. Biophys. **28,** 425–427; doi:10.4149/gpb_2009_04_425

Evans T. R., Mansi J. L., Bevan D. H., Dalgleish A. G., Harmer C. L. (1995): Primary non-Hodgkin's lymphoma of the thyroid with bone marrow infiltration at presentation. Clin. Oncol. **7,** 54–55; doi:10.1016/S0936-6555(05)80639-9

Ha C. S., Shadle K. M., Medeiros L. J., Wilder R. B., Hess M. A., Cabanillas F., Cox J. D. (2001): Localized non-Hodgkin lymphoma involving the thyroid gland. Cancer **91,** 629–635; doi:10.1002/1097-0142(20010215)91:4<629::AID-CNCR1045>3.0.CO;2-Q

Harrington K. J., Michalaki V. J., Vini L., Nutting C. M., Syrigos K. N., A'Hern R., Harmer C. L. (2005): Management of non-Hodgkin's lymphoma of the thyroid: the Royal Marsden Hospital experience. Br. J. Radiol. **78,** 405–410; doi:10.1259/bjr/31803121

Haugen B. R., Larson L. L., Pugazhenthi U., Hays W. R., Klopper J. P., Kramer C. A., Sharma V. (2004): Retinoic acid and retinoid X receptors are differentially expressed in thyroid cancer and thyroid carcinoma cell lines and predict response to treatment with retinoids. J. Clin. Endocrinol. Metab. **89,** 272–280; doi:10.1210/jc.2003-030770

So C. W., Dong S., So C. K. C., Cheng G. X., Huang Q. H., Chen S. J., Chan L. C. (2000): The impact of differential binding of wild-type RARα, PML-, PLZF- and NPM-RARα fusion proteins towards transcriptional co-activator, RIP-140, on retinoic acid responses in acute promyelocytic leukemia. Leukemia **14,** 77–83; doi:10.1038/sj.leu.2401643

Szabova L., Macejova D., Dvorcakova M., Blazickova S., Zorad S., Walrand S., Cardinault N., Vasson M-P., Rock E., Brtko J. (2003): Expression of nuclear retinoic acid receptors in peripheral blood mononuclear cells (PBMC) of healthy subjects. Life Sci. **72,** 831–836; doi:10.1016/S0024-3205(02)02307-X

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