The rest of the cellular types, independently from the lesions in which they are detected, retain heterozygosity at this locus. The LOH frequency in follicular lesions increases along with neoplastic transformation and the minimal common deleted region (MCDR) identified was localized at 7q21.2 (Trovato et al., 2004). These results suggest that a putative oncosuppressor gene might be localized around this genetic locus and support the true importance of a cellular distinction in the research of oncosuppressor genes or in the evaluation of the molecular alterations affecting thyroid tumors.

2

Analysis of the role of p53 and Galectin-3 in proliferation and apoptosis of thyroid carcinoma cell lines by specific RNA interference experiments

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P53 is an oncosuppressor gene mutated in 50% of human carcinomas. In human thyroid tumors p53 mutations are mainly encountered in anaplastic thyroid carcinomas (ATC) and are associated with a poor prognosis. Galectin-3 (Gal-3) is an antiapoptotic factor, proposed as a marker of thyroid malignancy. RNA interference (RNAi) is a rapidly emerging and powerful technique used to investigate gene function by degrading a specific mRNA target in a cell and thus knocking out or knocking down the levels of the encoded protein.

Recently, we demonstrated that wt p53 downregulates Gal-3 expression through an inhibitory effect at the promoter level and to study the role of these two factors in proliferation of human thyroid carcinoma cell lines using RNAi technique. Gal-3 expression was analyzed by Western blotting in 12 thyroid carcinoma cell lines (4 PTC-derived, 2 FTC-derived, and 6 ATC-derived), harboring different p53 mutations, and in the wt p53-expressing TPC-1 cell line, used as control. Gal-3 was overexpressed in all cell lines expressing a mutated p53, compared to TPC-1 control cells.

RNA interfering of mutated p53 (p53R273H) expression in ARO cells, caused a reduction of Gal-3 protein levels. Conversely overexpression of p53R273H in the TPC-1 cell line caused a significant increase of Gal-3 protein levels.

To understand the specific role exerted by mutated p53 and Gal-3 in proliferation of human thyroid carcinoma cells we stably interfered separately the expression of p53 and Gal-3 in ARO cells. Colony assay shows that interference of Gal-3 expression causes a dramatic reduction of proliferation of ARO cells. This effect is stronger than that observed in ARO cells interfered for mutated p53.

In conclusion, our results demonstrate that mutations of p53 not only loose the ability to repress promoter activity of Gal-3, but they acquire the de novo ability to stimulate the expression of this antiapoptotic factor. Moreover our RNAi experiments indicate that Gal-3 play a important role in proliferation of human thyroid cells suggesting that Gal-3 overexpression due to p53 mutations may represent a relevant event in the progression of anaplastic thyroid tumors.

3

Progress in the preoperative diagnosis of thyroid nodules: managing uncertainties and the ultimate role for molecular investigation

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The preoperative evaluation of thyroid nodules currently relies on a clinical assessment of risk factors and an algorithm based on imprecise tests. With serum TSH, thyroid ultrasound and ultrasound-guided fine needle aspiration (UG-FNA) accounting for the routine initial evaluation, indeterminate aspirates incite controversy and remain the major obstacle for confidently advising patients whether to have surgery or not. Another important controversy is whether the decision to perform an UG-FNA is based on thyroid nodule size or ultrasound appearance. Recent clinical guidelines have attempted to settle these and other controversies but many inherent errors of clinical testing result in delayed diagnosis and unnecessary surgery. A better solution may ultimately involve the use of molecular markers of thyroid carcinogenesis. Prime molecular markers to elucidate the nature of thyroid nodules include BRAF mutations, RET/PTC1 rearrangements and galec–

3/CD44v6 immunodetection for papillary thyroid cancer (PTC), PAX8-PPARY rearrangements for follicular variant of PTC and follicular thyroid cancer, and abnormalities in mitochondrial DNA for malignant Hürthle cell tumors. Coordinating UG-FNA with these molecular studies offer great promise but further research is still needed regarding the basic biology of thyroid cancer.