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Commentary

Genetics and Clinicopathological Findings in Thyroid Carcinomas Associated with Familial Adenomatous Polyposis

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The recent paper by Soravia et al[1] describes two kindreds with thyroid carcinoma associated with familial adenomatous polyposis (FAP). The former included three and the latter two FAP siblings with papillary thyroid carcinoma (PTC). The patients had a germline mutation of APC, the tumor suppressor gene responsible for FAP,[2] at codons 698 and 313, respectively, and activation of ret/PTC, a chimeric gene that is restricted to the papillary histotype,[3] in the thyroid tumoral tissue of three out of three subjects. Interestingly, ret/PTC was always found as its most frequent isoform, ret/PTC1.[3] This commentary discusses the issues of PTC as an extracolonic manifestation that is integral to FAP, genotype-phenotype correlations, the presence or absence of somatic mutations of the APC gene in the thyroid tumoral tissue, ret/PTC activation, possible cooperation among genes, histological significance of molecular alterations, and the natural history of these particular tumors.

FAP PTC Is an Extracolonic Manifestation Integral to FAP

Thyroid carcinoma has been considered a possible extracolonic manifestation of FAP since 1949.[4,5] However, it is a rare manifestation, reported in only 1–2% of patients included in the largest FAP registries. The Leeds Castle Polyposis Group has recently reported an incidence of 1.2% of thyroid carcinoma.[6] Is this the actual incidence, or would intensive screening for this tumor detect a greater number of affected patients, as suggested by some authors?[5] In a recent review of the literature we have identified 110 patients with FAP-associated thyroid carcinoma.[7] The mean age was 27.65 years (range 15–62); the female-to-male ratio among patients with at least two siblings in the same kindred was 17:1. Papillary histotype was quite constant, even if an unusual subtype, the so-called cribriform histotype, was very frequent.[5,7] This finding suggests that the follicular histotype, which has been described in some case reports, deserves careful re-evaluation, including analysis of ret/PTC, to confirm or exclude that these patients had a papillary tumor, even if it had prominent follicular areas. The APC gene has rarely been involved in the development of sporadic thyroid tumors (1/121) and a two-hit inactivation of the APC gene has not been observed, even in patients with APC germline mutations.[7] These observations raised questions as to whether thyroid carcinoma was integral to FAP syndrome. However, familial aggregation is indisputable. In particular, the observation of two kindreds (one from Soravia,[1] one from ourselves) with three siblings,[8] in addition to the six pairs of siblings with FAP-associated thyroid carcinoma already reported, confirms that thyroid carcinoma is undoubtedly an aspect of the FAP syndrome. This view is given further support by our recent observation of three FAP kindreds with thyroid carcinoma in association with hepatoblastoma,[9] a childhood tumor that is very rare but extremely frequent in FAP (estimated greater risk >1000:1).

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Genotype-Phenotype Correlation

Many reports suggest a close relationship between the site of APC mutation in a family and the occurrence of some extracolonic manifestations. In particular, it has been reported that patients with mutations in codons 463-1387 regularly develop congenital hypertrophy of the retinal pigment epithelium,[10] whereas those with mutations in codons 1445–1578 develop desmoid tumors but lack retinal lesions.[11] Soravia et al detected in their two kindreds the specific APC germline mutations at codons 313 and 698, respectively, and therefore not in the mutation cluster region (MCR) at codons 1286–1513, where more than 60% of somatic mutations have been found.[12] Interestingly, as a result of international cooperation, we have recently shown that 22 of 24 germline mutations in patients with FAP PTC were in the 5′ portion of the APC gene, outside the MCR.[7] Only two patients had mutations at codon 1309. None had mutations in the desmoid-associated area at codons 1445–1578.[7]

Somatic APC Mutations

Soravia et al screened only the MCR, where most somatic mutations have been located, for somatic mutations. The analysis of 9 different tumor sections from 4 thyroid tumors showed a deletion of 205 bp and a concomitant insertion of 160 bp between APC nucleotides 4366 and 4571 (codons 1455–1523) in the unusual patient with an aggressive tumor, which also had a p53 mutation. On the contrary, they did not find any somatic APC mutation in the other tumors. These data are in agreement with our previous findings, showing the absence of somatic APC mutations in six patients with FAP-associated thyroid carcinoma not only in the MCR, but also in the 5′ genomic area, where most of the germline mutations have been found in patients with FAP PTC.[13] This also accords with the infrequent finding of APC somatic mutations in sporadic thyroid carcinoma[7] and suggests an unusual behavior of PTC in comparison with other phenotypic manifestations of multitumoral inherited diseases, usually showing loss of heterozygosity of the basic tumor suppressor gene in the tumoral tissue. This could suggest (i) a dominant positive function, varying from tissue to tissue, analogously to what occurs in other multitumoral syndromes,[14] and/or (ii) that the APC tumor suppressor gene plays a basic role only in FAP PTC, not in sporadic PTC. In particular, in the former it could give simply a generic susceptibility to PTC that will require other cofactors for full phenotypic expression, namely modifier genes, sex-related genes (as suggested by the female-to-male ratio of 17:1), or environmental factors such as radiation.[15]

ret/PTC Activation

Soravia et al found ret/PTC activation in 3 out of 3 (of 5) patients with FAP PTC (100%). We have previously documented ret/PTC activation (always as ret/PTC1 isoform) in 4 out of 5 patients with FAP PTC.[16] This is the highest ratio of ret/PTC activation in any well defined subset of patients with PTC, even higher than that reported in children from Belarus after the Chernobyl nuclear accident (67–87%).[17] Interestingly, the data from Soravia et al confirm that, in contrast to Belorussian children, who usually showed the ret/PTC3 isoform,[17] ret/PTC1 was the constant isoform in FAP, detected in seven of seven patients (three by Soravia and four by ourselves). The only patient who, in addition to ret/PTC1 positivity, also had focal positivity for ret/PTC3, was patient III 11, kindred no. 1, who also had nuclear positivity for p53 and thyroid cancer recurrence 17 years after the initial removal of the thyroid tumor.[1] (Soravia et al report that neither of the patients with a recurrence had a total thyroidectomy as the initial operation.)

Cooperation Among Genes

We have suggested that there may be interaction between germline APC mutation and ret/PTC activation in the development of thyroid cancer in FAP patients.[16,18] We were cautious in our statement that loss of function of APC cooperates with ret/PTC in thyroid tumorigenesis, because the coexistence of alterations of these two genes in the same individual does not necessarily mean that they cooperate in the multistep process of carcinogenesis.[5,16] Soravia et al confirm the hypothesis that "genetic alterations in FAP-associated thyroid cancer involve loss of function of APC along with the gain of function of ret/PTC," also confirming that "alterations of p53 do not appear to be an early event in thyroid tumorigenesis."[1] However, Soravia et al raise a number of questions in their paper that are very important not only for the specific topic of thyroid carcinogenesis in patients with adenomatous polyposis, but also for mutual relationships and cooperation among genes and/or environmental factors, including tissue-specific cooperation of a tumor suppressor gene with different genes, sometimes mutually exclusive of each other, in different tissues of the same individual. It seems that, in the same kindred, a given germline APC mutation influences the occurrence of the tumoral phenotype in a way that differs according to the tissue of origin of the tumor. For instance, APC cooperates with ras and p53 for colonic polyps and cancer, and with p53 (but not with ras) for the occurrence of liver adenomas and carcinomas. In particular, ras activation and ret/PTC activation seem to be mutually exclusive in the progression of tumorigenesis in the thyroid tissue, the former restricted to the follicular histotype, the latter specific for the papillary one. The accumulated data strongly suggest that in the same individual, germline APC mutations cooperate with ras for the progression of colonic polyps to carcinoma, whereas they cooperate with ret/PTC, but not with ras, for the occurrence of thyroid carcinoma.[19] Therefore, the mutagenic stimulus for neoplastic proliferation varies from one tissue to another in the same patient, leading to the activation of oncogenes that are both tissue-specific and stimulus-related.[2,5]

Natural History of FAP-Associated Thyroid Carcinoma

On the basis of the cumulative findings in the literature, FAP PTC seems to be characterized by an unusual female preponderance, age at tumor diagnosis <30 years, and papillary differentiation (>95%). Despite frequent multicentricity and early lymph nodal involvement, FAP PTCs seem to be relatively indolent tumors.[2] All thyroid tumors associated with ret/PTC1 activation had a good prognosis.[5] Most of the 110 patients with FAP-associated tumors reported in the literature did not produce distant metastases, and the patients had a mean survival of >15 years without recurrence.[5,19]

The paper by Soravia et al is the first to give long-term information on follow-up of FAP PTCs, which included detection of both germline mutation of the APC gene and ret/PTC activation. On the basis of these observations, it seems important to screen for focal activation of ret/PTC3 in patients with tumor recurrence. These data suggest possible late recurrence, namely in patients with both ret/PTC1 and ret/PTC3 activation and concomitant p53 mutation. A different biological behavior has been proposed for ret/PTC1 and ret/PTC3.[19,20] If further confirmed, it may suggest that constitutive activation of ret in FAP PTCs determines a different carcinogenetic pathway, according to the different fused gene, with ret/PTC1 possibly having the better and ret/PTC3 the worse prognosis.[19,20]

Conclusion

FAP-associated PTC seems to be a specific type of thyroid carcinoma with a peculiar histological aspect that probably reflects cooperation among carcinogenetic genes different from that occurring in sporadic tumors. Recent findings have contributed to highlighting some aspects, but several questions still remain unanswered. However, due to the rarity of this extracolonic manifestation of FAP, only international multicenter cooperation, analyzing in detail the same genetic alterations in a sufficiently large number of patients, will give a better insight into FAP-associated thyroid carcinoma.

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