Nodulogenesis and goitrogenesis

R. Paschke
Department for Endocrinology and Nephrology, University of Leipzig, Liebigstrasse 20, 04103 Leipzig, Germany
Available online 20 April 2011

Résumé
La goitrogenèse est la conséquence d’un déficit relatif en iode qui interagit avec une prédisposition génétique d’inadaptation au déficit iodé. À long terme, la déficience en iode majore la production d’H\textsubscript{2}O\textsubscript{2} qui favorise les mutagenèses, avec pour conséquence l’apparition de mutations somatiques, et de ce fait de nodules thyroïdiens.

© 2011 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Mutations somatiques ; H\textsubscript{2}O\textsubscript{2} ; Mutagenèse ; Déficit iodé ; Goiter ; Nodules

Abstract
Goitrogenesis is the consequence of a relative iodine deficiency interacting with a genetic predisposition for maladaptation to iodine deficiency. In the long run, the iodine deficiency induces increased H\textsubscript{2}O\textsubscript{2} production that leads to an increased mutagenesis, resulting in somatic mutations with a proliferative advantage and thus the induction of thyroid nodules.

© 2011 Elsevier Masson SAS. All rights reserved.

Keywords: Somatic mutations; H\textsubscript{2}O\textsubscript{2}; Mutagenesis; Iodine deficiency; Goiter; Nodules

The heterogenous thyroid disorder benign nodular thyroid disease is highly prevalent in iodine deficient areas. It can be divided into solitary nodular and multinodular thyroid disease. Histologically, benign thyroid nodules are distinguished as (1) encapsulated lesions (true adenomas) or adenomatous nodules, which lack a capsule, and (2) by morphological criteria according to the WHO classification [1]. On functional grounds, nodules are classified as either “cold”, “normal” or “hot” depending on whether they show decreased, normal or increased uptake on scintiscan. Approximately 50–85% of all nodules are “cold”, up to 40% are scintigraphically indifferent and about 10% are “hot” [2,3], although the prevalence will vary geographically with the ambient iodine supply and with the clinical setting [4,5].

In contrast to solitary nodular thyroid disease, which has a more uniform clinical, pathologic and molecular picture, multinodular nontoxic goiter (MNG) and multinodular toxic goiter (MNTG) are a mixed group of nodular entities. Thus a combination of hyper-, hypo- or normally functioning thyroid lesions are usually found within the same thyroid gland. The overall balance of functional properties of individual thyroid nodules within a multinodular goiter ultimately determines the functional status in the individual patient, which may be euthyroidism (normal TSH and free thyroid hormone levels), subclinical hyperthyroidism (low or suppressed TSH and normal free thyroid hormone levels) or overt hyperthyroidism (suppressed TSH and elevated free thyroid hormone levels).

Until recently, nontoxic goiter was mainly regarded as a consequence of iodine deficiency. However, a number of goitrogens [6,7] and cigarette smoking are important environmental risk factors in the etiology of nontoxic goiter. Especially, the impact of smoking, most likely mediated by thiocyanate, which competitively inhibits the iodide transport into the thyroid, has been extensively studied [6,8]. Additional etiologically important factors are gender [9,10], age [11] and increased body mass index (BMI) [12]. The effect of a certain goitrogen is influenced by the degree of iodine sufficiency and therefore varies regionally and interindividually. However, it is most likely that interactions between environmental factors and individual genetic determi-
nants ultimately determine the onset of the goiter [9]. Nontoxic goiter appearing early in life, often clustering in families, suggests strong genetic susceptibility whereas the environmental determinants are more likely to have additive or triggering effects. However, in an individual it may be impossible to evaluate the relative contribution of genetic predisposition and a multitude of potential environmental factors.

In contrast to sporadic goiters, caused by spontaneous recessive genomic variations, most cases of familial goiter present an autosomal dominant pattern of inheritance, indicating predominant genetic defects [13–16]. Gene–gene interactions or various polygenic mechanisms (i.e. synergistic effects of several variants or polymorphisms) could increase the complexity of the pathogenesis of nontoxic goiter and offer an explanation for its genetic heterogeneity. A strong genetic predisposition is indicated by family and twin studies. Thus, children of parents with goiter have a significantly higher risk of developing goiter compared with children of nongoitrous parents [17]. The high incidence in females and the higher concordance in monozygotic than in dizygotic twins also suggest a genetic predisposition [9]. Moreover, there is preliminary evidence of a positive family history for thyroid diseases in those who have postoperative relapse of goiter, which can occur from months to years after surgery [18,19].

A first genome-wide linkage analysis has identified a candidate locus, MNG1 on chromosome 14q31, in a large Canadian family with 18 affected individuals [15]. This locus was confirmed in a German family with recurrent euthyroid goiters [20]. A dominant pattern of inheritance with high penetrance was assumed in both investigations. Moreover, a region on 14q31 between MNG1 and the TSHR gene was identified as a potential positional candidate region [20] for nontoxic goiter. However, in the earlier study by Bignell et al. [15] the TSHR gene was clearly excluded. Furthermore, an X-linked autosomal dominant pattern and linkage to a second locus MNG2 (Xp22) was identified in an Italian pedigree with nontoxic familial goiter [21]. To identify further candidate regions, the first extended genome-wide linkage analysis was performed to detect susceptibility loci in 18 Danish, German and Slovakian euthyroid goiter families [13]. Four novel candidate loci on chromosomes 2q, 3p, 7q and 8p were identified. An individual contribution was attributable to four families for the 3p locus and to one family to each of the other loci, respectively. On the basis of the previously identified candidate regions and the established environmental factors, nontoxic goiter can consequently be defined as a complex disease. For the first time a more prevalent putative locus, present in 20% of the families investigated, was identified [13,14].

Most goiters become nodular with time. From animal models of hyperplasia caused by iodine depletion [22], we have learned that besides an increase in functional activity a tremendous increase in thyroid cell number occurs. These two events very likely orchestrate a burst of mutation events. It is known that thyroid hormone synthesis goes along with increased H2O2 production and free radical formation [23], which may damage genomic DNA and cause mutations. Together with a higher spontaneous mutation rate, a higher replication rate will more often prevent mutation repair and increase the mutation load of the thyroid, thereby also randomly affecting genes crucial for thyrocyte physiology. Mutations that confer a growth advantage (e.g. TSHR or Gsa protein mutations) very likely initiate focal growth [23,24]. Hence, autonomously functioning thyroid nodules (AFTNs) are likely to develop from small cell clones, that contain advantageous mutations as shown for the TSHR in “hot” microscopic regions of euthyroid goiters [25].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


