SUMMARY

The human and mouse genome databases have provided powerful tools to probe many unanswered questions in thyroidology. Mechanistic knowledge regarding thyroid development, thyroid gland regulation by hypothalamic-pituitary function, thyroid hormone transport and action, thyroid autoimmunity and genetics, and thyroid oncogenesis have expanded enormously using molecular genetics. This basic information is providing the foundation for new clinical approaches to the diagnosis and therapy of thyroid disorders. For example, old dogma regarding the transport of thyroid hormones into cells being mediated by passive diffusion is being discarded as knowledge of new small molecule transporters has been discovered and related to human disease. The genetic basis for autoimmune thyroid disease is being unraveled by discovery of genetic variations associated with risk for autoimmune disease and important molecules in the disorder's pathogenesis. The translation of basic molecular genetic knowledge into clinical care is no better illustrated than in thyroid cancer, in which genetic mutations in molecules of the MAPK pathway have been shown to account for more than 70% of papillary thyroid cancers. Furthermore, certain mutations may predict clinical outcomes, such as cancer recurrence. The new molecular understanding of thyroid cancer causation is now opening a new therapeutic frontier as drugs are developed that modulate the MAPK pathway.

COMMENT

It is not customary for us to write commentaries on ‘reviews’ and ‘updates’ published in the literature. This update, however, is an exception worthy of a comment. From the beginning of 2006 to mid-2007, ~2,000 manuscripts dealing with the ‘thyroid’ have appeared in the medical literature. Thyroid cancer is on top of the list (~600) followed by hypothyroidism, hyperthyroidism, and thyroid genetics (~350 each).

Subclinical hypothyroidism (SCH) and cardiovascular risk: since 2001, there has been an increasing number of studies that have contributed important new information on the impact of SCH and the value of treating it (in contrast with the view of prior consensus panels). One important recent study showed that the administration of L-thyroxine to patients with a mild elevation in serum TSH yielded a significant improvement in total and LDL-cholesterol, as well as in flow-mediated dilation of arteries (see JCEM 92:1715, 2007).

Thyroid hormone transport: thyroid hormones are actively transported into cells and do not diffuse passively through cell membranes. Some tissues have a wide array of transporters (liver), whereas in other tissues the transport is largely mono-specific (brain). The discovery of thyroid hormone transporters has allowed to elucidate rare genetic disorders (such as the Allan-Herndon-Dudley syndrome of X-linked mental retardation, known - but not
understood - since 1944) by the demonstration of mutations (or deletion) in the MCT8 transporter (see Am J Hum Gen 74:168, 2004).

**Genetics of thyroid autoimmunity:**
There is now mounting epidemiological evidence for a major genetic influence on the development of AITD. To date, six genes have been shown to contribute to the development of AITD: CD40 (a member of the TNF-R receptor family expressed on B lymphocytes and other antigen-presenting cells), CTLA-4, HLA-DR, protein tyrosine phosphatase-22, Tg, and TSH receptor.

**Thyroid cancer:** One intriguing new finding is the association between serum TSH levels and the risk of thyroid cancer. In a recent study (see JCEM 91:4295, 2006), it was shown that the higher the basal TSH level, the more likely a nodule would be malignant. Another study also showed that the rate of recurrence (as well as mortality) was associated with higher serum TSH levels (see Thyroid 16:129, 2006). Explanations for such associations are not obvious, but one could consider that the chronic growth-stimulating action of TSH on thyrocytes might be directly implicated. Concerning the molecular pathogenesis of papillary cancer, much attention has been recently devoted to BRAF and the MAP kinase cascade. BRAF is mutated in approximately 45% of papillary thyroid cancers. Furthermore, when BRAF mutation is present, the cancers are more advanced (at diagnosis) and more aggressive. In brief, a cancer that harbours BRAF mutation is about twice as likely to show extra-thyroidal invasion, lymph node metastases, and advanced stage 3 or 4 disease.

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