HIGHLIGHTS

Thyrotropin receptor mutations in hyperfunctioning thyroid adenomas: new mutants, new second messenger and new frequency

Jérôme Bertherat
Service d'Endocrinologie, INSERM CFF 92-08, CHU Cochin, Paris, France

Activation of the cAMP pathway by TSH stimulates both cell proliferation and differentiation of thyrocytes. TSH is known to bind to a seven transmembrane receptor, coupled to heterotrimeric G proteins. Adenylate cyclase activity is increased by TSH through activation of Gs. But the human TSH receptor also activates the phospholipase C-diacylglycerol-inositol phosphate cascade. Hyperfunctioning thyroid adenomas are monoclonal and their growth and functional activity are TSH-independent. Therefore, somatic activating mutations in genes encoding proteins of the TSH signaling pathway (mainly the cAMP-regulatory cascade) were expected in these tumors. GoS activating mutations leading to TSH-independent constitutive adenylate cyclase activity were the first to be described. More recently, activating point mutations of TSH receptor were reported. The mutations studied initially cause constitutive activation of the cAMP-regulatory cascade only, without stimulation of the inositol phosphate-diacylglycerol one. The effect of TSH receptor and GoS mutations is dominant. TSH receptor activating mutations have been found in sporadic hyperfunctioning thyroid adenomas, in autosomal dominant non-autoimmune hyperthyroidism and in a sporadic case of congenital non-autoimmune hyperthyroidism (1, 2, 3). These mutations are somatic in sporadic tumors, while they are germline in the other cases.

The report by Parma et al. (1) now extends their previous studies on TSH-receptor mutations in sporadic toxic thyroid adenomas. This study is the first extensive report including the complete sequence of the tenth exon of the TSH receptor in these tumors. DNA from 11 tumors was sequenced and activating mutations were found in 9 of them. The activating mutations of the TSH receptor previously identified are located in the third intracellular loop, and in the third, sixth and seventh transmembrane segments. With this complete sequencing approach, three new mutations have been identified in three different tumors. They are located in the first and second extracellular loop of the TSH receptor (Ile486 mutated to Phe or Met and Ile488 mutated to Thr). These mutations are heterozygous and somatic (i.e. not found in the normal tissue from the same patient). Interestingly, these mutated receptors not only exhibit almost maximal intracellular cAMP accumulation in the absence of TSH stimulation, but also activate the inositol phosphate-diacylglycerol cascade. Transfection of these mutants in Cos-7 cells showed increased basal intracellular inositol phosphate levels, the Ile486 Phe mutant being the most active. Phospholipase C-dependent pathway activation by these new mutants might simply be explained by their very strong activity. Indeed, in human thyrocytes, higher TSH concentrations are required to stimulate inositol phosphate than cAMP accumulation. On the other hand, it could also be related to qualitative differences of the first and second extracellular loop mutants. Nevertheless, this raises the interesting issue of the role of the inositol phosphate-diacylglycerol cascade in the pathophysiology of hyperfunctioning thyroid adenomas. It remains to be determined whether the phenotype of the tumors harboring the mutations that activate both cAMP and phospholipase C-dependent cascades will turn out to be different. The other intriguing observation is that a large number of residues, with variable distribution over at least six different segments or loops, have already been found mutated in activated TSH receptors. Further studies on the structure and function of the TSH receptor will probably explain how these residues act to keep the receptor inactive. Finally, this study establishes clearly that TSH-receptor molecular defects are present in the majority (about 80%) of hyperfunctioning tumors of the thyroid. Along with GoS mutation, this could now explain constitutive adenylate cyclase activation in almost all the hyperfunctioning thyroid adenomas.

References

1. Parma J, Van Sande J, Swillens S, Tonacchera M, Dumont J, Vaesart G. Somatic mutations causing constitutive activity of the thyrotropin receptor are the major cause of hyperfunctioning thyroid adenomas: identification of additional mutations activating both the cyclic adenosine 3',5'-monophosphate and inositol phosphate-Ca2+ cascades. Mol Endocrinol 1995;9:725–33

Jérôme Bertherat, Service d'Endocrinologie, INSERM CFF 92-08, CHU Cochin. 27 Rue du Fg-St-Jacques, F-75014 Paris, France