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Editorial

Expression of somatostatin receptors may guide the use of somatostatin receptor imaging and therapy in differentiated thyroid cancer

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Thyroid carcinoma is the most frequent type of endocrine tumour. Most differentiated thyroid cancers (DTCs) have an excellent prognosis if diagnosed early and treated appropriately. Nevertheless, a number of patients with DTCs do not achieve remission after thyroidectomy and subsequent radioiodine administration, showing local or metastatic disease unresponsive to radioiodine treatment because of lack of radioiodine uptake by the dedifferentiated tumour cells.[1] Therefore, other therapeutic strategies could be helpful for metastatic DTCs refractory to radioiodine, for example, novel treatment options using radiolabeled somatostatin analogues. The rationale for somatostatin-based treatment should be the expression of somatostatin receptors in thyroid tumour cells, which allows diagnostic imaging and therapy by using radiolabeled somatostatin analogues.[2,3] The majority of currently available somatostatin analogues for diagnosis and therapy show a high binding affinity for somatostatin receptor subtype 2.[2]

Key words: Differentiated thyroid cancer, Endocrine tumors, Imaging, Nuclear medicine, Somatostatin analogues, Somatostatin receptors, Therapy

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Some studies assessed the expression of somatostatin receptors in thyroid tumours, in particular medullary thyroid carcinomas.[4] Results of somatostatin receptor detection in other thyroid diseases like DTCs are still scarce and often controversial, depending on the investigational method used (Table 1).[5-11]

In their article published in *Hormones*, Pazaitou-Panayiotou et al[5] have characterized the expression of somatostatin receptor subtypes in 47 cases of non-medullary thyroid carcinomas, thus providing a basis for future development of imaging and therapy with somatostatin analogues for patients with thyroid cancer who fail to respond to conventional therapies. Immunohistochemical staining was performed with five different polyclonal somatostatin receptor antibodies. These authors demonstrated that there was a high expression of all types of somatostatin receptors in human non-medullary thyroid carcinoma tissue, while the expression of somatostatin receptors was low or absent in the non-neoplastic thyroid tissue obtained from the same surgical material. Somatostatin receptor subtypes 2 and 3 appeared to be the most abundantly expressed.[5]

Immunohistochemical staining can reveal the cellular and subcellular pattern of somatostatin receptor expression. This technique has also been used in another study to demonstrate the expression of somatostatin receptor subtype 2 in different thyroid

Table 1. Expression of somatostatin receptors subtypes in non-medullary thyroid cancer: studies from the literature with more than 5 malignant thyroid tumours

Authors	Thyroid tumours evaluated	Methods	Somatostatin receptors detected
Pazaitou-Panayiotou et al 2012[5]	47 (38 PCs, 4 FCs, 2 ACs, 3 HCCs)	Immunohistochemisty for all SSTRs subtypes	SSTR 2 and 3 were expressed in all non-medullary thyroid carcinomas, SSTR 1 and 5 in 75% and SSTR 4 in 38%. The expression of SSTRs subtypes in normal thyroid tissue was low or absent.
Müssig et al 2012[7]	93 (67 PCs, 26 FCs)	Immunohistochemisty for all SSTRs subtypes	SSTR 1 to 5 were detected in 15% to almost 30% of thyroid tumours.
Sancak et al 2010[6]	17 PCs	Immunohistochemisty for SSTR 2	SSTR subtype 2 was expressed in PCs.
Klagge et al 2010[8]	45 (20 PCs, 20 FCs, 5 ACs)	mRNA expression for SSTRs	Thyroid tumours showed a predominant expression of SSTR 2 and SSTR 5, and a weak expression of SSTR 1 and SSTR 3.
Druckenthaner et al 2007[9]	17	mRNA expression for SSTRs correlated with immunochemistry for SSTR2	Thyroid tumours expressed SSTR 2, and less predominantly SSTR 3 and 5.
Forssell-Aronsson et al 2000[10]	9 PCs and 2 HCCs	mRNA expression	All thyroid tumours regularly expressed SSTR 1, 3, 4, and 5. SSTR 2 was not detected in PCs and was irregularly expressed in HCCs.
Ain et al 1997[11]	Cell lines derived from 2 PCs, 2 FCs and 4 ACs	mRNA expression for SSTRs in thyroid cancer cell lines	Most thyroid cancer cell lines expressed SSTR 3 and 5.

PCs: papillary carcinomas; FCs: follicular carcinomas; ACs: anaplastic carcinomas; HCCs: Hürthle cell carcinomas; SSTRs: somatostatin receptors.

diseases, including 17 papillary carcinomas.[6] On the other hand, in a recent study of Müssig K et al,[7] immunohistochemical analysis revealed the expression of somatostatin receptors only in one third of patients with DTC in contrast with the results of Pazaitou-Panayiotou et al,[5] underlining the fact that this topic is still controversial.

Several reports evaluated the expression of somatostatin receptors in non-medullary thyroid tumours by using mRNA analysis. Klagge et al[8] investigated the mRNA expression of different somatostatin receptor subtypes in benign and malignant thyroid tumours and compared them to normal surrounding thyroid tissues. Somatostatin receptor subtype 2 was the predominant subtype expressed in thyroid tumours (with a high expression pattern particularly in papillary carcinomas), this being in agreement with the results of the study of Pazaitou-Panayiotou et al.[5]

The discrepant findings in the literature as to somatostatin receptor expression in DTCs may result from methodological differences, such as analysis techniques (immunohistochemistry versus mRNA analysis through Northern blotting or reverse transcriptase polymerase chain reaction) and tissues analyzed (human thyroid tumour samples versus thyroid cancer cell lines) (Table 1).

Somatostatin receptor expression in DTCs may allow detection of iodine-negative tumours or metastatic disease via use of scintigraphy with somatostatin analogues labeled with Indium-111[10,12-20] or Technetium-99m,[21-23] or positron emission tomography with Gallium-68-somatostatin analogues.[2,24] So far, several studies have used somatostatin-based imaging methods with conflicting results, probably depending on the imaging protocol employed, size and site of the tumour lesions and differences in somatostatin receptor subtypes expression.

In conclusion, expression of somatostatin receptors could offer novel treatment options using somatostatin analogues labeled with Indium-111, Yttrium-90 or Lutetium-177 in the case of metastatic DTCs with deficient iodine uptake or refractory to conventional treatment, as demonstrated by some preliminary experiences.[15,25-27]

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