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Secretogranin III in human neuroendocrine tumours
A comparative immunohistochemical study with chromogranins A and B and secretogranin II

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ABSTRACT

Background: Different epitopes of the granin family of proteins, chromogranin (Cg) A, CgB and secretogranin (Sg) II, have been demonstrated in normal human pancreas, gastrointestinal tract, adrenal medulla and in several neuroendocrine tumours (NETs). SgIII has been recently reported in endocrine pancreas. The aim of the present study was to examine the expression of SgIII in different NETs and compare it with the expression of CgA, CgB and SgII epitopes.
Material and methods: Tissue specimens from 47 NETs were analyzed. Antibodies to CgA 250–284, CgB 244–255, SgII 172–186 (C-terminal secretoneurin) and SgIII 348–361 were used for immunostaining.
Results: SgIII was expressed in 41 of 47 NETs. The expression of SgIII agreed well with that of CgA, CgB and SgII, with exceptions of phaeochromocytomas, where more CgB and SgII immunoreactive cells were observed and parathyroid adenomas, which were only stained by CgA. In rectal NETs more cells expressed SgIII than CgA.
Conclusions: This is the first report on SgIII expression in various NETs. A majority of tumours studied displayed SgIII immunostaining, which indicates a functional relationship with the other granins.

1. Introduction

Granins constitute a family of acidic proteins that occur in the neuroendocrine (NE) system. The granin family comprises the chromogranins (Cgs; A and B) and secretogranins (Sgs; II–VII) which differ respectively by the presence or absence of an N-terminal disulfide-bonded loop.

CgA, the first granin studied, occurs in most NE cell types and has been used as a broad-spectrum marker for NE differentiation both in normal and neoplastic cells.

All granins contain multiple pairs of basic amino acids, which are potential cleavage sites by endogenous proteases, such as the prohormone convertases, giving rise to various smaller fragments some of them have biological activity [cf. 1].

Previous studies demonstrated that different epitopes of CgA, CgB and SgII are expressed to a varying extent in various normal NE cell types [2–5]. Different NE tumour (NET) types also express varying numbers of CgA epitopes [6–9], however, few studies of CgB and SgII epitopes in NETs have been reported [10–21].

Less well studied is the immunohistochemical expression of SgIII, which has recently been reported in pancreatic islet cells [22], but there are no reports about its occurrence in NETs. This granin is of special interest as a functional relationship between SgIII and CgA has been reported, where binding of CgA to SgIII is necessary for CgA targeting to secretory granules [23,24].

The present study was undertaken to evaluate the expression of SgIII in different NETs and compare it with the expression of CgA, CgB and SgII epitopes.

2. Material and methods

2.1. Tumours

Tissue specimens from forty-seven human NETs of different types were analyzed: lung NETs (n = 7), gastric enterochromaffin-like cell tumours (ECLomas) (n = 2), duodenal NETs (n = 3), endocrine pancreatic tumours (n = 6), ileal (n = 4), appendical (n = 3), colonic (n = 1), and rectal NETs (n = 6), medullary thyroid carcinomas (n = 4), parathyroid adenomas (n = 4) and phaeochromocytomas (n = 7).

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Table 1
Semi-quantitative grading of numbers of tumour cells displaying immunoreactivity to chromogranin (Cg) A, CgB, secretogranin (Sg) II and SgIII antibodies in various neuroendocrine tumours (NETs) (n = 47).

Granin Amino acid sequence	CgA LK2H10 250–284 [3]	CgB 244–255	SgII 172–186	SgIII 348–361
Lung NETs				
Typical carcinoids				
1	++++***	−	++++**(*)	+++*(**)
2	++++***	++++*	++++***	++++**
3	++*	−	++++**(*)	++**
4	+++**	−	++++**(*)	+**
Atypical carcinoids				
1	++++***	++++*(*)	++++**(*)	+++*
2	++++***	−	++++*(**)	++++*(*)
3	++++**	+*	++++***	++++*(**)
Gastric ECLomas Type I				
1	++++***	−	+++*	+*
2	++++***	−	+*	+*
Duodenal NETs				
1 (Somatostatinoma)	++++***	++*(*)	++**	+++*(**)
2 (Somatostatinoma)	+++***	++*	++++*(**)	++++*(**)
3 (Non-functional)	++++**(*)	+++*	++++***	++++**(*)
Islet cell tumours				
1 (calcitonin producing)	+++***	++++*(*)	+++*	−
2 (insulinoma, B)	++++***	++++**(*)	++++*(**)	++++*(**)
3 (insulinoma, M)	+++*(*)	+*	−	+++*(*)
4 (insulinoma, M)	++++***	+++*(*)	+++*(*)	+++*(*)
5 (insulinoma, M)	++++***	++++**	++++**(*)	++++***
6 (insulinoma, M)	++++***	++++*	−	+++**
Midgut carcinoids				
Ileum NETs				
1	++++***	++++*	+++*	+**
2	++++***	++++*(*)	+++*	+++*
3	++++***	+++*(*)	+++*(*)	+++*(*)
4	++++***	++++***	+++*(*)	+++*(*)
Appendix NETs				
EC-cell type				
1	++++***	+++*(**)	++*(*)	++*(*)
Goblet cell carcinoids				
2	++++***	−	−	−
3	++++***	++**	++**	+++**
Colon NET				
EC-cell type				
1	++*	+++*	+**(*)	+++*(**)
Rectal NETs				
EC-cell type				
1	++**(*)	+++***	+++***	+++**(*)
2	++*	+++*	+++***	++++***
3	+++**(*)	+++***	++++***	++++***
4	Partly − Partly +++***	+++*(*)	+++***	+++***
L-cell type				
5	−	+++*	+++**	++(+)*(*)
6	−	++*(*)	++++***	+++*(**)
Medullary thyroid carcinomas				
1	++++**	++++*	++++*(**)	++++*(**)
2	++++***	++++*	+++*(**)	++++***
3	++++***	++++*	++++*(**)	++++***
4	++++***	+++*(*)	++++*(**)	++++***
Parathyroid adenomas				
1	++++***	−	−	−
2	++++***	−	−	−
3	++++***	−	−	−
4	++++***	−	−	−
Phaeochromocytomas				
1	++++***	++++**	++++***	+**
2	++++**	++++*	++++**(*)	++++*(**)
3	++++***	++++*	++++**(*)	+*
4	++++***	++++*(**)	++++*(**)	+**
5	++++***	+++*	++++***	+*
6 (M)	++++***	++++*(*)	++++**(*) S	+*
7 (M)	++++**	++++*(*)	++++**(*) S	+*(*)

Numbers of tumour cells displaying immunoreactivity: −, negative; +, fewer than 10% of cells positive; ++, 10–50%; +++, 50–80%; and ++++, more than 80% positive.
Intensity of the immunoreactivity: *, weak; **, moderate; and ***, strong.
*(*), *(**) and **(*), means a variation in frequency between * and **, between * and ***, and between ** and ***, respectively.
B, benign; M, malignant; ECL, enterochromaffin-like; EC, enterochromaffin; S, spindle-like cells.