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Polysialylated N-CAM, chromogranin A and B, and secretogranin II in neuroendocrine tumours of the lung

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Abstract Highly α2–8-sialylated N-CAM (neural cell adhesion molecule) impairs N-CAM-mediated cell adhesion. We investigated polysiaN-CAM immunoreactivity in a range of neuroendocrine lung tumours: 15 typical carcinoids, 21 atypical carcinoids, 2 large cell neuroendocrine carcinomas and 12 small cell lung carcinomas were selected on a morphological basis and by their immunoreactivity for chromogranin A and B and secretogranin II. A progressive loss of chromogranin expression**,** particularly of chromogranin B, was paralleled by the up-regulation of polysiaN-CAM in histologically more aggressive tumours ($P = 0.001$). These data support the hypothesis that loss of cell–cell adhesion properties might be a relevant factor in the origin of the aggressivity of lung neuroendocrine tumours.

Key words Chromogranins · Polysialylated N-CAM · Lung · Neuroendocrine tumours

Introduction

Neural cell adhesion molecules (N-CAM) are a family of closely related membrane glycoproteins encoded by the same gene; they promote cell–cell (through a homophilic binding mechanism) and cell–substratum adhesion [1, 32]. Different isoforms of N-CAM are developmentally regulated and show tissue and cell specificity [11]. In addition, post-translational modifications that further increase N-CAM diversity occur; among them, the acquisition of α2–8-linked polysialic acid (polysia) chains appears to be relevant in human tumours. Originally described in embryonal tissues [29, 31], this modification has also been found in Wilms' tumour [30, 31, 40], lung tumours [17], and neuroblastomas [23]. The length of these chains is involved in the modulation of adhesive properties, as demonstrated by in vitro experiments [33, 39]. Highly sialylated forms of N-CAM promoting reduction of cell–cell adhesive properties of malignant cells have been related to the invasive and metastatic growth potential of tumour cells [18, 19, 22–24].

High-grade tumours such as small cell carcinomas of the lung (SCCLs) exhibit polysialylated N-CAM, whereas typical carcinoids (TCs) of the lung are reported to express the adult nonpolysialylated form of N-CAM [18]. TCs and SCCLs are known to be the ends of a spectrum of lung neuroendocrine neoplasias of different clinical behaviour, with well-differentiated neuroendocrine carcinomas (WDNCs) representing an entity with an intermediate course [3, 6, 20].

The pathological criteria for the diagnosis of WDNCs were firmly established by Gould's group [9, 10, 36, 37]; cytological diagnostic criteria have also been outlined [16]. The diagnostic criteria of WDNCs have since been widened, encompassing tumours lacking clear carcinoid architectural features; Travis et al. [35] provided further criteria for the diagnosis of the latter, which were renamed large cell neuroendocrine carcinomas of the lung (LCNECs). The description of this entity emphasizes that a wide spectrum of pulmonary neuroendocrine tumours exists.

We have now studied the expression of a molecule known to be involved in cell–cell and cell–matrix adhesion phoenomena in surgical specimens of pTNM-classified well-differentiated neuroendocrine carcinomas of the lung. We selected a series of neuroendocrine neoplasms of the lung varying in histological grade; to confirm their neuroendocrine phenotype, we tested them with a panel of monoclonal antibodies (MoAbs) to chromogranin A (CgA), chromogranin B (CgB) and secretogranin II (SgII), also called chromogranin C [8]. Since Cgs are well known to have a twofold distribution, over-

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lapping or complementary, a panel of MoAbs against these different molecules was thought to be suitable. CgA, CgB and SgII comprise a family of acidic glycoproteins stored in the matrix of the secretory granules of endocrine mammalian and nonmammalian cells. CgA, CgB and SgII have been localized in normal human tissues and in malignancies with neuroendocrine features [5, 21, 28, 34]. A further reason for interest in the detection of CgB synthesis relates to its role in adhesion phenomena [7]. In the present study we found an expression of CgB and polysiaN-CAM in WDNC intermediate between TC and SCCL. This result suggests that modifications of adhesion mechanisms might play a part in the aggressive behaviour of these neoplasms.

Materials and methods

Haematoxylin–eosin-stained sections from 71 neuroendocrine lung tumours from the files of the Ospedale Maggiore IRCCS of Milan between 1985 and 1993 were reviewed and classified separately by three of us (C.P., G.P., and R.B.). The original diagnoses were typical carcinoid, small cell lung carcinoma and well-differentiated neuroendocrine carcinoma: 12 small cell lung carcinomas, 15 typical carcinoids, 21 well-differentiated neuroendocrine carcinomas and 2 large cell neuroendocrine carcinomas were selected and classified according to the criteria of the World Health Organization nomenclature [14], Gould's group [36] and others [27, 35]. Cases harbouring squamous or glandular differentiation were dropped. Information on size, site of the primary and metastatic tumours, and pathological stage was available for all cases.

One formalin-fixed and paraffin-embedded block for each case underwent immunocytochemical analysis as follows: dewaxed and rehydrated tissue sections were immunostained for CgA monoclonal antibody (MoAb) A11, CgB (MoAbs B11 and B13) [25], SgII (MoAb 3C12) [26], and for polysialylated N-CAM (MoAb 735) [18] using the ABC staining procedure [15]. The specificity, working dilutions and sources of the primary MoAbs are reported in Table 1. Proteolytic digestion [1 mg/ml Trypsin (Sigma, St. Louis, Mo.) in TRIS-HCl 0.1 M pH 7.4 for 15 min at 37°C] of dewaxed sections was performed before immunostaining for CgA, CgB and SgII. Immunocytochemical negative controls included the omission of the primary antibody for chromogranin immunostaining and digestion of the sections with bacteriophage endoneuroaminidase E (Sigma) for polysialylated N-CAM. Indeed, this enzyme is reported to abolish polysialic acid immunostaining by digestion [18]. Formalin-fixed and paraffin-embedded sections from embryonal kidney and an ileal carcinoid were always included as positive controls for polysiaN-CAM and Cgs/SgII, respectively.

Results were quantified as follows: 1+, scattered immunoreactive cells, amounting to less than 20% of the neoplastic population; 2+, immunoreactive areas ranging from 20% to 50% of the neoplastic population; 3+, immunoreactivity in more than 50% of the neoplastic population.

Statistical analysis was performed by means of Chi-square method with Yates' correction. For each antibody utilized, contingency tables were obtained matching TCs with WDNCs and SCCLs.

Table 1 Antibodies used in the present study

MoAb	Specificity	m g/ml protein	Sources
A11	CgA	0.04	Dr.Siccardi/Dr.Pelagi
B11	CgB	2.14	Dr.Siccardi/Dr.Pelagi
B13	CgB	0.03	Dr.Siccardi/Dr.Pelagi
3C12	SgII	3.72	Dr.Siccardi/Dr.Pelagi
735	PolysiaN-CAM	5	Dr.Bitter Suermann

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Results

Chromogranins and secretogranin II

The morphological diagnosis of TC, WDNC, LCNEC and SCCL was reinforced by the immunohistochemical detection of CgA, CgB and SgII. Results are reported in Table 2. In summary, reactivity for at least one of the anti-Cgs or anti-SgII MoAbs was found in all tumours under study, with wide variability in the type of chromogranin present and in the percentage of the immunoreactive cells. As a rule, Cgs/SgII were more expressed in low-grade tumours (TCs) than in higher grade tumours (WDNCs, LCNECs and SCCLs). The majority (3+) of TC cells (Table 2) proved to be immunoreactive for both CgA and CgB as well as for SgII. Conversely, just subsets (1+ to 3+) of WDNC, LCNEC (Fig. 1) and SCCL cells reacted with Cgs/SgII MoAbs, CgB being the epitope most frequently expressed. It is noteworthy that 2 WDNCs thought to be devoid of CgB when tested with

Table 2 Immunohistochemical results (*TC* typical carcinoid, *WDNC* well-differentiated neuroendocrine carcinoma, *LCNC* large cell neuroendocrine carcinoma, *SCCL* small-cell carcinoma of the lung, *1+* scattered immunoreactive cells, amounting to less than 20% of the neoplastic population, *2+* immunoreactive areas ranging from 20% to 50% of the neoplastic population, *3+* immunoreactivity in more than 50% of the neoplastic population, *Cg* chromogranin, *Sg* secretogranin, *polysia* polysialylated

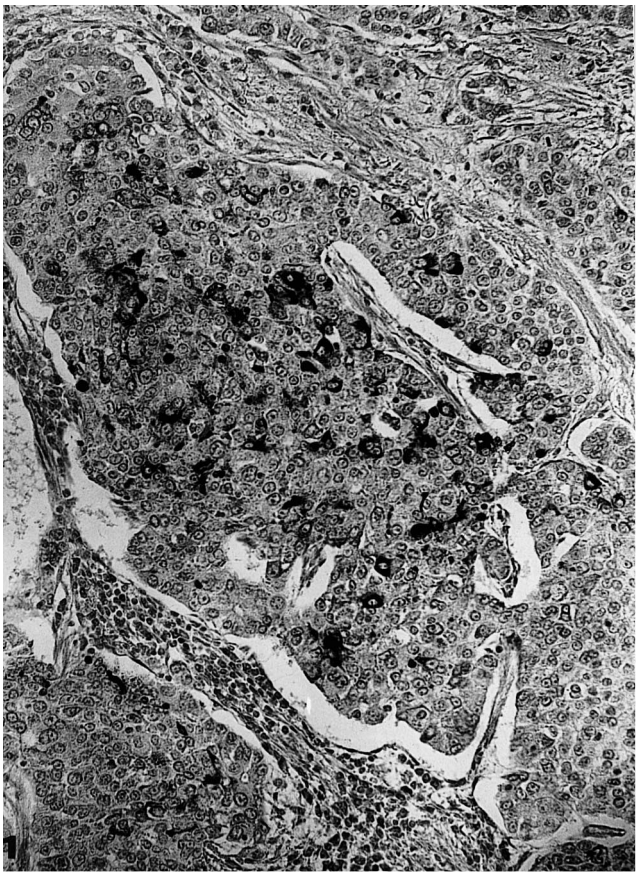
Diagnosis	PolysiaN-CAM	CgA	CgB	SgII
TC (no. 15)	0/15	15/15 (3+)	15/15 (3+)	15/15 (3+)
WDNC (no. 21)	13/21 (1+/2+)	8/21 (1+/2+/3+)	16/21 (1+/2+/3+)	8/21 (1+/2+/3+)
LCNC (no. 2)	1/2 (1+)	0/2	2/2 (1+)	0/2
SCCL (no. 12)	11/12 (1+/2+/3+)	8/12 (1+/2+)	7/12 (1+/2+)	5/12 (1+/2+)

Fig. 1 Scattered cells of large cell neuroendocrine carcinoma showing cytoplasmic immunoreactivity for chromogranin B. Haematoxylin counterstain, ×250

Fig. 2 Small cell lung carcinoma showing cytoplasmic membrane immunostaining of the overwhelming majority of the neoplastic population for polysialylated neural cell adhesion molecule (N-CAM) monoclonal antibodies (MoAb). ×250

Fig. 3 Cell membrane immunoreactivity for polysialylated N-CAM MoAb in ribbons and clusters of a well-differentiated neuroendocrine carcinoma. ×250

Fig. 4 Sheets of a well-differentiated neuroendocrine carcinoma showing scattered cells immunoreactive for polysialylated N-CAM. ×250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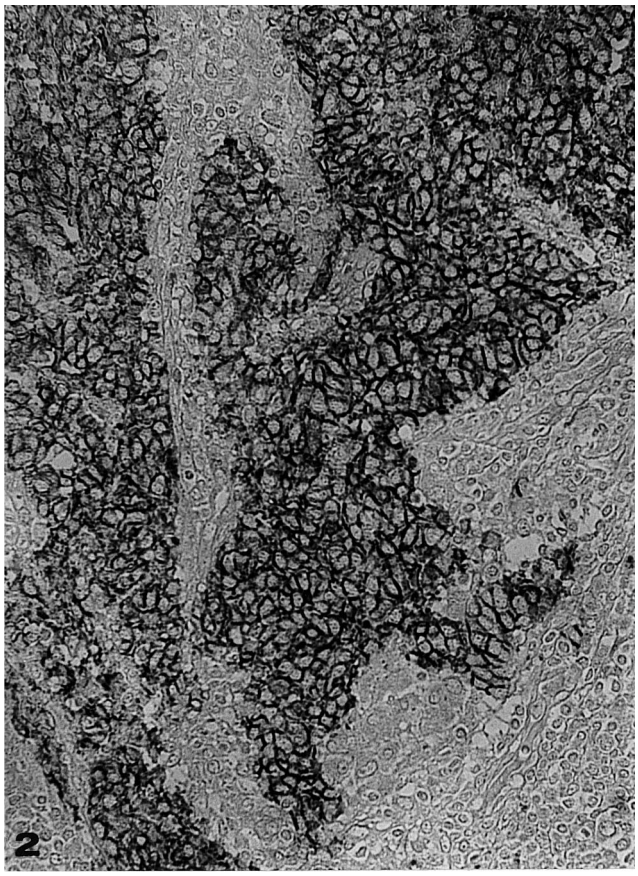
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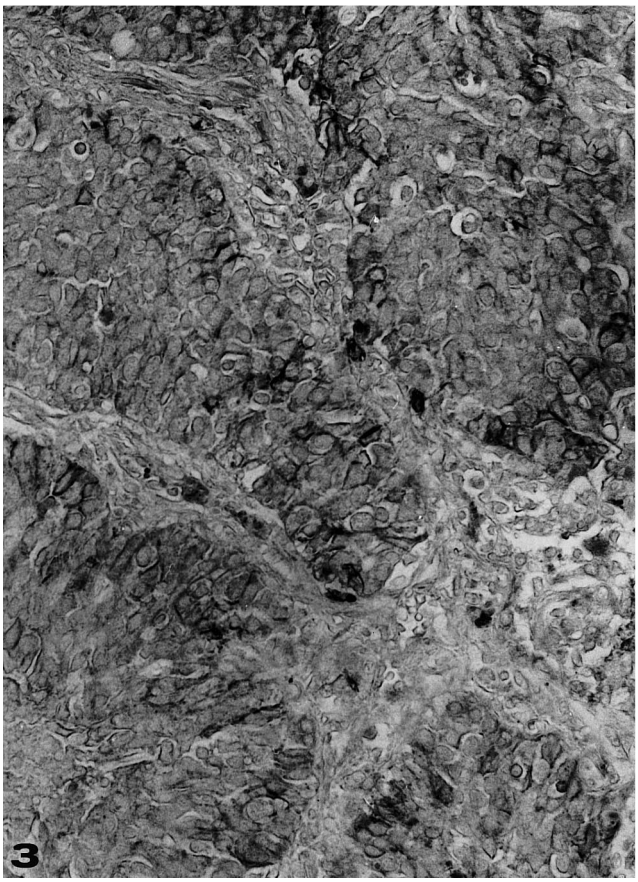
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B11 MoAb were subsequently classified as neuroendocrine tumours, being immunoreactive with the MoAb against CgB reported as B13 MoAb. CgB expression decreased from TCs to WDNCs and SCLCs, being detectable in all the TCs under study, in 16 of 21 (≈ 76%) WDNCs and 7 of 12 (≈ 58%) SCCLs, though this trend did not reach statistical significance according to Chi-square with Yates' correction ($P = 0.21$).

Scattered cells immunoreactive for CgA, CgB and SgII were detectable in non-neoplastic bronchial mucosa; SgII immunoreactivity was also detectable in bronchial nerves.

All MoAbs stained the cytoplasm of TC, WDNC and LCNEC cells in a coarsely granular pattern. Cell clusters of TCs, and to a lesser extent those of WDNCs and LCNECs, often displayed peripheral palisading with immunostaining concentrated in the basal pole of the cells. In the central areas of TC clusters, the immunoreactivity was distributed uniformly, the pattern being similar in WDNC and LCNEC cells. Finally, SCCL CgA immunoreactivity was represented by a paranuclear dot.

Polysialylated neural cell adhesion molecule

The results of the present study are summarized in Table 2. Non-neoplastic alveolar and bronchial epithelia and also tracheobronchial glands failed to react to MoAb 735 to the polysialylated N-CAM, while nerve trunks displayed strong immunoreactivity.

All but 1 of the SCCLs reacted with 735 MoAb (Fig. 2). The immunoreactivity ranged from a small subset (1+) to the majority of the neoplastic population (3+), irrespective of the WHO subgrouping.

Thirteen of 21 (≈ 62%) of the WDNCs showed immunoreactivity with MoAb 735, either confined to a small subpopulation of cells (1+) or more widely distributed (2+).

Finally, all of the TCs were unreactive with 735 MoAb. The number of positive cases increases, ranging from the slow-growing TCs through WDNCs with intermediate course to highly aggressive SCCLs ($P = 0.006$, Chi-square test with Yates' correction). MoAb 735 immunostained 1 of the 2 LCNECs present in the current study.

The pattern of immunostaining in WDNCs could be represented either by positive clusters intermingled with negative areas (Fig. 3) or by single positive cells surrounded by negative ones (Fig. 4). Tumour cells in close contact with vessels and lymphatic structures were usually more strongly immunostained.

Regardless of histotype, in all these tumours the staining was strictly confined to the cytoplasmic membrane, with a continuous or punctate pattern. This staining pattern was never polarized. Cytoplasmic immunostaining was focally present in some cases, and was unscored. The stroma, scanty or abundant, was not stained with MoAb 735.

No correlations were found between immunoreactivity to MoAb 735 and malignancy criteria such as number of mitoses, cell size, extent of necrosis and organoid structures suggested as a basis for subtyping of the WDNCs [35, 36], and pTNM.

Chromogranins and polysialylated neural cell adhesion molecule

A differential expression of Cgs, particularly of CgB, and polysiaN-CAM was found: polysiaN-CAM was not detectable in any TC, while it was present in 13 of the 21 WDNCs and in all but 1 of the SCCLs ($P = 0.006$). Conversely, all the TCs, 16 of the 21 WDNCs and 7 of the 12 SCCLs were immunoreactive to B11 MoAb. This distribution, when analysed by the Chi-square test with Yates' correction, was highly significant ($P = 0.001$).

Discussion

N-CAM is a glycoprotein involved in intercellular adhesion mechanisms [32]. Multiple α2–8-polysialylated units are coupled to the N-CAM protein core in the Golgi compartment by several sialyltransferase isoforms in embryonal life [29–31, 40]. The function of N-CAM is modulated by the degree of sialylation, that is to say that interference with cell–cell adhesive phenomena has been related to the presence of N-CAM in the embryonal form [1, 33]. Other sialylated molecules are retained to exert the same functions [13, 38]. In human adult tumours, N-CAM carrying long chains of polysialic acid units has been often detected [17–19, 22–24].

Our results emphasize the similarities between WDNCs and SCCLs: in fact, both were consistently immunoreactive with MoAb 735 that failed to react with TCs [18]. These findings agree with those of others [22]. It is noteworthy that TCs are consistently unreactive, as shown in this and other studies [17, 18]. Our results are also in keeping with the putative correlation between the presence of highly sialylated N-CAM forms and tumour aggressivity. Indeed, polysiaN-CAM immunoreactivity is not detectable in the presence of morphological evidence of a cohesive architecture characteristic of TCs. Conversely, loosely arranged carcinomas such as SCCLs were positive for polysiaN-CAM. Similarly, these immunoreactivities emphasize the close linkage between polysiaN-CAM expression and differentiation of the whole category of neuroendocrine tumours.

From the analysis of data reported in Table 2, an inverse relationship between the distribution of Cgs/SgII and polysiaN-CAM emerges ($P = 0.001$). Highly differentiated neoplasms including TCs consistently showed immunoreactivity for the MoAbs to Cgs/SgII in more than 50% (3+) of neoplastic cells. Conversely, SCCL cells immunoreactive to Cgs/SgII were few, amounting to under 50% (1+ to 2+), and usually did not express more than one antigen. WDNCs showed neuroendocrine features in a percentage of cells intermediate between TCs and SCCLs (1+ to 3+). Down-regulation of the neu-

roendocrine features progressed from WDNCs to SCCLs only for CgB, a trend also reported by others [3]. Analysis of the functional significance of CgB in tumours merits some interest. CgB has two putative heparin-binding motifs in a region without homologies to CgA [7]. Interestingly, this region has a high degree of sequence conservation between species, suggesting a functional significance. CgB has an adhesive potency in the range of fibronectin, collagen and laminin. Our data show an inverse relationship between CgB and polysiaN-CAM expression in the tumours in our series: the number of CgB immunoreactive cells was highest in low-grade tumours where polysiaN-CAM was lacking. Conversely, the high expressors of polysiaN-CAM were high-grade neoplasms that displayed few CgB immunoreactive cells or none at all. In addition, the cells of a series of tumours identified by a MoAb against CgA were recently proved to be in a postmitotic phase [2, 4]; accordingly, Cgs/SgII immunoreactivity was used as a marker of the resting population of the tumour.

Finally, Grogan et al. [12] reported high polysialylated N-CAM expression in lymphomas of the central nervous system (CNS). Although highly neurotropic carcinomas such as SCCL do express polysiaN-CAM, we were not able to find a correlation between its expression in WDNCs and CNS metastases at the time of the diagnoses.

In summary, the expression of polysialylated N-CAM and possibly that of CgB in WDNCs does not show clear-cut clinico-pathological correlations; however, the inverse correlation of polysiaN-CAM and CgB with the degree of differentiation of neuroendocrine tumours of the lung strongly support the pivotal role of adhesion phenomena in tumour aggressivity.

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