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Oral granular cell lesions

An immunohistochemical study with emphasis on intermediate-sized filaments proteins

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Summary. Six cases of oral granular cell lesions were studied with respect to intermediate-sized filaments (IF), peanut lectin binding (PNL) and muramidase activity by means of the peroxidase antiperoxidase technique. The tumours included three granular cell myoblastomas of the tongue (GCM) two cases of congenital gingival granular cell tumour (CGGT) and one granular cell ameloblastoma (GCA). Every tumour studied showed intracytoplasmic PNL binding whereas muramidase was negative in all cases. Vimentin expression was demonstrated in the CGGT and to a lesser extent in the GCM, but was absent in the GCA which was positive for keratin. Desmin and glial fibrillary acidic protein (GFAP) were not present in any of the lesions. These data demonstrate that PNL binding might be considered to be a common feature of granular cells regardless of their histogenesis. Lysosomes are supposed to represent the intracellular binding sites for this marker. Moreover it is shown that histomorphological identity between the granular cells of CGGT and GCA does not signify identity in histogenesis since the former are of mesenchymal derivation while the latter, from their intermediate filament protein types appear to originate from epithelium.

Key words: Congenital gingival granular cell tumor – Granular cell myoblastoma – Granular cell ameloblastoma – Peanut lectin – Intermediate-sized filaments

Granular cell myoblastoma (GCM) and congenital gingival granular cell tumor (CGGT) have both been the subject of considerable controversy with respect to histogenesis. Abrikossof (1926) who first described GCM believed this lesion to be derived from striated muscle. This opinion could not be maintained and in the course of time, a neural origin (Feyrter 1935;

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Fust and Custer 1949), and derivation from Schwann cells (Fisher and Wechsler 1962; Garancis et al. 1970; Weiser 1978), perineural fibroblasts (Pearse 1950), primitive mesenchymal cells (Moscovic and Azar 1967; Aparicio and Lumsden 1969; Sobel et al. 1973a, b; Regezi et al. 1979; Matthews and Mason 1982) or histiocytes (Azzopardi 1956; Eversole and Sabes 1971) have been proposed.

Support for a Schwann cell origin came from the demonstration of S-100 protein in the granular cells (Stefansson and Wollmann 1982; Nakazato et al. 1982) but the recent detection of this protein in an extensive range of other cell types (Kahn et al. 1983) makes the value of S-100 protein as a marker for neural tissues questionable.

Regarding CGGT, most opinions with respect to histogenesis have been developed by inference from the morphological similarity of the granular cells of the lesion to those occurring in GCM, resulting in the same series of presumed precursor cells as summarized above (Fuhr and Krogh 1972). Few studies have been devoted exclusively to the histogenesis of CGGT. A derivation from odontogenic epithelium was originally suggested by Massin (1894) and has since been supported by Hoke and Harrelson (1967); Kay et al. (1971); and most recently by Sunderland et al. (1983). Custer and Fust (1952) agreed with an odontogenic origin but make no statements whether odontogenic epithelium or mesenchyme acts as a source. Support for an origin from odontogenic mesenchyme also came from the similarity between CGGT and ameloblastic fibroma granular cell type (Waldron et al. 1963; White et al. 1978). A derivation from subepithelial connective tissue fibroblasts was proposed by Bauer and Bauer (1953) and Bhaskar and Akamine (1955). Rohrer and Young (1982) concluded that origin from pericytes was highly probable whereas Lack et al. (1982) supposed gingival stromal cells with a fibrohistiocytic character represented the precursor cells.

Whether CGGT and GCM are the same tumour has been subject of a debate almost as extensive as that about their histogenesis. Ultrastructural studies have generally failed to demonstrate significant differences between the granular cells in the lesions (Navarette and Smith 1971; Regezi et al. 1979; Rohrer and Young 1982; Lack et al. 1982); and histochemical staining methods have not been succesful in this respect (O'Brien 1972; Sunderland et al. 1983). It has however been stressed that morphological similarity does not signify identity or origin from the same parent tissue (Campbell 1955; McCallum and Cappel 1957) and therefore, there is no basis for those who advocate identity between CGGT and GCM (Dixter et al. 1975; Skoglund and Holst 1983) or those who disagree with this theory (Custer and Fust 1952; O'Brien 1972).

We attempted to solve some of the problems concerning CGGT and GCM by means of studying the intermediate-sized filaments of the cytoskeleton. These intermediate filaments (IF) are tissue specific in so far that epithelial, mesenchymal, muscle, and neural tissue types can be distinguished by the use of specific antibodies to keratin, vimentin, desmin and neurofilaments or glial filaments respectively (Osborn et al. 1983; Ramaekers et al. 1983a). This paper reports the IF pattern of GCM and CGGT. The observations were extended by an assay for muramidase and for peanut lectin

(PNL) binding capacity. This particular lectin has been reported to be a histochemical marker for granular cells (Schwechheimer et al. 1983). Moreover, a case of granular cell ameloblastoma (GCA) was subjected to the same procedures for evaluation of the relation between CGGT and GCA granular cells. Morphological identity between CGGT and GCA granular cells has been considered evidence for an epithelial derivation of CGGT in the past (Hoke and Harrelson 1967) and a comparison of their respective cytoskeletons may shed new light on this aspect.

Material and methods

Six specimens from different patients were selected from our biopsy files. They included three GCM of the tongue, two cases of CGGT and one GCA (reported in detail by de Wilde et al. in press). 5 micron sections of formalin-fixed and paraffin embedded tissue were obtained using a microtome with C-knives (Leitz Germany).

Antisera. The following antisera directed against IF were used in this study: (1) a rabbit antiserum against keratin from human skin calluses prepared essentially as described by Franke et al. (1979) (2) a rabbit antiserum to bovine eye lens vimentin (Ramaekers et al. 1981, 1982, 1983a); (3) a rabbit antiserum directed against desmin from chicken gizzard (Geisler and Weber 1980) and (4) a rabbit antiserum to glial fibrillary acidic protein (GFAP) essentially prepared as described by Dahl and Bignami (1976).

PNL and rabbit antiserum to PNL were purchased from E.Y. Lab., USA. Normal swine serum, swine anti-rabbit serum, rabbit PAP complex and antiserum to human muramidase were obtained from DAKO, Denmark. Peroxidase reaction was visualized using 3,3′ diaminobenzidine tetrahydrochloride (DAB; Sigma, USA) as a chromogen.

Procedures. The Sternberger PAP technique was employed (Sternberger 1979). For detecting PNL binding the method as described by Roholl et al. (in press) was used and can be summarized as follows: xylene (3 × 10 min), ethanol (3 × 5 min.), 1% H_2O_2 in methanol (30 min), phosphate buffered saline (PBS) (2 × 10 min.), normal swine serum 1:5 (45 min), PNL 15 ng/ml (45 min), PBS (3 × 10 min), rabbit antiserum to PNL 1:800 (overnight at 4° C), PBS (3 × 10 min), swine anti-rabbitserum 1:200 (45 min), PBS (3 × 10 min), rabbit PAP complex 1:250 (45 min), PBS (3 × 10 min), Tris buffer (50 mM, 1 N HCl, pH 7.6, 10 min) DAB (10 min), tap water (10 min), Mayer haematoxylin as counterstain.

Intermediate filaments were visualized by conforming to the technique as described by Ramaekers et al. (1983a), briefly as follows. Initial steps up to PBS after treatment with 1% H_2O_2 were identical with the PNL procedure as mentioned before. Thereafter the sections were incubated with undiluted normal swine serum (30 min) followed by the first antiserum. Sera were used at the following dilutions: anti-keratin 1:40; anti-vimentin 1:100; anti-desmin 1:120; anti-GFAP 1:500. Furthermore vimentin antisera which had been preabsorbed with keratin or vimentin were used as controls. Sections were incubated overnight at 4° C. After PBS (3 × 10 min), sections were incubated with swine anti-rabbit serum 1:30 (30 min). Next steps included PBS (3 × 10 min), rabbit PAP complex 1:100 (30 min), PBS) (3 × 10 min.), DAB (3 min), tap water (10 min) and Mayer haematoxylin as counterstain.

Some sections had to be pretreated with pronase (1 mg/ml in 50 mM Tris-buffer 1 N HCl, pH 7.6, 15–30 min at 37° C) in order to expose keratin antigenic determinants and allow its detection by our antiserum. It is our experience that with formalin-fixed paraffin embedded tissues immunoperoxidase staining for keratin occasionally may give rise to false negative results (Schlegel et al. 1980; Ramaekers et al. 1983b). These may occur as a result of destruction or masking of keratin antigenic determinants, a phenomenon which should be kept in mind when interpreting the results presented here for the keratin antibody.

Muramidase was tested according to the method described by Mason and Taylor (1975) with anti-muramidase serum at a dilution 1:50. Control studies were performed by substituting the first antibody by PBS.

Results

Keratin IF are present in the GCA granular cells which exhibit a positive reaction to keratin antiserum that is most intense at the periphery of the cell (Fig. 1c). It seems as if the filaments of the cytoskeleton are compressed against the cellular membrane by the cytoplasmic granules. CGGT and

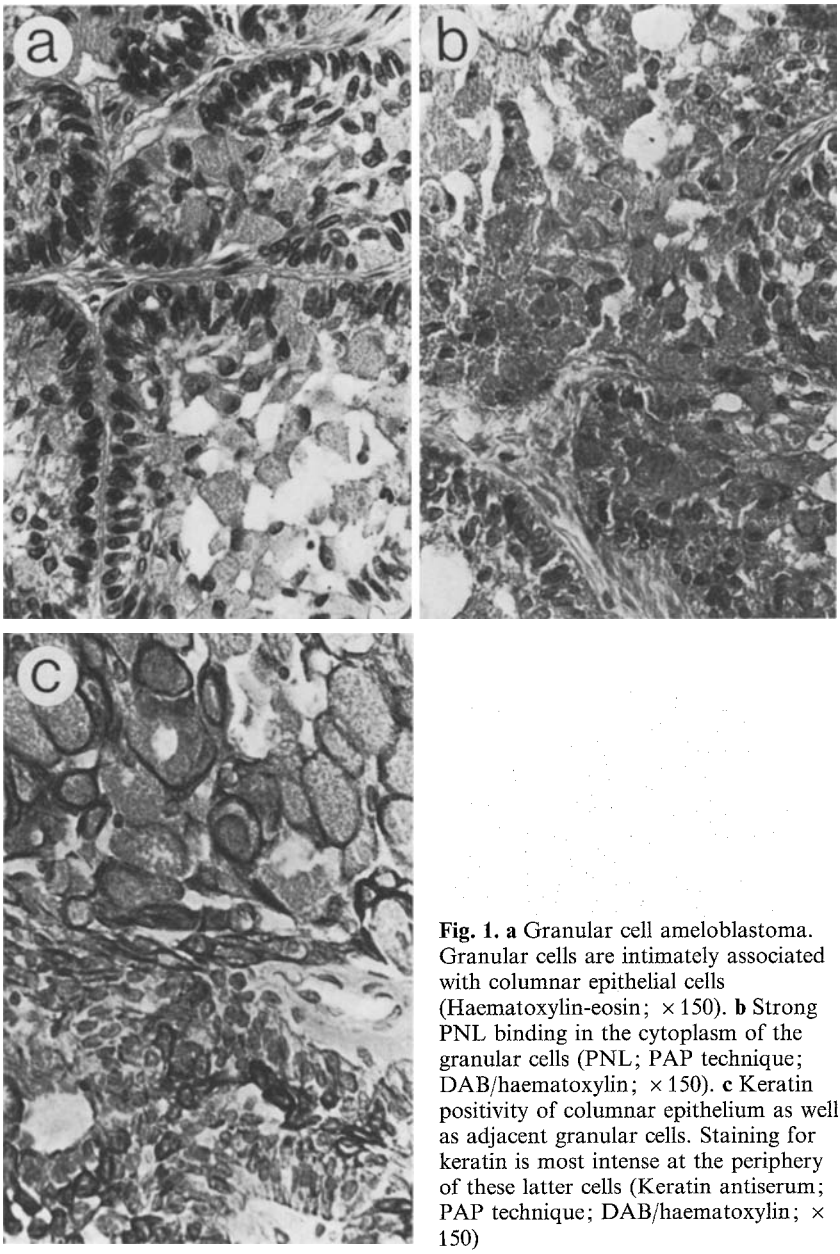

Fig. 1. a Granular cell ameloblastoma. Granular cells are intimately associated with columnar epithelial cells (Haematoxylin-eosin; ×150). **b** Strong PNL binding in the cytoplasm of the granular cells (PNL; PAP technique; DAB/haematoxylin; ×150). **c** Keratin positivity of columnar epithelium as well as adjacent granular cells. Staining for keratin is most intense at the periphery of these latter cells (Keratin antiserum; PAP technique; DAB/haematoxylin; × 150)

GCM granular cells do not show the presence of keratin IF. Vimentin IF are present in CGGT granular cells. In the GCM granular cells the vimentin antiserum yields weak and variable results which might be due to a smaller amount of vimentin in GCM granular cells than is present in CGGT granular cells. A fixation artifact as source of this difference in vimentin reactivity can be ruled out as no differences in vimentin reactivity

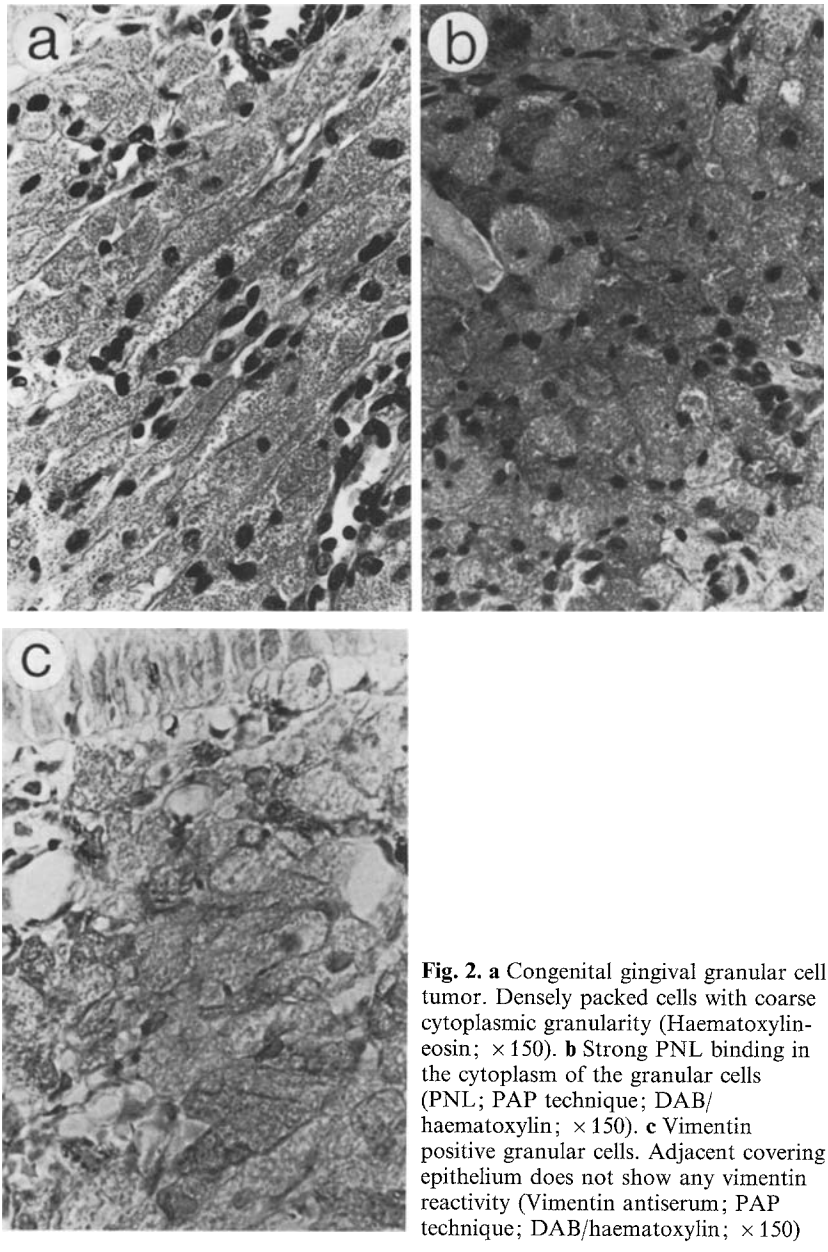

Fig. 2. a Congenital gingival granular cell tumor. Densely packed cells with coarse cytoplasmic granularity (Haematoxylin-eosin; ×150). **b** Strong PNL binding in the cytoplasm of the granular cells (PNL; PAP technique; DAB/haematoxylin; ×150). **c** Vimentin positive granular cells. Adjacent covering epithelium does not show any vimentin reactivity (Vimentin antiserum; PAP technique; DAB/haematoxylin; ×150)

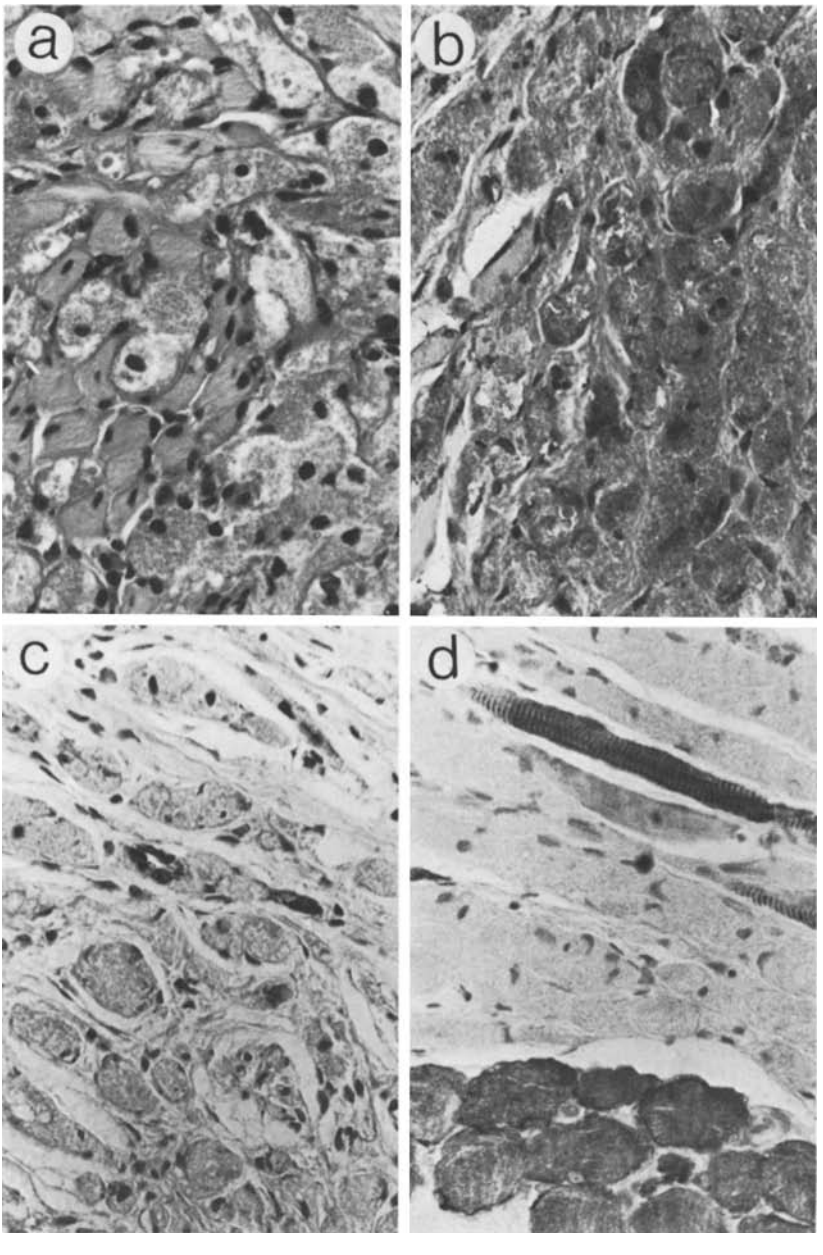

Fig. 3. a Granular cell myoblastoma. Granular cells are dispersed between striated muscle fibers (Haematoxylin-eosin; ×150). **b** Strong and uniform PNL binding in the cytoplasm of the granular cells (PNL; PAP technique; DAB/haematoxylin; ×150). **c** Vimentin reactivity in the granular cells is weak and variable (Vimentin antiserum; PAP technique; DAB/haematoxylin; ×150). **d** Pre-existing striated muscle is strongly positive for desmin antiserum whereas adjacent granular cells do not show any reactivity (Desmin antiserum; PAP technique; DAB/haematoxylin; ×150)

are observed in the supporting stromal areas in either kind of granular cell lesion. GCA granular cells do not exhibit the presence of vimentin IF. No desmin or GFAP IF can be detected in any of the granular cells in the various lesions examined. Covering epithelium, stromal areas and blood vessels, striated muscle and peripheral nerves showing a strong positive reaction with the various antisera serve as intrinsic positive controls.

From these results it is obvious that the antibodies to vimentin, desmin and GFAP are capable of detecting their respective antigens with high sensitivity in routine sections without pretreatment of the paraffin embedded tissue. Keratin can also be detected by the technique described above, but occasionally only after pretreatment of the sections with pronase in order to expose masked keratin antigenic determinants. Fresh frozen sections of the GCA that were studied by immunofluorescence microscopy showed the same IF staining pattern as described above for the paraffin sections (de Wilde et al. in press) and serve as an additional control for the reliability of the results that were obtained by the PAP technique.

Anti-muramidase serum yields negative results in all granular cell lesions. Histiocytes in concomitant inflammatory infiltrates showing a positive reaction serve as positive controls for this antiserum. PNL binding can be demonstrated in all granular cell lesions examined (Figs. 1–3). The reaction is very strong in all granular cells regardless of the lesion of which they form part.

The granular cells in GCA arise through transformation of columnar epithelium and an increasing PNL binding parallels this metamorphosis (Fig. 1b). Similar precursor cells from which the granular cells could arise cannot be identified in the other granular cell lesions.

The various results are summarized in Table 1. Controls substituting the first antibody by PBS or preabsorbed serum yield negative results.

Table 1. Differential staining patterns of granular cells using various immunohistochemical markers

Material	No.	Antisera used in the immunoperoxidase assay					
		keratin	vimentin	GFAP	desmin	muramidase	PNL
GCM	3	−	+/−	−	−	−	+
CGGT	2	−	+	−	−	−	+
GCA	1	+	−	−	−	−	+

GCA = granular cell ameloblastoma
GCM = granular cell myoblastoma
CGGT = congenital gingival granular cell tumour
PNL = peanut lectin
GFAP = glial fibrillary acidic protein

Discussion

The IF pattern of the various oral granular cell tumours may shed some new light on controversies concerning their histogenesis. In summary, discussion centers around the question of the origin of the granular cells in GCM and CGGT and the unsolved problem of whether or not the granular cells in CGGT are of mesenchymal or odontogenic epithelial derivation. The question whether or not the GCA granular cells have properties in common with the CGGT granular cells also needs to be resolved.

The IF pattern of the CGGT granular cells clearly denies an epithelial origin as is demonstrated by positive staining with the vimentin antiserum, and negative results with the keratin anti-serum which is specific for epithelial tissues. Since IF staining patterns of the GCA granular cells showed the opposite result – cells negative for vimentin but positive for keratin, indicating an epithelial origin, it is evident that the morphological similarity of the CGGT granular cells when compared with those occurring in GCA and those encountered in fetal tooth germ (Sunderland et al. 1983) does not immediately imply that these cells originate from the same progenitor tissue.

The proposed identity between the CGGT granular cells and the GCM granular cells (Dixter et al. 1975; Skoglund and Holst 1983) does not gain support from our observations. Both lesions exhibited vimentin reactivity in the granular cells, consistent with a mesenchymal character, but the degree of vimentin expression varied from uniform and unequivocal in the CGGT granular cells to weak and variable in the GCM granular cells. It seems that in the CGGT the cytoplasmic granules do not interfere with the cytoskeleton whereas in the GCM, the vimentin expression is suppressed in some way.

With regard to the controversies on histogenesis of CGGT and GCM the following remarks can be made. The myogenic theory of histogenesis of GCM, first advocated by Abrikossof (1926) but since then generally refuted (Sobel et al. 1973a, b) does not gain support from our observations. No desmin reactivity could be detected in any type of granular tumor cell while, however, adjacent pre-existent muscle tissue exhibited a strong positive reaction with the desmin antiserum. These findings agree with the study of Matthews and Mason (1982) in which antiserum to actin failed to produce conclusive evidence for myoblast origin of GCM granular cells.

The neurogenic theory can neither be substantiated nor denied from our study. GFAP reactivity was not noted in the granular cells. This is not surprising since GFAP is specific for astrocytes and tumours derived from them (Tascos et al. 1982), while schwannomas do not seem to contain this IF protein (Ramaekers et al. 1983a). The demonstration of vimentin in CGGT and GCM is, strictly speaking, not in contradiction with Schwann cell derivation, since this IF protein has been demonstrated in schwannomas (Altmannsberger et al. 1982). Since however vimentin is present in many other mesenchymal cell types, its presence cannot be considered strictly as evidence for a Schwann cell origin. The same is true for a histiocytic

derivation of granular cells which can neither be rejected nor proven by vimentin positivity. Absence of staining for muramidase neither supports nor excludes the histiocytic cell as a precursor for CGGT or GCM granular cells, since not all kinds of histiocytes contain muramidase (Pinkus and Said 1977; Watanabe et al. 1983). Previous reports have already mentioned the muramidase negativity of GCM granular cells (Matthews and Mason 1982; Schwechheimer et al. 1983).

Our data on PNL binding of the various granular cells confirm the observations of Schwechheimer et al. (1983) that PNL is a marker for granular cells regardless of their location and histogenesis. PNL binding was demonstrated not only in the mesenchymally derived granular cells of the GCM and CGGT but also in the epithelial granular cells of the GCA. In the latter lesion granular transformation is based on the appearance of lysosome-like granules in the cytoplasm which are the ultrastructural counterpart of the granular eosinophilic cytoplasm (Navarette and Smith 1971). Therefore it is tempting to speculate that these lysosomes are the intracellular binding sites for PNL.

When summarizing the main objectives of our study, we conclude that the IF staining pattern rules out an epithelial origin for the CGGT and GCM granular cells. Furthermore, the myogenic theory does not gain support from our observations. On the other hand we have not succeeded in substantiating or ruling out a possible Schwann cell or histiocytic derivation of the CGGT and GCM granular cells. Future development of other, more specific markers for these tissues may solve this problem.

It is obvious from our results, however, that although of similar morphology, granular cell types may have different biochemical properties, indicating different lines of origin.

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