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Comparative histogenesis and morphogenesis of mucoepidermoid carcinoma and pleomorphic adenoma

An ultrastructural study

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Summary. Current classifications of salivary gland tumors separate mucoepidermoid carcinoma from other neoplasms on the basis of a number of histological features, in particular the lack of participation of neoplastic myoepithelial cells. However, ultrastructural examination of low- and intermediate-grade mucoepidermoid carcinomas and pleomorphic adenomas reveals many common organizational and cellular features. Of prime importance is the relationship of intermediate cells to the luminal cells in mucoepidermoid carcinomas, which is remarkably similar to that seen between modified myoepithelial cells and luminal cells in pleomorphic adenomas. The results suggest that intermediate cells of mucoepidermoid carcinoma are the counterpart of the modified myoepithelial cells of pleomorphic adenoma. The generally accepted hypothesis that the former tumor develops from an excretory duct reserve cell, while the latter originates from an intercalated duct stem cell does not seem to be valid; pleomorphic adenoma and mucoepidermoid carcinoma appear to be closely related morphologically.

Key words: Salivary gland – Neoplasm – Mucoepidermoid carcinoma – Electron microscopy – Histogenesis

Introduction

Mucoepidermoid carcinomas are infrequent tumors of the salivary glands, a fact that may account for the limited specialized studies of their histogenesis (Dardick et al. 1984; Chaudhry et al. 1989) and even of their histopathology (Hubner and Kleinsasser 1970; Nicolatou et al. 1977; Chen 1979; Klacsmann et al. 1979; Chomette et al. 1982; Miura et al. 1986; Nikai et al. 1986; Kumasa et al. 1988; Hamper et al. 1989). Theoretically, this neoplasm is considered to develop in association with a specific reserve cell located in the excretory duct system (Healey et al. 1970; Hubner and Kleinsasser 1970; Eversole 1971; Thackray and Lucas 1974; Regezi and Batsakis 1977; Batsakis et al. 1980; Chaudhry et al. 1989). This is thought to account for morphological differences between this tumor and many of the other lesions of the salivary glands, which are suggested to arise from specific stem cells in the intercalated duct region. This has been referred to as the semipleuripotential bicellular concept for tumor induction (Eversole 1971; Regezi and Batsakis 1977).

This hypothesis postulates that all neoplasms of salivary gland originate from a population of reserve stem cells, fully differentiated cells participating rarely, if ever. However, this concept is not supported by experimental or other scientific observations. In fact, it has been demonstrated in experimental models that the capacity for cellular proliferation is shown by all cell types, even acinar, in the mature and immature salivary gland (Barka 1965; Walker and Gobe 1987; Dardick et al. 1990), an observation that is difficult to reconcile with the semipleuripotential bicellular hypothesis (Eversole 1971). Consequently, it is necessary to question the basis for segregation of mucoepidermoid carcinoma from the many other entities said to originate from the intercalated duct reserve cell (Regezi and Batsakis 1977; Batsakis et al. 1980; Batsakis and Luna 1988).

One of the principal reasons that has been suggested for mucoepidermoid carcinomas differing histogenetically from other salivary gland tumors is the apparent absence of myoepithelial cells in this lesion (Spiro et al. 1978; Batsakis 1985). Furthermore, the concept that mucoepidermoid carcinomas originate from reserve cells of the excretory duct has been fostered by the suggestion that myoepithelial cells are only associated with intercalated duct and acinar cells (Cutler et al. 1974; Regezi and Batsakis 1977; Batsakis 1985). This is thought to contrast with such tumors as pleomorphic adenoma and adenoid cystic carcinoma in which modified myoepithelial cells have such a cardinal role in the development of their unique histologies (Batsakis et al. 1983; Erland-

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son et al. 1984; Dardick et al. 1983a, b; Dardick and van Nostrand 1985; Lam 1985; Orenstein et al. 1985) – thus their apparent origin from intercalated duct cells (Eversole 1971; Regezi and Batsakis 1977).

It is now clear that myoepithelial cells are more widely distributed in the duct system than originally thought (Chaudhry et al. 1987; Dardick et al. 1987), and basal cells of the excretory ducts share certain features with myoepithelium (Born et al. 1987; Dardick et al. 1987, 1988; Geiger et al. 1987; Burns et al. 1988; Leoncini et al. 1988). Because of this, it seemed timely to compare basic ultrastructural features of mucoepidermoid carcinoma with those of pleomorphic adenoma.

Materials and methods

For this comparative study, eight mucoepidermoid carcinomas (five low-grade and three intermediate grade) and three pleomorphic adenomas (all with extensive cellular regions in addition to typical myxo-chondroid differentiation) were selected from the files of the Toronto General and Mount Sinai Hospitals. All cases had glutaraldehyde-fixed and epon-embedded tissues available in addition to paraffin blocks.

Following review of toluidine blue-stained plastic sections from at least three epon blocks from each case, thin sections were cut from one or two blocks, mounted on 100-mesh copper grids, double-stained with uranyl acetate and lead citrate, and selected areas photographed using a Philips EM400 electron microscope at 60 kV.

Results

Comparative ultrastructure

To allow appreciation of patterns of differentiation and the organization of tumor cells in both mucoepidermoid carcinoma and pleomorphic adenoma, representative micrographs from each of these lesions are provided in pairs. The principal ultrastructural features of these two types of tumors are initially described and, subsequently, the diagnosis is provided.

Organizational aspects of mucoepidermoid carcinoma and pleomorphic adenoma are illustrated in the two micrographs comprising Fig. 1. In both cases, three key features were seen: (1) a central lumen enclosed by a single layer of glandular epithelial cells bearing microvilli on the apical surface; (2) multiple layers of irregularly and variably shaped, non-luminal tumor cells positioned on the outer aspect of the glandular cells; and (3) a distinct, narrow basal lamina lining one or more surfaces of the non-luminal cells (Fig. 1). Comparing the two lesions, non-luminal cells, particularly, had some differing ultrastructural features such as the frequency of surface projections and desmosomes (Fig. 1A) or the amounts of tonofilaments (Fig. 1B). Otherwise, the basic architectural features were present in both pleomorphic adenoma (Fig. 1B) and low-grade mucoepidermoid carcinoma (Fig. 1A). In addition, both revealed differentiation of two cell types. All five low-grade and the three intermediate-grade mucoepidermoid carcinomas displayed these fundamental features.

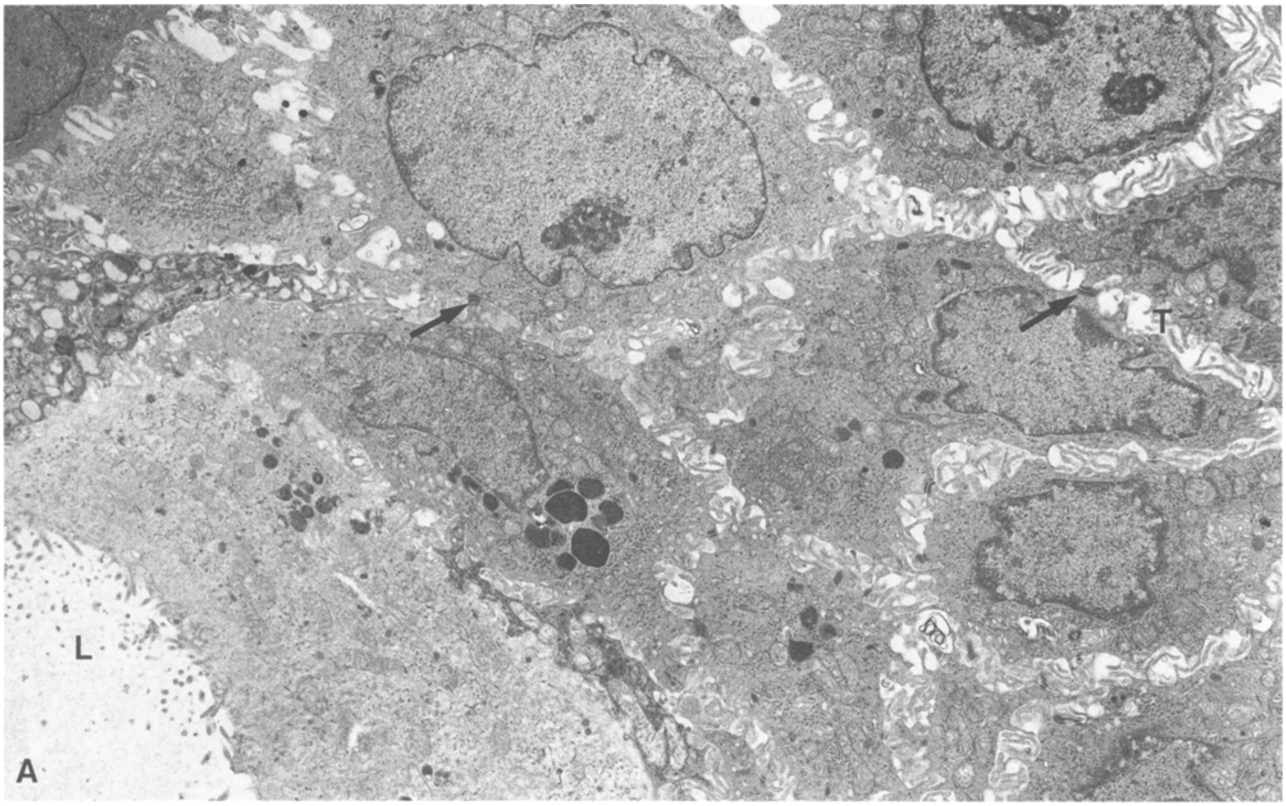
Figure 2 illustrates an additional feature, i.e., secretory activity by the luminal cells. In Fig. 2A, each luminal cell contained round to darkly stained secretory granules, often in considerable numbers; each lumen also contained a homogeneous, deeply stained secretory product. The ductal structures were surrounded by smaller, angular, slightly separated tumor cells that were joined by desmosomes. A number of basal lamina-lined intercellular spaces were associated with the latter cell type (Fig. 2A). In the tumor depicted in Fig. 2B, luminal cells, bearing microvilli, had secretory granules containing a flocculent material and an eccentrically located, denser region. Loosely organized cells, joined by desmosomes and bearing many short surface projections, arranged in either a single or a few layers were seen below the luminal cells. The former were separated from the stromal tissues by an undulating basal lamina following the irregular contour of the base of the cells (Fig. 2B). A typical pleomorphic adenoma provided Fig. 2A and a low-grade mucoepidermoid carcinoma Fig. 2B, both being different cases from those used in Fig. 1. Some duct-like structures in pleomorphic adenomas also were surrounded by a single layer of tumor cells, a feature emphasizing the organizational similarities of the two types of tumors.

Comparative histopathology

In the cases of pleomorphic adenoma examined ultrastructurally, the regions of tumor came from cellular areas in which there were readily identifiable duct-type lumina and a surrounding component of angular and slightly separated modified myoepithelial cells (Fig. 3A). At times, the latter tumor cells formed a single layer around the duct, while in other areas these cells were multilayered or formed extensive sheets devoid of obvious luminal differentiation. In some regions of certain pleomorphic adenomas, the modified myoepithelial cells were more closely packed and polygonal in shape (Fig. 3B).

Well-differentiated (low-grade) mucoepidermoid carcinomas were characterized by glandular structures in which the lumina were expanded with an excessive content of mucosubstances (Fig. 4A). The luminal cell lining was formed by variable numbers of goblet cells and flattened, cuboidal or columnar cells without evidence of a specific differentiation. In addition, in each of the five low-grade tumors, and as part of the glandular structures, a single layer of flattened to polygonal-shaped tumor cells and/or multiple layers of intermediate cells were present below the surface epithelium (Fig. 4A, B). In the three intermediate-grade lesions, cystic spaces were smaller and less frequent. However, duct-type lumina and goblet cells were still identifiable and again were surrounded by either a single or a few layers (Fig. 4C), or by larger numbers of intermediate cells (Fig. 4D), similar in appearance to those seen in the low-grade tumors (Fig. 4A, B).

By comparing organizational features, as well as the cytological aspects of the modified myoepithelial cells



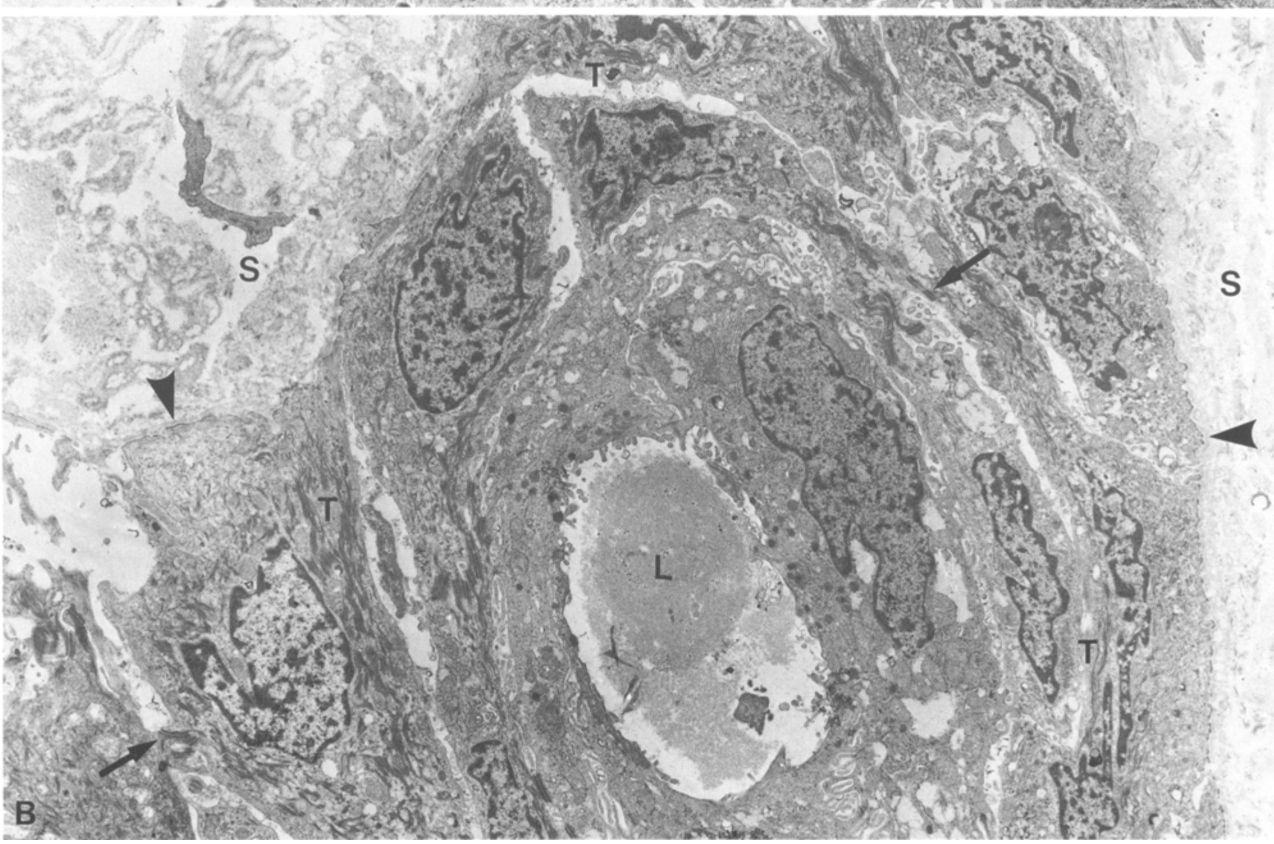


Fig. 1. In both **A** and **B**, a number of organizational aspects of the tumor cells are similar. Centrally placed cells bearing microvilli enclose a glandular lumen (*L*). Luminal cells are surrounded by a second population of more irregularly shaped and slightly separated tumor cells that are joined by desmosomes (*arrows*) and are separated from the stroma (*S*) (not shown in **A**) by a basal lamina (*large arrowheads*). Abluminal cells contain only a few tonofilament (*T*) aggregates in **A**, but many (*T*) in **B**. **A** ×5800; **B** ×6600

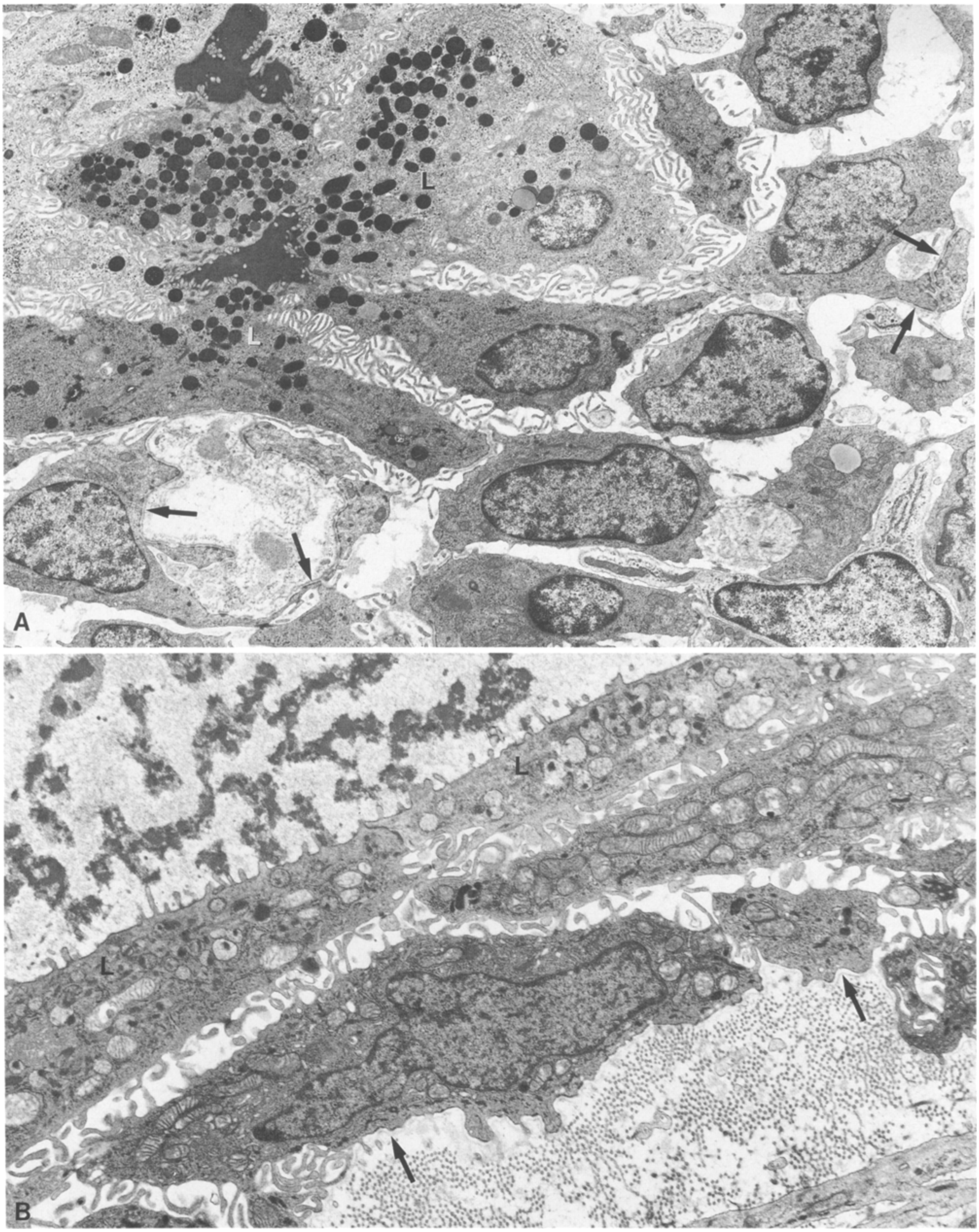


Fig. 2 A, B. In both tumors, luminal cells (*L*) contain many secretory granules. In **A**, the granules are homogeneously, and mainly, densely staining, while in the lesion represented in **B**, the granules have two compartments with only the eccentric or central core darkly stained. In **A**, the non-luminal cells are associated with a number of intercellular, basal lamina-lined (*arrows*) spaces, and in **B**, the one or more layers of abluminal cells also produce a basal lamina (*arrows*). **A** ×6000, **B** ×10900

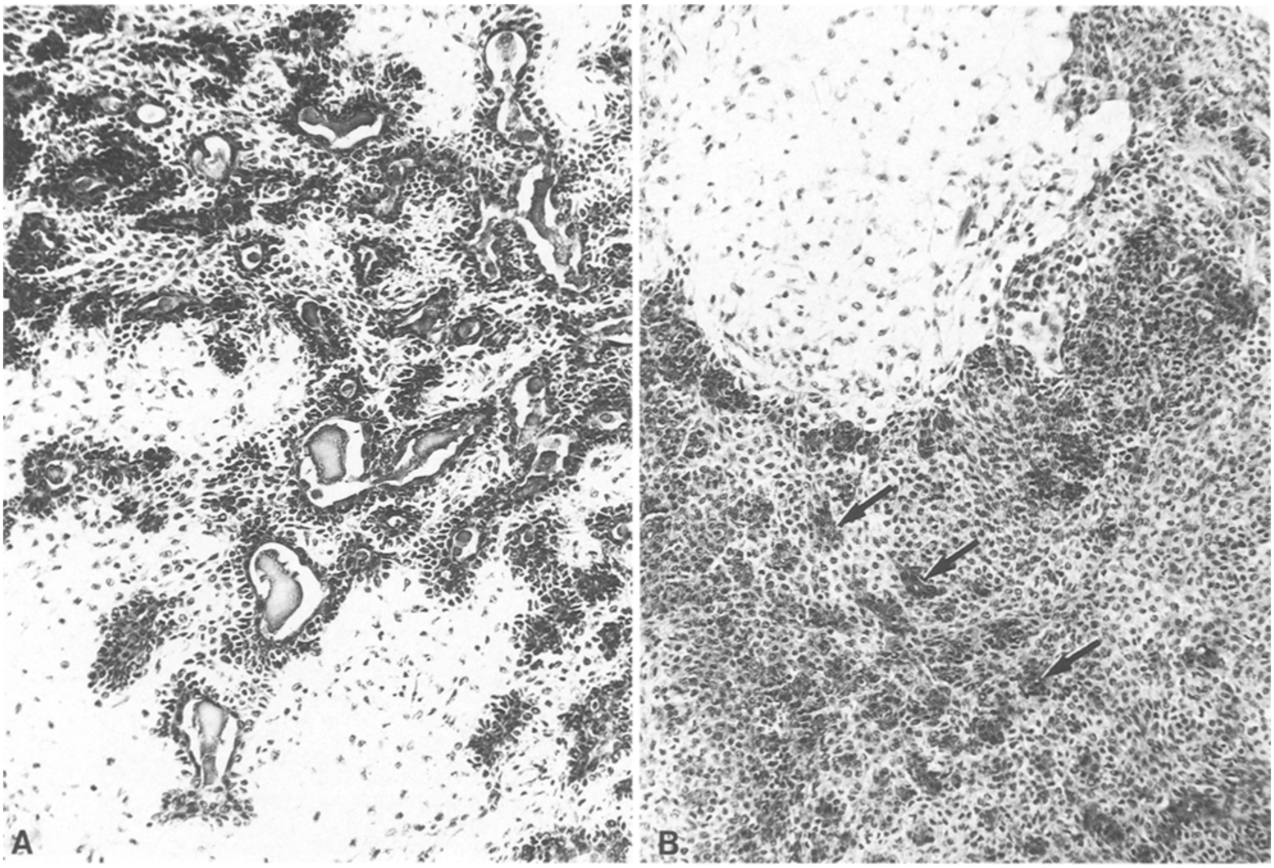


Fig. 3A, B. Pleomorphic adenoma. **A** Characteristic area with ductular elements surrounded by one or more layers of angular, slightly separated modified myoepithelial cells. Similar cells are increasingly separated forming scattered myxoid regions. **B** In this same adenoma, more compactly organized duct-type epithelial cells (*arrows*) are surrounded by sheets of modified myoepithelial cells. The appearance and arrangement of the latter cells should be compared to the intermediate cells in the low- and intermediate-grade mucoepidermoid carcinomas illustrated in Figs. 4**A** and **D**. **A** and **B** H&E, ×125

in pleomorphic adenomas (Fig. 3) with the intermediate cells in mucoepidermoid carcinomas (Fig. 4), basic similarities between these two tumors are evident even at the light microscopic level.

Specialized ultrastructural features in mucoepidermoid carcinoma

An area within the well-differentiated mucoepidermoid carcinoma illustrated in Fig. 4A revealed the typical interplay of goblet and intermediate cells forming microcystic structures. Ultrastructural examination of this neoplasm showed that the mucous granule-laden goblet cells had a definite relationship to the underlying tumor cells (Fig. 5); the latter represent the intermediate cells noted in Fig. 4A. Figure 6 presents the details of a multilayered zone of intermediate cells just below the goblet cells seen in Fig. 5. These elongated, somewhat angular cells had many surface projections, a number of which were slightly broader and were joined to neighboring intermediate cells by well-formed desmosomes complete with tonofilament bundles (Fig. 6). This feature along with the interrupted, widened intercellular spaces and the cytoplasmic tonofilaments are characteristic of squamous differentiation. The intermediate cells even in this region developed basal lamina on their stromal aspect (Fig. 6).

Whether organized as a single layer, that is as basal cells, or as a more extensive proliferation of intermediate cells, some tumor cells adjacent to the basal lamina exhibited additional features such as micropinocytotic vesicles and hemidesmosomes (Fig. 7). In some such cells, a band of filaments was organized in the outer aspect of the longitudinal axis of the cell; myofilament differentiation was not evident in this region and typical tonofilament bundles were scattered in the rest of the cytoplasm (Fig. 7). Prominent tonofilaments were seen in a proportion of intermediate cells, as well as in some luminal cells (Fig. 8); the latter emphasizes that squamous differentiation can occur in mucoepidermoid carcinomas by more than one pathway.

Infrequently, groups of intermediate cells in mucoepidermoid carcinoma exhibited an additional important feature, that is, small, intercellular foci lined by basal lamina that contained glycosaminoglycans and collagen fibers (Fig. 9). Some of these were remote from the similar basal lamina separating the intermediate cells from

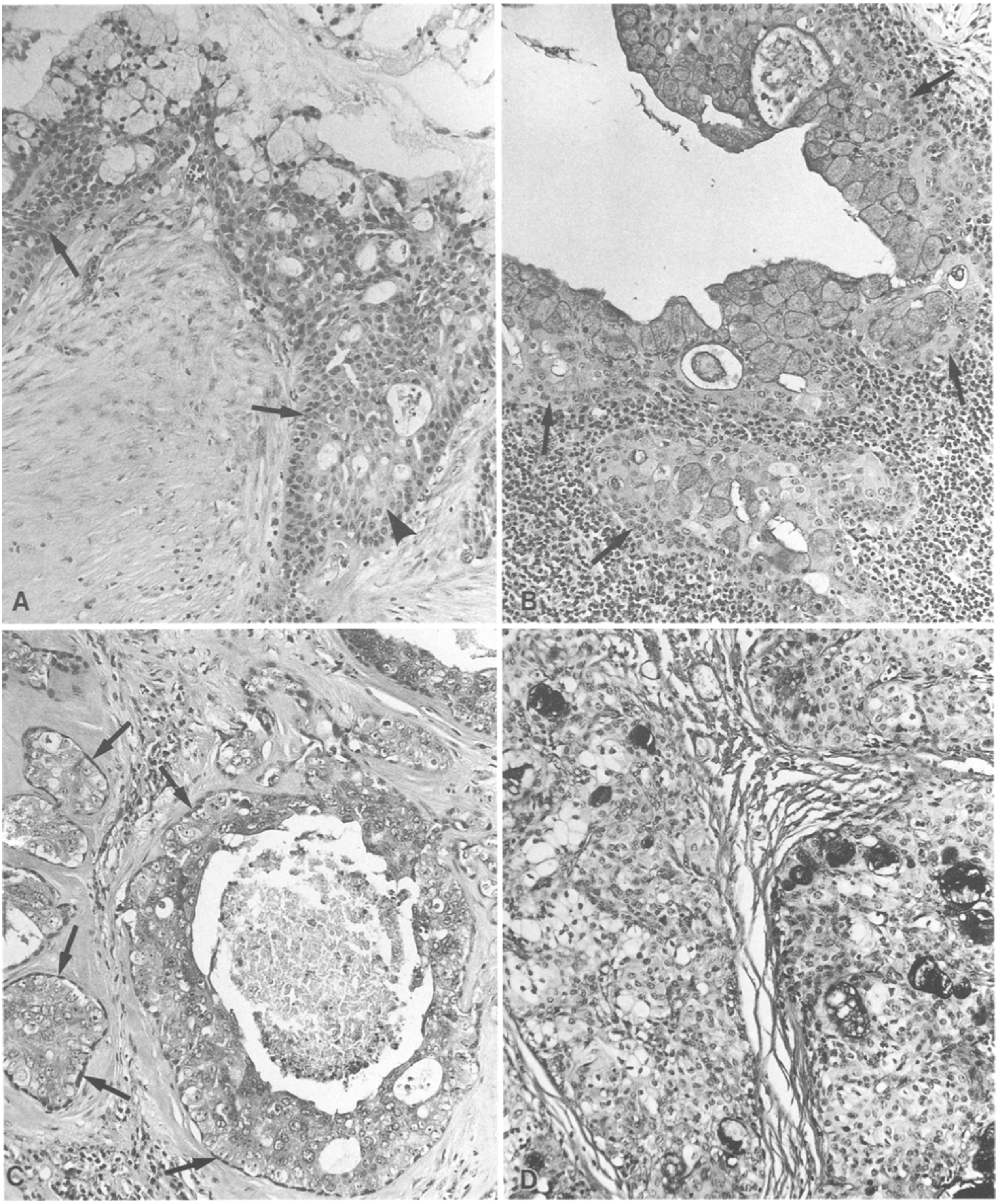


Fig. 4 A–D. Mucoepidermoid carcinoma. **A**, **B** Well differentiated; **C**, **D** intermediate-grade. **A** In microcystic regions, there are a few to many layers of intermediate cells (*arrows*) immediately below the surface layer of goblet cells. Focally, the intermediate cells have increased amounts of cytoplasm and assume a squamoid appearance (*arrowhead*). **B** In another example, the single layer or at most few layers of intermediate cells (*arrows*) are more difficult to appreciate below the goblet cells. **C** The clusters of squamoid appearing tumors cells (in this case likely modified luminal cells) are completely or partially surrounded by a flattened, darkly staining layer of tumor cells (*arrows*). **D** Aggregates of intermediate cells (some with clear cytoplasm, others with a squamoid appearance) isolate groups of mucus-containing tumor cells. **A**, **C**, H&E; **B** mucicarmine and hematoxylin; **D** PAS (without diastase) and hematoxylin; all ×125

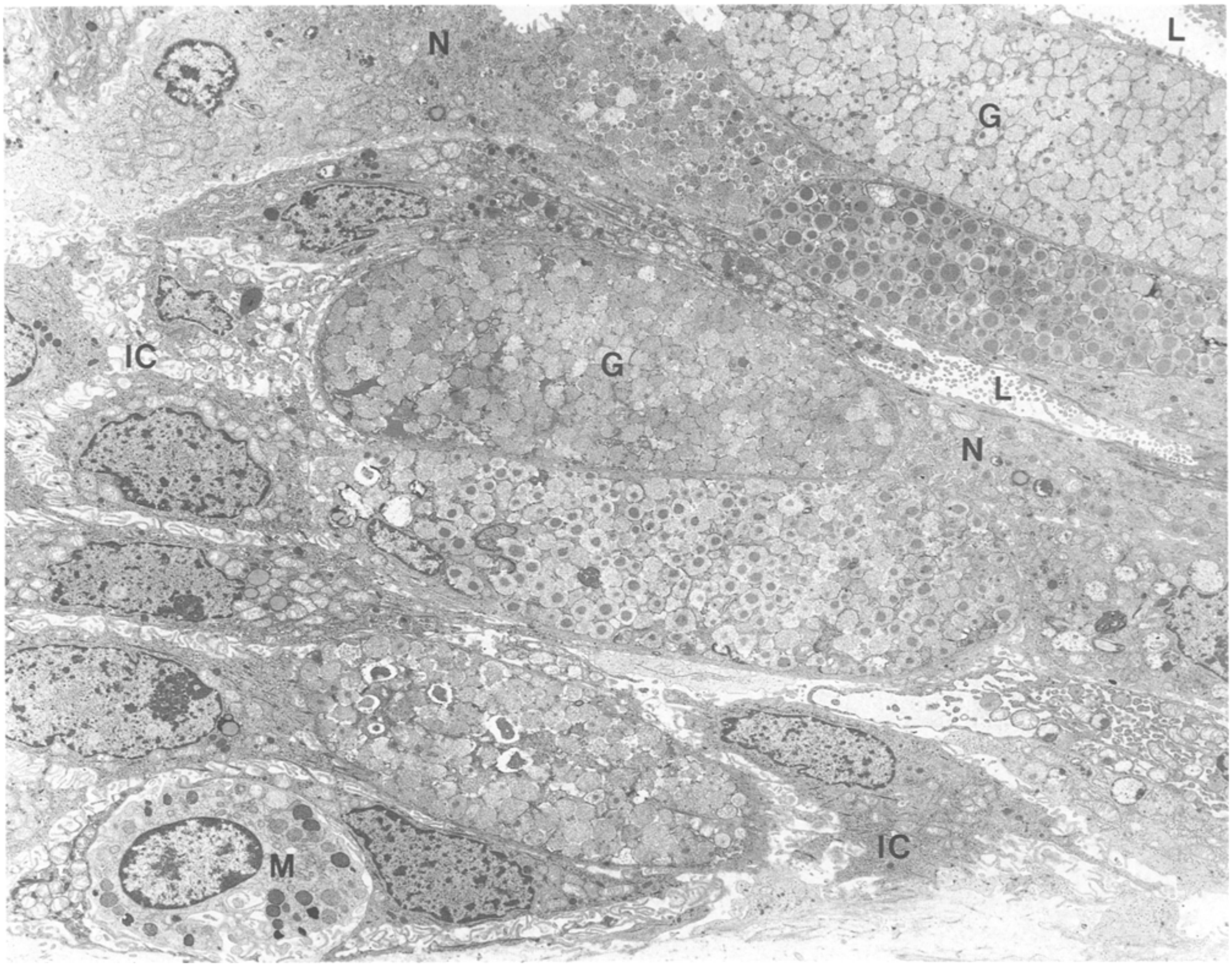


Fig. 5. Mucoepidermoid carcinoma (same case as Fig. 4A). A tangential section reveals the apical regions and lumens (*L*) of a number of goblet (*G*) and non-secretory luminal (*N*) cells. On the left side and at the bottom, the glandular cells interface with the smaller, slightly separated intermediate cells (*IC*). A mast cell (*M*) is present among the intermediate cells. ×4000

the true stroma and were even close to the luminal cells. Such extracellular foci (Fig. 9) were comparable to the basal lamina-lined spaces evident in electron micrographs of pleomorphic adenomas (Figs. 1, 3).

Discussion

Pattern recognition is one of the essential tools used by pathologists to classify tumors. The well and intermediately differentiated (grades 1 and 2) mucoepidermoid carcinomas have a readily recognizable histological profile. It is therefore reasonable to investigate the type of cells and their organization in these subtypes before attempting to better define the relationship to high-grade lesions and the factors underlying modifications in their histopathology, particularly in view of the relationship between histological appearance and prognosis in mucoepidermoid carcinoma (Spiro et al. 1978; Accetta et al. 1984; Evans et al. 1984; Conley and Tinsley 1985; Jensen et al. 1988; Hamper et al. 1989).

Current classification of salivary gland tumors relies on the concept that tumor development occurs from two specific duct stem cells (Eversole 1971; Regezi and Batsakis 1977; Batsakis et al. 1989). In formulating such a histogenetic classification, mucoepidermoid and squamous cell carcinomas are segregated from other salivary gland tumors and are presumed to originate from reserve (stem?) cells associated with the excretory duct. However, no experimental evidence to support this hypothesis has been published (Regezi and Batsakis 1977; Batsakis 1980). Despite recent assertions that such a segregation continues to be valid, at least for mucoepidermoid carcinoma (Batsakis 1985; Batsakis et al. 1986, 1989), the only reasoning offered seems to be the absence of myoepithelial cell participation in this lesion. At the opposite end of the classification scheme is pleomorphic adenoma, postulated to arise from a stem cell associated with the intercalated duct (Eversole 1971; Regezi and Batsakis 1977; Batsakis et al. 1989). It is this lesion that is cited as the prime example of a salivary gland tumor in which myoepithelial cells participate (Batsakis et al.

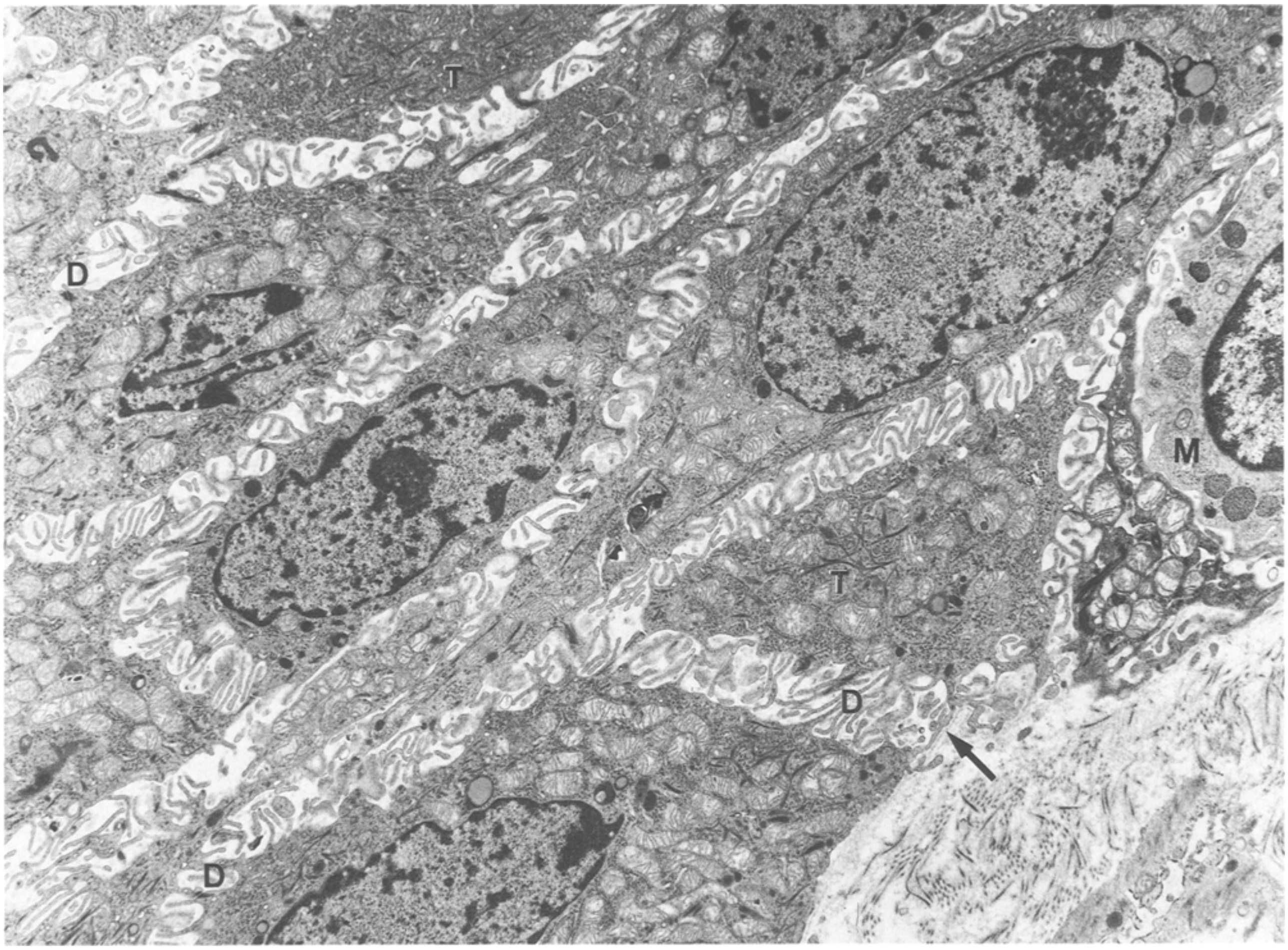


Fig. 6. Mucoepidermoid carcinoma (same case as Figs. 4A and 5). The features of the intermediate cells, and the mast cell (*M*), at the base of the goblet cells in Fig. 5 are more apparent at higher magnification. Widened intercellular spaces contain numerous fine and slightly broader cytoplasmic processes. The latter are joined by desmosomes (*D*) that are tonofilament associated. Some intermediate cells contain foci of tonofilament bundles (*T*). Basal lamina is present on one aspect of the cells (*arrow*). × 6900

1983, 1986, 1989; Dardick et al. 1983a, b; Erlandson et al. 1984; Lam 1985; Mori et al. 1987; Palmer et al. 1985). In fact, it is the neoplastic differentiation of myoepithelium that is considered responsible for the rich variety of lesions in this gland when compared to other organs such as the pancreas (Batsakis et al. 1989).

The spectrum of neoplastically modified myoepithelial cells, not only in pleomorphic adenoma but even in myoepitheliomas, is recognized (Sciubba and Brannon 1982; Mori et al. 1988; Dardick et al. 1989a, b). Since mucoepidermoid carcinoma has many differing and unusual histological characteristics and tends to arise most often in tissues containing myoepithelial cells, e.g., skin, breast, lung and salivary gland, a more detailed evaluation of cellular populations and comparative studies with such tumors as pleomorphic adenoma is required, which is the rationale for the current study.

Previous ultrastructural studies of mucoepidermoid carcinoma have illustrated a multiplicity of cell types. In addition to the readily recognized mucous, squamoid, and intermediate cells, others have been characterized as glycogen-, ribosome-, tonofilament-, and mitochondrial-rich (Hubner and Kleinsasser 1970; Tomita et al. 1977; Chen 1979; Nicolatou et al. 1979; Miura et al. 1986; Chaudhry et al. 1989). However, as we (Dardick et al. 1984) and others (Hanna and Kahn 1985) have shown previously and again in the current series of low- and intermediate-grade mucoepidermoid carcinomas, there are in essence two basic types of tumor cell, luminal and intermediate, that have a specific organizational relationship. While the former is responsible for the goblet cell differentiation and the mucous secretion, both cell types can express tonofilaments and so account for the squamoid histological patterns [for luminal cells with prominent tonofilaments see Fig. 9 and Chen (1979), his Fig. 7]. Again, both cell types can accumulate excess glycogen and produce the clear cell component evident in some mucoepidermoid carcinomas (Nicolatou et al. 1979; Miura et al. 1986). Thus descriptive studies of mucoepidermoid carcinomas may be of marginal importance compared to an understanding of the relationship between luminal and intermediate cells.

Based on original observations of routinely stained sections of mucoepidermoid carcinomas, the designation "intermediate cells", seemed appropriate as these cells were suggested to exhibit bidirectional differentiation to

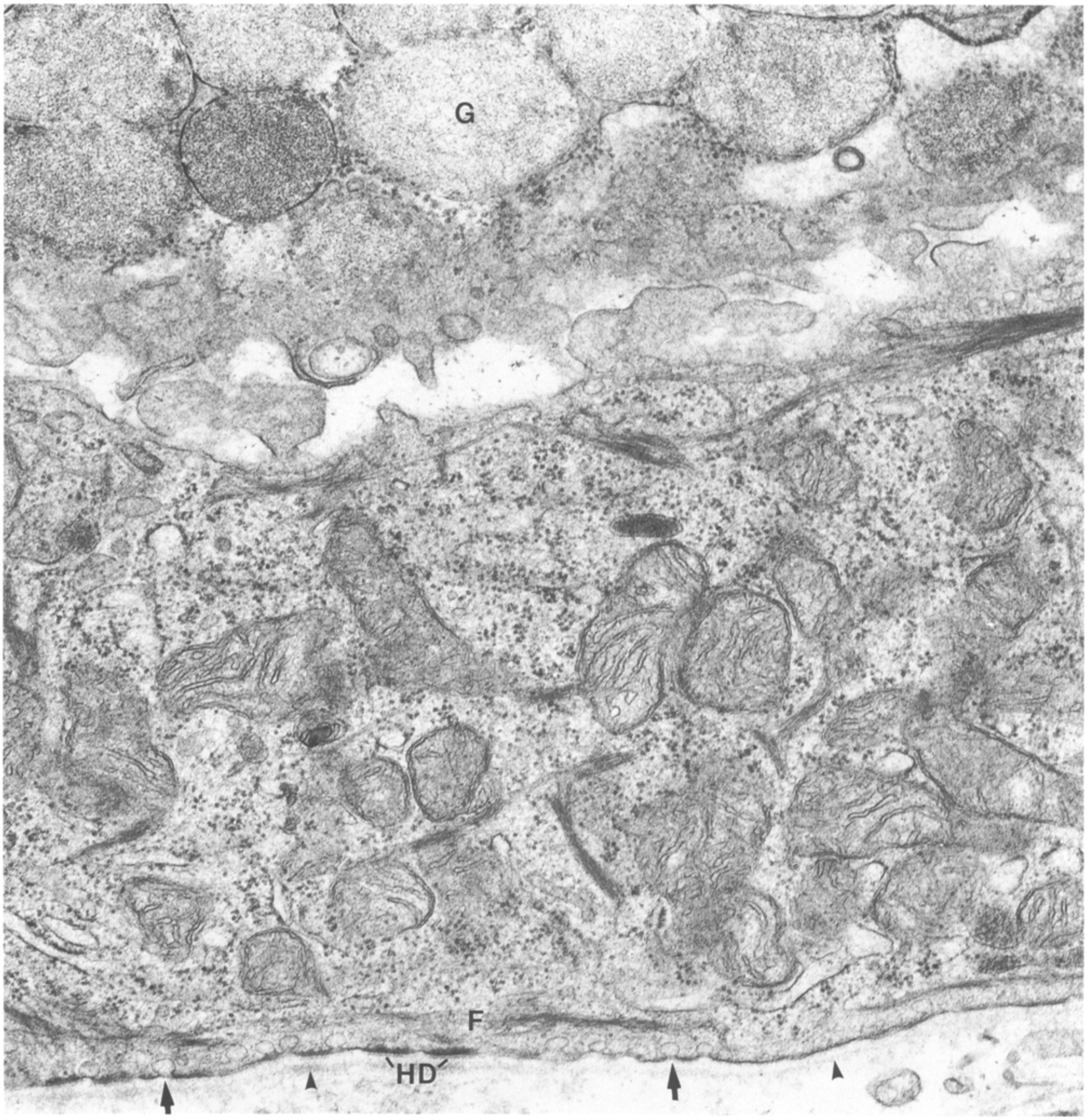


Fig. 7. Mucoepidermoid carcinoma. Another low-grade example has a layer of slightly flattened, basal cells below the mucus-granule (*G*) containing luminal cells. In addition to tonofilaments, the basal cells exhibit micropinocytotic vesicles (*arrows*), hemidesmosomes (*HD*), basal lamina (*arrowheads*), and a layer of filaments (*F*) adjacent to the outer margin. ×48000

both goblet cells and squamous cells. Neither histochemical nor electron microscopic studies support such a concept (Dardick et al. 1984; Hanna and Kahn 1985; Nikai et al. 1986; Chaudhry et al. 1989). Indeed, as this comparative study shows, the intermediate cells of mucoepidermoid carcinoma are almost certainly the counterpart of the modified myoepithelial cells of pleomorphic adenoma. Not only are they positioned similarly to those observed in pleomorphic adenomas (Figs. 1, 3), and even in adenoid cystic carcinomas (Orenstein et al. 1985), but intermediate cells share many ultrastructural features with modified myoepithelial cells in both pleomorphic adenoma and adenoid cystic carcinoma (Dardick et al. 1983a, b; Erlandson et al. 1984; Orenstein et al. 1985; Dardick and van Nostrand 1985, 1987). Ultrastructurally, some intermediate cells even resemble the normal myoepithelial cell (Hanna and Kahn 1985; Chaudhry et al. 1989).

One of the major differences between mucoepidermoid carcinoma and both pleomorphic adenoma and adenoid cystic carcinoma is the development of basal lamina-lined extracellular spaces in the latter; this fea-

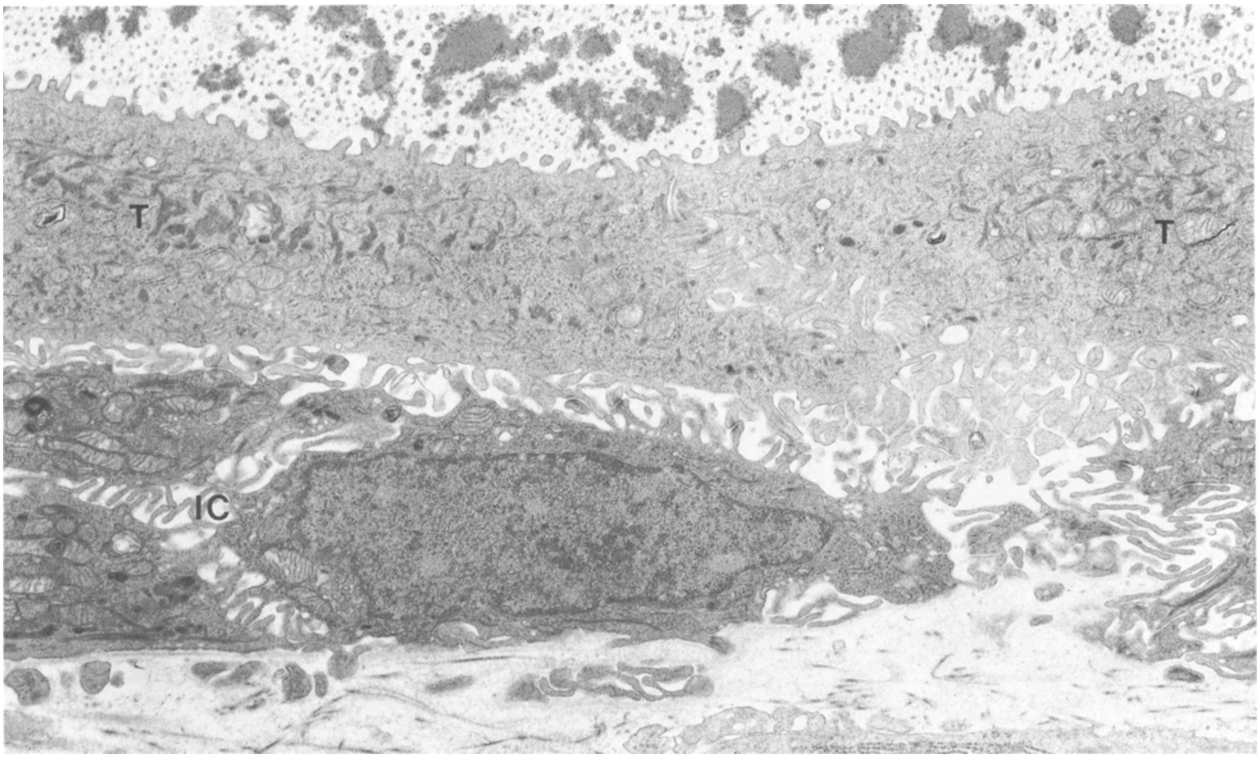


Fig. 8. Mucoepidermoid carcinoma, low-grade (same case as Fig. 4B). A further example again reveals two cell-types, but in this case the luminal cells express more tonofilaments (*T*) than the intermediate cells. ×9400

ture is responsible for the formation of myxoid "stroma" in pleomorphic adenoma and the cribriform growth pattern in adenoid cystic carcinoma. Although such important differential diagnostic characteristics are absent in mucoepidermoid carcinomas, the potential for intermediate cells to be associated occasionally with similar extracellular materials [Fig. 9 and Dardick et al. (1985)], is further support for a close developmental relationship between these tumor cells and modified myoepithelial cells.

As we have shown in histological sections, even the modified myoepithelial cells associated with ducts in pleomorphic adenomas can be similar to intermediate cells in mucoepidermoid carcinomas. Using histochemical techniques, Nikai et al. (1986) have also illustrated comparable staining patterns of myoepithelial cells in these two tumors. In pleomorphic adenoma, glial fibrillary acidic protein (GFAP) is not uncommonly expressed in the tumor cell component at the periphery of the duct-like structures, that is, the modified myoepithelial cells (Burns et al. 1988; Gustafsson et al. 1989); in one mucoepidermoid carcinoma, GFAP has been noted in a similar distribution (Gustafsson et al. 1989). The relationship between luminal and intermediate cells is readily appreciated in low- and intermediate-grade mucoepidermoid carcinomas, but may be more difficult to display in high-grade tumors. However, this does not preclude common ancestral growth patterns within the histological spectrum of mucoepidermoid carcinoma, as we have shown increasing modifications of the two main cell-types in carcinoma ex pleomorphic adenoma as such lesions proceed from carcinoma in situ to invasive carcinoma (Dardick et al. 1989a).

The rationale for suggesting that pleomorphic adenoma and adenoid cystic carcinoma develop following neoplastic induction of intercalated duct cells while mucoepidermoid carcinoma has a histogenetic derivation from excretory duct reserve cells (Batsakis et al. 1989; Chaudhry et al. 1989) is not readily apparent. Clearly, all three types of tumor share basic morphogenetic characteristics and, thus, are more closely related than has been suggested in the past. Perhaps the division of salivary gland tumors on the basis of origin from specific segments of the duct system is not essential, since it may bear no relationship to the biological behavior of these lesions. All parts of the duct system are bicellular, that is, luminal and basal/myoepithelial cells (Born et al. 1987; Dardick et al. 1987, 1988; Geiger et al. 1987; Leoncini et al. 1988), and myoepithelial cells are even present on intralobular striated ducts (Chaudhry et al. 1987; Dardick et al. 1987). So tumors such as pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma could develop from a variety of cell types in any segment of the ducts and yet have similar histological appearances.

The neoplastic counterpart of the uniquely specialized myoepithelial cell (Dardick et al. 1989b) may be the major factor responsible for the histological variety seen in salivary gland tumors and this may be as true of mucoepidermoid carcinoma as it is of pleomorphic

Fig. 9. Mucoepidermoid carcinoma (same case as Figs. 4B and 8). The intermediate cells not only form an external lamina (*arrows*) adjacent to the true stroma (*S*), but also develop basal lamina-lined intercellular spaces (*IS*); some of these are remote from the true stroma and one (*asterisk*) is even adjacent to a luminal cell (*L*). ×11000

adenoma. The obvious differentiation of two cell types and their arrangement in mucoepidermoid carcinoma, the similarities of modified myoepithelial cells in pleomorphic adenoma and the intermediate cells in mucoepidermoid carcinoma, and the location of focal accumulations of extracellular materials in both lesions all support such a conclusion. Labelling cells with an undifferentiated appearance as "stem" cells in tumors such as mucoepidermoid carcinoma (Chaudhry et al. 1989) is unhelpful since the biological potential of such cells cannot be determined simply by a description of cytological features in electron micrographs.

Until experimental data is available to substantiate a classification of salivary gland tumors on the basis of histogenetic concepts, the ultimate differentiation of the neoplastic cell, the synthetic processes of tumor cells and their eventual organization – all morphogenetic processes – would appear to constitute a more clinically relevant basis for classification.

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