MYOEPITHELIAL CELLS: REVISITED
- Review -
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Summary
Myoepithelial cells are important components of salivary gland which are stellate shaped with cytoplasmic extensions and present between the basement membrane and the plasma membrane of the acinar structures and ductal cells. They have structural features of both epithelium and smooth muscle cells and so they are called the myoepithelial cells. They enable the contraction of the structural apparatus and this expulses the secretions from the acinar cells. They can be demonstrated by special stains and enzyme histochemistry. The article reviews on the developmental process of the myoepithelial cells, structure, function, the differentiation patterns and its role in salivary gland tumours

Keywords: differentiation, immunohistochemistry, salivary gland, secretion.

Introduction
The human salivary gland system is composed of three major salivary gland and numerous minor salivary glands. The Myoepithelial cells are important component salivary gland and are located beneath the basement membrane and the basal plasma membrane of the acinar cells. They are usually found in the glandular epithelium as a thin layer beneath the luminal cells. They are seen in sweat glands, lacrimal glands, mammary glands and salivary glands.

Myoepithelial cells are spindle shaped and the cell body contains four to eight cytoplasmic processes which normally run parallel to the direction of the duct. Myoepithelial cells are also called as basket cells as they have a stellate shaped appearance with embracing cytoplasmic process the secretary unit. They are present in both minor and major salivary glands (Raubenheimer et al., 1987; Gnepp., 2001). This structural unit was first described by Zimmerman in 1898. The myoepithelial cells of the salivary gland are ectodermal in origin and envelope the acinar, glandular and ductal elements of the salivary gland. They are predominant in the acinar areas followed by the intercalated duct and it is almost absent in the excretory ducts (Dardick et al., 1984)

Prenatal and Postnatal development of myoepithelial cells:
Early development stage (10-18 weeks):
The primitive myoepithelial cells appear in the salivary gland epithelium at about 15-16 weeks of gestation even before the cytodifferentiation of acinar and ductal luminal cells takes place. At this phase they demonstrate irregular fibrillar demonstration. These cells are immature initially and gradually over a period of time increase in number and they get closely apposed to the tubule alveolar structure of the salivary gland (Caselitz et al., 1981)
Early intermediate developmental stage (19-24 weeks):
The myoepithelial cells in the fetal salivary gland express actin filaments before the maturation of the acinar and ductal luminal cells takes place. This suggests that myoepithelial cells antedate the secretary epithelium during embryogenesis. With maturation of the acinar cells, the myoepithelial cells undergo cytoplasmic extension and took place in the basal portins of the acini and intercalated duct and they were extruded in the excretory and striated ducts (Caselitz et al., 1981; Lee et al., 1991).
Late intermediate developmental stage (25-32 weeks):
The myoepithelial cells undergo morphological changes during this phase and the cells get further flattened and dendritic at the basal portions of the acinar and intercalated duct structures. The development of myoepithelial cells and secretary cells begins at the same time. However the myoepithelial cells differentiate asynchronously with the secretary cells. The dendritic myoepithelial cells mature at 25-26th week and become more conspicuous. They increase in number during this stage and mature earlier to push the secretary material out of the acini towards the excretory ducts against the amniotic fluid pressure (Lee et al., 1991; Chi et al., 1996).

Late developmental stage (33-40 weeks):

The myoepithelial cells increase in number and develops contractile properties. The cells which first developed in the acinar and intercalated ductal areas move towards the excretory ducts through the basal portions of the duct (Lee et al., 1991; Chi et al., 1996).

Structure of myoepithelial cells:

Myoepithelial cells appear to have the same morphology, irrespective of the organ or species in which they are studied. The cells embracing the acini are the secretary endpieces which contains four – eight cytoplasmic process. The cytoplasmic process gives two or more secondary branches and this gives an appearance of an octopus sitting on a rock appearance (Young et al., 1978). The myoepithelium contains an outer and inner surface. The outer surface contains caveolar invaginations and they are numerous in areas where nerve fibres are present. The inner surface or the visceral surface is smooth and they are attached to the secretary cells by desmosomes. The cytoplasmic process of the cell contains extension of the cytoplasmic membrane which are protruded deep inside (Tandler., 1965).

Electron microscopy shows an ellipsoidal cell containing few ribosomes and mitochondrial scattered through the cytoplasm of the body. Other organs including the golgi apparatus, endoplasmic reticulum are seen in the juxtranuclear position (Young et al., 1978). They contain cytoplasmic filaments which are uniform in diameter. They have varying densities with varying distance between the individual elements. They have a compact distribution resembling the dense bodies and terminate in the attachment devices. Intermediate sized filaments are demonstrated in the cytoplasm are of cytokeratin type (Caselitz et al., 1981).

Myoepithelial cells demonstrate an electron lucent cytoplasm devoid of any organelles adjacent to the cells. These cells are believed to be clear cells which had undergone a transformation. The myoepithelium therefore has properties of a secretary intercalated duct cell suggesting an ancestral origin (Riva et al., 1976).

Functions of myoepithelial cells:

The role of myoepithelial cells begins from the embryonic development from the branching morphogenesis and promotes epithelial cell differentiation. The myoepithelial cells of the salivary gland have a dual innervations by sympathetic and parasympathetic synapses and the impulses from both results in contraction of a cell (Garrett et al., 1979). The diffusion of transmitter substances synchronizes with the contraction made by the gap junction and the overlap between the myoepithelial cell process (Tamarin., 1966; Brocco et al., 1979). The myoepithelial contraction helps in expulsion of the secretions by the rupture of a ripe mucous cell, preventing distention of secretary endpiece thus reducing the luminal volume. The secretary cells lacking the myoepithelial cells usually secrete a watery or serous saliva (Tandler., 1965).

The contraction of the myoepithelial cells decrease the surface area of the secretary apparatus exposed to interstitial fluid and thereby modifies the salivary secretion The myoepithelial cilia act as chemoreceptors and has a sensory function. Contraction of the myoepithelial cells around the intercalated ducts results in
reduction of the luminal volume and shortens and widens the structure decreasing the peripheral resistance (Young et al., 1977).

The myoepithelial cells also helps in transportation of the metabolites to and from the secretory cells. The basal surface of the myoepithelium demonstrates numerous infoldings which increase the surface area exposed to the tissue fluid (Nagai et al., 1985). There is presence of pinocytic vesicles, which demonstrates positivity for iron binding protein ferritin, increased alkaline phosphatase and magnesium dependent adenosintriphosphatase activity (Toto et al., 1985; Yoshikara et al., 1984).

The myoepithelial cells helps in formation and maintainence of the basement membrane components namely fibronectin, laminin and elastin (Toto et al., 1985). These are not just essential for the epithelial proliferation and differentiation, but also plays a role in epithelial mesenchymal junctions through which the metabolites of or role as a tumour suppressor the saliva are communicated (Han et al., 1976; Kleinman et al., 1981).

Myoepithelial cells beyond all these functions, have a major role as a tumour suppressor by exerting paracrine antiinvasive role by promoting epithelial differentiation, basement membrane secretion, by secreting proteinase inhibiting angiogenesis (Ellis., 1991; Batsakis et al., 1983).

Morphologic patterns of the myoepithelial cells in tumours:

Neoplastic myoepithelial cells takes complex patterns resulting from interplay of three factors namely the (i) Cytological Differentiation (ii) Extracellular matrix production and (iii) Architectural patterns

Cytological Differentiation:

The myoepithelial cells differentiates into cells of various morphological types. The forms taken by these cells are angulate/ basaloid cells( demonstrate small hyperchromatic nuclei with faint eosinophilic cytoplasm), epitheloid cells ( cells are polygonal with vesicular nuclei and ample cytoplasm), clear cells ( contain clear cytoplasm due to glycogen), spindle cells ( elongates and fusiform with pale cytoplasm) and plasmacytoid cells ( contains bright eosinophilic cytoplasm with eccentric nuclei) (Fig 1). A tumour undergoing myoepithelial cell differentiation has a morphological heterogeneity and sometimes they also undergo metaplastic changes such as chondroid, squamous and oncocytic area (Ellis., 1991; Batsakis et al., 1983).
Figure 1: The differentiation pattern of myoepithelial cell in tumours

Extracellular matrix production:
Neoplastic myoepithelial cells alters the matrix synthesizing property and produces excess of basement membrane and non basement membrane components. Chondroitin sulfate is a non Basement membrane matrix which is produced in excess resulting in bluish gray appearance which is alcian blue positive. They also produce eosinophilic hyalinized material (type IV collagen and laminin) related to basement membrane and the components of interstitial matrix (Fibronectin, type I, II Collagen).(Fig 2) Accumulation of these materials in varying proportions results in alteration of the basement membrane structure on salivary gland tumours (Raubenheimer et al., 1987; Dardick et al., 1984; Ellis., 1991; Dardick et al., 1989).

Architectural Patterns:
Dardick et al. (1989) suggested the diverse architectural patterns of myoepithelial cells which are enumerated as follows. The various patterns that a myoepithelial cell can produce are myxoid pattern, solid pattern, reticular pattern, microcytic pattern, cribriform pattern (Fig 1). The myxoid pattern demonstrates loosely arranged tumour cells which are produced due to production of abundant chondromyxoid matrix. The solid pattern are non myxoid in which the cells are arranged in the form of nests and sheets seen in intervening hyaline stroma. Reticular pattern shows anatamosing pattern composed of epithelial myoepithelial cells intervened by extracellular material. Microcystic pattern are otherwise called as pseudocystic pattern and shows cystic space formed by accumulation of myxoid matrix within nests of tumour cells. Cribriform pattern are called pseudoglandular pattern in which the epithelial cells form cribriform structures and pseudoumen due to myxoid matrix production (Ellis., 1991; Batsakis et al., 1983).

Role of myoepithelial cells in benign and malignant salivary gland tumours:
Pleomorphic adenoma and myoepithelioma:
The tumours are benign tumours with various morphological diversities. The predominant myoepithelial differentiation in these tumours are responsible for the mesenchymal components and morphological diversity. Myoepithelially differentiated cells are arranged in the form of Sheets and islands with varying proportions of spindle cells, clear cell, plasmacytoid, and epitheloid cells. Most tumors are composed of a just a single cell type but combinations of two or more types may occur (Hirano et al., 1990)

Basal cell adenoma and myoepithelial cells:
The basal cell adenoma was first described in 1967 by Kleisasser and they
lack the myxochondroid component and are generally monomorphic. Myoepithelial cells participate in this tumour and produce a hyalinized matrix. Variable amounts of myxoid matrix also occur and the neoplastic myoepithelial cells produce basement membrane related and interstitial matrix. This results in formation of hyaline droplets in this tumour (Zarbo et al., 2000)

**Adenoid cystic carcinoma and myoepithelium:**

ACC exhibits a dual differentiation pattern of epithelial and myoepithelial cells resulting in three patterns: the cribriform, solid and tubular pattern. The myoepithelial cells are arranged in the form of small basaloïd aggregate of angulated cells in the periductal location and cribriform areas. The solid variant also demonstrates scatted or peripheral basaloïd myoepithelial cells arranged in the form of small sheets/nests. The myoepithelial differentiation also gives rise to a collagenous and hyalinized stroma with a bluish myxoid material in cribriform pattern (Szanto et al., 1984)

**Epithelial Myoepithelial carcinoma:**

This tumour similar to the adenoid cystic carcinoma shows a dual epithelial myoepithelial differentiation and this is reflected as a nodular growth pattern with the epithelial tubules cuffed by myoepithelial cells. Bimorphic type is similar to ACC but the stainin pattern differs. The outer cells are clear with expression of myoepithelial markers. However when all the cells are predominantly having myoepithelial differentiation, it is difficult to distinguish from primary clear cell carcinoma, clear cell myoepithelial carcinoma and hyalinizing clear cell carcinoma (Simpson et al., 1991; Hagiwara et al., 1995)

**Polymorphous low grade adenocarcinoma:**

The myoepithelial differentiation is rarely present in this tumour and only a focal stain with smooth muscle markers has been demonstrated. The participation of myoepithelial cells in this tumour is however suggested by the presence of a myxoid hyalinized matrix as seen in other tumours (Batsakis et al., 1983; Dardick et al., 1989).

**Mucopeidermoid carcinoma and myoepithelial cells:**

The histopathology of MEC as reported by Dardick et al. (1989), suggests the presence of luminal epithelial cells surrounded by modified intermediate cells. They are believed to be the modified myoepithelial cells. However, whether the tumour originates from the reserve duct cells or the myoepithelial cells is still controversial. The two theories of histogenesis reported by Dardick states that the MEC differentiates from the luminal epithelial cells or from the modified myoepithelial cells. The modified myoepithelium corresponds to the intermediate cells and shows possibilities for undergoing squamous metaplasia (Dardick et al., 1989).

**Conclusion:**

The myoepithelial cells are important because they play a fundamental role in secretion of saliva by its contractile function. They are also considered as the key for various morphogenetic processes as they give various histological appearances to the gland. The role of myoepithelial cells in salivary gland tumours needs to be understood because they differentiate into a variety of morphological pattern. Knowledge on the differentiation pattern thus paves a way for the diagnosis of salivary gland tumours.

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