

The Biology of Clara Cells -Review Paper

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INTRODUCTION

Clara cells, the nonciliated population in the epithelial lining of bronchioles, are one of the most heterogeneous and multifunctional cell types in the mammalian lung. The best-defined markers for Clara cell differentiation in adult mammals are the ultrastructural features (Table 1).

Clara cells are characterised as low cuboidal cells with minimal apical projections, bound to each other by junctional complexes on the luminal aspects of the basolateral membrane^[1,2]. The distribution of organelles within the cytoplasm shows little polarization and includes small amounts (<10%) of rough (RER) and smooth (SER) endoplasmic reticulum, mitochondria and Golgi apparatus. The nucleus is approximately one-third of the total volume of the cells and is centrally placed. The apical portions of the cytoplasm generally contain a small number of ovoid, electron-dense membrane-bound secretory granules. This structural composition has been defined for humans and in three species of macaque monkeys^[1].

The ultrastructure of the most of the mammalian species is slightly different from each other and is characterised by:

- Extensive apical projections into the airways
- A polarized organisation of organelles

In most species there is an abundance of apical smooth endoplasmic reticulum. In mouse, hamster, rat, guinea pig rabbit, pig, sheep and horse more than 40% of the cytoplasmic volume consists of smooth endoplasmic reticulum^[3,7].

Clara cell functions: Clara cells have at least four roles in the normal lung function:

- Contribute a secretion to the extracellular lining fluid
- Progenitor cells for both themselves and for ciliated cells

- Contain a variety of cytochrome p-450 monooxygenases that have an active role in metabolism of xenobiotics.
- Regulate fluid balance in the distal conducting airways

Table 1: Comparison of volumes (μm^3) of cellular components in Clara cells adapted from^[1]

Component	Rabbit	Cat	Bonnet monkey
Cell	471.8±51.8	496.1±40.8	418.9±36.1
Nucleus	83.0±7.0	132.5±45.6	119.9±18.4
SER	213.4±51.0	38.9±24.4	15.6±9.9
Glycogen	37.5±13.1	222.9±36.4	0
RER	25.8±19.4	1.56±3.38	38.9±1.2
Mitochondria	75.4±17.7	70.9±34.9	42.0±8.3
Granules	12.5±6.7	0	6.3±1.4
Golgi apparatus	5.7±5.7	14.6±13.1	24.1±2.8

Secretion products: Clara cells secrete a number of proteins including surfactants SP-A, B and D, Clara cell 10-kDa protein/uteroglobin, leukocyte protease inhibitors, β -galactoside binding lectin and a trypsin-like protease^[2,8,9]. It was proposed that Clara cell secretion is both apocrine and merocrine, the former predominating^[8].

Clara cells 10-kDa protein (CC10) is the predominant product of Clara cells and is distributed mainly in the bronchiole^[10,11]. The protein has also been referred to as Clara cell 16-kDa protein according to results using electrospray/mass spectrometry. This protein was first identified in urine of patients with renal failure and purified later from lung lavage^[12,14]. The entire human CC16 gene has been sequenced and localised to chromosome 11, p12-q13, a region occupied by several genes involved in the regulation of allergy and inflammation^[12]. Human CC10 is identical to human Urinary Protein 1 (UP1) and Human Uteroglobin (UG)^[11,15].

Changes in CC10 levels in sera and bronchoalveolar lavage (BAL) fluid have been reported in various lung diseases and in patients exposed to different toxins including cigarette smoking^[15,19]. Although the function of CC10 is unclear, it may play a role in regulation of inflammation.

Surfactant proteins and the mRNA for SP-B have been localised in the Clara cells^[20]. The detection of SP-B

in Clara cells is more consistent than that of SP-A. SP-A and SP-D are believed to be involved in host defence against micro-organisms by their lectin like activity^[21]. The role of the surfactant proteins secreted by Clara cells is still unclear^[2,19].

The 29-kDa β -galactoside binding lectin may be the same as the 30-kDa Clara cell tryptase, but their function and physiological role is still not clear. Clara cell tryptase has been shown to cleave haemagglutinin and activate infectivity of influenza A virus^[22,24].

The leukocyte protease inhibitor has been immunohistochemically localised to Clara cells. This protein inhibits leukocyte proteases, especially elastase^[25].

Progenitor cells: Clara cells are self replicative but also terminally differentiate into ciliated cells in the bronchioles^[1,26,28]. Clara cells isolated from the lungs of rabbit were shown to be able to re-populate denuded tracheas^[29]. Clara cells were shown not to be necessary for pulmonary neuroendocrine cell hyperplasia^[19].

Metabolism of xenobiotics: Among the other epithelial cells found in the lung epithelial bronchiolar region, Clara cells are distinguished for their ability to metabolise xenobiotics via the cytochrome P-450 (CYP) monooxygenase system and flavin-containing monooxygenases^[30,32]. Bronchiolar Clara cells are considered to be one of the principal targets in the mammalian lung pulmonary toxicants. These include a wide variety of compounds including furans, chlorinated hydrocarbons and aromatic hydrocarbons. Many compounds injure Clara cells in most of the species but Clara cells in different species do not have the same level of sensitivity to any one compound^[6,26,33].

Changes in Clara cells are manifested as early as 1 hour after exposure and involve clumping and margination of nuclear chromatin, mitochondrial swelling, dilation of endoplasmic reticulum membrane and disruption of cell junctions. Within 24 h of exposure the injury there is cellular enlargement and formation of large numbers of membrane-bound vacuoles^[31,33,34].

There are a large number of studies showing the ability of Clara cells to metabolise a number of xenobiotics including naphthalene and its metabolites^[35,40], ozone^[18], styrene and its compounds^[41,42], benzo (α) pyrene and its derivative compounds^[43,44,45], cigarette smoke^[46,48], coumarin^[49,50], methylene chloride^[51,52], trichloroethylene^[53,54], amines^[55] and nitrogen dioxide^[56]. Diallyl sulfone, a derivative of garlic, was found to protect against Clara cell injury caused by 1,1-dichloroethylene by conjugating a glutathione with its reactive metabolites^[57].

Regulation of fluid balances: Due to the fact that

bronchiolar epithelium has lateral projections, it has been suggested that the airways epithelium of distal conducting airways is involved in re-absorption and clearance of airway-lining fluid^[3,58]. It was shown that there is a net movement of sodium ions (Na^+) from the mucosal to the serosal side in cultured monolayers of rabbit Clara cells. This movement is amiloride-sensitive and occurs under short- or open-circuit conditions, thus most likely Clara cells are involved in fluid re-absorption. Chloride ions (Cl^-) secretion was observed to be induced by amiloride, but no net Cl^- movement was observed under basal conditions^[60]. Cl^- channels that can be stimulated by c-AMP-activating agents and extracellular ATP were described in Clara cells. These channels share many bio-physiological properties with the Cystic Fibrosis Transmembrane Regulator (CFTR)-related Cl^- channel (1997).

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