Progress in Retinal and Eye Research 54 (2016) 49–63

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Goblet cells of the conjunctiva: A review of recent findings

Ilene K. Gipson

Schepens Eye Research Institute, Department of Ophthalmology, Harvard Medical School, 20 Staniford Street, Boston, MA 02114, USA

ARTICLE INFO

Article history:
Received 25 February 2016
Received in revised form
11 April 2016
Accepted 14 April 2016
Available online 16 April 2016

Keywords:
Goblet cell
Goblet cell differentiation
Conjunctival epithelium
Ocular surface
SPDEF
Dry eye

ABSTRACT

Goblet cells within the conjunctival epithelium are specialized cells that secrete mucins onto the surface of the eye. Recent research has demonstrated new characteristics of the cells, including factors influencing their differentiation, their gene products and their functions at the ocular surface. The following review summarizes the newly discovered aspects of the role of Spdef, a member of the Ets transcription factor family in conjunctival goblet cell differentiation, the newly discovered goblet cell products including claudin2, the Wnt inhibitor Frzb, and the transmembrane mucin Muc16. The current concepts of conjunctival goblet cell function, including debris removal and immune surveillance are reviewed, as are changes in the goblet cell population in ocular surface diseases. Major remaining questions regarding conjunctival cell biology are discussed.

Contents

1. Introduction

A continuous layer of cells termed the epithelium covers the surface of the human body. The epithelial surface is primarily of the dry, keratinized and stratified type on the outer epidermal surface of the body, but as the epithelium involutes internally to cover the ocular surface, and the respiratory, gastrointestinal, and urogenital surfaces, it becomes a wet surfaced and non-keratinized, mucosal epithelium. At the transition zones from outer to internal epithelium, the wet surfaced epithelia remain stratified but become a simple single cell layer upon reaching more protected internal

E-mail address: Ilene_gipson@meei.harvard.edu.

http://dx.doi.org/10.1016/j.preteyeres.2016.04.005
1350-9462/

surfaces. If one were to travel over the entire surface of the epithelium covering the body surfaces, including the involuted epithelial glands, one would encounter an astounding variety of specialized epithelial cells. One such specialized cell present within several regions of the internal wet surfaced mucosal epithelia of the body is the mucin producing goblet cell. In drying, cicatrizing diseases of the ocular surface, which in their most severe stages have the potential of resulting in corneal blindness, goblet cell numbers are reduced; thus understanding their differentiation in the conjunctival epithelium is imperative.

Goblet cells are found intercalated within the epithelia of the conjunctiva, respiratory epithelium, and gastrointestinal epithelium. In the respiratory epithelia they are found as single cells interspersed in the columnar epithelium of the conducting tubes of the trachea, bronchi and large bronchioles and in the gastrointestinal epithelium they are present within the columnar epithelium of the stomach, and small and large intestine. Uniquely, in the conjunctiva, goblet cells are interspersed within a stratified epithelium. The distribution patterns of goblet cells within the conjunctival epithelium are species specific. In humans (Fig. 1A) and in dogs, the greatest density of goblet cells per area of epithelium is in the nasal region, with fewer of the cells in superior and inferior bulbar regions (Kessing, 1968; Moore et al., 1987). In humans, goblet cells can occur individually or within clusters, albeit in regions with sparser numbers, individual cells are predominant (Figs. 1B and 2A) (Gipson and Tisdale, 1997; Greiner et al., 1981). In the so called lid wiper region at the tarsal lid border adjacent to the mucocutaneous junction, goblet cells were recently found to occur individually or in clusters, and they were also present within cryptal epithelial infoldings (Fig. 1 B) (Knop et al., 2012). In rodents, goblet cells occur in basket-like clusters (Figs. 1C and 2 and Gipson and Tisdale, 1997).

2. Conjunctival goblet cell structure

Goblet cells of the conjunctiva are plump, rounded cells, the basal membrane of which is in contact with the epithelial basement membrane, thus the goblet cell extends the entire thickness of the stratified epithelium to the apical surface (Fig. 3A). Mucin granules fill the cell leaving a thin rim of cytoplasm, rich in golgi apparati, and a nucleus crowded toward the basal cell membrane of the cell (Fig. 3A). High resolution transmission electron microscopy demonstrates a granule membrane and a “filamentous” substructure to the mucin granule content (Fig. 3B), which may reflect the packaging of the large secretory mucin glycoprotein, MUC5AC in humans (Inatomi et al., 1996), or Muc5ac or 5b in mice (Marko et al., 2014), within the granule. Packaging of the very large, heavily O-glycosylated mucins within the mucin granule is dependent on having a high concentration of multivalent cations within the granule (Perez-Vilar, 2007) and disruption of calcium levels in epithelia due to vitamin D receptor knockdown, alters goblet cell mucin levels and mucin granules in the conjunctiva of the mice (Paz et al., 2003). Membranes surrounding mucin granules in the human conjunctival goblet cells were recently demonstrated to bind antibodies to the membrane anchored mucin MUC16 (Fig. 4) (Gipson et al., 2015). The function of this membrane-associated mucin at the granule membrane is unknown. In humans but not mice, MUC16 is present on the apical cell membrane of apical cells of the cornea and conjunctival epithelium where it provides barrier function (Gipson et al., 2014) but also a dysadhesive function, preventing adherence of cells and pathogens and secreted mucin (MUC5AC) to the ocular surface (Govindarajan and Gipson, 2010). Perhaps the function of MUC16 in the goblet cell mucin granule membrane may be to facilitate expulsion of the secretory mucins from the granule membrane upon secretion.

Phalloidin staining of whole mounts of conjunctival epithelium show that an actin filament rich zonula adherens surrounds the apical-basal border of the cell (Fig. 2C) (Gipson and Tisdale, 1997) and in those species where goblet cell clusters predominate, the zonula adherens of adjacent cells form an outer circular annulus around the goblet cell cluster. This outer ring of actin appears to form an orifice to the acinar-like basket of goblet cells (Fig. 2C). These actin structures may be useful in propelling mucin from the cell as demonstrated in Fig. 2D or alternatively keep the orifice closed to prevent mucin granule expulsion.

Goblet cells form tight junctions with neighboring stratified epithelial cells (Gipson et al., 2005). Recent data indicates that in the human and mouse, the conjunctival goblet cell expresses specific claudins, transmembrane components of tight junctions that associate with ZO-1 and form the junction “strands” visible in freeze fracture preparations. In humans, claudin 10 has been demonstrated to surround some of the conjunctival goblet cells

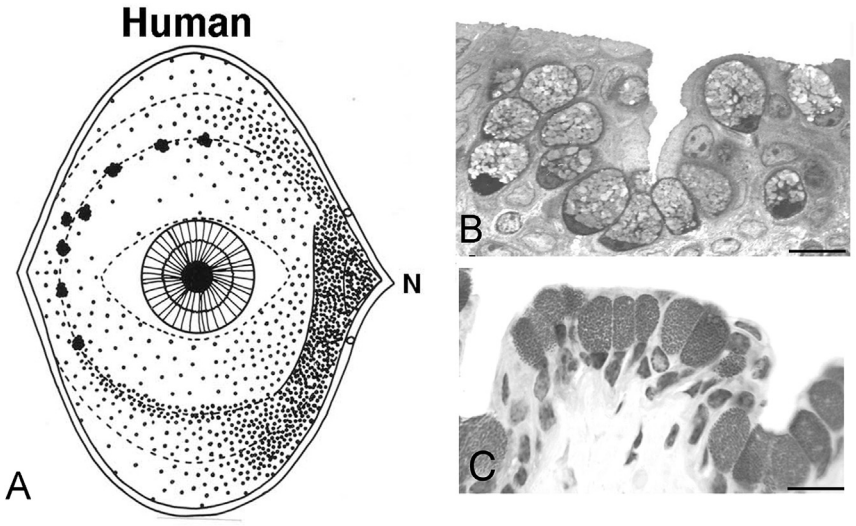

Fig. 1. Goblet cell distribution on the human ocular surface (A, after (Kessing, 1968) and histologic appearance of goblet cells in (B) human and (C) mouse conjunctival epithelium. Note that the goblet cells in humans can appear singly in regions of sparse density and that they can also occur in clusters in the forniceal region as shown in A. Such a cluster is present in the section of human conjunctiva in B. In mice (C), clusters are present throughout the conjunctiva. Bars, B = 10 μm, C = 20 μm.