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Review

Pathophysiology of ocular surface squamous neoplasia

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ABSTRACT

The incidence of ocular surface squamous neoplasia (OSSN) is strongly associated with solar ultraviolet (UV) radiation, HIV and human papilloma virus (HPV). Africa has the highest incidence rates in the world. Most lesions occur at the limbus within the interpalpebral fissure particularly the nasal sector. The nasal limbus receives the highest intensity of sunlight. Limbal epithelial crypts are concentrated nasally and contain niches of limbal epithelial stem cells in the basal layer. It is possible that these are the progenitor cells in OSSN. OSSN arises in the basal epithelial cells spreading towards the surface which resembles the movement of corneo-limbal stem cell progeny before it later invades through the basement membrane below. UV radiation damages DNA producing pyrimidine dimers in the DNA chain. Specific CC → TT base pair dimer transformations of the p53 tumour-suppressor gene occur in OSSN allowing cells with damaged DNA past the G1-S cell cycle checkpoint. UV radiation also causes local and systemic photo-immunosuppression and reactivates latent viruses such as HPV. The E7 proteins of HPV promote proliferation of infected epithelial cells via the retinoblastoma gene while E6 proteins prevent the p53 tumour suppressor gene from effecting cell-cycle arrest of DNA-damaged and infected cells. Immunosuppression from UV radiation, HIV and vitamin A deficiency impairs tumour immune surveillance allowing survival of aberrant cells. Tumour growth and metastases are enhanced by; telomerase reactivation which increases the number of cell divisions a cell can undergo; vascular endothelial growth factor for angiogenesis and matrix metalloproteinases (MMPs) that destroy the intercellular matrix between cells. Despite these potential triggers, the disease is usually unilateral. It is unclear how HPV reaches the conjunctiva.

1. Introduction

Ocular surface squamous neoplasia (OSSN) comprises of a spectrum of tumours that affect the ocular surface ranging histologically from intraepithelial neoplasia to different grades of invasive squamous cell carcinoma (Lee and Hirst, 1995). Early lesions of varying size usually occur at the limbus, the area of transition between the cornea and conjunctiva (Lee and Hirst, 1997; Waddell et al., 2006). Advanced stages may involve the eyelids and may invade the orbit. Curiously OSSN usually affects only one eye (Chisi et al., 2006).

OSSN occurs worldwide but the peak incidence is found at a latitude of 16° South (Gichuhi et al., 2013). The mean age-standardised incidence rate worldwide is 0.18 and 0.08 cases/year/100,000 among males and females, respectively and the highest incidence rate is found in Africa (1.38 and 1.18 cases/year/100,000 in males and females) (Gichuhi et al., 2013). In temperate countries OSSN predominantly affects males while in Africa both sexes are affected equally. Systematic reviews and meta-analysis show that the main risk factors are solar ultraviolet (UV) radiation, HIV and human papilloma virus (HPV); while vitamin A deficiency is a potential risk factor but has not been investigated (Gichuhi et al., 2013; Carreira et al., 2013). This paper reviews the pathophysiological mechanisms underlying the development of OSSN.

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2. Ocular surface anatomy

The ocular surface consists of the cornea, limbus and conjunctiva but in a wider anatomical and embryological sense the mucosa of the ocular adnexa (lacrimal gland and lacrimal drainage system) is included. The epithelia of the cornea, conjunctiva and eyelid are formed from differentiation of the surface ectoderm during embryonic development. The corneal endothelium and the corneal stroma, conjunctiva and eyelids are formed when periocular mesenchymal cells of neural crest origin migrate and differentiate (Cvekl and Tamm, 2004; Kao et al., 2008).

The cornea has a stratified squamous non-keratinizing epithelium with five to seven cell layers. It is immunologically privileged due to its lack of blood vessels and lymphatics, with dendritic cells present usually only in the peripheral cornea (Akpek and Gottsch, 2003).

The limbal epithelium is 8–10 cells thick and is constantly being replenished from stem cells in the basal layer (Schermer et al., 1986). The limbal basement membrane has undulating peg-like inter-digitations into the underlying stroma called the palisades of Vogt, which increase the surface area and protect against shearing forces (Fig. 1). The palisades are unique for individuals (like fingerprints) and have distinct radial vascular loops that leak fluorescein in the late phase of angiography suggesting a protective function for stem cells (Goldberg and Bron, 1982). The basal cells are protected from UV light by melanin within deep limbal crypts, where melanocytes contain melanin granules oriented towards the apex of each cell, acting as a pigmented cap facing the ocular surface (Higa et al., 2005). Among darker pigmented races the limbus is heavily pigmented, perhaps offering greater protection from UV radiation.

The conjunctiva consists of an epithelium on a basement membrane and underlying loose connective tissue called the lamina propria. The lamina propria is loosely anchored to the episclera and sclera making the conjunctiva easily mobile. The epithelium varies between 2–3 and 10–12 cell layers, depending on whether it is the bulbar, fornix or tarsal portion. Lymphocytes and plasma cells are abundant in the conjunctiva (Hingorani et al., 1997). They form the conjunctiva-associated lymphoid tissue (CALT) in the lamina propria (Knop and Knop, 2007).

3. Limbal stem cell biology

Stem cell biology is a rapidly progressing field. A stem cell is a special undifferentiated progenitor cell capable of giving rise to many more cells of the same type, and from which other kinds of cells arise by differentiation. There are three types of stem cells. Embryonic stem cells originate from pre-implantation embryos and can develop into tissues that belong to one of the three germ layers (Martin, 1981). Non-embryonic adult stem cells (termed somatic) are undifferentiated cells found in special niches of various organs where they divide and differentiate to replace damaged tissue while some may transdifferentiate to other tissues (Gonzalez and Bernad, 2012). Their origin remains unclear. Limbal epithelial cells would fall in this category. Lastly, induced pluripotent stem cells are created in the lab by genetically reprogramming somatic cells to an embryonic stem cell-like state (Takahashi et al., 2007; Obokata et al., 2014).

Corneo-limbal lineage is distinct from conjunctival lineage (Wei et al., 1996). Evidence suggests the existence of corresponding stem cell reservoirs. Corneo-limbal epithelial stem cells are located in the limbal basal layer while conjunctival stem cells are distributed throughout the bulbar and forniceal conjunctiva, but some propose that they are concentrated in the fornix (Nagasaki and Zhao, 2005;

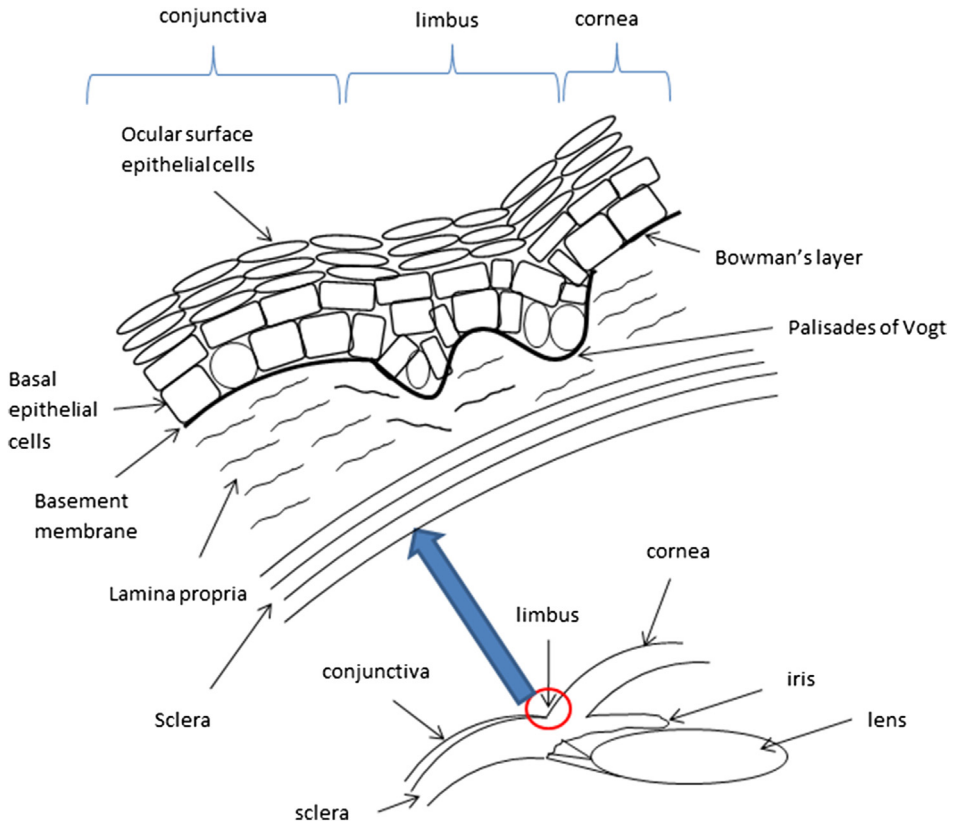

Fig. 1. Anatomy of the limbus.