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Ocular surface pathogenesis associated with precocious eyelid opening and necrotic autologous tissue in mouse with disruption of *Prickle 1* gene

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ABSTRACT

Ocular surface disease is one major type of eye diseases. Different etiologies trigger distinct pathological responses of the ocular surface. We previously reported that genetically engineered mice with ablation of *Prickle 1* manifested precocious eyelid opening with ensuing cornea dysplasia. The current study aimed to characterize the molecular traits and the direct cause of ocular pathology associated with precocious eyelid opening in the *Prickle 1* mutant mouse. *Prickle 1* mutant mice exhibited a slew of ocular surface pathology including cell proliferation, cell fate transformation and inflammatory infiltration coinciding with the timing of the precocious eyelid opening. Forced eyelid opening in wild type mice did not induce cornea pathology comparable to that of the *Prickle 1* mutants. Necrotic tissue debris was found associated with the lesioned cornea. RNAseq analysis of the mutant cornea revealed an expression profile shared by a range of dermatological diseases involving immune responses and cancer. Taken together, the data suggest that the necrotic eyelid debris plays an important role in ocular pathogenesis of the *Prickle 1* mutant mouse, which may represent a type of non-infectious keratoconjunctivitis caused by damaged autologous tissues. Additionally, *Prickle* 1 mutant cornea pathogenesis may offer molecular insights into other types of epithelial pathogenesis.

1. Introduction

Ocular surface disorders can be caused by a variety of foreign stimuli including non-infectious atopic and immunopathic agents and immunogenic damaged tissues, and infectious microbial pathogens. The ocular surface pathology is often manifested as keratitis, conjunctivitis or both (keratoconjunctivitis), which may also be accompanied with hyperplasia, metaplasia, or squamous neoplasia with abnormal growth of the ocular surface epithelium (http://eyewiki.aao.org/Ocular_Surface_Squamous_neoplasia).

The eyelids in conjunction with the ocular surface play vital roles in maintenance of the normal eye function. The outer surface of the eyelid is keratinized skin tissue, a physical barrier against mechanical injuries and microbial invasions. The inner lining is conjunctival epithelium harboring goblet cells producing mucins of the inner layer of the tear film over the cornea. In between is the eyelid pocket comprising the Meibomian gland, continuously secreting lipid components forming the outer layer of the tear film, and the retractors and nerves responsible for eyelid blinking to refresh otherwise dry or irritants-contaminated tear film. Additionally, resident and bone marrow-derived immune cells in the eyelid serve as sentinels constantly performing surveillance of foreign pathogens and irritants (Foulsham et al., 2018; Suzuki et al., 2015; Ueta and Kinoshita, 2010, 2012).

In human embryonic development, the eyelid starts to form about 40–45 days of gestation and is completely closed about 15 days later. Eyelid does not reopen until seven months of fetal life (Pearson, 1980; Sevel, 1988). The closed eyelid during this period is thought to create an isolated environment from potentially toxic amniotic fluid to ensure proper development of the ocular surface (Sevel, 1988; Zieske, 2004). In rodents such as the mouse, eyelid remains closed postnatally for a couple of weeks. Despite this difference, the closed eyelid is considered to have similar protective function as in humans for the developing ocular surface (Zieske, 2004). A series of changes in ocular surface epithelial differentiation were correlated with the timing of postnatal eyelid reopening (Chung et al., 1992; Watanabe et al., 1993; Zieske, 2004), suggesting that ithe integrity of eyelid might be crucial for maturation of the ocular surface differentiation. Nevertheless, the essence of the postnatal on-time opening of the eyelid in mouse in regard

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