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## Emerging importance of ACE2 in external stratified epithelial tissues

Nihal Kaplan<sup>a,1</sup>, Elena Gonzalez<sup>b,1</sup>, Han Peng<sup>a,\*\*\*</sup>, Daniel Batlle<sup>b,\*\*</sup>, Robert M. Lavker<sup>a,\*</sup>

<sup>a</sup> Department of Dermatology, Northwestern University, Chicago, IL, USA

<sup>b</sup> Department of Medicine (Nephrology and Hypertension), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

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### ABSTRACT

Angiotensin converting enzyme 2 (ACE2), a component of the renin-angiotensin system (RAS), has been identified as the receptor for the SARS-CoV-2. Several RAS components including ACE2 and its substrate Ang II are present in both eye and skin, two stratified squamous epithelial tissues that isolate organisms from external environment. Our recent findings in cornea and others in both skin and eye suggest contribution of this system, and specifically of ACE2 in variety of physiological and pathological responses of these organ systems. This review will focus on the role RAS system plays in both skin and cornea, and will specifically discuss our recent findings on ACE2 in corneal epithelial inflammation, as well as potential implications of ACE2 in patients with COVID-19.

### 1. Introduction

The renin-angiotensin system (RAS) encompasses an enzymatic cascade of reactions with the hormone Angiotensin II (Ang II) as the pivotal product. Two important enzymes in RAS are angiotensin converting enzyme (ACE) and its homolog angiotensin converting enzyme 2 (ACE2). ACE converts Ang I to Ang II, while ACE2, a monooxycarboxypeptidase first described in 2000 (Donoghue et al., 2000; Tipnis et al., 2000), hydrolyzes and degrades Ang II to Ang 1–7, a peptide that has effects generally opposite to those of Ang II (Wysocki et al., 2019; Batlle et al., 2012; Marquez et al., 2020).

Ang II is important for maintenance of volume and blood pressure as it causes vasoconstriction and kidney sodium retention, but it can have detrimental effects at the tissue level when chronically sustained (Dzau, 1988; Schlueter et al., 1994; Bader and Ganten, 2008). Ang II exerts its effects through two principal receptors, Ang II type 1 and type 2 receptors (AT1R and AT2R) (Crowley et al., 2006). The entire RAS system plays a critical role in the regulation of systemic hemodynamics and fluid volume, but its effects go beyond that, and RAS is involved in cell proliferation and tissue remodeling. Most components of the RAS are produced locally in various tissues, a concept known as tissue RAS (Bader and Ganten, 2008; Stock et al., 1995).

The discovery of the novel Coronavirus SARS-CoV-2 has drawn attention to RAS located in the cornea, as this tissue represents a potential port of entry for the infection (Gralinski and Baric, 2015; Zhou et al., 2020; Batlle et al., 2020). Interestingly, ACE2 has been identified as the receptor for the spike (S) protein of SARS-CoV-2 (Zhou et al., 2020; Lu et al., 2020) and there is increasing interest in ACE2 as a potential target for COVID-19 treatments (Batlle et al., 2020). Upon engagement with the virus, ACE2 becomes down-regulated (Zhou et al., 2020; Xu et al., 2020; Verdecchia et al., 2020; Zhang et al., 2020). This paper will review the presence of tissue RAS in skin and cornea, two distinct stratified squamous epithelial tissues with somewhat overlapping properties and will primarily focus on the critical roles of Ang II and ACE2 in wound healing and inflammation. Since there is a recent review on the functions of RAS and its pathophysiology in skin (Silva et al., 2020), we will focus our attention more to our recent findings in the cornea (Wang et al., 2020a) as well as potential implications of interactions of SARS-CoV-2 and ACE2 in the cornea of patients with COVID-19. Thus, understanding the biology of ACE2 in the context of the cornea and skin is exceedingly timely.

\* Corresponding author. Department of Dermatology, Northwestern University, 303 East Chicago Avenue, Ward 9-124, Chicago, IL, 60611, USA.

\*\* Corresponding author. Department of Medicine (Nephrology and Hypertension), Northwestern University, 320 E. Superior Street, Searle 10-511, Chicago, IL, 60611, USA.

\*\*\* Corresponding author. Department of Dermatology, Northwestern University, 303 East Chicago Avenue, Ward 9-120, Chicago, IL, 60611, USA.

E-mail addresses: [han-peng@northwestern.edu](mailto:han-peng@northwestern.edu) (H. Peng), [d-batlle@northwestern.edu](mailto:d-batlle@northwestern.edu) (D. Batlle), [r-lavker@northwestern.edu](mailto:r-lavker@northwestern.edu) (R.M. Lavker).

<sup>1</sup> authors contributed equally.

## 2. RAS in the cornea and skin

Although the eye and skin are quite different organs, they share similarities, particularly when comparing the cornea with the skin (Cotsarelis et al., 1990; Cotsarelis et al., 1989; Fuchs, 2018; Lavker and Sun, 2003). Both: (i) have a primary barrier function; (ii) are covered by a stratified squamous epithelium (corneal epithelium and the epidermis); (iii) have well-defined epithelial stem cell populations that govern the homeostasis of self-renewing tissues; (iv) respond similarly to external stresses; and (v) mount comparable inflammatory responses, characterized by the release of proinflammatory cytokines from epithelial cells, recruitment of immune cells and enhanced neovascularization.

The expression of the components of RAS in skin has been well documented (Silva et al., 2020; Nehme et al., 2015). RAS components are expressed in epidermis, dermal fibroblasts, dermal vessel walls, subcutaneous fat, and human hair follicles as well as in cultured primary keratinocytes, melanocytes, and dermal microvascular endothelial cells (Takeda et al., 2002; Steckelings et al., 2004; Aleksiejczuk et al., 2019). Moreover, ACE, AT1 and AT2 were detected in human keratinocyte cultures and normal human skin (Steckelings et al., 2004). Interestingly, ACE and ACE2, two key enzymes of RAS, are both highly expressed in epidermal basal cells (Hamming et al., 2004; Akershoek et al., 2018). ACE2 positive cells were also detected in suprabasal and granular cells (Xue et al., 2020). ACE2 expression was significantly higher in keratinocytes than other cell types in the skin. Moreover, highest ACE2 expression was noted in the basal and differentiating keratinocytes. This expression pattern of ACE and ACE2 was reduced or lost in either basal cell and squamous cell carcinomas (Grzegorzolka et al., 2013). However, the expression of ACE2 was increased in basal keratinocytes of psoriatic skin in an IL17 dependent manner (Krueger et al., 2020). The expression pattern of these two key enzymes of RAS suggests that RAS plays a critical role in keratinocyte biology and opens the possibility of lining epithelia as an entry point for the SARS-CoV-2 (Xue et al., 2020).

Expression of several RAS components have been reported in different structures of the eye (Xu et al., 2020; Vaajanan et al., 2015; Holappa et al., 2015; White et al., 2015). Such ocular expression has been associated with important physiologic functions as well as several pathologies such as diabetic retinopathy and glaucoma (Xu et al., 2020; Giese and Speth, 2014; Passos-Silva et al., 2015; Wang et al., 2015). For example, the aqueous humor has been shown to have significant levels of ACE, ACE2 and Ang 1–7 (Holappa et al., 2015), supporting the idea that intraocular RAS may be involved in the regulation of intraocular pressure (IOP). In this sense, pharmacological activation of intrinsic ACE2 significantly decreased the IOP of glaucomatous rats (Foureaux et al., 2013). ACE2 expression has also been detected in conjunctival cells and pterygium (Ma et al., 2020), an overgrowth of the subconjunctival tissue onto the corneal epithelium (Sarkar and Tripathy, 2020). Interestingly, both ACE and Ang II show increased nuclear expression in pterygium epithelial cells compared with normal conjunctival epithelium (Demurtas et al., 2014; Demurtas et al., 2013). Inhibition of ACE/Ang II signaling by valsartan, an AT1R antagonist, suppresses cell growth and migration in pterygium fibroblasts (Kucuk et al., 2020). These expression patterns of RAS, and the effects of Ang II signaling inhibition on outgrowths suggest a possible role of ACE2 and Ang II in pterygium pathogenesis. The expression and roles of ACE2 and Ang II in cornea were unclear until recently. We demonstrated that ACE2 and its substrate Ang II were present in both corneal and limbal epithelia and that they played an important role in regulating corneal inflammation (Wang et al., 2020a).

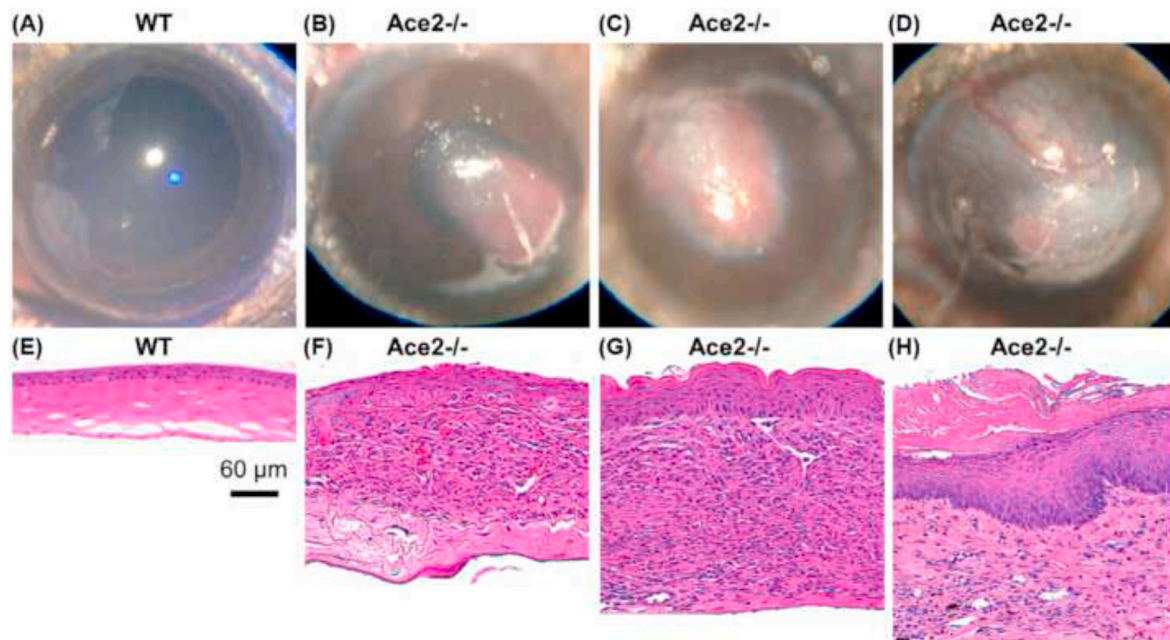
## 3. RAS in re-epithelialization and wound repair

Wound healing is a dynamic process that consists of three components: inflammation, tissue formation, and tissue remodeling. Successful tissue remodeling requires the interaction of soluble mediators, blood

cells, extracellular matrix, and parenchymal cells (Singer and Clark, 1999). RAS system plays a critical role in the process of wound healing in various tissues including skin and cornea (Bernasconi and Nystrom, 2018; Abdallah et al., 2016; Abadir et al., 2018). ACE/Ang II has been identified as the pro-inflammatory, pro-proliferative and pro-fibrotic axis of the RAS whereas ACE2/Ang 1–7 has a counteracted role as the anti-inflammatory, anti-proliferative and anti-fibrotic axis (Bernasconi and Nystrom, 2018). ACE expression was markedly increased in scratch wounded keratinocyte monolayers as well as in human wounded skin at 12 days post injury (Steckelings et al., 2004). Consistently, cutaneous tissue ACE activity was significantly increased in human wounded skins with normal healing process (Morihara et al., 2006). These findings indicate that RAS system in human skin plays important roles in cutaneous homeostasis as well as wound healing (Steckelings et al., 2004). Interestingly, the ACE activity in pathologic scar tissues was dramatically higher than in both normal and wounded skins without scar (Morihara et al., 2006), suggesting that dysregulation of ACE may contribute to cutaneous pathologic scar formation similar to that seen in the cardiovascular system (Morihara et al., 2006). Interestingly, ACE/Ang II promotes fibrosis in cardiovascular and kidney tissues via induction of TGF $\beta$  (Wenzel et al., 2001; Alzayadneh and Chappell, 2014; Bockmann et al., 2019), a key regulator of fibrosis (Lichtman et al., 2016; Jimenez et al., 1996). This is consistent with our observation that increased Ang II levels due to decreased ACE2 expression may have an anti-fibrotic function in the cornea (Wang et al., 2020a). Furthermore, increase in Ang II expression is associated with lacrimal gland fibrosis, which can be reversed by blocking AT1R signaling (Yaguchi et al., 2015).

The roles of RAS have been evaluated in several preclinical models of cornea and skin repair. Topical treatment of NorLeu3A (1–7), an analog of Ang 1–7, accelerated healing of full-thickness corneal injuries as well as resolution of edema and inflammation without evidence of fibrosis and angiogenesis (Abdallah et al., 2016). Interestingly, NorLeu3A(1–7) has also been shown to play a beneficial role in healing of full thickness excisional wounds (punch wound model) in skins of rat and diabetic mice (Rodgers et al., 2003a,b; 2005). Furthermore, NorLeu3A(1–7) enhances the healing of incisional wounds (longitudinal cutting parallel to the midline on the dorsal side through epidermis, dermis and subcutaneous tissue down to the muscle) in rat skins (Rodgers et al., 2003a, b; 2005). More importantly, treatment with NorLeu3A (1–7) reduced scarring. Recently, we reported that loss of ACE2 in the mouse cornea significantly delayed corneal epithelial healing and promoted haze formation following a small circular debridement wound (Wang et al., 2020a), which is the type of wound that does not result in a significant inflammatory infiltrate (Stepp et al., 2014). These observations suggest that ACE2/Ang1-7 axis has a translational potential in promoting re-epithelialization and preventing fibrosis in cornea.

An upregulation of AT1 and AT2 receptors was found in different tissues from human cutaneous wounds demonstrating the importance of Ang II in cutaneous wound healing (Steckelings et al., 2005). For example, dysregulation of RAS system with increased AT1R and decreased AT2R was shown to play a role in chronic wounds of diabetic skin (Abadir et al., 2018; Hao et al., 2011). Ang II binding to its receptors, AT1R or AT2R, leads to a complex cascade of signaling events with opposed consequences. AT1R signaling has been associated with enhanced migration and proliferation of keratinocytes and myofibroblasts (Kurosaka et al., 2009; Tamarat et al., 2002; Takeda et al., 2004). Ang II contributes to accelerated closure of full-thickness skin injuries in animal models (Rodgers et al., 1997). This property is closely linked to the positive influence of Ang II on keratinocyte and fibroblast migration during wound healing (Yahata et al., 2006). It has been suggested that Ang II signaling induces phosphorylation of the epidermal growth factor receptor (EGFR) via the AT1R receptor (Yahata et al., 2006). ACE/Ang II signaling also induces TGF $\beta$  expression (Wenzel et al., 2001; Alzayadneh and Chappell, 2014; Bockmann et al., 2019), which is a ligand of EGFR. Consistent with the positive role of Ang II in skin wound healing,



**Fig. 1.** ACE2-deficient mice show corneal inflammation and epithelial defects. (A–D) Representative clinical images of WT (A) and Ace2<sup>-/-</sup> mouse eyes (60–80 weeks old) (B–D) were taken using a dissecting scope. Clear and transparent corneas were observed in aged WT mice eyes (A), while increased central cornea haze with corneal neovascularization were noted in aged Ace2<sup>-/-</sup> mice eyes (B–D). (E–H) Representative H&E stained histological images of WT mouse cornea with intact corneal epithelium and regular stroma (E) and Ace2<sup>-/-</sup> mouse corneas (F–H) with markedly thickened cornea and a large number of polymorphonuclear, mononuclear, and lymphocytic infiltrates along with numerous vascular profiles (Wang et al., 2020a).

knock-out of AT1R markedly delayed wound healing in these mouse skins (Yahata et al., 2006). This *in vivo* observation strongly indicates that AngII via AT1R has protective effects during wound healing. Interestingly, Ang 1–7 signaling can stimulate cell migration by activating AKT, a key downstream effector of EGFR signaling (Zheng et al., 2015). This raises a question of whether AngII-AT1R and Ang 1-7-MAS have a similar positive effect on wound healing. Finally, Ang II is a potent regulator of angiogenesis, which is also fundamental for wound repair (Bell and Madri, 1990). Taken together, it becomes apparent that further studies are necessary to elucidate the underlying mechanisms by which both Ang II and Ang 1–7 are involved in wound healing.

#### 4. ACE2 and inflammation in ocular tissues

ACE2 plays essential roles in regulating inflammation in various ocular tissues (Mirabito Colafella, Bovee and Danser, 2019). For example, overexpression of ACE2 by subretinal administration of AAV8-ACE2 decreased the clinical and histological scores and the expression of inflammatory cytokines (e.g., IL-6, CCL2, IL-1 $\beta$ ) in experimental autoimmune uveitis (Qiu et al., 2016). Such anti-inflammatory effects of ACE2 are associated with the inhibition of MAPK, NF- $\kappa$ B and STAT3 pathways (Qiu et al., 2016). *In vitro*, pharmacological activation of ACE2, which inhibits MAPK and NF- $\kappa$ B pathways, prevents lipopolysaccharide-induced inflammation in human retinal pigment epithelium (Tao et al., 2016). Furthermore, overexpression of ACE2 reduces the inflammatory response in an *in vitro* model of age-related macular degeneration (AMD) via inhibiting overproduction of cytokines such as IL-1 $\beta$  and CCL-2 (Fu et al., 2017). Intravitreal administration of ACE2 or Ang-(1–7)-AAV reduces diabetes-induced inflammation in the retina (Verma et al., 2012). Recently, we demonstrated that Ang II and ACE2 are present in both human and mouse limbal and corneal tissues and when the Ang II/ACE2 balance becomes disturbed, mice are prone to a significant inflammatory response that alters corneal epithelial and stromal tissues (Wang et al., 2020a).

A marked increase in Ang II expression is observed in the corneal

epithelium of ACE2-deficient mice compared with wild type mice. Such disruption of the Ang II/ACE2 balance significantly elevates expression of interleukins (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6), chemokines (CCL2, CXCL8), and TNF- $\alpha$ , resulting in a cytokine storm-like phenotype (Wang et al., 2020a). Once initiated, a chronic inflammation persists, which remodels the stromal microenvironment (Fig. 1). Inflammatory infiltrates in the stroma were identified as macrophages, T cells, and dendritic cells (Fig. 2). This microenvironmental change results in a wide range of epithelial phenotypes (Wang et al., 2020a). The most dramatic is a cell fate switch from the transparent corneal epithelium to a keratinized, stratified squamous, psoriasiform-like epidermis (Figs. 1 and 3). A mild perturbation can induce marked inflammation and a cytokine storm in Ace2<sup>-/-</sup> mice indicating that these ACE2 deficient mice are “primed” for an inflammatory response (Fig. 3). Finally, treatment with the AT1R antagonist losartan, partially rescues the upregulation of cytokine expression, suggesting that the observed effect was mediated by Ang II acting on its main receptor (Wang et al., 2020a). Consistent with our findings, telmisartan treatment, another AT1R antagonist, can rescue suturing-induced neovascularization, recruitment of macrophages, and upregulation of cytokines (e.g., IL-6) in the mouse cornea (Usui et al., 2008). Having defined the corneal phenotype in Ace2<sup>-/-</sup> mice and establishing a pivotal role of ACE2 and Ang II in the corneal inflammatory response, we now have a foundation for future studies to investigate the molecular mechanisms by which ACE2 and Ang II balance inflammation.

#### 5. Role of autophagy in ACE2-regulated corneal inflammation

Autophagy is the process of degradation of damaged organelles and cytoplasmic components often in response to stress (Eskelinen and Saffig, 2009; Klionsky et al., 2016). Autophagy can promote cell death as well as insure cell survival. In addition to cell death and survival, we have demonstrated that autophagy functions to help maintain the proliferative capacity of limbal epithelial stem cells and to ensure proper corneal epithelial differentiation (Park et al., 2016). Recently, it has been demonstrated that ACE2 has a negative role in the activation of

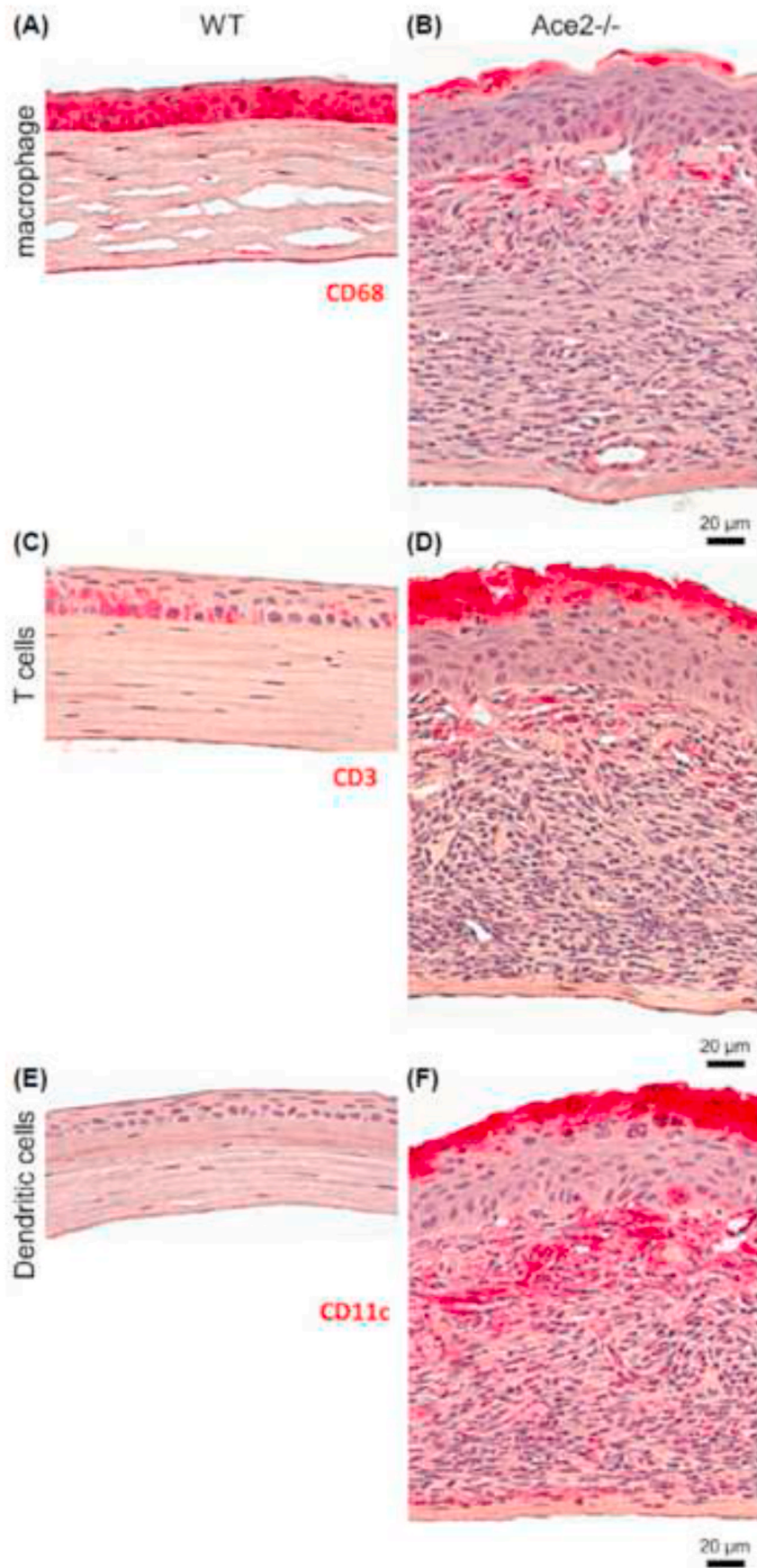
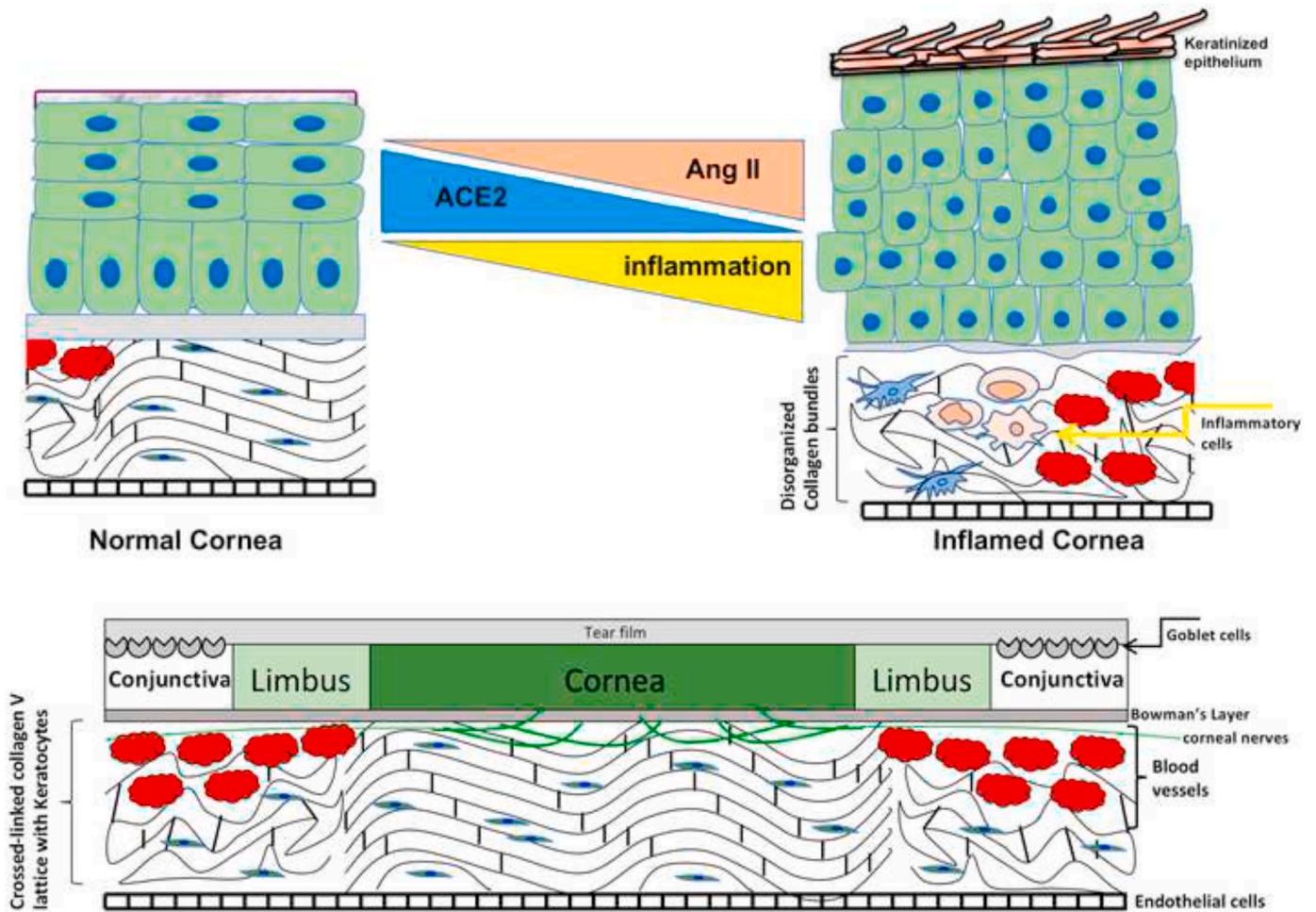


Fig. 2. ACE2-deficient mice show infiltration of immune cells. WT (A, C, E) and *Ace2*<sup>-/-</sup> (B, D, F) mouse corneas were stained for CD68 (marker for macrophage), CD3 (marker for T cells), and CD11c (marker for dendritic cells). N = 3 (Wang et al., 2020a).



**Fig. 3. Deficiency in ACE2 primes the cornea for chronic inflammation.** A reduction in ACE2 levels leads to a cloudy corneal phenotype. Haze accompanied by chronic inflammation, corneal edema and neovascularization is evident in mice deficient in *Ace2* (Wang et al., 2020a). In severe cases, a cell-fate switch from a transparent corneal epithelium to a keratinized, stratified squamous, psoriasiform-like epidermis can be observed.

autophagy, resulting in attenuated inflammation in lung and cardiac tissues (Lai et al., 2017; Zhang et al., 2019). Inhibition of miR-122-5p suppressed Ang II-mediated pro-inflammatory and anti-autophagic effects in rat aortic adventitial fibroblasts by activating ACE2 signaling (Song et al., 2020). Increased expression of ACE2 in the vascular endothelium is associated with activation of AMPK and inhibition of p-mTOR, thus promoting autophagy (Wang et al., 2020b). Vitamin D is a potential activator of autophagy in skin (Das et al., 2019). Lipopolysaccharide (LPS) stimulates acute lung injury via inducing ACE and AT1R expression, and inhibiting ACE2 expression, which can be rescued by vitamin D treatment (Xu et al., 2017). Hydroxychloroquine an inhibitor of autophagy (Klionsky et al., 2016), is a widely used drug for malaria and autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis). Even though it is no longer recommended, as a treatment for COVID-19, hydroxychloroquine has anti-SARS-CoV-2 effects in vitro, attributable to a deficit in the glycosylation of the SARS coronavirus receptor ACE2 (Vincent et al., 2005; Wang et al., 2020c; Bonam et al., 2020). These observations suggest that the regulatory role of ACE2 in inflammation may be associated with alteration of autophagy activity in a tissue specific manner. Thus, it would be interesting to investigate whether the corneal inflammation induced by loss of ACE2 is due to regulation of autophagy.

### 6. Implications for COVID 19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

is responsible for the current COVID-19 pandemic. Accumulating evidence shows that patients with severe COVID-19 might have a cytokine storm syndrome (Xu et al., 2020). SARS-CoV-2, like SARS-CoV, utilizes human ACE2 as the receptor for entry (Gralinski and Baric, 2015; Zhou et al., 2020; Batlle et al., 2020; Davidson et al., 2020; Hoffmann et al., 2020). Co-expression of ACE2 and TMPRSS2 is a prerequisite for the SARS-CoV-2 induced infection, and this co-expression pattern was shown to be specific for corneal epithelial cells, rather than conjunctival epithelium (Ma et al., 2020). This suggests that the cornea is a possible entry point for the virus, not the conjunctiva. SARS-CoV spike protein binding with ACE2 may reduce ACE2 expression (Kuba et al., 2005). Injection of SARS-CoV spike protein worsens acute lung failure in mice with the enhanced renin-angiotensin pathway (Kuba et al., 2005). Considering the correlation of reduced ACE2 expression after SARS-CoV infection and the anti-inflammatory role of ACE2, this could explain the possible occurrence of conjunctivitis in patients with SARS-CoV-2 infection. SARS-CoV-2 infection downregulates ACE2, leading to unregulated inflammation including interstitial mononuclear inflammatory infiltration in both lungs, mimicking the cytokine storm syndrome (Xu et al., 2020). This phenotype bears striking similarities to what we have observed in the corneas of *Ace2*<sup>-/-</sup> mice (Fig. 3) (Wang et al., 2020a).

Skin related manifestations of SARS-CoV2 were seen mostly in children with a prevalence of skin lesions with erythema, resembling of Kawasaki disease (Khalili et al., 2020; Gkoutzourelas et al., 2020). Interestingly, a recent study found concomitant expression of ACE2 and

TMPRSS2 in epidermal keratinocytes (Ma et al., 2020). This suggests that the skin might also be a potential target for SARS-CoV2 based on the high expression of two receptors for virus invasion in keratinocytes. It also suggests that keratinocytes may be a potential target cell for the viral infection when a patient is in a state of viremia (Xue et al., 2020). Taken together, these findings indicate a central role of ACE2 in COVID-19 pathology of the skin and the eye.

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