REVIEW

The impact of aging on epithelial barriers

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ABSTRACT

The epithelium has many critical roles in homeostasis, including an essential responsibility in establishing tissue barriers. In addition to the fundamental role in separating internal from external environment, epithelial barriers maintain nutrient, fluid, electrolyte and metabolic waste balance in multiple organs. While, by definition, barrier function is conserved, the structure of the epithelium varies across organs. For example, the skin barrier is a squamous layer of cells with distinct structural features, while the lung barrier is composed of a very thin single cell to minimize diffusion space. With the increased focus on age-dependent alterations in organ structure and function, there is an emerging interest in the impact of age on epithelial barriers. This review will focus on the impact of aging on the epithelial barrier of several organs, including the skin, lung, gastrointestinal tract and the kidney, at a structural and functional level.

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Introduction

The percentage of the US population over 65 is now 12%, by the year 2040 it is expected to rise to 21%¹ and will be accompanied with a corresponding increase in age-related disease.² Both structural and functional changes are associated with aging, which is linked to increased fibrosis and inflammation in multiple organs.^{3–6} Given these changes, it is not surprising that aging is linked several acute and chronic diseases in multiple organs, including the skin, lung, digestive system and the kidney.^{7–12}

Epithelial cells form barriers that separate air- or fluid-filled tissue compartments and their role is not limited to just separating spaces. The epithelial barrier, via cellular transport processes, also defines fluid composition. While functionally conserved, there are organ-specific functions of the barrier and structurally, the epithelial barrier is distinct between organs. The skin barrier is multi-cellular, with a highly organized, layered structure that provides a critical defense mechanism.¹³ The lung barrier is extremely thin, designed to maximize gas exchange across the air:fluid interface.¹⁴ The kidney has 2 epithelial barriers—the relatively ‘leaky’ glomerular barrier facilitating fluid filtration, and the tubular epithelial barrier required for waste removal and water balance.^{15,16} The intestinal barrier is

designed for absorption and also partitions the gut microbiome from the rest of the body.¹⁷ In the context of aging, the blood-brain barrier has received considerable attention and will not be covered as there are several excellent reviews on the topic.^{18,19}

A key feature of the epithelial barrier, and critical regulator of permeability, are cell adhesion complexes.^{20,21} A great deal of progress has been made in our understanding of the cell adhesion complexes mediating cell-cell interactions in epithelial cells. Specifically, in epithelial cells, tight junctions, and cadherin/catenin complexes are the major regulators (Fig. 1). Tight junctions (zonula occludens) are defined as a dense condensation at the apical surface of polarized cells where the plasma membranes of adjacent cells appear fused. The tight junction has 2 critical functions; the ‘fence’ function prevents intra-domain movement of membrane proteins and phospholipids, while the ‘gate’ function blocks the paracellular movement of solutes.²² Occludin, claudins and junctional adhesion molecule (JAM) are transmembrane components of tight junctions. Occludin has 4 transmembrane domains, 2 extracellular domains, and a long cytoplasmic (C-terminal) domain.²³ Claudins are a multigene family of transmembrane proteins that also have 4 transmembrane

Figure 1. Representation of the Cell Adhesion Complexes Present in Proximal Tubular Epithelial Cells. Most proximal to the apical membrane is the tight junction that is composed of transmembrane (occludin, claudins, and JAMs) and cytosolic proteins (ZO-1, ZO-2) that link the complex to the actin cytoskeleton. The adherens junction (cadherin/catenin complex) is located basal to the tight junction. Cadherins are single transmembrane proteins whose cytoplasmic domain is bound by β - (or γ -catenin). α -Catenin does not directly bind cadherins but links the complex to the actin cytoskeleton and may also interact with tight junctions via ZO-1.

domains and 2 extracellular domains.²⁴ JAMs are members of the IgG superfamily and are structurally distinct from occludin and claudins.²⁵ ZO-1, ZO-2, and ZO-3 are cytoplasmic proteins that are members of the membrane-associated guanylate kinase (MAGUK) gene superfamily and have common structural features including 3 PDZ domains, an SH3 domain, and a guanylate kinase homology region (GUK).²⁶ It is thought that ZO-1 and -2 link transmembrane tight junction components to the actin cytoskeleton.

The cadherin gene superfamily encodes for transmembrane proteins that regulate Ca^{2+} -dependent cell-cell adhesion.²⁷ Type-I (classical) cadherins comprise a large family of proteins that share significant structural conservation and include E-[epithelial], N-[neuronal] and P-[placental] cadherin.²⁸ The extracellular domain contains 4 highly conserved Ca^{2+} -binding 'cadherin repeats' (EC1–4) and one membrane proximal extracellular domain (EC5). Type-II (atypical) cadherins have a similar structure, but lack the conserved His-Ala-Val (HAV) sequence in the EC1 domain. A functional cadherin adhesion complex

requires interaction with cytoplasmic catenin proteins (Fig. 1). α -Catenin does not directly bind to cadherins, but it interacts with the cytoplasmic domain of cadherins via β - or γ -catenin. p120-catenin binds to the cadherin cytoplasmic domain, and shares sequence homology with β - and γ -catenin, but does not bind α -catenin.²⁹ The binding of p120 to the cadherin intracellular domain stabilizes cadherin expression at the plasma membrane, whereas the absence of p120 is associated with cadherin endocytosis and degradation.³⁰ α -Catenin has a role in linking the cadherin cell adhesion complex to the actin cytoskeleton.^{31,32} Cadherin-mediated adhesion influences actin cytoskeleton organization and actin cytoskeleton integrity is necessary for cadherin-mediated adhesion.³³ Therefore, the relationship between the cadherin/catenin complex and the actin cytoskeleton is bidirectional, with each regulating the other. Even though tight junctions and cadherin/catenin complexes are distinct molecular structures, they are functionally interrelated. α -Catenin binds ZO-1³⁴ and the cadherin complex plays an important role in the formation of tight junctions and the establishment of the epithelial barrier.^{35,36}

Age-dependent alterations in the epithelial barrier

Skin

Age-dependent changes in the barrier function of the skin have long been recognized (Table 1).^{37,38} In aged human skin, there is a decrease in the expression of the tight junction components claudin-1 and occludin.³⁹ An appropriate balance of claudin expression is critically important as overexpression of claudin-6 in mice decreases barrier function of the skin.⁴⁰ Further studies have shown that expression of a claudin-6 mutant decreased claudin-1 expression and reduced barrier function; this transgenic mouse has been proposed as a relevant model to investigate the aging skin.⁴¹

The aging skin is more susceptible to maceration, which may lead to development of lesions.⁴² Following insult, the skin barrier has a decreased ability to recover in aged patients (> 80 years); similar results are seen in aged mice.⁴³ While aged human skin has structurally normal stratum corneum lamellar bilayers, they are reduced in number. There is also a decrease in lipid content of the

stratum cornea.⁴³ This is consistent with the finding that topical application of mevalonic acid promotes recovery of the skin barrier in aged mice, putatively via acceleration of cholesterol synthesis.⁴⁴ In addition, administration of cholesterol-dominant lipid mixture containing free fatty acids enhances recovery in aging human and mouse skin.⁴⁵ More recently, administration of a plant oil emulsion improves epidermal barrier formation and corrects the lipid ratios in the aged stratum cornea.⁴⁶

The decreased ability to recovery may also be due to alterations in interleukin-1 (IL-1) signaling; injury stimulates the release of IL-1 α .⁴⁷ Importantly, knock-out of the IL-1 type 1 receptor exacerbates barrier dysfunction, and decreases recovery, demonstrating the important role of this signaling pathway in establishment and maintenance of the skin barrier.⁴⁷

While there are differences between intrinsic and extrinsic aging skin⁴⁸ - the latter often uses ultraviolet (UV) exposure of skin to simulate aging - extrinsic aging has been used to delineate mechanisms associated with barrier dysfunction. UV exposure of skin (photoaging) is associated with decreased E-cadherin and β -catenin expression and was exacerbated in ovariectomized mice that simulate menopause.⁴⁹ These changes in adhesion molecule expression were associated with increased skin permeability to tretinoin, a lipophilic compound. Conversely, other studies have shown that intrinsic and photoaging did not increase skin absorption of rhodamine123 or hydroquinone, despite alterations in TJ components.⁵⁰

Taken together, the majority of data suggest that the epidermal barrier of the skin is disrupted during aging, and following insult there is decreased recovery of function. Several mechanisms may underlie this pathophysiology, including loss of specific homotypic cell adhesion proteins, as well as alterations in cytokine signaling and lipid content.

Lung

The air-blood brain is structurally designed to maximize gas exchange across a small diffusion space; however, this single cell structure is highly susceptible to damage. Given the structural and functional changes associated with aging in the lung,⁵¹ it is rather surprising that little is understood about age-dependent changes in the air-blood barrier (Table 1). In senescent mice, lung permeability, as assessed by clearance

of soluble particles, is increased despite a decrease in alveolar surface area.⁵² This may be due, in part, to decreased expression of matrix metalloproteinase-14 (MMP-14), which is critical for structural integrity of the alveoli,⁵³ in aging mice.⁵⁴ In mice, age-dependent changes in lung structure and function are strain-dependent,⁵⁵ and the loss of MMP-14 expression during aging correlates with these differences.⁵⁴

Acute lung injury is more severe in aging mice (18 mon) - injury is associated with increased vascular permeability as demonstrated by elevated albumin influx.⁵⁶ *In vitro*, senescent lung endothelial cells exposed to lipopolysaccharide (LPS) exhibited greater permeability, which was attenuated by inhibition of Nox4.⁵⁶ The role of Nox4 suggests a critical role for oxidative stress in the disruption of the air-blood barrier. The disruption of the barrier by LPS is supported by *in vivo* studies. Aged mice are more susceptible to LPS-induced disruption of the air-blood barrier as evidenced by elevated protein and inflammatory cells in the bronchoalveolar lavage fluid; decreased occludin expression correlated with these functional deficits.⁵⁷ These data indicate that the air-blood barrier is impacted by aging, and has implications for both acute and chronic respiratory pathophysiology.

Gastrointestinal

Both animal and human studies demonstrate an age-dependent increase in permeability of the gastrointestinal barrier and a role for decreased intestinal barrier function in disease has been reviewed (Table 1).^{58,59} Three decades ago, it was shown that aged rats have decreased intestinal barrier function as assessed by diminished capacity to exclude polyethylene glycol 900 (a medium size molecule) from penetrating the mucosa.⁶⁰ There was also a significant increase in permeability to PEG 400 and mannitol, but not to the large macromolecule inulin, in aged rats.⁶¹ Interestingly, as compared with many age-dependent changes in the rat, lifelong caloric restriction did not attenuate this deficit. There are age-related changes in structure that may, in part, underlie decreased barrier function. Increased endothelial gaps in the villous plexus correlate with increased permeability in aged rats.⁶² There is also decreased ZO-1 and occludin expression in the ileum linked with discontinuous TJs.⁶³ Age-related changes in the intestinal barrier are also seen in aging non-human primate models. In tissue from aged

Table 1. Age-Dependent Changes in the Epithelial Barrier.

Organ	Affected Adhesion Complexes	Mechanisms of Barrier Disruption
Skin	Tight Junction Cadherin/Catenin	Inflammation Lipid Metabolism Oxidative Stress
Lung		Inflammation Oxidative Stress
Intestinal	Tight Junction	Inflammation Secondary to Stroke
Kidney	Tight Junction Cadherin/Catenin	Unknown

baboons, there was a decrease in ZO-1, occludin, and JAM-A, as well as increased claudin-2 expression.⁶⁴ Aged vervet monkeys have reduced intestinal barrier function, leading to increased microbial translocation associated with systemic inflammation.⁶⁵

As assessed by lactulose or mannitol absorption, permeability of the aging human (> 60 yr) small intestine is not increased compared with young controls.⁶⁶ However, in ileal biopsies from aged patients (67–77 yr), there is reduced transepithelial electrical resistance.⁶⁷ While there was no difference in ZO-1, occludin, or JAM-A1 expression, there was an increase in claudin-2 expression associated with barrier dysfunction. Elevated claudin-2 expression was associated with increased IL-6, but not interferon- γ , tumor necrosis factor- α or IL-1 β .⁶⁷

Disruption of the intestinal barrier can also occur secondary to other insults. In an interesting recent study, it was shown that middle cerebral artery occlusion increased gut permeability in young (2–3 mon) and aged (18–20 mon) mice.⁶⁸ This led to bacterial translocation from the gastrointestinal tract that was quickly resolved in young, but not aged mice, and was associated with sepsis in the aged animals.⁶⁸

Given the important role of the intestinal barrier in sequestering the gastrointestinal microbiome from the internal environment, disruption of this barrier during aging has tremendous implications in several pathophysiology. In addition, data suggests that the barrier may be disrupted by other insults, including stroke. Therefore, further understanding of both the implications of increased intestinal permeability, and the mechanisms underlying barrier disruption, have important translational implications.

Kidney

Our laboratory has a long-standing interest in the mechanism(s) leading to renal dysfunction in the aging kidney.^{69–76} We have demonstrated that the aging kidney is characterized by a loss of N-cadherin and α -catenin expression in the proximal tubular epithelium,^{69,70} and that hypermethylation of the N-cadherin promoter underlies decreased expression of in the aging kidney.⁷⁵ To delineate the impact of decreased α -catenin expression on tubular epithelial cell function, we have developed a cell line with stable knockdown of α (E)-catenin. These cells are characterized by increased apoptosis following cisplatin challenge, presumably due to increased Fas signaling,^{71,72} and decreased wound healing due to disrupted migration.^{70,73} This increased susceptibility to apoptosis could explain, in part, the increased severity of AKI following cisplatin in aged rats,⁷¹ while the decreased wound healing may be an underlying mechanisms of the decreased ability of the aging rat to repair following AKI.⁷⁶ The impact of these age-related changes in the tubular epithelial cadherin/catenin complex, however, have not been definitively linked to changes in either basal- or injury-induced

Table 2. Age-Dependent Changes in Adhesion Molecule Expression.

Adhesion Protein	Organ	Mechanism of Regulation	Effect	Reference
↓ZO-1	Intestine	Unknown	Correlates with ↑permeability	64
↓Occludin	Intestine	Unknown	Correlates with ↑permeability	64
↓JAM-A	Intestine	Unknown	Correlates with ↑permeability	64
↓Claudin-1	Skin	Secondary to claudin-6 overexpression	↓Barrier function	41
↑Claudin-1	Kidney	Unknown	Unknown	78
↑Claudin-2	Intestine	Unknown	Correlates with ↑permeability	64, 67
↓Claudin-2	Kidney	Unknown	Unknown	78
↓Claudin-3	Kidney	Unknown	Unknown	78
↓Claudin-4	Kidney	Unknown	Unknown	78
↓Claudin-5	Kidney	Unknown	Unknown	78
↓Claudin-7	Kidney	Unknown	Unknown	78
↓E-cadherin	Skin	Unknown	Correlates with ↑permeability	49
↓N-cadherin	Kidney	Hypermethylation	Unknown	69, 75
↓ α -catenin	Kidney	Unknown	Linked with ↑apoptosis and ↓migration in vitro	70–73
↓ β -catenin	Skin	Unknown	Correlates with ↑permeability	49

permeability of the epithelial barrier that could lead to backleak of the glomerular filtrate.

Age-related changes in adhesion molecular expression are not limited to the cadherin/catenin complex, or tubular epithelium (Table 1). In aged rats there are a decreased number of podocytes concomitant with increased parietal epithelial cells that express podocyte markers (WT-1) and these changes are corrected by caloric restriction⁷⁷ and may have implications on the glomerular filtration barrier. In the aging medulla of female and male mice, claudin-1 is elevated while claudins-2, -3, -4, -5 and -7 are decreased.⁷⁸ In addition, claudin-5 expression was present in young, but not aged, glomeruli.

Taken together these data suggest, but do not directly demonstrate, that glomerular and tubular epithelial barriers may be altered in the aging kidney. Both tight junction and cadherin/catenin complexes are affected by aging and while several pathways downstream of these changes have been characterized, a complete picture of the role of adhesion molecules changes in the structural and functional deficits associated with aging has not been elucidated.

Eye

There is also evidence for barrier disruption in the aging eye, specifically an increase in corneal permeability. There is a correlation between patient age and corneal fluorescence 45 min after application of sodium fluorescein to the conjunctival sac, indicating an increase in epithelial permeability.⁷⁹ However, in aged rabbit corneas (3–4 yr), there was a significant decrease in permeability to large hydrophilic compounds, which may have implications in nutrient delivery.⁸⁰ Currently, the impact of aging on the corneal barrier in the eye is unclear, and represents a pressing need for future research.

Conclusions

Given the critical role of the epithelial barrier in homeostasis, and the impact of aging on organ structure and function, understanding of the impact of aging on epithelial barriers is limited. While there is sound evidence that, in fact, aging may perturb epithelial barriers in several organs, little information is available on the mechanism(s) underlying these changes. Given the unique differences in the structure and function of the epithelial barrier in organs, it is suggested that there may not be a common

mechanism underlying age-related changes. For example, a decrease in claudin-1 expression is associated with decreased function of the skin barrier, but claudin-1 is elevated in the aging kidney (Table 2). While further research on the effect of aging on barrier structure and function is needed, it is also important to examine the aged epithelial barrier in the context of insult and repair, as evidenced by the abundant data that injury is more severe, and recovery inhibited, in aging skin. This emerging field has more unanswered questions than answers, and may provide novel therapeutic targets to combat age-related pathophysiologies in multiple organs.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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