Tight junction proteins, claudin and occludin in pathological conditions and aging of skin and oral mucosa : A review

〔Review〕

Tight junction proteins, claudin and occludin in pathological conditions and aging of skin and oral mucosa：A review

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Abstract

The epithelium is the first line of defense against noxious environmental stimuli through different barrier mechanisms. These barrier mechanisms are maintained by various junctions that can be broadly classified into tight junctions (TJ), gap junctions and adherence junctions. TJ is the most important epithelial barrier system and forms a continuous, circumferential belt like structures at the apical compartment of epithelial sheets. The junctional proteins of TJ play a major role in holding epithelial cells together. The integral junctional proteins of TJ are claudin and occludin. Claudin and occludin have been shown to alter in various diseases of skin and oral mucosa. Also, their alteration with aging has been demonstrated to cause poor epithelial barrier function. Although, various studies have been focused on claudin and occludin, the findings are dispersed. In this review, we summarize the altered expression of the TJ proteins, claudin and occludin, in different pathological conditions including carcinoma of skin and oral mucosa. Also, we summarize the changes in these proteins with aging in both skin and oral mucosa. The findings of our review suggest that the altered expression, not alone downregulation or upregulation of these proteins are responsible for causing various epithelial barrier related skin and oral diseases. The role of these proteins is crucial in the invasion and metastasis of various carcinomas. The understanding of altered expression of these proteins is important in pathogenesis of various age related diseases.

Introduction

The epithelium is the first line of defense against noxious environmental stimuli through different barrier mechanisms. These barrier mechanisms are maintained by various junctions that can be broadly classified into tight junctions (TJ), gap junctions and adherence junctions (Dokladny et al., 2016). TJ acts as an occluding junction that seals the adjacent epithelial cells and prevent the paracellular passage of small solutes and molecules. Adherence junctions are calcium dependent attachment plaques which connects cell−cell or cell－matrix via actin and intermediate filaments to strengthen the cytoskeleton. Gap junctions are composed of connexin proteins involved in connecting cells and create channels to transport small molecules and ions between the cells (Balda & Matter, 2008).

TJ is the most important epithelial barrier system, and forms the continuous and circumferential belt like structures at the apical compartment of epithelial sheets. This protein complex is composed of integral membrane proteins that constitute TJ strands, cytoplasmic proteins and cytoskeletal proteins. It also has roles in maintaining cellular polarity, cell differentiation and signal transduction (Gonzalez−Mariscal et al., 2003)

The junctional proteins of TJ play a major role in holding epithelial cells together (Buckley & Turner, 2018). Claudin, occludin and junctional adhesion molecules (JAM) are the integral junctional proteins of TJ (Chiba et al., 2008).

Claudin and occludin are the backbone in forming TJ strands, whereas JAM is not essential to TJ formation in epithelial cells but involved in various biologic processes like inflammatory reactions and tumorigenesis (Reglero−Real et al., 2016).

Claudin and occludin have been shown to alter in various diseases of skin and oral mucosa. Their alterations with aging have been demonstrated to cause poor epithelial barrier function (Saitoh et al., 2009). Although various studies have been focused on claudin and occludin, the results so far are controversial. In this review, we summarize the altered expression of claudin and occludin in different pathological conditions, carcinoma and aging of skin and oral mucosa.

Role of TJ proteins in barrier mechanism and its regulation

TJ is the apical component of cell membrane in polarized epithelium and endothelium, which is involved in the cell−cell interactions at the lateral domains (Bauer et al., 2014). Claudin, a 20−27kDa membrane protein, is composed of 27 members expressed in TJ of epithelial cells including skin and oral mucosa (Günzel & Fromm, 2013) . Claudin is also transmembrane protein which is composed of two intracellular N and C segment and two extracellular loops. The first loop, with high content of tyrosine and glycine residues, is responsible for paracellular charge selectivity. The second loop, the carboxy terminal domain, rich in serine, threonine and tyrosine residues is a target for a number of proteins and tyrosine kinases, and acts as a co−receptor for bacterial toxins (Weber, 2008). Paracellular flux is regulated by pore pathway allowing passage to small ions and macromolecules, or leaky pathway which allows larger molecules to pass through (Capaldo & Nusrat, 2009). Claudin−1, −3, −5, −11 and −19 are considered as the sealing components, and claudin −2, −10, −15 and −17 are considered as the channel forming components of TJ (Bauer et al., 2014). Occludin, a 60kDa protein, has four transmembrane domains, three cytoplasmic domains (long COOH terminal, short NH_2 terminal domains and short intracellular turn), and two extracellular loops (Förster, 2008). The C−terminal of the occludin plays an essential role in paracellular channel formation, and N−terminal is essential for TJ barrier functions and extracellular loops helps to retain occludin to TJ strands (Cummins., 2012). The C−terminal half of the occludin also binds with peripheral membrane proteins like zona occludens (ZO) and comprises ZO−1, −2 and −3. ZO proteins interact directly with most of the transmembrane proteins including occludin and claudin and acts as a scaffold which allows numerous protein−protein interactions and a cross linker between cytoplasmic proteins and actin based cytoskeleton (Pummi et al., 2001).

The structures of TJ is dynamic and is regulated by various protein phosphorylation and dephosphorylation in response to signaling molecules which determine the compositional and functional integrity of TJ proteins. The disruption of TJ is caused by the activation of various signaling proteins such as MAPKs, Rho GTPase signaling mechanisms and protease activator receptor in response to different noxious stimuli such as oxidative stress, inflammatory mediators, growth factors (Enjoji et al., 2014). It has been shown that the expression of claudin was increased and TJ assembly was enhanced by the inhibition of PP2A (McCole, 2013). The expression of specific genes, which are important for epithelial differentiation and morphogenesis, is activated by the subsequent translocation into the nucleus (Gottardi et al., 1996) and are responsible for cellular differentiation, actin cytoskeleton regulation and TJ functions remodulation (Matter & Balda, 2007).

TJ protein in healthy skin and oral mucosa

Skin is composed of several layers. Stratum corneum, the uppermost layer mainly composed of keratinocytes, is the first line of barrier to the environmental insults such as allergen, microbiome, irritants and pollutants. Once the barrier function of stratum corneum is compromised, the next barrier is performed by TJ proteins, mainly claudin and occludin, in the stratum granulosum layer (Brandner et al., 2015). Oral mucosa is classified as keratinized or non−keratinized tissue. The stratum corneum is absent from non−keratinized tissue. In gingiva, the oral epithelium is keratinized, sulcular epithelium is predominantly non−keratinized and junctional epithelium is non−keratinized (Caffesse et al., 1977). The role of TJ proteins becomes more critical in the non−keratinized oral tissue including sulcular epithelium and junctional epithelium. This might be a cause that sulcular epithelium and junctional epithelium are especially affected in periodontal diseases.

Claudin and Occludin in different pathological conditions of skin and oral mucosa

The altered expression of claudin and occludin are mostly observed in various pathological conditions of skin depending on the severity of the disease, bacterial concentration and epidermal differentiation (Table 1). Increased expression of occludin and decreased expression of claudin−1 and 7 are observed in the early or late stages of psoriasis with more prominent effects in later (Brandner, 2002 ; Kirschner et al., 2009). The expression of claudin−1, 2 and 3 are downregulated in atopic dermatitis facilitating entry of pathogen through epidermis, however compensatory mechanism to maintain barrier integrity leads to the overexpression of claudin−4 (Guttman et al. 2006). It is reported that TJ proteins are altered in human epidermal keratinocytes during different bacterial infections. A study showed that the increased expression of TJ proteins as a rescue mechanism was observed by the exposure of *Staphylococcus aureus* and *Staphylococcus epidermidis* to epithelial cell for 3 hours, while the significantly decreased expression was observed by the exposure for 7−10 hours due to the loss of transepithelial resistance (TER). No alteration of TJ proteins is observed in the epithelial barrier by the exposure at the concentration of $< 10^4$ bacteria/ml for 5 hours, while downregulated expression of claudin−1, 4 and 7 is observed by increasing bacterial load up to the concentration of 10^6 bacteria/ml (Ohnemus et al., 2008). Hailey−Hailey disease and Darrier's disease are autosomal dominant skin diseases where alteration of TJ proteins is associated with epidermal differentiation and calcium gradient. In both, increased expression of claudin−1, 4 and occludin is observed with the

Table 1 : Altered expression of Claudin and Occludin in various skin diseases ; TJ, Tight Junction ; NISCH, Neonatal ichthyosis−sclerosing cholangitis.

Pathological condition (Skin)	Proteins	Explained Impact	References
A. *In Vitro study*			
Bacterial (*S.aureus & S.epididermis*) infection i) Early−3hrs of infection Late−7.5 hrs of infection ii) 10^4/ml bacteria−5hr 10^6/ml bacteria−5hr	Early− Claudin−4 ↑, Occludin ↑ Late− Claudin−4 ↓, Occludin ↓ Claudin−1, 4,Occludin−No change Claudin−1,−4,Occludin ↓	Early rise of TJ proteins may be due to rescue mechanism during bacteria−keratinocyte interaction. Dyslocalization of TJ proteins occurred after bacteria invade the epidermis.	(Ohnemus et al., 2008)
B. *In Vivo study*			
Psoriasis vulgaris (Early stage) Psoriasis (Plaque type)	Occludin ↑ Claudin−1 ↓, −7 ↓ Occludin ↑ Claudin−1 ↓, −7 ↓	1) Broader expression of occludin and claudin is to keep barrier functions results in thicker epidermal layer. 2) Further loss of claudin is a consequence of various stimuli like bacterial infections leading to impairment in the TJ barrier functions.	(Brandner, 2002 ; Watson et al., 2007 ; (Kirschner et al., 2009)
Atopic Dermatitis	Claudin−1 ↓,−2 ↓,−3 ↓, Claudin−1 ↓ (lesional area) Claudin−4 ↑ (non−lesional area)	1)Decreased Claudin−1,23 enhance the penetration of environmental antigens leading to greater allergen sensitization. 2)Increased Claudin−4 is a compensatory mechanism to maintain stratum corneum barrier integrity.	(Guttman et al., 2006 ; De Benedetto et al., 2011)
Impetigo Contagiosa	Occludin ↑ Claudin−1 ↓	Early rise of TJ proteins may be due to rescue mechanism. Downregulation of TJ proteins occurred after bacteria invade the epidermis.	(Ohnemus et al., 2008)
Hailey−Hailey disease i) Low calcium ii) High calcium	Claudin−1 ↓ i) Claudin−4,Occludin ↓ ii) Claudin−4,Occludin ↑	Acantholytic process alters the dynamics of TJ proteins. Altered expression of TJ may be due to aberrant epidermal differentiation and calcium concentration.	(Raiko et al., 2009 ; Raiko et al., 2012)
Lichen Planus Ichthyosis Syndrome	Occludin ↑	Alteration in stratum granulosum layer leads TJ proteins to relocalize to stratum spinosum which results in hyperkeratotic lesion.	(Pummi et al., 2001)
Darrier's Disease	Claudin−1 ↓	Acantholytic process alters the dynamics of TJ proteins which highlight the importance of intercellular calcium in TJ regulation.	(Raiko et al., 2009 ; Raiko et al., 2012)
NISCH syndrome	Claudin−1 ↓ Claudin−2 ↑	Decreased Claudin−1 increases the paracellular permeability due to poor anchoring among the claudin in epithelial cells. The relative overexpression of claudin−2 in the patient liver is due to compensatory mechanism.	(Hadj−Rabia et al., 2004)
Mouse−model	Claudin−1 knockout	Died immediately after birth due to transepidermal water loss and skin dehydration.	(Furuse et al., 2002)

low calcium concentration while significant downregulations were observed by increasing calcium gradient and epidermal differentiation (Raiko et al., 2012).

In experimental models of periodontitis, the expression of TJ proteins depends on the duration or the grade of periodontitis, bacterial concentration and apical or basolateral exposure *in vitro*. The expression of claudin－4, 15 is upregulated in case of biofilm challenge and minimally inflamed gingival epithelium for 24 hour (Guo et al., 2017) while claudin−4, 15 and occludin is downregulated in pocket epithelium. These suggest that the expression of TJ proteins is decreased by the chronicity of diseases. *Porphyromonas gingivalis* (*Pg*) along with its virulence factors is one of the major etiologic agents in the pathogenesis and progression of periodontal disease. Significant upregulation of claudin−4 is shown by the exposure of *Pg* to gingival epithelial cell for 4 hours, with no effect on claudin－1 and occludin. In contrast, the expression of claudin－4, 15 and occludin is downregulated by the exposure of *Pg Lipopolysachharide* (*Pg LPS*) for 4 hours. Also, claudin−1 is upregulated by the exposure of *Pg* to gingival epithelial cells after 4 hours while is significantly downregulated by the chronic exposure of LPS for 3 weeks. *Pg* is an opportunistic pathogen which relies on fermentation of amino acids for metabolic energy and tends to grow in nutritional environment forming subgingival plaque. Subsequent changes in the local environment which may be host related factor or symbiotic pathogens can differentially regulate its virulence factors. LPS is the most potent endotoxin which exerts its effect through activation of Toll like receptor 4 (TLR4) (Tada et al., 2013). The studies have shown to activate TLR4 after 6 hours of LPS exposure to oral epithelial cells. Based on the above results, we can hypothesize the pathogenesis of *Pg* in two ways. In the early stage of infection, epithelial cells, which are the first line of immune defense, respond strongly to *Pg* mediated low grade inflammation. At later stage, virulence

Table 2 : Altered expression of Claudin and Occludin in various oral pathological conditions ; TJ, Tight Junction ; *Pg*, *Porphyromonas gingivalis* ; LPS, Lipopolysaccharide ; FHHNC, Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis ; TER, Transepithelial Electrical Resistance.

Pathological condition (Oral)	Proteins	Explained Impact	References
A. *In Vitro study*			
24 hour Biofilm challenge	Claudin−4 ↑	24hr challenge with biofilm without 'red complex' bacteria shows upregulation of Claudin−4 which may not deliberate any biological relevance.	(Guo et al., 2018)
Pg and *Pg LPS* induced alteration of TJ−4hr	i) *Pg* 4hr− Claudin−4 ↑, Claudin−15 ↓ ; *Pg* 72hr− Claudin−1 ↑ ii) *Pg LPS* 4hr− Claudin−4 ↓, Claudin−15 ↓, Occludin ↓, Claudin−1 ↑	Early upregulation of TJ proteins is due to compensatory mechanism for barrier protection. Chronic exposure of pathogen altered the immune defence mechanism and hence alter TJ expression resulting in epithelial disruption.	(Guo et al., 2018 ; Tada et al., 2019)
Pg induced epithelial disruption i) $>10^9$ bacteria/ml , 2−4hr− Basolateral exposure− ↓TER ii) $>10^9$ bacteria/ml, 2−4hr− Apical exposure− ↑TER	i) Occludin ↓ ii) Occludin ↑	Decreased TER observed between 2−4 hour− Bacterial pathogen exposed from basolateral surface are more susceptible for epithelial disruption. Increase in TER observed up to 24hours and decreased between 24－48 hour− Apical exposure of bacterial pathogen require more time to induce epithelial disruptions.	(Katz et al., 2000)
T.denticola induced TJ protein alteration i) 10^4 −6hr−Basolateral ii) 10^4 −6hr−Apical	i) Claudin−1 ↓, Occludin− ↓ ii) No change in expression	Basolateral surfaces are more susceptible than apical surfaces to the effects of *T.denticola* and threshold of bacteria is required to alter epithelial barrier proteins.	(Kikuchi et al., 2018)
i) Minimal gingival inflammation ii) Pocket epithelium	i) Claudin−4 ↑, Claudin 15 ↑, Occludin− ↑ ii) Claudin−4− ↓, Claudin−15 ↓, Occludin− ↓	Ligation of CD24 facilitates increase expression of TJ proteins that mediate epithelial barrier functions as a protective mechanism against periodontal pathogens.	(Ye et al., 2014)
B. *In Vivo study*			
Chronic *LPS* challenge periodontitis−3wks	Claudin−1 ↓	Disruption of barrier functions and initiation of periodontal diseases	(Fujita et al., 2010)
Periodontitis in HIV patients−5 days treatment of oral epithelial cells with HIV−tat and gp120	Claudin−1 ↓,−3 ↓,−4 ↓, Occludin− ↓	Activated immune cells produce larger amount of proinflammatory cytokines which disrupt epithelial barriers, facilitates secondary invasion to human papilloma virus.	(Tugizov, 2016)
Enamel defects Amelogenesis Imperfecta in patients with FHHNC	Claudin−3 ↓,16 ↓,19− ↓	1) Hypoplastic and hypomineralised tooth. 2) Enamel loss, easily breakable enamel with underlying dentin exposure in molars, and decreased mineralization in continuously growing lower incisors in patients with FHHNC.	(Bardet et al., 2016)

factor like LPS activates TLR4 leading to series of inflammatory cascade resulting in tissue destruction (Kocgozlu et al., 2009).

By the exposure of Treponema denticola (*Td*) at a concentration of $>10^9$ bacteria/ml for 2−4 hours, transepithelial electrical resistance (TER) is decreased in the basolateral area, while is increased in the apical area (Katz et al., 2000). At concentration of 10^4 bacteria/ml for 6 hours, TER is significantly decreased in the basolateral area, while no change is observed in the apical area. At concentration of 10^2 bacteria/ml for 16 hours, Claudin−1 is decreased in both apical and basolateral area (Kikuchi et al., 2018). These signify that the disruption of epithelial junctional proteins is caused by the critical threshold of bacterial load and exposure duration.

Claudin and occludin maintains barrier integrity from the early development of tooth germs when ameloblast and odontoblast differentiates (João & Arana−Chavez, 2004). Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare kidney disease caused by the mutation of claudin−16 and −19. These patients show severe enamel defects, which are similar to amelogenesis imperfecta with impaired TJ structure and enamel matrix deposition. The loss of claudin−16 results in the modification of environmental factors such as pH, impairment of the processing of enamel matrix proteins and disturbance of enamel formation, in the patients with FHHNC and in the $Cldn16^{-/-}$ mice (Bardet et al., 2016). Claudin−3 and −19 deficiency in patients with FHHNC presented hypoplastic or hypomineralised enamel in both secretory and maturational stages (Bardet et al., 2017). These highlights the importance of claudin and occludin from early stages of tooth development

Table 3 : Altered expression of Claudin and Occludin in various skin cancer ; TJ, Tight Junction ; DMBA, Dimethylbenz(a)anthracene ; TPA, Tetradecanoyl−phorbol−13−acetate.

Cancer (Skin)	Proteins	Explained Impact	References
A. *In Vitro study*			
DMBA/TPA induced skin Papilloma	Claudin−1↓,6↓,11↓,12↓,18↓ (in cell membrane)	Translocalization of claudin away from cell membrane may suggest endocytosis leading claudin retention in cytoplasmic vesicles which may lead to altered cell polarity and barrier.	(Arabzadeh et al., 2007)
B. *In Vivo study*			
Squamous cell carcinoma (SCC) Well−differentiated (early stage/low grade)	Claudin−1↑ Claudin−11↓ Claudin−4↑ Occludin↑	Increased claudin−1 facilitates invasive potential Loss of claudin is a biomarker for tumor progression Claudin−4 and occludin are concentrated around cancer−pearl which indicates the presence of TJ is not for barrier function rather than their relation to keratinization.	(Ouban et al., 2012 ; Nissinen et al., 2017 ; Morita et al., 2004)
SCC Less−differentiated (late stage/high grade)	Claudin−1↓ Claudin−7↑ Claudin−11↑ Occludin↓	May express other pathogenetic mechanism to regulate invasion. Expression of Claudin−7 is late event in epidermal neoplastic process. Expression of claudin−11 is associated with progression of tumor to invasive stage. Downregulated occludin decrease cell−cell adhesion, altered epidermal differentiation and calcium homeostasis.	(Ouban et al., 2012 ; Hintsala et al., 2013 ; Rachow et al., 2013 ; Nissinen et al., 2017)
Merkel Cell Carcinoma	Claudin−3,4↑, Occludin↑ Claudin−5−Mild expression	The increased expression may signify TJ may play role in self-isolation of tumor from environment. Expression of claudin−5 in certain areas signifies the formation of vessels within tumor mass	(Haass et al., 2003)
Metastatic melanoma	Claudin−1↑ Claudin−1↓	Expression of claudin increases MMP−2 activity thereby increasing melanoma cell motility. Claudin−1 produced by melanocytes may not assemble with TJ structures	(Cohn et al., 2005 ; Leotlela et al., 2007)
Precursor tumors of SCC			
Atopic keratosis	Claudin−1↓ Claudin−2↑ Claudin−4↑	Diminish TJ barrier functions. Overexpression of Claudin−2 is associated with leakage of barrier. Alteration of Claudin−4 is induced by UV radiation	(Hintsala et al., 2013 ; Rachow et al., 2013)
Bowen's diseases	Claudin−1, Claudin−4 & Occludin↑ (in keratinized part)	TJ−associated molecules altered in relation to keratinization (individual cell keratinization).	(Morita et al., 2004)
Ankyloblepharon−Ectodermal Dysplasia Clefting (AEC)	Claudin−1↓	Claudin−1 may be a transcriptional target of p63 gene, which has undergone mutation in AEC patients, so its downregulated expression causes skin fragility.	(Lopardo et al., 2008)

in creating suitable environment for enamel deposition and maturation by their role as barrier maintaining proteins.

Claudin and occludin in cancer of skin and oral cavity

Cell to cell interaction is important phenomenon in maintaining tissue integrity and homeostasis. The loss of cell−cell adhesion is considered as the initiation in the process of invasion and metastasis in carcinoma. The altered expression of TJ proteins can increase epithelial permeability, loss of contact inhibition, polarity and abnormal signaling leading to inhibition or activation of various growths signaling mechanism. Although the exact mechanism of altered TJ proteins in cancer is still unclear, the involvement can be confirmed by the deregulated expressions with migration, invasion and metastasis of cancer in tissue specific manner (Martin & Jiang, 2009). The bewildering expressions of TJ proteins in various cancers are due to solitary or synergistic actions of above mechanisms.

The alterations of claudin and occludin in dysplasia and cancer in skin and oral tissues are shown in Table 3 and Table 4 respectively. The expression patterns of TJ proteins might have some correlation with the type of tumor grade, site or keratinization.

As ultraviolet (UV) radiation is the major risk factor for benign and malignant lesion of skin, the effect of UV radiation on TJ proteins may also precede the conditions. The downregulation of claudin−1 and upregulation of claudin−2 and −4 are shown in the precursor tumors such as atopic keratosis, and it resulted in diminished TJ barrier function which is a typical feature of dysplastic lesion (Hintsala et al., 2013). The expression of claudin−1, −4 and occludin is altered in Bowen's disease (Morita et al., 2004). Claudin−1 is upregulated in the early stage of cutaneous squamous cell carcinoma (cSCC) and is downregulated in advanced stage (Sappayatosok & Phattarataratip, 2015). Claudin−4 and occludin are upregulated in well differentiated cSCC, while their concentrated expression is observed around the keratin pearl instead of cell−cell border (Morita et al., 2011). Claudin−4 expression is increased in keratinized portion of SCC whereas downregulated in non−keratinized part (Vicente et al., 2015). The expression of claudin−7 and −11 is upregulated in undifferentiated cutaneous SCC, and is more significantly upregulated in the later event in epidermal neoplastic process (Hintsala et al 2013; Nissinen et al., 2018). The decreased expression of occludin is shown in other carcinoma derived from non−keratinized epithelia such as hepatic carcinoma, gastric carcinoma, breast carcinoma and endometrial carcinoma (Sawada et al., 2003). This indicates that TJ proteins might be related to keratinization.

Furthermore, the summary of TJ proteins in other skin carcinoma such as malignant melanoma (MM) and merkel cell carcinoma (MCC) have been studied. Loss of Claudin−1 in metastatic MM (MMM) as compared to benign melano-

Table 4 : Altered expression of Claudin and Occludin in various oral diseases ; TJ, Tight Junction ; OSCC, Oral Squamous Cell Carcinoma ; KCOT ; Keratocystic Odontogenic Tumour

Cancer (Oral)	Proteins	Explained Impact	References
OSCC- Early stage	Claudin−1 ↓ Claudin−4,−7 ↑, Occludin− ↓	May involve other regulating factors than claudin to increase invasive potential. Claudin overexpression result in enhanced cell adhesion and decreased tumor aggressiveness. Upregulation may interfere with TJ interactions and signaling cascades	(Joãoj & Arana−Chavez, 2004 ; De Vicente et al., 2015 ; Sappayatosok & Phattarataratip, 2015)
OSCC- Late stage	Claudin−1 ↑ Claudin−4 ↓ Claudin−7 ↓	Claudin−1 enhances tumor invasion by degradation of extracellular matrix deposition. Claudin−4 play a role in maintaining the architecture of cell nests and keratin pearls, however downregulation is accompanied with decrease e−cadherin expression which enhance migration, invasiveness and metastasis Loss of Claudin−7 directly promote neoplastic process due to destruction of TJ	(Joãoj & Arana−Chavez, 2004 ; Oku et al., 2006 ; El−Bolok, 2011 ; De Vicente et al., 2015 ; Sappayatosok & Phattarataratip, 2015)
KCOT−lining epithelium	Claudin−1 ↑,−3 ↓ Claudin−4 ↑ Claudin−7 ↑	Increased in an attempt to maintain cell–cell attachments at the sites of cystic degeneration. Over expression of Claudin−4 in keratinocytes surface may be associated with abnormal TJs formation. May play a role in the formation of Rushton hyaline bodies.	(Siar & Abbas, 2013)
KCOT- Vascular epithelium	Claudin−5− mild to moderate	Claudin−5 is the only claudin member expressed in endothelium. Subcellular localization of Claudin− 7 in lining epithelium may result in formation of Rushton hyaline bodies.	(Siar & Abbas, 2013)
Mild Oral Epithelial Dysplasia	Claudin−1 ↓	Staining intensity increasing with high grade of tumor may suggest the involvement of claudin−1 in progression of dysplasia	(Kwon, 2013 ; Carvalho et al., 2010)

cytic nevi may be due to failure of claudin produced by melanocytes cells to assemble with TJ structures (Cohn et al., 2005). In experimentally induced skin papilloma of mice with 7, 12−dimethylbenz (a) anathracene, the downregulated expression of claudin−1, −6, −11, −12, −18 is observed. The downregulation of TJ proteins may be due to the involvement of transcriptional factors silencing the expression of claudin (Arabzadeh & Turksen., 2007).

The expression of claudin and occludin depends on the histopathological grade of cancer. Claudin−1, −4 and −7 are the major TJ proteins altered in oral cancer. In mild epithelial dysplasia and early stage of Oral SCC (OSCC), the expression of claudin−1 is downregulated, thereby leading to the disorganization of epithelial cancer cells. The low expression of claudin−1 may be a predictor of disease recurrence and poor prognosis. The increased expression of claudin−1 with cancer progression enhances the invasive potential with degradation of extracellular matrix. Claudin−4 and −7 are upregulated in the early stages of OSCC and are downregulated in the late stages. The upregulation in the early stages interferes with TJ functioning and signaling whereas the downregulation in the late stages is accompanied with the destruction of TJ structure enhancing migration, invasion and metastasis. The expression of TJ proteins in the lining epithelium of keratocystic odontogenic tumor (KCOT) is found to be associated with keratinization. The concentrated presence of claudin−1, −3, −4 is found in the area of keratin pearls. The increased expression of claudin−1 is associated with compensatory mechanism to maintain barrier integrity. The increased expression of claudin−4 and −7 is found to be associated with their role in Rushton hyaline body formation. The loss of claudin−3 caused the altered barrier formation and the loss of cell polarity which simulate the biological behavior of KCOT. Claudin−5 is only observed in the vascular lining of KCOT. Claudin−5 is the only protein of claudin family expressed in the endothelium. Similarly the upregulation of claudin−1 in the invasive ductal breast, cervical and colorectal carcinoma, and the downregulation of claudin−4 and −7 in the invasive esophageal and prostrate carcinoma are observed. Also the downregulation of claudin−1 in other invasive carcinomas such as hepatocellular and prostate carcinoma is observed.

The role of claudin and occludin in tumorigenesis is complicated. The impaired cell−cell contacts leading to series of changes with its reduced expression are clearly understandable, but the overexpression of certain proteins in many metastatic lesions creates paradigm that how stabilizing proteins enhances cell motility of tumor cells. The alteration of TJ functions is caused by either underexpression or overexpression of TJ proteins. The transcriptional regulator should be taken into consideration. Decreased expression leading to cell detachment process is understandable but increased expression of claudins are often observed in tumor cells. The enhanced expression may also be an initial step which disturbs the balance of TJ in the cells and is associated with proliferation, invasion and metastasis of the tumor cells. The expression of TJ proteins for carcinomas are not consistent. These may be due to multifactorial complex where TJ performs barrier function, cellular signaling and differentiation. These may act through specific pathway to potentiate or protect tumorigenesis.

TJ proteins in skin and oral mucosa with aging

Aging is a progressive decline in the physiological function leading to onset of organ specific functional deterioration. The clinical presentation of aged skin exhibit hypo−/hyper−pigmented lesions, wrinkle scaly appearances or pallor fragility. Some studies have attributed these changes to the change of thickness in the stratum corneum composition and basement membrane (Farage et al., 2013), while another study highlighted the role of TJ (Bhattacharyya & Thomas, 2004). The intrinsic factor for aging changes is due to the continuous physiological remodeling of tissues which was generated by some stresses over time period (Quan & Fisher, 2015). The accumulation of reactive oxygen species (ROS) causing stress to cells is led by the extrinsic factors such as UV radiation, pollution, smoking, hypoxia, or poor nutrition. These oxidative stresses may lead to the post−translation mostly including phosphorylation at serine and threonine residues, and may result in altering the phosphorylation pattern and the barrier integrity.

Few Studies have been reported regarding the expression and regulation of TJ proteins in skin and oral mucosa with physiological and experimental models of aging skin. In a study, no significant alteration of TJ proteins in human young or intrinsically aged epidermis is confirmed even though the decreased expression is confirmed in rodent epidermis (Althubaiti., 2012). However, the changes in barrier functions and TEWL are noted in physiologically aged skin. This might be due to the various signaling pathway associ-

ated with TJ proteins. In an experimental model of aging skin, claudin−1 is downregulated, and claudin−7 and −12 are upregulated in the photoaged skin as compared to the photoprotected skin (Althubaiti, 2012). The UV radiation may change TJ protein levels by ROS mediated signaling associated with degradation of MMP or directly affecting the genes at the transcriptional level. The barrier disruption is caused by the downregulation of claudin−1 and upregulation of claudin−7 and −12. The wrinkled skin with increased TEWL caused by the downregulation of claudin−1 is observed in the aging mice (Parrish., 2017). These changes are accompanied by the marked downregulation of claudin−1. The epidermal barrier disruption is shown by the claudin−1 knockdown aged mice with atopic dermatitis as compared to claudin$^{+/+}$mice (Tokumasu et al., 2017). Normal morphological phenotype is shown by the transgenic mice overexpressing an epidermal targeted claudin−6 at a young age, while severe dermatitis associated skin barrier function is shown by a high sensitivity for epidermal injury with aging (Troy et al., 2009).

In aging mice, Claudin−2, −3, −4 and −5 are downregulated in the kidney epithelium and pancreas. Claudin−1 is upregulated in the liver and kidney and claudin−7 is upregulated in the pancreas (D'Souza et al., 2009). Although the exact mechanism and regulation of their expression in aging tissue are still not clear, these are considered as the effect on TJ functionality which is responsible for some of the aging related changes.

Conclusion

TJ proteins, including mainly claudin and occludin, plays a major role in maintaining epithelial integrity. The altered expression, of these proteins are responsible for skin and oral diseases. The role of these proteins in various carcinomas is crucial in the invasion and metastasis. The understanding of altered expression of these proteins in the age−related diseases is important and studies are limited. Further research is needed to be focused on this aspect.

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