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Cleavage of transmembrane junction proteins and their role in regulating epithelial homeostasis

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Abbreviations: TJ, tight junction; AJ, adherens junction; DM, desmosome; CTX, cortical thymocyte marker in Xenopus; JAM-A, junctional adhesion molecule A; CAR, coxsackie adenovirus receptor; CLMP, CAR-like membrane protein; ZO, zonula occludens; MAGI, membrane-associated guanylate kinase with inverted orientation; E-cadherin, epithelial-cadherin; N-cadherin, neural-cadherin; P-cadherin, placental-cadherin; AF, afadin; Dsg, desmoglein; Dsc, desmocollin; MMP, matrix metalloprotease; ADAM, a disintegrin and metalloprotease; EMMPRIN, extracellular matrix metalloprotease inducer; IFN-γ, interferon-gamma; sE-cadherin, soluble E-cadherin; EGFR, epidermal growth factor receptor; HtrA, high temperature requirement protease A; SPINK5, serine protease inhibitor of kazal type 5; HAV, His-Ala-Val; EC, extracellular; MT1-MMP, membrane-type matrix metalloprotease; HER, human epidermal growth factor receptor; PI3K, phosphoinositide-3 kinase; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; TLR, toll-like receptor; STAT, signal transducer and activator of transcription; CTF, C-terminal fragment; Tcf, T cell factor; EpCAM, epithelial cell adhesion molecule; FHL2, four and a half LIM-domain protein; Lef, lymphoid enhancer-binding factor; RTK, receptor tyrosine kinases; HIV, human immunodeficiency virus; TACE, tumor necrosis factor-α-converting enzyme; TGFβ, transforming growth factor-beta; IL-1β, interleukin-1 beta; LPS, lipopolysaccharide; TNFα, tumor necrosis factor-alpha; PMA, phorbol-12-myristate-13-acetate; PKD1, protein kinase D1; HGF/SF, hepatocyte growth factor/scatter factor; EGF, epidermal growth factor; LPA, lysophosphatidic acid; TPA, 12-O-tetradecanoylphorbol-13-acetate; PMN, polymorphonuclear leukocyte; IGF1R, insulin-like growth factor 1 receptor; NTF, N-terminal fragment; EA, extracellular anchor

Epithelial tissues form a selective barrier that separates the external environment from the internal tissue milieu. Single epithelial cells are densely packed and associate via distinct intercellular junctions. Intercellular junction proteins not only control barrier properties of the epithelium but also play an important role in regulating epithelial homeostasis that encompasses cell proliferation, migration, differentiation and regulated shedding. Recent studies have revealed that several proteases target epithelial junction proteins during physiological maturation as well as in pathologic states such as inflammation and cancer. This review discusses mechanisms and biological consequences of transmembrane junction protein cleavage. The influence of junction protein cleavage products on pathogenesis of inflammation and cancer is discussed.

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Introduction

Epithelial tissues form a physical barrier that separates the external environment and tissue compartments thereby playing a pivotal role in host defense. In simple epithelia such as in the gut, this barrier is formed by a single layer of cells joined by a series of intercellular junctions: tight junctions (TJs), adherens junctions (AJs) and desmosomes (DMs).[1] Intercellular junctions affiliate with the cytoskeleton that in turn controls junction function. It is now evident that intercellular junctions are dynamic structures that not only control the epithelial barrier, but also influence overall epithelial homeostasis.

TJs, the most apical epithelial junctions, are visualized as belt-like structures in a region where membranes from adjoining cells comes into very close apposition forming a selective seal that regulates paracellular movement of ions and solutes.[1,2] In addition to its role as a gate, TJs also function as a fence that prevents free movement of proteins from the apical to the basolateral membrane. Thus, TJs contribute to maintenance of epithelial apical-basolateral polarity.[2] A vast repertoire of TJ proteins have been identified that can be broadly grouped into transmembrane, cytoplasmic plaque and signaling proteins. Key transmembrane proteins include claudins, occludin/tricellulin and the cortical thymocyte marker in Xenopus (CTX) family members

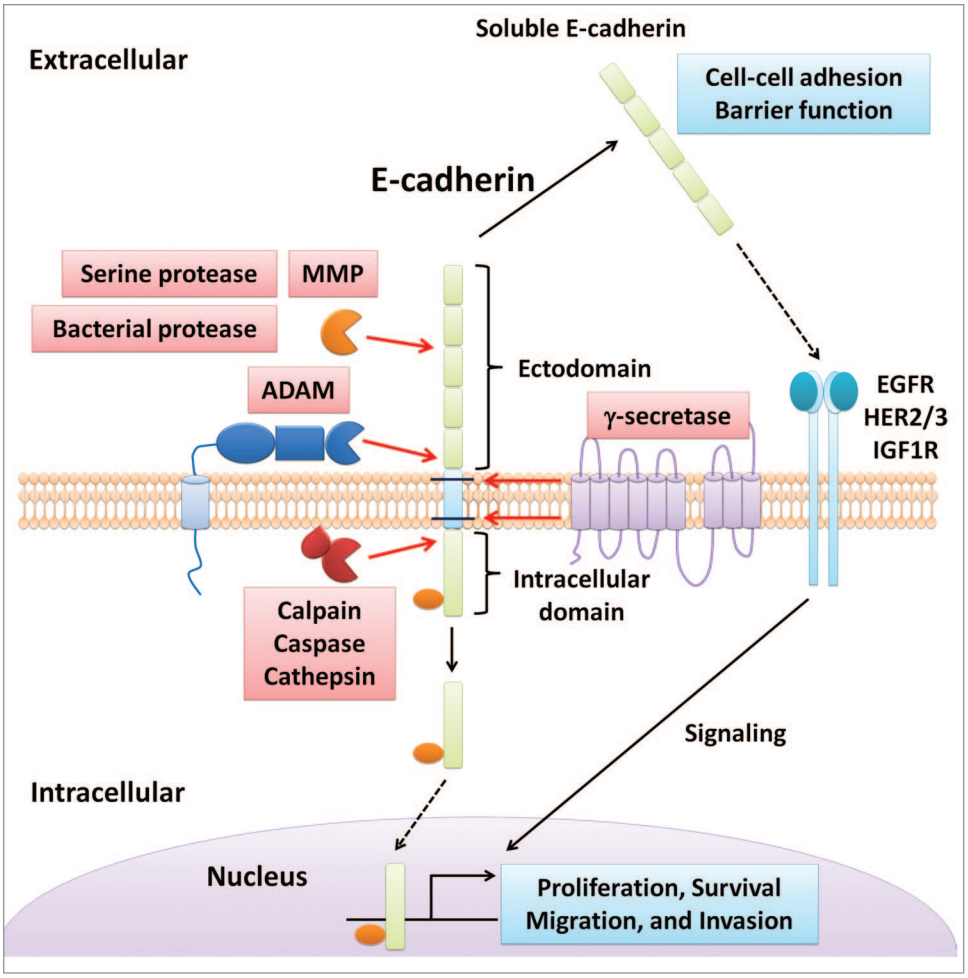

Figure 1. E-cadherin cleavage and its influence on epithelial homeostasis. This figure summarizes extracellular and intracellular cleavage of E-cadherin as detailed in the review.

[junctional adhesion molecule A (JAM-A), coxsackie adenovirus receptor (CAR) and CAR-like membrane protein (CLMP)]. These transmembrane proteins affiliate with the underlying apical perijunctional F-actin belt via peripheral membrane proteins, such as zonula occludens (ZO)-1 and membrane-associated guanylate kinase with inverted orientation (MAGI)-1.[2-6]

AJs are localized immediately subjacent to the TJ and by electron microscopy appear as regions where membranes of two neighboring cells run parallel to each other.[1] Analogous to TJs, AJs circumscribe the cell periphery and play an important role regulating cell-cell adhesion. AJs consist of a central core of transmembrane proteins that include nectin, classical cadherin family members such as epithelial (E)-cadherin, neural (N)-cadherin, placental (P)-cadherin and cytoplasmic plaque proteins, which are linked to the actin cytoskeleton via plaque proteins.[7,8] Plaque proteins in the AJ include afadin/AF-6 (for nectin), α-catenin and several members of the armadillo family that include β-catenin and p120-catenin (for classical cadherin).[8] It is noteworthy to mention that the AJ plaque protein β-catenin is one of the principal transcription factors that regulate epithelial proliferation and differentiation.[9,10] Thus, establishment and maintenance of functional AJs is a central event that controls epithelial homeostasis.

DMs are spot-like adhesions located in the lateral membrane of the epithelial cells[11,12] and comprised of desmosomal cadherins: desmoglein (Dsg) and desmocollin (Dsc). To date, four isoforms of Dsg (Dsg1–4) and three isoforms of Dsc (Dsc1–3) have been identified in the human epidermis.[13] However, simple epithelia such as intestinal epithelium expresses only Dsg2 and Dsc2.[12,14] Desmosomal cadherins indirectly associate with keratin intermediate filaments via plaque proteins, that include plakoglobin, plakophilin and the plakin family member, desmoplakin.[11] DMs provide resistance to mechanical stress in the epithelium and also in several nonepithelial tissues such as cardiac muscle and meninges.[12] In concert with other intercellular junctions, DMs are reservoirs for signaling molecules that control several biological processes.[11,14,15] Dysfunction of desmosomal cadherins has been linked to pathogenesis of diseases such as pemphigus vulgaris.[16-18]

Given their essential role in maintenance of the epithelial barrier, cell junctions need to function as dynamic structures that are continuously assembled and disassembled. The dynamic nature of cell junctions allows epithelial cells to respond to external stimuli by modifying strength and distribution of cell junction proteins. Remodeling of cell junctions can be achieved by mechanisms that include: de novo synthesis,[19] internalization,[20,21] exocytosis[22] and proteolytic processing of structural proteins at cell junctions.[14,23,24] Indeed, proteolysis of transmembrane junction proteins by cellular and bacterial proteases has emerged as a novel mechanism to regulate intercellular junctions and epithelial homeostasis. In this review, we will focus on the mechanisms of transmembrane junction protein cleavage and their physiological, pathological and biological significance.

Extracellular Cleavage of Epithelial Transmembrane Junction Proteins

Proteases that mediate extracellular cleavage of transmembrane junction proteins. In epithelial tissues, the extracellular domains of the transmembrane junction proteins are located along the lateral membrane in the paracellular space formed by between two adjacent cells. In the intercellular space,

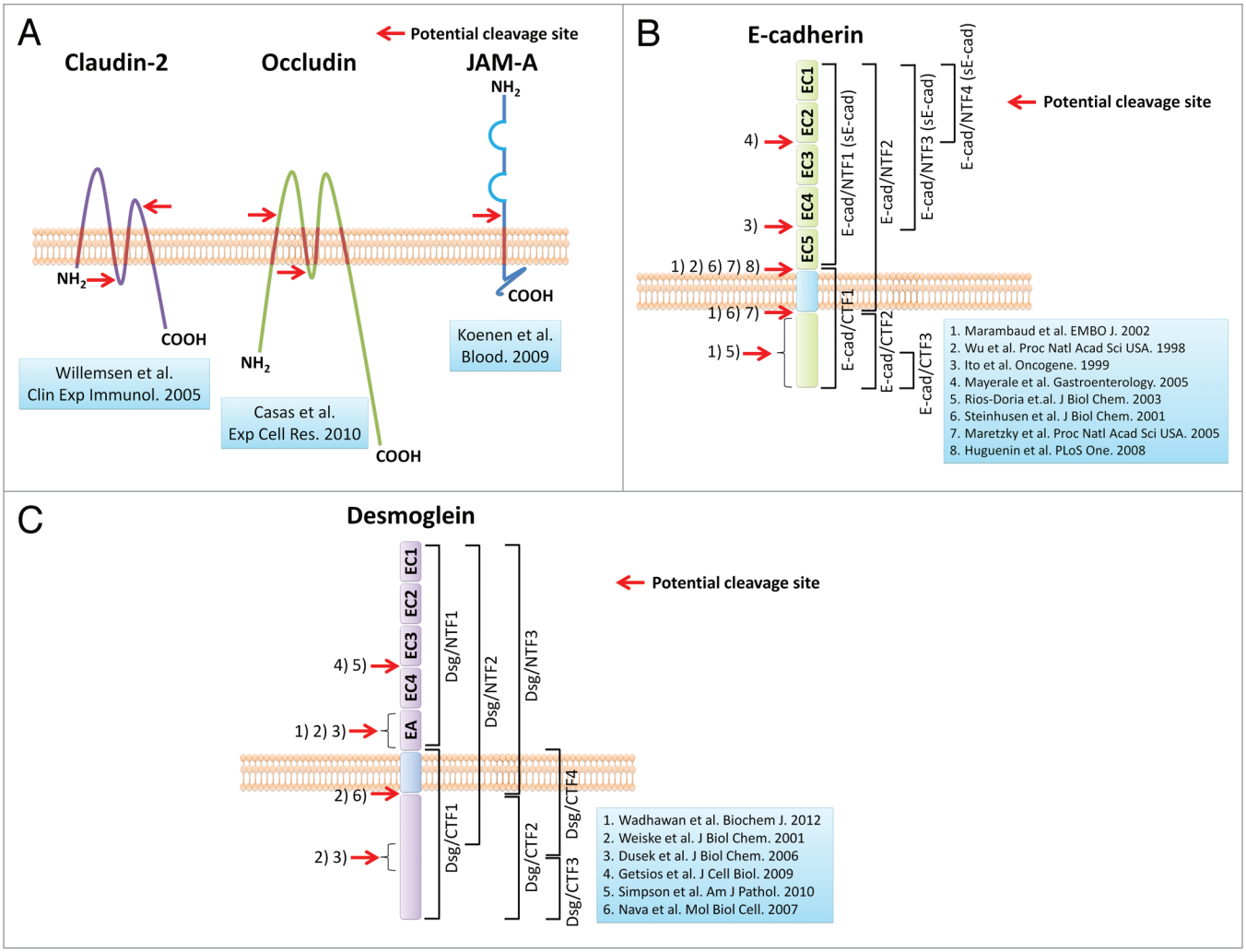

Figure 2. Potential cleavage sites in transmembrane junctional proteins. These figures demonstrate potential cleavage sites of representative transmembrane junctional proteins in epithelial cells. (**A**) Tight junction proteins; (**B**) E-cadherin; (**C**) desmoglein.

ectodomains of two neighboring cells form cell junctions. Thus, the ectodomains are exposed to several insults including extracellular proteases referred to as "sheddases." Sheddases can cleave unprotected extracellular domains of the proteins in the paracellular space (**Fig. 1**). Such proteases include diverse proteins derived from the epithelium, endothelium, immune cells and bacteria. Many sheddases are misregulated in pathological states such as inflammation and cancer. In fact, one of the mechanisms by which cancer cells overcome cell adhesion to induce cell proliferation and metastasis is by upregulating the expression/activity of several sheddases that are capable of cleaving the extracellular domain of cell adhesion molecules.[25,26] As shown in **Figure 2**, cleavage of transmembrane proteins most often occurs at defined sites close to transmembrane regions of junction proteins. Interestingly, the extracellar cleavage products can modulate epithelial cellular processes such as cell-cell adhesion, cell migration and cell proliferation. In this review, we discuss proteases that generate cleavage products of junctional proteins which exert biological effects on epithelial homeostasis. Matrix metalloprotease (MMP), a disintegrin and metalloprotease (ADAM), γ-secretase, serine proteases (kallikrein and plasmin) and bacterial proteases represent proteases that are involved in the cleavage of extracellular domain of junction proteins (**Table 1** and **Figure 1**). It is noteworthy to mention that γ-secretase also functions as an intracellular protease for transmembrane junction proteins.[27]

Tight junction. Given the role of TJs as gatekeepers, cleavage of transmembrane proteins that form these structures is often associated with epithelial barrier breakdown. However, despite their importance in controlling epithelial barrier function, extracellular cleavage of integral proteins in TJs during physiological and pathological conditions is not well characterized. Huet et al. have reported that the induction of MMP9 by the extracellular matrix metalloprotease inducer (EMMPRIN; also termed CD147) results in cleavage of occludin extracellular domain and disruption of barrier function associated with pathogenesis of dry eye disease.[28] Willemsen et al. have also shown that interferon-gamma (IFNγ) activates cellular serine proteases that cleave claudin-2 extracellular domain.[29] Occludin has also been shown to be cleaved by several bacterial proteases including the cysteine

Table 1. Extracellular cleavage of transmembrane junction proteins in epithelial cells

Junction protein	Protease		Model epithelial cell line	Functional output of cleavage product	Stimulus	Reference
Claudin-2	Serine protease		T84 (Colon)		IFNγ	29
EpCAM	ADAM17 (TACE)		HEK293 (Kidney), FaDu (Hypopharynx)			93
	γ-secretase		HEK293 (Kidney), HT29 (Colon)			124
JAM-A	ADAM10, 17 (TACE)		HEK293 (Kidney)	Neutrophil transmigration↓	PMA	35
Occludin	MMP		MDCK (Kidney)	Barrier function↓	Methyl-β-cyclodextrin	125
	MMP2		Primary human ectocervical epithelial cells, CaSki (Cervix)			126
	MMP7		Primary human normal vaginal-cervical epithelial cells		Estrogen	127
	MMP9		Human corneal epithelial cells, MMP9 knockout mouse			66
			Human corneal epithelial cells		Extracellular matrix metalloprotease inducer	28
	Serine protease	Plasmin	Primary human ectocervical epithelial cells, CaSki (Cervix)			126
	Bacterial protease	Aerolysin	HT29/B6 (Colon)			32
		Haemagglutinin/ protease	MDCK (Kidney)			31
	Protease K		Primary human ectocervical epithelial cells, CaSki (Cervix)	Barrier function↓		126
E-cadherin	MMP	Membrane-bound	SW480, HT29 (Colon), A431 (Skin), TE12, TE13 (Esophagus)		Mechanical scraping, ionomycin	84
	MMP2		LNCapFGC (Prostate)	Cell proliferation↓	PKD1	128
	MMP3		MDCK (Kidney), DU145 (Breast)	Cell invasion↑, cell-cell adhesion↓	PMA	40
			SCp2, SCg6 (Breast)	Cell-cell adhesion↓		73
			HC11 (Breast)	Cell invasion↑	FK506-binding domain dimerizer (AP20187)	74
	MMP7		MDCK (Kidney)	Cell-cell adhesion↓, cell migration↑, cell polarization↓, cell proliferation↑		129
			MDCK (Kidney), MCF-7 (Breast)	Cell invasion↑, cell-cell adhesion↓	PMA	40
			LNCaP-FGC (Prostate)	Cell-cell adhesion↓, cell invasion↑	HGF/SF	39
			A549 (Lung)	Cell migration↑		130
			NUGC-3, MKN-28 (Stomach)	Cell invasion↑	HGF	131
	MMP9		OVCA433 (Ovary)	Barrier function↓, cell-cell adhesion↓	Bead-immobilized α_3 or β_1 integrin antibody	41
			MDCK (Kidney), DU145 (Breast)	Cell proliferation↓	PKD1	128
			SCC10A (Head and neck)	Cell migration↑, cell invasion↑	EGF	132
	Meprinß		MDCK (Kidney), Caco-2 (Colon)	Cell-cell adhesion↓		133

Table 1. Extracellular cleavage of transmembrane junction proteins in epithelial cells, cont.

Junction protein	Protease		Model epithelial cell line	Functional output of cleavage product	Stimulus	Reference
	ADAM10		HaCaT (Skin)	Cell migration↑		43
			Primary human keratinocyte cells		TGF-β, IL-1β, LPS, IFNγ + TNFα	134
			NCI-N87 (Stomach)		*Helicobacter pylori*	135
			MDCK (Kidney)		Ephrin-B1	136
	ADAM15		SKBr3 (Breast)	Cell prolieration↑, cell migration↑		77
	γ-secretase		Caco-2 (Colon)	Barrier function↓	*Candida albicans*	137
	Serine protease	Kallikrein 6	HEK293 (Kidney)	Cell-cell adhesion↓		138
		Kallikrein 7	BxPC-3 (Pancreas)	Cell invasion↑, cell-cell adhesion↓		63
		Plasmin	MDCK (Kidney)	Cell-cell adhesion↓, cell invasion↑		62
			OVCA429 (Ovary)	Cell invasion↑	LPA	115
	Bacterial protease	Fragilysin	HT29/C1 (Colon)			45
		Gingipain	MDCK (Kidney)			46
		HtrA	MKN-28 (Stomach)	Bacteria invasion↑, bacterial ransmigration↑		44
	Leukocyte elastase		Rat pancreatic tissue, primary rat pancreatic acinar cells	Leukocyte transmigration↑, cell-cell adhesion↓	Cerulein	139
	Cysteine protease	Cathepsins: B, S, L	Mouse pancreatic cancer model	Cell invasion↑		140
Nectin-1α	MMP		MDCK (Kidney)		TPA, HGF/SF	48
Nectin-4	ADAM17 (TACE)		CHO (Ovary), T47D (Breast)		PMA	49
Desmoglein 1	MMP		A431 (Skin)		UV	141
	Serine protease	Plasmin	Human skin tissue			142
		Exfoliative toxin A	Mouse skin	Cell-cell adhesion↓		53
			HaCaT (Skin)			54
			Organotypic raft model of human epidermis, primary human epidermal keratinocytes			50, 52
		Kallikrein 5	SCC25 (Tongue)			51
Desmoglein 2	MMP		SKCO-15 (Colon)			86
	ADAM10		CHO (Ovary), A431 (Skin), ADAM10 knockout mouse		EGF	58
	ADAM17 (TACE)		SCC68 (Skin)	Cell-cell adhesion↓		143
			CHO (Ovary), A431 (Skin), ADAM10 knockout mouse		EGF	58
			A431 (Skin)			144
	Serine protease	Kallikrein 7	Panc-1, BxPC-3 (Pancreas)			145
		Matriptase	HCT-116 (Colon)	Cell-cell adhesion↓		57
Desmoglein 3	MMP		HaCaT (Skin)		Staurosporine	146
Desmocollin 3						

protease Der p 1 from house dust mite,[30] haemagglutinin/protease (metalloprotease) from *Vibrio Cholerae*,[31] and secreted pore-forming toxin aerolysin produced by *Aeromonas hydrophila*.[32] Paracellular barrier compromise by haemagglutinin/protease and aerolysin has been linked to clinical diarrhea. Epithelial barrier disruption by house dust mite and pollen extract contributes to allergic diseases such as asthma.[30,33,34] Koenen et al. reported that cleavage and shedding of the TJ protein, JAM-A is mediated by ADAM17 and 10 during inflammation resulting in inhibition of neutrophil transendothelial diapedesis.[35] These findings highlight cleavage of transmembrane TJ proteins is essential mechanism that mediates disruption of epithelial barriers.

Adherens junction. The AJ intercellular space (~200 Å)[1] contains extracellular domains of classical-cadherin family members and nectins, which constitute the two major family of integral membrane proteins in this region. Nectins and cadherins control several physiological processes including cell-cell adhesion, cell signaling, proliferation and differentiation.[36-38] For example, soluble E-cadherin (sE-cadherin) fragment resulting from cleavage of the E-cadherin extracellular domain by MMPs[39-41] can function as a paracrine/autocrine signal to prevent cell death by activating epidermal growth factor receptor (EGFR) signaling and inhibiting apoptosis.[42] Shedding of sE-cadherin fragment has also been reported for other cellular proteases such as ADAMs[43] and γ-secretase.[27] In addition to cellular proteases, the extracellular domain of E-cadherin is targeted by several bacterial proteases that include HtrA protease from *Helicobacter pylori*,[44] fragilysin from *Bacteroides fragilis*[45] and the gingipains from *Porphyromonas gingivali*.[46] These bacterial proteases influence epithelial homeostasis analogous to cellular proteases. In addition to E-cadherin, other integral membrane AJ proteins such as the nectin-1 ectodomain are cleaved in neurons by MMPs.[47] The entire ectodomain of nectin-4 and nectin-1α are shed by MMPs in cancer and during cell spreading.[48,49] The stability of these fragments in different body fluids suggests a putative role of these ectodomains as mediators of diverse biological processes.

Desmosome. Analogous to E-cadherin, desmosomal cadherins including Dsg and Dsc family members undergo extracellular domain cleavage during inflammation and cancer.[18,50,51] Indeed, extracellular domain cleavage of desmosomal cadherins has been reported to influence epithelial homeostasis.[18,51,52] In keratinocytes, where desmosomal cadherins are the major adhesion molecules, cleavage of desmosomal cadherins contributes to pathogenesis of diseases. For instance, the staphylococcal exfoliative toxin, which is causative agent of bullous impetigo and staphylococcal scalded skin syndrome have been shown to specifically target the ectodomain of Dsg1.[53,54] In Netherton syndrome, which is an autosomal skin disease characterized by skin inflammation and scaling, Dsg1 cleavage occurs as a consequence of kallikrein hyperactivation due to the inactivation of the serine protease inhibitor of kazal type 5 (SPINK5).[55,56] Additionally, shedding of desmosomal cadherin ectodomains by cellular proteases has been reported during cancer progression and metastasis implying a role of these molecules in modulating invasion and metastasis. For example, cleavage of Dsg2 in intestinal epithelial cells by matriptase has been associated with decreased cancer cell–cell adhesion.[57] ADAM17 and 10 have also been implicated in the shedding of Dsg2 during cancer development.[58] A similar mechanism has been described in the pathogenesis of oral squamous cell carcinoma where cleavage of Dsg1 by kallikrein 5 is necessary to reduce cell-cell adhesion in order to enhance cell migration.[51] Thus, understanding the mechanisms that regulate desmosomal cadherin cleavage is important in understanding the pathogenesis of several diseases.

Biological effects of epithelial junction protein extracellular cleavage fragments. Recent evidence suggests that cleavage fragment of junctional proteins possess different biological activities.[26] These fragment not only control normal homeostatic event in the epithelia such as cell proliferation, migration and apoptosis but also contribute to pathogenesis of mucosal inflammation and cancer. In this section, we describe the biological effects of soluble intercellular junction protein cleavage fragments.

Cell-cell adhesion. Cell-cell adhesion in epithelial cells is mediated by AJ and desmosomal proteins. It's well known that disruption of cell-cell adhesion contributes to metastasis of cancer cells. Several reports have shown that extracellular cleavage of intercellular junction proteins results in loss of cell-cell adhesion.[59,60] Moreover, recent findings have also shown that soluble extracellular cleavage products of intercellular junction proteins can regulate epithelial cell-cell adhesion by paracrine or autocrine signaling. Wheelock et al. reported that the 80 kd sE-cadherin fragment disrupts cell-cell adhesion in a human mammary carcinoma cell line.[61] Symowicz et al. have also demonstrated that recombinant sE-cadherin promotes cell junction disruption and metastasis of ovarian carcinoma cells.[41] Additionally, extracellular E-cadherin fragments released by serine proteases, plasmin and kallikrein 7 inhibit cellular aggregation.[62,63] These findings suggest that extracellular E-cadherin fragments have functional effects that inhibit endogenous cell-cell junction protein function. However, it still remains unknown how these cleavage products interact with cell-cell junction proteins and whether or not extracellular cleavage products of other intercellular junction proteins such as nectins or desmosomal cadherins have similar biological effects on cell-cell adhesion.

Barrier function. Epithelial tissues provide physical and permeability barriers in vertebrates. In simple epithelium the barrier is formed by epithelial cells where the paracellular space is sealed by intercellular contacts. MMPs actively participate in the disruption of epithelial barrier under several conditions. For example, during inflammation, proinflammatory cytokines released in the milieu of ocular epithelium enhance MMP9 expression and activation that promotes cleavage of the TJ protein occludin thereby resulting in increased corneal epithelial permeability.[28,64-66] Of interest MMP9 expression and activity has been directly linked to dry eyes in human patients with ocular rosacea and rheumatoid arthritis.[64,65] Moreover, virulence factors can also perturb epithelial barrier function by inducing cleavage of specific transmembrane epithelial junction proteins. The effects of these bacterial proteases are broad in range and some are very well characterized. Fragilysin from *Bacteroides fragilis* cleaves the extracellular domain of E-cadherin to disrupt barrier

function.[45] In contrast, the zinc-containing metalloprotease from *Vibrio cholerae* decreases epithelial barrier function by targeting the extracellular domain of occludin.[31] In addition to its role in compromising the epithelial barrier, mimetic peptides of transmembrane junction proteins and virus-derived proteins can transiently modulate epithelial barrier function. Interestingly, the efficiency and reliability of this system has been used in recent years to transiently compromise the paracellular pathway in order to promote drug delivery across the epithelium.[67-71]

Migration and invasion. Epithelial cells are less mobile than most other cell types. Disruption of cell adhesion to enhance cell migration and invasion is an integral event in cancer metastasis.[72] As mentioned above, cleavage of transmembrane junction proteins by proteases reduces cell-cell adhesion and directly enhances cell migration and invasion.[59,60] Interestingly, it has been shown that the extracellular cleavage products from intercellular junction proteins can also induce cell migration and invasion. The role of sE-cadherin in cell migration and invasion is well known.[40,62,73,74] Most recently, Brouxhon et al. have demonstrated that sE-cadherin promotes cell migration and tumor invasion by activating MMP2 and 9 in murine skin squamous carcinoma cell lines.[75] Furthermore, in human lung tumor cells, the presence of sE-cadherin in conditioned media and E-cadherin HAV peptides simulating E-cadherin EC1 domain induce MMP2, 9 and MT1-MMP transcription and activation resulting in cell invasion.[76] Taken together, these findings suggest that sE-cadherin has functional properties that promote cell migration and invasion by inducing MMP activity. Increased junction protein cleavage, reported in inflammation, exerts biological effects on mucosal homeostasis. Soluble JAM-A ectodomain fragments have been reported to modulate endothelial cell migration and prevent neutrophil extravasation.[35] However, mechanisms by which soluble extracellular junction protein cleavage fragments modulate cell migration are complex and not well understood.

Cell proliferation and apoptosis. Several reports have linked junction extracellular cleavage products to cell proliferation and apoptosis.[42,59,75,77] These studies have also highlighted underlying signaling pathways that mediate the biological effect of junction protein cleavage fragments. In skin cancer cells, exogenous sE-cadherin can interact with EGFR and human epidermal growth factor receptor (HER) 2 to activate them and their downstream singnaling proteins: phosphoinositide-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK). Ultimately, the cleavage fragments induce cell proliferation.[75] Najy et al. have also shown the interaction between exogenous sE-cadherin and HER2-HER3 heterodimer in breast cancer cells where sE-cadherin promotes cell proliferation via HER2-HER3 and extracellular signal-regulated kinase (ERK) activation.[77] In addition to proliferation, recent evidence indicates that extracellular cleavage products can regulate cell survival. For example, Inge et al. have revealed that sE-cadherin can suppress apoptosis thereby promote cell survival and these effects are mediated by activation of EGFR signaling via PI3K/Akt and ERK1/2.[42] However, cleavage or loss of the transmembrane proteins in cell junctions has also been linked to the presence or appearance of pro-apoptotic signals.[78] In fact, metalloprotease cleavage of desmosomal cadherins during keratinocyte apoptosis has been reported.[79] Additionally, and in simple epithelium, cleavage of E-cadherin by sheddases is an essential step in the onset of apoptosis.[80,81]

Intracellular Cleavage of Epithelial Transmembrane Junction Proteins

Proteases that mediate intracellular cleavage of junction proteins. Transmembrane junction proteins associate with an underlying actin cytoskeleton via scaffold proteins that constrains their intracellular domains. Intracellular domains can also be targeted by proteases that are in the vicinity of the cytoplasmic surface of the plasmamembrane.

Several proteases that are activated during inflammation and cancer mediate intracellular cleavage of cell-cell junction proteins. Additionally, increased expression/activity of proteases that cleave adhesion proteins facilitates cancer cell proliferation and metastasis.[25,26] Interestingly, following extracellular domain shedding, the membrane-associated proteins undergo proteolytic processing thereby generating soluble intracellular fragments that exert biological effects. Cleavage of such protein fragments is mediated by intracellular and membrane associated proteases such as calpain, caspase, cathepsin and γ-secretase.[27] Intracellular proteases promote intracellular cleavage of junction proteins that in turn induces cytoskeletal restructuring as well as modification in scaffold and signaling proteins to maintain epithelial homeostasis (**Fig. 1**). Recent reports have highlighted biological effects of intracellular cleavage fragments of junction proteins (**Table 2**).

Tight junction. Little is known about the intracellular cleavage of TJ proteins. Sumitomo et al. have demonstrated that calpain activated by Streptolysin S from Group A *streptococcus*, cleaves occludin and disrupts barrier function of intestinal epithelial cells and keratinocytes.[82] Willemsen et al. have also shown that cellular serine protease activated by IFN-γ treatment can cleave intracellular domain of claudin-2.[29] Additionally, toll-like receptor (TLR) 2-induced calpain cleaves intracellular domain of occludin and promotes polymorphonuclear leukocyte transmigration.[83]

Adherens junction. The intracellular fragment of E-cadherin that remains attached to the cellular membrane after cleavage by membrane-bound metalloproteases, generates a cytosolic fragment (33 kDa) when γ-secretase is activated. The 33 kDa cytosolic fragment promotes intracellular signaling and cell proliferation.[27,84] In addition to cleavage by membrane associated proteases, the cytosolic domain of E-cadherin has been shown to be further cleaved by intracellular proteases such as calpain.[23] However, the fragments generated by calpain have been shown to induce apoptosis instead of proliferation in epithelial cells.[81] Interestingly, it has also been proposed that during apoptosis the 33 kDa fragment generated by γ-secretase is also targeted by caspase-3 to generate a 29 kDa fragment. However, the function of this cleavage fragment has not been characterized, but its localization and distribution suggest a putative role in the regulation

Table 2. Intracellular cleavage of transmembrane junction protein in epithelial cells

Junction protein	Protease		Model epithelial cell line	Functional output of cleavage product	Stimulus	Reference
Claudin-2	Serine protease			T84 (Colon)	IFNγ	29
EpCAM	γ-secretase	Presenilin 2	HEK293 (Kidney)	Cell proliferation↑	Extracellular cleavage product of EpCAM	93
			HEK293 (Kidney), HT29 (Colon)			124
Occludin	MMP		MDCK (Kidney)	Barrier function↓	Methyl-β-cyclodextrin	125
	Cysteine protease	Calpain	Caco-2 (Colon), HaCaT (Skin)	Barrier function↓, bacterial translocation	Streptolysin S	82
			16 HBE, 1HAEo (Lung/ Bronchus)	Polymorphonuclear leukocytes (PMNs) transmigration	Toll-like receptor 2 ligands	83
		Der p 1	MDCK (Kidney), 16HBE14o (Lung/Bronchus)	Barrier function↓		30
E-cadherin	MMP7		MDCK (Kidney)	Cell-cell adhesion↓, cell migration↑, cell polarization↓, cell proliferation↑		129
	MMP	Membrane-bound	SW480, HT29 (Colon), A431 (Skin), TH12, TE13 (Esophagus)		Mechanical scraping, ionomycin	84
	MT1-MMP (MMP14)		NRK-52E (Kidney)	Cell-cell adhesion↓		147
	ADAM10		Primary human keratinocyte cells		TGFβ, IL-1β, LPS, IFNγ + TNFα	134
	γ-secretase		Caco-2 (Colon)	Barrier function↓	*Candida albicans*	137
			T47D, MCF-7 (Breast)	Cell-cell adhesion↓	Staurosporine	148
			A431 (Skin), MCF-7 (Breast), MDCK (Kidney)			91
		Presenilin 1	Murine embryonic fibroblast, SW480 (Colon)			90
			A431 (Skin)	Cell-cell adhesion↓	Ionomycin	27
	Caspase		HER313A (Retina)			149
		Caspase-3	H184A1 (Breast)		Staurosporine	80
	Cysteine protease	Calpain	LNCaP (Prostate), MCF-7, SKBR3 (Breast)		TPA, ionomycin	23
			16 HBE, 1HAEo (Lung/ Bronchus)	PMNs transmigration	Toll-like receptor 2 ligands	83
			Caco-2 (Colon), HaCaT (Skin)	Barrier function↓, bacterial translocation	Streptolysin S	82
		Cathepsins (B, S, L)	Mouse pancreatic cancer model	Cell invasion↑		140
Nectin-1α	γ-secretase	Presenilin 1	CHO (Ovary)		TPA	150
Desmoglein 1	Caspase		HaCaT (Skin)		Staurosporine	79
		Caspase-3	A431 (Skin)		UV	141
Desmoglein 2			T84 (Colon)		Camptothecin	14
		Caspase-3	HaCaT cells (Skin), HT29 (Colon)	Cell-cell adhesion↓	Staurosporine	85
	Cysteine protease	Calpain	T84 (Colon)		Camptothecin	14
Desmoglein 3	Caspase		HaCaT (Skin)		Staurosporine	146

of epithelial cell apoptosis.[80] Thus, proteolysis of epithelial cadherin allows the formation of several intracellular fragments that have biological activities. Furthermore, E-cadherin intracellular fragments are important in activating signaling pathways that control physiological and pathological events.

Desmosome. In simple epithelium, cleavage of desmosomal cadherins by cysteine proteases has been shown to be an important step in the disassembly of the DMs.[85] Desmosomal disassembly may directly contribute to the detachment of the dead cells observed in epithelial tissues. The cytosolic fragments generated by Dsg2 cleavage have been observed in human colon tissues.[86] We have observed that an intracellular Dsg2 cleavage fragment promotes apoptosis in the intestinal epithelium.[14] We have also reported a similar Dsg2 cleavage fragment in nasal polyps after cytokine exposure.[87] However, in addition to apoptosis, we cannot rule out the possibility that the cytosolic fragments generated after Dsg2 cleavage serve to promote cell proliferation. In fact, Brennan et al. have demonstrated that Dsg2 proteolytic products are elevated in vivo in skin tumors from transgenic mice overexpressing Dsg2.[88] These results suggest that the cytosolic fragment of Dsg2 may be responsible for the regulation of several mitogenic signaling pathways such as Akt, MAPK and the signal transducer and activator of transcription (STAT) 3.[89]

Biological effects of junction protein intracellular cleavage products. As described above, several intracellular proteases including γ-secretase, calpain and caspase are responsible for cleavage of intercellular junction proteins that in turn exert biological effects. We have previously observed that an intracellular Dsg2 cleavage fragment generated by serine proteases promotes apoptosis in intestinal epithelial cells.[14] Some cleavage fragments can translocate to the nucleus to regulate transcriptional activity and cell survival. For instance, 35 kDa E-cadherin C-terminal fragment (CTF) generated by presenilin 1 regulates β-catenin/T cell factor (Tcf)-4 transcriptional activity.[90] E-cadherin/CTF translocates to the nucleus to influence Kaiso-regulated gene transcription. Nuclear localization of E-cadherin/CTF is also enhanced by p120-catenin.[91] Furthermore, presenilin 1 induces E-cadherin cytoplasmic cleavage, generating products that promote disassembly of E-cadherin-catenin complex by sequestering β-catenin in the cytosol.[27] Additionally, calpain induced cleavage of intracellular E-cadherin domain generates a 100 kDa cleavage product that regulates cell survival in prostate epithelial cells.[81] Similar to E-cadherin, presenillin promotes the release of the CTF in N-cadherin which also plays an important role in the regulation of β-catenin signaling.[92]

In addition to cadherins, intracellular domains of epithelial cell adhesion molecule (EpCAM) generated by presenilin 2 translocates to the nucleus with four and a half LIM-domain protein (FHL) 2 and β-catenin to promote lymphoid enhancer-binding factor (Lef)-1 transactivation and epithelial proliferation.[93] Interestingly, truncated Dsg1 and 2 generated by extracellular domain cleavage can influence cell-surface desmosomal cadherins through the interaction of raft-associated protein, caveolin-1 and plakoglobin.[50,88]

Signaling Pathways Triggered by Cleavage of Transmembrane Junction Proteins

Transmembrane junction proteins regulate cell proliferation, differentiation and apoptosis by controlling several signaling pathways. The mechanism by which the cleavage fragments regulate these processes is incompletely understood. Dimerization and autophosphorylation of receptor tyrosine kinases (RTKs) by the extracellular cleavage products of cadherin family members can regulate epithelial homeostasis. For example, sE-cadherin results in RTK ligand-independent dimerization, activation of the receptor and stimulation of several intracellular signaling pathways including MAPK, PI3K, Akt and mTOR.[94,95] These signaling pathways influence biological events such as cell proliferation,[94,95] growth,[94] and cell migration.[96] As a consequence of RTK interaction with sE-cadherin, activation of pro-proliferative and anti-apoptotic signaling pathways was observed. Thus, the presence of sE-cadherin in the serum has been associated with poor prognosis in cancer patients.[77,97] However, given that shedding of the cadherin ectodomain has also been reported in physiological conditions or in other pathologies such as inflammation,[50,52-54,98-100] it is easy to speculate that these soluble fragments have additional biological functions that need to be investigated.

Cleavage of transmembrane junctional proteins can directly trigger the activation of pro-proliferative signaling by releasing intracellular scaffolding molecules that often associate with their intracellular domains. For instance, intracellular cleavage of E-cadherin and N-cadherin promotes translocation of β-catenin from the plasmamembrane to nucleus thereby resulting in β-catenin/TCF transactivation and increase in cell proliferation.[43,84,92] In addition to its role in cell proliferation, β-catenin transactivation can also increase the expression and secretion of metalloproteases.[101,102] Thus, it is tempting to speculate that β-catenin redistribution after E-cadherin or N-cadherin cleavage could result in the activation of metalloproteases that in turn enhance shedding of their ectodomains. This process will increase epithelial cell proliferation through stimulating RTK receptors in a paracrine manner.

Relevance to Pathologic States

Cancer. A continuous turnover of intercellular junction proteins in healthy individuals is required for the maintenance of epithelial tissues and therefore, a low level of E-cadherin cleavage product has been observed in the healthy serum.[99] However, in pathological conditions such as inflammation and cancer, proteolytic activity is increased.[103] Since cleavage products have biological activity that influences cell-cell adhesion, migration and proliferation, they contribute to the pathogenesis of disease. As a result, increased soluble junctional proteins such as E-cadherin,[40,99,104,106-116] N-cadherin,[105] and nectin[49] can be observed in body fluids (serum, urine and ascites) and cancer tissue of patients. Given the ectodomain stability of cell junction proteins in several body fluids, the detection of cleavage products as biomarkers for disease has been considered. For example, increased sE-cadherin is seen in serum or at other sites (cancer

tissue, urine, cyst and ascites) in cancer patients. Such cleavage product has been detected in cancers from many areas that include bladder,[106,107] colorectal,[108,109] esophageal squamous cell carcinoma,[104] gastric,[99,110] liver,[99,111] lung,[112,113] ovarian,[41,114,115] prostate,[116] and skin tissue.[117] Given the biological function of intercellular junction protein ectodomains, their upregulation may play a role in the progression of cancer and metastasis. However, some reports have failed to detect increased serum E-cadherin cleaved products in some cancer patients.[118-120] Thus, additional studies are needed to verify the role of such cleavage products in cancer pathogenesis and detection. Analogous to E-cadherin, the ectodomains of nectin-4 are increased in the serum of patients with metastatic ductal breast carcinoma compared with healthy subjects.[49] Furthermore, soluble N-cadherin is significantly elevated in serum of prostate cancer patients.[105] These findings indicate the potential use of such products as diagnostic tools.

Inflammation. Knowledge of junctional protein cleavage fragments in inflammation is limited compared with cancer reports. Mayerle et al. have shown that leukocyte elastase cleaves extracellular domain of E-cadherin and disrupt cell-cell contacts in the rat pancreas, thereby promoting leukocyte transmigration into epithelial tissues in the initial phase of experimental pancreatitis.[100] Furthermore, extracellular cleavage of Dsg1 by *Staphylococcus aureus* exfoliative toxin A (serine protease) disrupts cell-cell adhesion, which leads to bullous impetigo or Staphylococcal scalded skin syndrome.[50,52-54] These reports suggest that the extracellular cleavage of intercellular junction proteins disrupts cell-cell adhesion contributing to loss of epithelial barrier function and mucosal inflammation. However, the utility of detecting junctional protein cleavage products as inflammation biomarkers remains incompletely understood. Pittard et al. identified increased concentration of sE-cadherin in patients with systemic inflammatory response syndrome and multi-organ dysfunction.[98] On the contrary, Weiss at al. did not observe significant difference in serum sE-cadherin in healthy control individuals and patients with inflammatory bowel disease.[109] The presence of the ectodomains of other junction proteins such as JAM-A and JAM-C[121] in body fluids suggests a putative role of these fragments as diagnostic tools in such pathologies.

Others. Cleavage of transmembrane junction proteins has been observed in several other pathologies. Dry eye disease is a common disease that develops as a result of changes in tear fluid, leading to osmotic stress and perturbed epithelial barrier function. Huet et al. have shown a relationship of MMP9-mediated cleavage of occludin in human corneal epithelial cells and dry eye disease.[28] In HIV infection, abnormal distribution of E-cadherin has been observed in the intestinal epithelium, which leads to increased systemic levels of sE-cadherin. Additionally, sE-cadherin level in plasma correlates with viral load in HIV patients. Interestingly, sE-cadherin can inhibit HIV-1-specific antiviral activity of $CD8^+$ T-cell function.[122] Thus, cleavage products of intercellular junctional proteins also regulate immune response. Additionally, it has to be noted that some pathological states induced by bacterial pathogens such as diarrhea[45] and skin blister formation[123] are mediated by targeting extracellular domains of cell adhesion molecules by bacterial proteases.

Conclusion

A continuous turnover of transmembrane intercellular junction proteins is observed in healthy individuals and is required for the maintenance of epithelial barriers. Physiologically low levels of cleavage products have been identified in the serum. The cleavage products are generated by a variety of proteases during epithelial cell junction rearrangement. Extracellular proteases such as MMP, ADAM, γ-secretase, serine and bacterial proteases can cleave the ectodomain of the proteins. On the other hand, proteases including calpain and caspase cleave intracellular domain of junction transmembrane proteins. Interestingly, the cleavage products generated by these proteases have distinct biological functions. In pathological conditions such as cancer and inflammation, increased junction protein cleavage products are often detected in the tissue and body fluids. These cleavage products influence epithelial behavior that includes proliferation, migration and apoptosis. In addition to exerting biological activity, detection of junction protein cleavage fragment can serve as biomarkers to follow disease progression.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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