Minireview

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Collagenous Transmembrane Proteins: Recent Insights into Biology and Pathology*S

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Is collagen just the workhorse of the extracellular matrix with few roles other than merely giving the body structural platforms? Hardly so. The collagen family has now swelled to at least 27 distinct members and thus is full of promise for functional diversity (1). Granted, some collagens belong to the best known and most abundant structural proteins. However, collagens also control sophisticated organ or tissue functions by means which are unexpected, fascinating, and often bewildering. Like other matrix macromolecules, collagens are functional only after aggregating into tissue suprastructures. They form complex alloys or composites containing not only several collagen types but also other kinds of molecules. Even tiny fractions of "minor" collagens astoundingly control suprastructural assembly and thus cell-matrix interactions dictating cellular activities such as growth, survival, differentiation, gene expression, and metabolism.

This minireview will focus on a growing subgroup of collagens, the collagenous transmembrane proteins, which have dual functions as cell surface receptors or as matrix components. If their extracellular domains are cast off by limited proteolysis, they can begin to signal to cells as soluble molecules. Collagenous transmembrane proteins are widely expressed and are involved in cell adhesion, epithelial-mesenchymal interactions during morphogenesis, neuromuscular signaling, and host defense against microbial agents. Correspondingly, they are associated with genetic and acquired human diseases, *e.g.* epidermolysis bullosa, ectodermal dysplasias, bullous pemphigoid, or Alzheimer disease, and mouse models implicate them in the etiology of further pathological conditions.

Structure and Functions of Collagenous Transmembrane Proteins

The designations of most collagenous transmembrane proteins are related to their structures or functions or to diseases caused by mutations in their genes (2). The group includes several collagens, *i.e.* types XIII, XVII, XXIII, and XXV, which have a number of consecutive triple helical regions flanked and separated by non-helical sequences (Fig. 1). Other group members contain single and sometimes small collagenous triple helical stretches, *e.g.* ectodysplasin A, the class A macrophage scavenger receptors, the MARCO[1] receptor, as well as the newly discovered "collagen repeat plus olfactomedin domain-containing proteins," or colmedins (3). Collagens XIII and XVII are components of morphologically distinct cell adhesion structures, *i.e.* focal adhesions and hemidesmosomes, respectively (4–7). Because they share structural features, collagen XXIII and ectodysplasin A may also be part of the cell adhesion machinery. Collagen XXV, also called CLAC-P (collagen-like Alzheimer amyloid plaque component precursor), is brain specific, and its ectodomain is a stabilizing component of Alzheimer amyloid plaques. The macrophage scavenger receptors and the MARCO receptor are involved in host defense and the colmedins in neuromuscular signaling (3, 8–10).

All collagenous transmembrane proteins are trimers of identical polypeptides, called α-chains. They contain an N-terminal intracellular domain, a single transmembrane stretch, and a large extracellular C terminus, *i.e.* a structure characteristic of membrane proteins in type II orientation (Fig. 1). The length of the α-chains varies between 135 amino acids for the shortest isoform of ectodysplasin A and 1497 amino acids for the largest group member, collagen XVII. The intracellular domains comprise about 10% of the total mass with the exception of collagen XVII, where it is roughly one-third. The hydrophobic membrane-spanning domains consist of 21–26 amino acids. The ectodomains protruding into the extracellular space have rigid, rodlike shapes because they contain one or several triple helical regions. If present, the interruptions separating the triple helical domains provide for structural flexibility within the ectodomains.

Extracellular, juxtamembranous stretches of 59–116 amino acids form "linker regions" between the plasma membrane and the first collagenous domains. These linker regions contain trimeric α-helical coiled-coils thought to prompt trimerization and subsequent zipper-like folding of the adjacent triple helices, presumably in the N- to C-terminal direction (11–15).

Proteolytic processing within the linker region results in soluble, shorter forms of collagens XIII, XVII, XXIII, XXV, and ectodysplasin A that have been isolated from tissues or cell cultures. The cleavage is catalyzed by a group of cell surface enzymes, collectively referred to as sheddases, which release the ectodomains from the cell surface in analogy to the processing of a variety of biologically active molecules such as growth factors and their receptors, proteoglycans, or cell adhesion molecules (16). The soluble forms, retaining some of the interaction capacities of their cell-bound counterparts, may have altered biological activities in that they modulate ligand binding or fine-regulate signal transduction and/or cell attachment during proliferation and differentiation. Thus, ectodomain shedding can influence the interaction of cells with their environment in multiple ways.

It is not clear whether the same sheddases cleave the ectodomains of all collagenous transmembrane proteins. Because most members of the group contain a furin consensus sequence within the linker region, furin has been proposed as the relevant sheddase (12, 17–22). However, processing of collagen XVII is more complex and will be discussed below in more detail.

Collagen XVII: Role Model of Collagenous Transmembrane Proteins

Collagen XVII is one of the best studied collagenous transmembrane proteins and well exemplifies the characteristics of the entire group. The protein, initially identified as the 180-kDa bullous pemphigoid antigen (BP180) in the skin, is a keratinocyte surface protein in the epidermis.

Biochemical Features and Ligand Interactions—Collagen XVII is a component of hemidesmosomes, supramolecular structures mediating adhesion of basal epidermal keratinocytes and certain other epithelial cells to their underlying basement membrane. Its cytosolic N terminus is located within the hemidesmosomal plaque, whereas the extracellular domain resides in the region of the anchoring filaments in the basement membrane zone. The collagen

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[1] The abbreviations used are: MARCO, macrophage receptor with collagenous structure; ADAM, a disintegrin and metalloproteinase; TACE, tumor necrosis factor-α-converting enzyme; JEB, junctional epidermolysis bullosa; EDA, ectodysplasin A; SRCR, scavenger receptor cysteine-rich; OLF, olfactomedin.

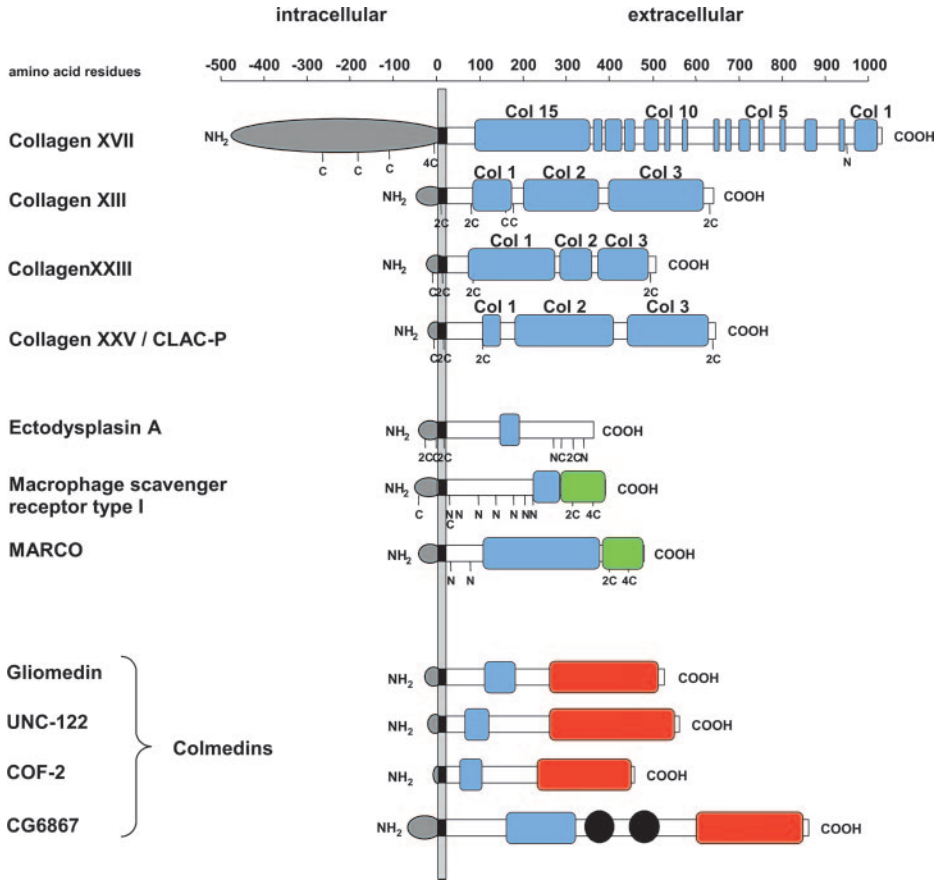

FIG. 1. **Schematic representation of the structure of collagenous transmembrane proteins.** The group includes four transmembrane collagens and at least seven related type II transmembrane proteins. The *vertical gray line* depicts the cell membrane and the *black box* the transmembrane domain. The *horizontal white areas* correspond to non-collagenous domains; *blue areas* to collagenous domains; *green areas* to SRCS domains; *red areas* to OLF domains; and *black circles* to IgG-like domains. *C*, cysteine; *N*, potential *N*-glycosylation site. The *scale* shows amino acid residues. Null represents the relative border position between the cytosolic domain and the ectodomain. Negative values define intracellular amino acid residues and positive values transmembrane and extracellular amino acid residues.

XVII molecule comprises three α1(XVII) chains with a molecular mass of 180 kDa. The intracellular domain, the short transmembrane stretch, and the extracellular, rodlike domain are 466, 23, and 1008 amino acids in length, respectively (2). The ectodomain contains 15 collagenous (COL1–COL15) and 16 non-collagenous sequences (NC1–NC16), some of which are *N*-glycosylated. The overall structure of the ectodomain is that of a flexible rod (13, 17). The intracellular ligands of collagen XVII include β_4-integrin, plectin, and BP230 in the hemidesmosomal plaque (4), and the extracellular ligands α_6-integrin and laminin 5 in the anchoring filaments (23, 24). Further binding partners are likely to exist but still await identification. Thus, collagen XVII contributes to stable adhesion of epithelial cells by multiple protein-protein interactions. Its pivotal role in this process is indirectly demonstrated by genetic and acquired skin diseases in which the loss of function of collagen XVII leads to diminished epidermal adhesion and skin blistering (see below).

Collagen XVII Is Shed by ADAMs—A landmark feature of collagen XVII is its constitutive shedding yielding a shorter and soluble form of the molecule (17, 25) that essentially spans the entire ectodomain (see Fig. 2S in supplemental material). There is a furin consensus sequence within the juxtamembranous linker region NC16A of human collagen XVII, and a specific furin inhibitor abolishes shedding. However, other species, *e.g.* pig, dog, mouse, rat, or chicken, do not have a furin consensus sequence in the NC16A domain, and at least murine collagen XVII and a human deletion mutant lacking the furin site are efficiently processed nonetheless. Collagen XVII is not directly cleaved by furin convertases but rather by proteinases of the ADAM family (26, 27), which, in turn, are activated by furin. It remains to be seen whether furin also can activate sheddases other than ADAMs. The prototype sheddase ADAM-17, or TACE, appears to be the major and physiologically relevant sheddase for collagen XVII, but ADAM-9 and -10 may substitute. Being integral membrane proteins themselves, ADAMs generally act near the extracellular cell surface and release soluble forms of many type I or type II transmembrane proteins (16, 28, 29). It is believed that shedding of membrane-bound precursors depends less on sequence specificity than on structural convergence or accessibility of the cleavage sites and their distance to the cell surface (30). In the case of collagen XVII, the stretch of amino acids 528–547 within the NC16A linker domain seems essential for sheddase recognition and cleavage. Deletion of this stretch prevented shedding and reduced thermal stability (26). This observation led to the proposal that the conformation of the NC16A domain and steric availability of the cleavage site influence shedding. This notion is supported by the fact that the soluble ectodomains isolated from human skin and from cultured HaCaT cells have different N termini (31).

Biological Significance of Collagen XVII Shedding—The biological consequences of collagen XVII shedding are not yet fully understood. An initial prediction was that ectodomain cleavage favors keratinocyte detachment during morphogenesis, differentiation, and regeneration. Presumably, the cleavage of collagen XVII releases the cell from some of its binding partners and allows it to embark on other functions. This is supported by the finding that inhibition of collagen XVII processing preserved hemidesmosomal attachment in cultured keratinocytes (32). In the meantime it has become obvious that cell adhesion and motility involve a number of receptors and ligands depending on the spatial and temporal biological context (4) and that these processes are quite complex (24, 27, 33, 34).

Hereditary and Acquired Collagen XVII Diseases—Mutations in the human collagen XVII gene, *COL17A1*, lead to the absence or structural alterations of collagen XVII. The functional consequences include diminished epidermal adhesion and skin blistering in response to minimal shearing forces. The disorder is called junctional epidermolysis bullosa (JEB), a skin disease with variable clinical phenotypes (2, 35, 36). Morphological characteristics of JEB are rudimentary hemidesmosomes and subepidermal tissue separation. Clinical hallmarks, in addition to blisters and erosions of the skin and mucous membranes, include nail dystrophy, loss of hair, and dental anomalies. More than 50 different *COL17A1* mutations have been disclosed in JEB. Studies on genotype-phenotype correlations have not only revealed the molecular pathomechanisms in JEB but have augmented our understanding of the normal functions of collagen XVII and its individual subdomains (2, 24, 26, 33).

Collagen XVII also plays a role as an autoantigen. It was initially identified as the 180-kDa bullous pemphigoid antigen (hence the

name BP180). Today we know that the pemphigoids are a heterogeneous group of autoimmune skin disorders with tissue-bound and circulating autoantibodies to collagen XVII. Most immunodominant epitopes lie within the NC16A domain, and the binding of the autoantibodies perturbs adhesive functions of the collagen, and this (together with inflammation-related processes) leads to epidermal-dermal separation and skin blistering. Also the shed ectodomain is targeted by IgG and IgA autoantibodies and, in some cases, is the preferential target (37, 38). Therefore, it is likely that shedding of collagen XVII generates neoepitopes by inducing conformational changes in the new N terminus of the ectodomain.

Other Collagenous Transmembrane Proteins and Associated Diseases

Collagen XIII—This transmembrane collagen has a small cytosolic domain and a large ectodomain rich in collagenous sequences (39). Apart from a 60-amino acid linker region, most of the ectodomain consists of three collagenous domains, COL1–3, and short non-collagenous interruptions, NC1–4. The ectodomain of recombinant collagen XIII has a rodlike structure with two flexible hinges, which coincide with the NC-2 and -3 domains (5). Furin convertases appear to cleave the ectodomain of collagen XIII, both within the trans-Golgi network and at the plasma membrane (21). Collagen XIII exhibits a wide tissue distribution and multiple splice variants. It occurs at cellular junctions and cell-matrix interaction sites in epithelial, mesenchymal, and neural tissues. In cultured fibroblasts, collagen XIII is a component of focal adhesions (6). It interacts with the collagen-binding integrin $\alpha_1\beta_1$ as well as with the matrix macromolecules fibronectin, nidogen-2, perlecan, and heparin, suggesting involvement in multiple cell-matrix interactions (5, 7). The phenotypes of collagen XIII transgenic mice are manifold. Muscle cell attachment to basement membranes is deficient in mice with collagen XIII lacking the cytosolic and transmembrane domains (40), and a deletion within the COL2 domain led to embryonic lethality due to placental or cardiovascular defects (41).

Collagen XXIII—The cDNA for human collagen XXIII predicts a 540-amino acid polypeptide, which consists of an N-terminal cytoplasmic domain of 24 amino acids, a transmembrane stretch, and an extracellular domain of 481 amino acids with three collagenous domains flanked by short non-collagenous sequences (20). Thus, collagen XXIII shows structural homology with collagens XIII and XXV. The functions of this novel collagen still are unknown. Its mRNA is expressed in placenta, kidney, skin, and neural cells.[2] Recombinant collagen XXIII is synthesized as a ~75-kDa protein, which can be released from the cell surface by furin-mediated proteolysis. The cleavage produces a 60-kDa soluble ectodomain that forms a multimeric complex, which binds heparin with low affinity (20).

Collagen XXV—This molecule is an intriguing member of the group (8). First identified in Alzheimer amyloid plaques, it is now known to be exclusively produced by neurons. The human *COL25A1* gene encodes a polypeptide of 654 amino acids, which shows structural homology to collagens XIII and XXIII in that it harbors three large collagenous subdomains in the extracellular domain. The ectodomain of recombinant collagen XXV is shed from the cell surface by furin, and both the soluble and transmembrane forms bind to and stabilize aggregates of amyloid β-peptides but not the intact amyloid precursor protein. Therefore, collagen XXV has been linked to β-amyloidogenesis and neuronal degeneration in Alzheimer disease (8, 42).

Ectodysplasin A (EDA)—EDA is a short transmembrane protein with two small collagenous segments within the ectodomain and a tumor necrosis factor ligand motif in the C terminus (43). The *N*-glycosylated ectodomain is shed from the cell surface, presumably by furin, to produce a diffusible signaling molecule which binds to EDA receptors (EDAR, XEDAR). EDA occurs in several splicing isoforms, all of which include a short intracellular domain, the transmembrane domain, and 73 amino acids of the extracellular domain. The two main isoforms, EDA-A1 and -A2, are 391 and 389 amino acids in length, respectively. The insertion of two residues determines receptor specificity. EDA-A1 binds to EDAR whereas EDA-A2 binds to a related, but distinct, ectodysplasin-A2 receptor XEDAR, derived from an X chromosomal gene (44). Mutations in EDA, EDAR, or other molecules of this signaling pathway cause ectodermal dysplasias characterized by defective development of skin, hair, teeth, and exocrine glands, such as sweat glands, presumably due to impaired NF-κB responses. Mutations in the EDA gene *ED1* cause X-linked anhydrotic ectodermal dysplasia, a human disease characterized by sparse hair, abnormal teeth, and the absence of sweat glands, and in the mouse the *Tabby* phenotype (22, 45, 46). Interestingly, amino acid substitutions of Arg-156 are frequent in patients with X-linked anhydrotic ectodermal dysplasia. This amino acid is part of the furin cleavage site within the linker region common to all EDAs, and it has been postulated that inhibition of furin cleavage prevents paracrine and juxtacrine signaling by the soluble ectodomain of EDA (19). EDAR mutations underlie human hypohydrotic ectodermal dysplasia, a similar but less severe disease than the anhydrotic form, and the mouse *downless* phenotype (47). Studies with mice either lacking the functional proteins of EDAR pathway or overexpressing the ligand or receptor suggest that EDA-A1-EDAR signaling has multiple roles in ectodermal organ development regulating their initiation, morphogenesis, and differentiation (48).

The Macrophage Scavenger Receptors Type I, II, and III—The class A scavenger receptors are trimeric integral membrane glycoproteins implicated in tissue macrophage functions such as endocytosis, adhesion, phagocytosis, and intracellular signaling. There are three forms of the receptor derived by alternative splicing of a single gene. Each isoform contains six predicted structural domains that differ in the location and function of their C-terminal, scavenger receptor cysteine-rich (SRCR) domain. The SRCR domain is found in diverse secreted and cell-surface proteins and is thought to mediate protein-protein interactions and ligand binding (49). The collagenous domain is presumed to be a ligand binding domain that can recognize a wide range of negatively charged macromolecules including oxidized low density lipoprotein, β-amyloid fibrils (similarly to collagen XXV), damaged or apoptotic cells, or pathogenic micro-organisms (50), denatured collagens I and III, as well as native, but not denatured, collagen IV (51). Employing their scavenger receptors, macrophages clean up cellular debris and other materials and exert initial host defense. Under pathological conditions, the receptors mediate recruitment, activation, and transformation of macrophages and other cells (9, 52).

The Macrophage Receptor MARCO—MARCO also belongs to the class A scavenger receptors (53). In addition to one large 270-residue collagenous region, the extracellular C terminus of MARCO contains an SRCR domain involved in binding of Gram-positive and -negative bacteria (10). MARCO is constitutively expressed in macrophages of the spleen and lymph nodes (54), and MARCO-mediated phagocytosis in the lung is essential for the innate defense against pneumococcal infection (55).

Colmedins (Collagen Repeat Plus Olfactomedin-containing Proteins)—The first member of this newly termed group, UNC-122 (uncoordinated locomotion), was discovered in *Caenorhabditis elegans* as a molecule essential for locomotion (3). Together with structurally similar proteins predicted from DNA sequences of *C. elegans*, *Drosophila*, and vertebrates, UNC-122 forms the family of "colmedins," type II transmembrane proteins, which contain a collagen-like and a cysteine-rich olfactomedin (OLF) domain (Fig. 1, *Col 3*). UNC-122 occurs in muscle and coelomocytes, the immunocytes of the coelom, and localizes to the postsynaptic surface of certain neuromuscular junctions. On the basis of motifs in the UNC-122 protein sequence that are characteristic of extracellular matrix proteins, it has been proposed that UNC-122 is involved in maintaining a structural microenvironment that allows efficient neuromuscular signaling. The *unc-122* gene encodes a 598-amino acid type II transmembrane protein, with a small intracellular and a large extracellular part, which is probably released from the cell surface. The latter contains both a collagen-like and an OLF domain. The other colmedin of *C. elegans* is COF-2 (colmedin family member number 2), a protein of 486 amino acids with an intracellular N terminus of only 7 amino acids and an ectodomain containing a collagen-like and an OLF domain. *Drosophila* has only one colmedin gene, *CG6867*, encoding for a putative 949-amino acid type II transmembrane protein with one collagenous, one OLF, and two immunoglobulin domains not found in other OLF domain proteins. Recently, gliomedin was identified as a putative vertebrate ortholog of UNC-122; it contains the three structurally defining

[2] M. Koch, personal communication.

features of colmedins: a type II transmembrane domain, a collagen domain, and an OLF domain (GenBank™ data base accession number NP852047). Its functions remain to be investigated. The prototypic OLF motif also occurs in olfactomedin, an extracellular matrix protein of unknown function, originally discovered in amphibian olfactory neuroepithelium and subsequently found also in mammalian brain (56). Biochemical assays showed that OLF domain-containing proteins can form disulfide-bonded multimers and, thus, may be structural proteins (57, 58).

Summary and Perspectives

Common denominators of collagenous transmembrane proteins are the following. First, they all are type II transmembrane proteins spanning the plasma membrane of the cells expressing them and they can bind to extracellular and, sometimes, also intracellular ligands. Second, all members of the group explicitly studied in this respect are subject to shedding *in vivo* and *in vitro*. Therefore, shedding is likely to be a general feature of these proteins. There is no unique sheddase although furin is likely to be involved, directly or indirectly, and there is no well defined shedding consensus sequence within the substrates. Third, all collagenous transmembrane proteins discovered so far consist of three identical polypeptides folded into at least one collagen-like triple helical domain of variable length.

Although many structural and functional features of the group are known, a number of questions still remain unanswered. The biological advantage of the optionally membrane-bound structure still is incompletely understood with the possible exception of collagen XVII and EDA. The former is likely to be a membrane-bound matrix receptor and the latter, in its soluble form, a signaling factor. The potential functions of the shed proteins are presumably manifold, and it will be intriguing to learn about different biological events triggered by shedding. Further, the role of furin in regulating or effecting shedding is likely to provide novel insights not only into proteolytic processing but also into the ways in which cells communicate with their environment. Finally, as the details of the biological roles of collagenous transmembrane proteins are unraveled, novel strategies of developmental mechanisms are likely to become apparent, and consequently we also shall learn a great deal about the etiopathology of several rare (and probably also of more common) human diseases.

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REFERENCES

1. Myllyharju, J., and Kivirikko, K. I. (2004) *Trends Genet.* **20,** 33–43
2. Franzke, C. W., Tasanen, K., Schumann, H., and Bruckner-Tuderman, L. (2003) *Matrix Biol.* **22,** 299–309
3. Loria, P. M., Hodgkin, J., and Hobert, O. (2004) *J. Neurosci.* **24,** 2191–2201
4. Koster, J., Borradori, L., and Sonnenberg, A. (2004) in *Handbook of Experimental Pharmacology* (Behrens, J., and Nelson, W. J. (eds) Vol. 165, pp. 243–280, Springer Science + Business Media, Berlin
5. Tu, H., Sasaki, T., Snellman, A., Gohring, W., Pirila, P., Timpl, R., and Pihlajaniemi, T. (2002) *J. Biol. Chem.* **277,** 23092–23099
6. Hägg, P., Vaisanen, T., Tuomisto, A., Rehn, M., Tu, H., Huhtala, P., Eskelinen, S., and Pihlajaniemi, T. (2001) *Matrix Biol.* **19,** 727–742
7. Nykvist, P., Tu, H., Ivaska, J., Kapyla, J., Pihlajaniemi, T., and Heino, J. (2000) *J. Biol. Chem.* **275,** 8255–8261
8. Hashimoto, T., Wakabayashi, T., Watanabe, A., Kowa, H., Hosoda, R., Nakamura, A., Kanazawa, I., Arai, T., Takio, K., Mann, D. M., and Iwatsubo, T. (2002) *EMBO J.* **21,** 1524–1534
9. Matsumoto, A., Naito, M., Itakura, H., Ikemoto, S., Asaoka, H., Hayakawa, I., Kanamori, H., Aburatani, H., Takaku, F., Suzuki, H., Kobari, Y., Miyai, T., Takahashi, K., Cohen, E. H., Wydro, R., Housman, D. E., and Kodama, T. (1990) *Proc. Natl. Acad. Sci. U. S. A.* **87,** 9133–9137
10. Sankala, M., Brannstrom, A., Schulthess, T., Bergmann, U., Morgunova, E., Engel, J., Tryggvason, K., and Pikkarainen, T. (2002) *J. Biol. Chem.* **277,** 33378–33385
11. Engel, J., and Kammerer, R. A. (2000) *Matrix Biol.* **19,** 283–288
12. Snellman, A., Tu, H., Väisänen, T., Kvist, A. P., Huhtala, P., and Pihlajaniemi, T. (2000) *EMBO J.* **19,** 5051–5059
13. Areida, S. K., Reinhardt, D. P., Muller, P. K., Fietzek, P. P., Kowitz, J., Marinkovich, M. P., and Notbohm, H. (2001) *J. Biol. Chem.* **276,** 1594–1601
14. McAlinden, A., Smith, T. A., Sandell, L. J., Ficheux, D., Parry, D. A., and Hulmes, D. J. (2003) *J. Biol. Chem.* **278,** 42200–42207
15. Latvanlehto, A., Snellman, A., Tu, H., and Pihlajaniemi, T. (2003) *J. Biol. Chem.* **278,** 37590–37599
16. Hooper, N. M., Karran, E. H., and Turner, A. J. (1997) *Biochem. J.* **321,** 265–279
17. Schäcke, H., Schumann, H., Hammami-Hauasli, N., Raghunath, M., and Bruckner-Tuderman, L. (1998) *J. Biol. Chem.* **273,** 25937–25943
18. Elomaa, O., Pulkkinen, K., Hannelius, U., Mikkola, M., Saarialho-Kere, U., and Kere, J. (2001) *Hum. Mol. Genet.* **10,** 953–962
19. Chen, Y., Molloy, S. S., Thomas, L., Gambee, J., Bachinger, H. P., Ferguson, B., Zonana, J., Thomas, G., and Morris, N. P. (2001) *Proc. Natl. Acad. Sci. U. S. A.* **98,** 7218–7223
20. Banyard, J., Bao, L., and Zetter, B. R. (2003) *J. Biol. Chem.* **278,** 20989–20994
21. Väisänen, M. R., Väisänen, T., and Pihlajaniemi, T. (2004) *Biochem. J.* **380,** 685–693
22. Schneider, P., Street, S. L., Gaide, O., Hertig, S., Tardivel, A., Tschopp, J., Runkel, L., Alevizopoulos, K., Ferguson, B. M., and Zonana, J. (2001) *J. Biol. Chem.* **276,** 18819–18827
23. Hopkinson, S. B., Baker, S. E., and Jones, J. C. (1995) *J. Cell Biol.* **130,** 117–125
24. Tasanen, K., Tunggal, L., Chometon, G., Bruckner-Tuderman, L., and Aumailley, M. (2004) *Am. J. Pathol.* **164,** 2027–2038
25. Hirako, Y., Usukura, J., Uematsu, J., Hashimoto, T., Kitajima, Y., and Owaribe, K. (1998) *J. Biol. Chem.* **273,** 9711–9717
26. Franzke, C. W., Tasanen, K., Borradori, L., Huotari, V., and Bruckner-Tuderman, L. (2004) *J. Biol. Chem.* **279,** 24521–24529
27. Franzke, C.-W., Tasanen, K., Schäcke, H., Zhou, Z., Tryggvason, K., Mauch, C., Zigrino, P., Sunnarborg, S., Lee, D., Fahrenholz, F., and Bruckner-Tuderman, L. (2002) *EMBO J.* **21,** 5026–5035
28. Black, R. A., and White, J. M. (1998) *Curr. Opin. Cell Biol.* **10,** 654–659
29. Peschon, J. J., Slack, J. L., Reddy, P., Stocking, K. L., Sunnarborg, S. W., Lee, D. C., Russell, W. E., Castner, B. J., Johnson, R. S., Fitzner, J. N., Boyc, R. W., Nelson, N., Kozlosky, C. J., Wolfson, M. F., Rauch, C. T., Cerretti, D. P., Paxton, R. J., March, C. J., and Black, R. A. (1998) *Science* **282,** 1281–1284
30. Schlondorff, J., and Blobel, C. P. (1999) *J. Cell Sci.* **112,** 3603–3617
31. Hirako, Y., Nishizawa, Y., Sitaru, C., Opitz, A., Marcus, K., Meyer, H. E., Butt, E., Owaribe, K., and Zillikens, D. (2003) *J. Invest. Dermatol.* **121,** 1554–1556
32. Hirako, Y., Yoshino, K., Zillikens, D., and Owaribe, K. (2003) *J. Biochem. (Tokyo)* **133,** 197–206
33. Tasanen, K., Eble, J. A., Aumailley, M., Schumann, H., Baetge, J., Tu, H., Bruckner, P., and Bruckner-Tuderman, L. (2000) *J. Biol. Chem.* **275,** 3093–3099
34. Nykvist, P., Tasanen, K., Viitasalo, T., Kapyla, J., Jokinen, J., Bruckner-Tuderman, L., and Heino, J. (2001) *J. Biol. Chem.* **276,** 38673–38679
35. Fine, J.-D., Eady, R. A. J., Bauer, R. R., Briggaman, R. A., Bruckner-Tuderman, L., Christiano, A., Heagerty, A., Hintner, H., Jonkman, M. F., McGrath, J., McGuire, J., Moshell, A., Shimizu, H., Tadini, G., and Uitto, J. (2000) *J. Am. Acad. Dermatol.* **42,** 1051–1066
36. Bruckner-Tuderman, L. (2002) in *Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects* (Royce, P., and Steinmann, B., eds) pp. 687–725, John Wiley & Sons, Inc., New York
37. Schumann, H., Baetge, J., Tasanen, K., Wojnarowska, F., Schacke, H., Zillikens, D., and Bruckner-Tuderman, L. (2000) *Am. J. Pathol.* **156,** 685–695
38. Zone, J. J., Taylor, T. B., Meyer, L. J., and Petersen, M. J. (1998) *J. Invest. Dermatol.* **110,** 207–210
39. Hägg, P., Rehn, M., Huhtala, P., Vaisanen, T., Tamminen, M., and Pihlajaniemi, T. (1998) *J. Biol. Chem.* **273,** 15590–15597
40. Kvist, A. P., Latvanlehto, A., Sund, M., Eklund, L., Vaisanen, T., Hagg, P., Sormunen, R., Komulainen, J., Fassler, R., and Pihlajaniemi, T. (2001) *Am. J. Pathol.* **159,** 1581–1592
41. Sund, M., Ylönen, R., Tuomisto, A., Sormunen, R., Tahkola, J., Kvist, A. P., Kontusaari, S., Autio-Harmainen, H., and Pihlajaniemi, T. (2001) *EMBO J.* **20,** 5153–5164
42. Verdier, Y., and Penke, B. (2004) *Curr. Protein Pept. Sci.* **5,** 19–31
43. Ezer, S., Bayes, M., Elomaa, O., Schlessinger, D., and Kere, J. (1999) *Hum. Mol. Genet.* **8,** 2079–2086
44. Yan, M., Wang, L. C., Hymowitz, S. G., Schilbach, S., Lee, J., Goddard, A., de Vos, A. M., Gao, W. Q., and Dixit, V. M. (2000) *Science* **290,** 523–527
45. Kere, J., Srivastava, A. K., Montonen, O., Zonana, J., Thomas, N. S. T., Ferguson, B. M., Munoz, F., Morgan, D., Clarke, A., Baybayan, P., Chen, E. Y., Ezer, S., Saarialho-Kere, U., la Chapelle, A., and Schlessinger, D. (1996) *Nat. Genet.* **13,** 409–416
46. Ferguson, B. M., Brockdorff, N., Formstone, E., Ngyuen, T., Kronmiller, J. E., and Zonana, J. (1997) *Hum. Mol. Genet.* **6,** 1589–1594
47. Monreal, A. W., Ferguson, B. M., Headon, D. J., Street, S. L., Overbeek, P. A., and Zonana, J. (1999) *Nat. Genet.* **22,** 366–369
48. Pispa, J., and Thesleff, I. (2003) *Dev. Biol.* **262,** 195–205
49. Hohenester, E., Sasaki, T., and Timpl, R. (1999) *Nat. Struct. Biol.* **6,** 228–232
50. Yamada, Y., Doi, T., Hamakubo, T., and Kodama, T. (1998) *Cell. Mol. Life Sci.* **54,** 628–640
51. Gowen, B. B., Borg, T. K., Ghaffar, A., and Mayer, E. P. (2001) *J. Leukocyte Biol.* **69,** 575–582
52. Takahashi, K., Takeya, M., and Sakashita, N. (2002) *Med. Electron Microsc.* **35,** 179–203
53. Elomaa, O., Sankala, M., Pikkarainen, T., Bergmann, U., Tuuttila, A., Raatikainen-Ahokas, A., Sariola, H., and Tryggvason, K. (1998) *J. Biol. Chem.* **273,** 4530–4538
54. Ito, S., Naito, M., Kobayashi, Y., Takatsuka, H., Jiang, S., Usuda, H., Umezu, H., Hasegawa, G., Arakawa, M., Shultz, L. D., Elomaa, O., and Tryggvason, K. (1999) *Arch. Histol. Cytol.* **62,** 83–95
55. Arredouani, M., Yang, Z., Ning, Y., Qin, G., Soininen, R., Tryggvason, K., and Kobzik, L. (2004) *J. Exp. Med.* **200,** 267–272
56. Karavanich, C. A., and Anholt, R. R. (1998) *Mol. Biol. Evol.* **15,** 718–726
57. Snyder, D. A., Rivers, A. M., Yokoe, H., Menco, B. P., and Anholt, R. R. (1991) *Biochemistry* **30,** 9143–9153
58. Hillier, B. J., and Vacquier, V. D. (2003) *J. Cell Biol.* **160,** 597–604

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