Physiological and pathological implications of laminins: From the gene to the protein

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Abstract

The extracellular matrix plays an important role in modulating the behavior of cells with which it interacts. There are a number of families of extracellular matrix (ECM) proteins including collagens, proteoglycans and laminins (LM). LM are the major component of the basal lamina (BL). Here, we review the current knowledge on their structure, self-assembly, binding mechanisms, diverse tissue-expression patterns and its impact on pathology. Studies and hypothesis exploring the role of LM and their polymorphic genes on autoimmune diseases (AIDs) such as systemic lupus erythematosus and Sjögren's syndrome (SS) are also discussed.

Keywords: *Laminin, extracellular matrix, basal lamina, systemic lupus erythematosus, Sjögren's syndrome*

Introduction

Laminins (LM) are a family of glycoproteins that are the basic components of the extracellular matrix (ECM), whose heterotrimeric structure is made up of three different polypeptide subunits, alpha, beta and gamma (α, β and γ), each of which is encoded by its own gene [1]. LM interact with the cell surface components such as dystroglycan and integrins, to attach cells to the ECM and further participate in the regulation of cell differentiation, proliferation mobility, anchoring and cellular death; in addition, they play a significant role in the transmission of intercellular signals—functions, being modulators of tissular homeostasis. LM are the main component of basal lamina (BL) [2], which is a structure that is indispensable for the maintenance of the tissular architecture; moreover, they provide the tissues mechanical stability and act as a protective barrier against cell invasion. BL is made up of glycoproteins and proteoglycans, including LM as well, besides, type IV collagen (CIV), type XV collagen (CXV), type XVIII collagen (CXVIII), nidogen, perlecan, agrin, fibulin and osteonectin [3] (Figure 1).

The structure of BL is composed of two networks. The first one is created by CIV molecules that develop through covalent and non-covalent bonds with adjacent monomers and the second is made up of LM molecules that are associated by means of non-covalent bonds between the N-terminal regions of each one of the chains (α, β, γ). Both networks integrate with each other through nidogen and possibly, perlecan molecules [4].

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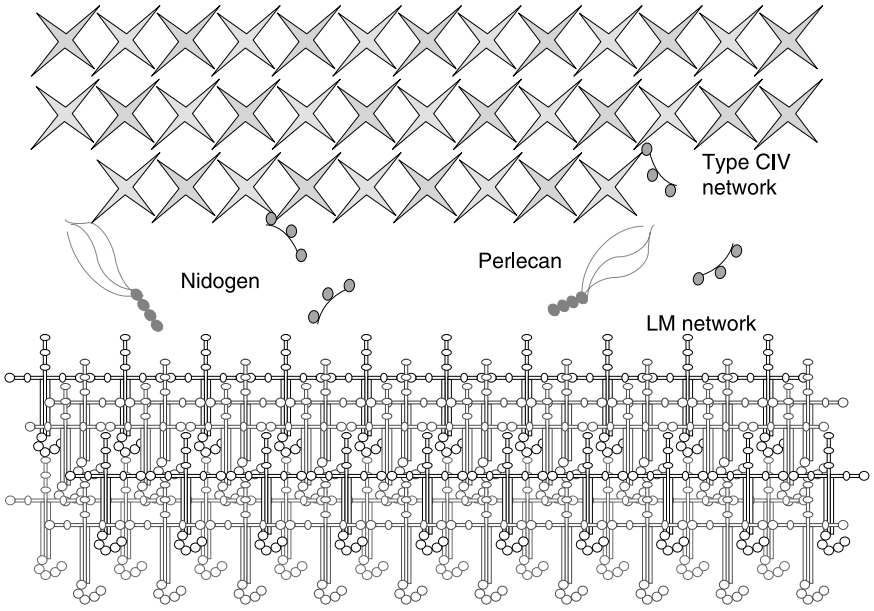

Figure 1. Main components of the BL. Modified from Quondamatteo et al. [4].

Structure and formation of the protein

LM were initially identified as heavy weight molecular proteins assembled by means of disulfide bonds that seemed to be made up of two main components. This concept has been modified after more than a decade of study. Currently, LM are recognized as trimers composed of the assembly of three polypeptides each of which possesses three or more isoforms, which was the first reliable structure as proposed by Burgenson effectively employed to introduce the nomenclature that has been utilized for more than 11 years (Table I) [5,6]. However, Aumailley and coworkers [7], recently proposed a new nomenclature for LM, based on the domains that compose it in order to facilitate their recognition (Table I). In this review, the preceding nomenclature is used and the new one is indicated in parenthesis.

Table I. Nomenclature for LM isoforms.

Name current practice	Chain composition	Abbreviated new nomenclature
LM-1	*α1 β1 γ1*	LM-111
LM-2	*α2 β1 γ1*	LM-211
LM-3	*α1 β2 γ1*	LM-121
LM-4	*α2 β2 γ1*	LM-221
LM-5, or 5A	*α3A β3 γ2*	LM-332 o LM-3A32
LM-5B	*α3B β3 γ2*	LM-3B32
LM-6, or 6A	*α3 β1 γ1*	LM-311 o LM-3A11
LM-7, or 7A	*α3A β2 γ1*	LM-321 o LM-3A21
LM-8	*α4 β1 γ1*	LM-411
LM-9	*α4 β2 γ1*	LM-421
LM-10	*α5 β1 γ1*	LM-511
LM-11	*α5 β2 γ1*	LM-521
LM-12	*α2 β1 γ3*	LM-213
LM-14	*α4 β2 γ3*	LM-423
-	*α5 β2 γ2*	LM-522
LM-15	*α5 β2 γ3*	LM-523

Independent of this diversity, there is a general structure that makes it possible to distinguish various domains that the majority of the LM have in common and that, starting from the extreme C-terminal, are: Domain G (LG1–LG5 domains), which is only present in the α-chains and the domains that are designated I through VI, which are made up of the three chains, α, β and γ. Of these domains (I through VI), the first two constitute the long arm of the LM and the other four, which go to the extreme N-terminal, make up the three short arms of this molecule, partially or completely truncated based on the isoform of the LM (Figure 2). However, the high selectivity in the association of the chains that constitutes each LM is still uncertain. In addition, it is believed that the diversity in reservoir of LM isoforms could be due to their expression in specific tissues and their presence in defined stages of development. The most important aspects of each one of the domains that have been described will be highlighted below.

Domain G (LG1–LG5 domains)

Domain G (LG1–LG5 domains), is made up of the extreme C-terminal of the α-chains, which can be divided into five sub-domains, organized in sequence and designated as LG1, LG2, LG3, LG4 and LG5. Although they represent a third of the amino acids (900 residues) in the sequence of the α-chain, they are doubled or folded into compact structures that resemble a lesser molecular size [8]. Domain G (LG1–LG5 domains), is composed of 14 β filaments,

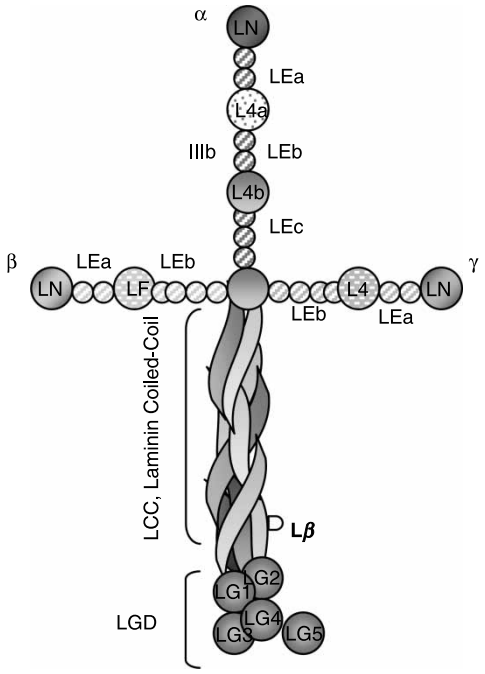

Figure 2. Schematic model of LM-1 and current recommendation for the domain nomenclature. Modified from Tunggal et al. [8].

which are organized in two layers that resemble a sandwich, with its extremes representing sites for binding with the Ca^{2+} ions (LG5) and for other ECM molecules such as perlecan, fibulin-1, α-dystroglycans and heparin (LG4). It also interacts with the cell surface by means of integrin-like receptors, mainly α3 and α6 [9].

Domains I and II (LCC, laminin coiled-coil)

These are formed by the binding of fragments from the three chains-α, β and γ, which create a triple α-helical coil and coil that corresponds to the longest portion of protein. Its formation in repeated heptads can be seen in Figure 3. Each single α-helix of about

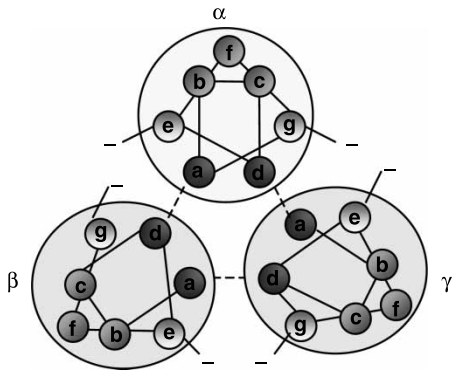

Figure 3. Projection of the triple-helical heptad repeat structure found in domain LCC. The dashed lines depict the hydrophobic interactions between residues *a* and *d* and the electrostatic interactions between residues in positions *e* and *g* are indicated by showing typical charges. Modified from Tunggal et al. [8].

600 amino acids consists of a series of heptad repeats, (*abcdefg*)*n*, where *a* and *d* are typically hydrophobic, *e* and *g* charged and *b*, *c* and *f* hydrophilic residues. Toward the extreme N-terminal, the three chains combine through the action of the disulfide bridges, thus providing greater stability for the trimer assembly [8], since it was precisely in the middle of this extreme where the main connection site (C8–9) for agrin was identified [9]. In the β-chains, domains I and II (LCC) are separated by an additional domain, not present in the α- and γ-chains; this extra domain, previously called α, is now represented as domain B (L*β*), as it is specific for the β-chains. The three-dimensional structure and function of domain α(L*β*), is still not known, but its domain is relatively small (33–35 amino acid residues) and is rich in glycine and cysteine [8].

Domains III (LEb) and V (LEa)

Domains III (LEb) and V (LEa) are segments that are located on the short arms of the LM and possess 3–22 copies of epidermoid growth factor (EGF)-like modules referred to as LE modules, *laminin-type EGF-like,* toward their extreme N-terminal. From the third to the fourth segment, the sequence of these modules is composed of amino acid residues that have a high homology with the EGF [10]. These structures are important in ligand–receptor interaction in particular with nidogen.

Two other globular domains, IV and VI (LN), have been described; domain IV constitutes two parts L4 (*a* or *b*) in α- and γ-chains and LF for β-chains; and domain VI constitutes a *laminin* N-terminal globular called LN. The domain IV (L4 and LF) is considered the main binding site for fibulin-2, while VI (LN) represents the most conserved region in the trimer [8].

Tissular expression

LM represent the structural component of the BL in all the tissues, but their expression can be associated with specific stages of development such as in the case of LM-1 (LM-111), which is expressed predominantly in pre- and post-implantation stages, where these molecules are relevant for epithelial development during organogenesis [5]. Likewise, their expression is tissue specific as is the case of LM-1 (LM-111) in the placenta, LM-5 (LM-332) in the skin and salivary gland and LM-10 (LM-511) and 11 (LM-521) in the kidneys [1]. Table II illustrates the main organs in which the different α-, β- and γ-chains of the LM have been identified [11].

LM receptors

The LM receptors are predominantly integrins like heterodimeric glycoproteins, which are characterized

Table II. The tissue distribution of diverse chains of LM [11].

Gene	System	Tissue
LAMA1	Nervous	Brain, spinal cord
	Secretory	Liver, pancreas, prostate, salivary glands
	Immune	Spleen, thymus
	Others	Lung, kidney (fetal and neonatal), retina,placenta
LAMA2	Muscular	Cardiac muscle, skeletal muscle
	Nervous	Peripheral nerve, meninges
	Secretory	Pancreas, adrenal glands, salivary glands
	Others	Lung, placenta, kidney, lung, bladder skin, capillaries, testis
LAMA3	Nervous	Brain
	Secretory	Prostate, intestinal epithelial
	Others	Skin, lung, epithelial of urinary tract
LAMA4	Nervous	Brain
	Muscular	Cardiac muscle
	Secretory	Liver
	Others	Ovary, intestines, placenta, lung, blood vessels, dermis, muscle
LAMA5	Muscular	Skeletal muscle
	Secretory	Prostate, liver
	Others	Lung, retina, kidney, placenta
LAMB1	Nervous	Brain, spinal cord
	Muscular	Cardiac muscle
	Secretory	Prostate, pancreas
	Others	Lung, kidney
LAMB2	Nervous	Brain, spinal cord
	Muscular	Cardiac muscle, skeletal muscle (synaptic cleft)
	Secretory	Prostate, pancreas
	Others	Lung, kidney
LAMB3	Nervous	Brain, spinal cord
	Others	Skin, lung y kidney
LAMC1	Muscular	Cardiac and skeletal muscle
	Nervous	Brain
	Secretory	Prostate, liver, pancreas
	Others	Lung, kidney
LAMC2	Muscular	Skeletal muscle
	Nervous	Brain, spinal cord
	Secretory	Prostate, pancreas, salivary glands
	Others	Lung, kidney, epithelial cells in embryoid bodies
LAMC3	Nervous	Brain
	Secretory	Prostate, liver, pancreas
	Others	Lung, skin, reproductor tract, kidney

as transmembrane receptors that play an important role in both cell to cell and in cell to ECM adhesions. So far, 18 α-chains and eight β-chains in vertebrates have been described at the molecular level for these receptors. Most of them exist under multiple isoforms generated by alternative splicing. Based on molecular classification, three subfamilies are recognized: the *β1 integrin subfamily* with 12 members (α1–α11, αv), the *β2 integrin subfamily* with four and the *αv subfamily* in which five members have been described [12].

These receptors possess a intracytoplasmatic C-terminal domain that is involved not only in the transduction of activation signals, but also in cytoskeleton assembly where it exerts a determining regulatory function in a different cellular structure [13].

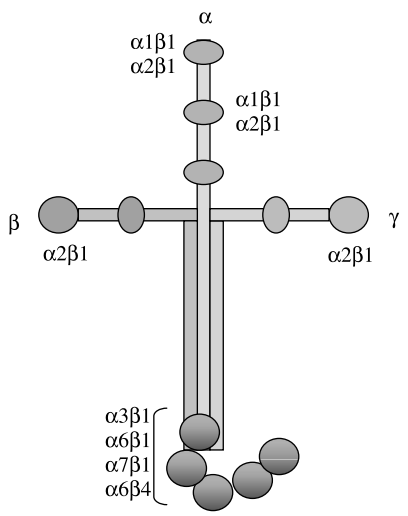

Figure 4. Integrin-interaction sites on the laminin α, β and γ chains. Modified from Belkin et al. [12].

Different studies have focused on identifying the specific integrin receptors for each LM. However, the multiple isoforms of these receptors and the diversity of LM that have been described make their study difficult. In addition, the evidence of integrin: ligand-binding specificity for each chain of the same LM, makes this problem more complex than it initially appears (Figure 4) [12].

Among the integrin receptors for the LM, six members of the β1 integrin subfamily (α1β1, α2β1, α3β1, α6β1, α7β1 and α9β1) and three of the αv subfamily (αvβ3, αvβ5, αvβ8) are described. Receptor α6β4 from the first group is described as well, but it is considered separately due to the fact that it has its own characteristics. It has been successfully determined that certain LM bind with greater affinity to specific integrins, for example, LM-5 (LM-332), LM-10 (LM-511) and LM-11 (LM-521) bind specifically with integrins like α3β1 [14], while LM-2 (LM-211) and LM-4 (LM-221) bind specifically mostly with α7β1 [15,16]. Together, LM-5 (LM-332), LM-6 (LM-311), LM-7 (LM-321), LM-8 (LM-411) and LM-9 (LM-421) cannot bind to receptor α1β1 because its binding domain is located on the short arm of the α-chain which is truncated in these LM [17].

Not all of the LM receptors are integrin-like. Domains for specific bonding for molecules such as heparin, α-dystroglycans, galactosyltransferase, glycolipids, lectins and elastin have also been reported [18].

Physiological implications

Preimplantation, implantation, placentation and embryonic development

Of the 16 LM isoforms, only LM-1 (LM-111) and LM-10 (LM-511) are expressed in the early stages of

embryogenesis. It was successfully determined in murine models that, in the blastocyte, LM-1 (LM-111) is expressed in the internal cellular mass and in the BL of the trophectoderm, while the LM-10 (LM-511) does the same in the uterus among the cells of the internal cellular mass and the BL of the polar trophectoderm. In the implantation process, not only LM-1 (LM-111) but also LM-10 was found in the embryonic BL and in the Reichert's membrane. However, LM-1 (LM-111) is predominated in the Reichert's membrane while LM-10 (LM-511) was more detectable in the embryonic BL [19]. LM-1 (LM-111) is considered the only component of BL which is fundamental for its formation in the early stages of development in mammals. The LM-1 (LM-111) γ1 and β1-chains are found in pre-implantation murine embryos at the 8-cell stage, while the expression of the α1-chain occurs later on in embryos at the 16-cell stage. This chain continues to be expressed predominantly in the epithelial cells during the entire period of organogenesis not only in mice, but also in humans [20]. LM-1 (LM-111) is directly involved in the process of differentiation of the epiblast, as well as indirectly in the correct assembly of the BL [21].

The results obtained with knockout mice for the *LAMC1* or *LAMB1* gene further support the basic role of LM-1 (LM-111) in the early phases of embryonic development [22]. These mice are characterized by a defective assembly of BL due to the altered polymerization of the LM trimers, which impedes the differentiation of the endoderm along with the disorganization of embryonic tissue and apoptosis. These processes lead to the early lethality of the embryo (6th day of development) [22].

After the implantation stage, the trophoblast invades not only the maternal deciduas, but also the stroma, thus establishing a connection with the maternal vascularity. This process is characterized by the replacement of the endothelium by endovascular trophoblast and the destruction of the elastic muscular fibers and nervous tissue, which in the absence of maternal vasomotor control, generates low resistance to flow and assures the satisfactory perfusion of the placenta and the embryo [23]. In experiments that were done by using knockout mice for the LM-1 (LM-111) α1, β1, or γ1-chain, it was successfully demonstrated that α1 and β1-chains are required for the normal development of embryogenesis. In the absence of the γ1-chain (*LAMC1*-/-), mouse embryos would die on the first day of implantation, given that this is required for endodermic differentiation and the formation of BL. Consistent with this, it was observed that the mouse embryos that lacked α1 and β1-chains (*LAMA1* and *LAMB1*) behaved in a fashion that was similar to the *LAMC1*-/-. However, those that only lacked the α1-chain succeeded in forming BL, the embryonic ectodermic cavity and differentiating the endoderm, apparently through partial compensation by LM-10 (LM-511). In the *LAMC1*-/- and *LAMB1*-/- mice, a reduced number of invading trophoblasts was evident [24].

The above mentioned findings directly correlate with the findings of Qureshi et al. [25], who analyzed cell cultures from biopsies of chorionic villi taken from human placentas at 6–7 weeks of gestation. These cultures were enriched with LM-1 (LM-111) at different concentrations and later treated with anti-LM-1 antibodies. In the first case, a stimulation of the trophoblastic adherence and migration was observed and in the second, an inhibition of these same processes was evident, which completely reverted when purified LM-1 (LM-111) was added. These findings confirm that LM-1 (LM-111) exercises a dose-dependent effect on the process of adherence and migration of the invading trophoblast during the early embryonic development [25]. These experimental results strongly correlate with the clinical findings in which it has been possible to demonstrate the association between elevated levels of anti-LM-1 (IgG) and recurrent miscarriage [26] and infertility associated with endometriosis [27].

The role that LM plays in the process of the implantation of the fertilized ovule is a field of special research interest in reproductive biology. This is especially true in autoimmune diseases (AIDs) that are associated with a greater frequency of early loss in gestation or infertility such as systemic lupus erythematosus (SLE) and in pathologies that are directly related to alterations in implantation and placentation such as preeclampsia.

Kidneys

The glomerular basal lamina (GBL) is mainly responsible for establishing and initiating the process of plasmatic ultrafiltration. At the renal level, LM-10 (LM-511) is the most abundant laminin and is located throughout the entire system. Nevertheless, LM-11 (LM-521) also expresses itself significantly in the GBL and in the arteriolar BL, where it apparently plays a significant role in satisfactory renal functioning. Knockout mice for *LAMB2*-/- (the gene that encodes for the β2-chain of LM-11/(LM-521)) have an ultrastructurally normal BL but the podocytes do not fuse together correctly, generating defects in the filtration process with marked proteinuria and early death two to three weeks after birth [28]. In addition, the expression of LM-1 (LM-111) has an influence on the differentiation of the mesenchyme to the transition epithelium, an important step in nephrogenesis [29].

Neuromuscular system

The neuro-muscular system (NMS) comprises seven classes of LM chains: α1, α2, α4, α5, β1, β2 and γ1,

which generate seven LM trimers: 1, 2, 4, 8, 9, 10 and 11. These LM have been described in different BL in the NMS, in the muscle (myotendinous junction, synaptic cleft and extrajunctional muscle) and in the nerves (perineurial, endoneurial and terminal Schwann cells) [30].

Among the LM that has been mentioned, LM-2 (LM-211) plays an important structural role in supporting the muscular plasmatic membrane and is considered the more relevant isoform in NMS to promote adhesion, migration, differentiation and/or survival of muscle cells and Schwann cells; while LM-4 (LM-221) regulates myoblastic migration, adhesion and differentiation in the myotendinous connection. According to their relevant role, they have also been called merosins, since they are the most frequent ones in mature NMS similar to the integrin α7β1 receptor. In addition, the fact that LM-11 (LM-521) regulates the differentiation of the terminal nerve and the motility of the Schwann cells has been described [31].

Studies conducted on knockout mice for *LAMB2* (β2-chain) that is associated with a lack of LM-4 (LM-221), LM-9 (LM-421) and LM-11 (LM-521), reveal different changes in the NMS. Among them are the separation of the terminal nerve from the synapsis and a poor pre-synaptic differentiation, which are changes that generate a dystrophic phenotype and early death due to neuromuscular failure [32]. Discoveries such as these shed light on and enable us to understand some diseases associated with irregularities in the human motor plaque.

Central nervous system (CNS)

LM are important factors in neuronal and glial interactions. The main storage sites for these molecules are the cerebral blood vessels, the choroid plexus and astrocytes [33].

The dynamic role of the LM in neuronal migration was finally confirmed upon treating nervous tissue with anti-LM antibodies, demonstrating that neuronal growth and migration underwent inhibition. This effect was corroborated upon being reversed with the addition of soluble LM [34]. At the same time, children with congenital muscular dystrophy, which is caused by the presence of mutations in the *LAMA2* that encodes for the α2-chain, showed significant alterations in the white matter and different cerebral structural abnormalities associated with alterations in the myelination process of CNS. Furthermore, comorbidity with epilepsy has also been described, although the physiopathological mechanism that is implicated has not been answered yet [35].

The main LM associated with the defective development of the cerebrum is the α5-chain (*LAMA5*), where almost 60% of the knockout mice for this gene exhibit exencephaly, which is secondary to failure of anterior neural tube closure [35]. Variants in the interaction site for nidogen (located on the γ-chain), inhibit its interaction with LM and generate a process of aberrant neuronal migration [36].

Skin

The most important laminin for the epidermis is LM-5 (LM-332), which is exclusively produced by the basal keratinocytes in the form of a precursor protein. LM-5(LM-332), is found in abundance in the hemidesmosomes, the specialized anchoring structures that connect the basal keratinocytes of the epidermis to the LM-5 (LM-332) of the BL by means of integrin like α6β4 receptors. LM-5 (LM-332) is connected to the dermis stroma through its interaction with type VII collagen (Figure 5) [37,38]. Both interactions are crucial for the firm establishment of epithelial adhesion to BL, thus assuring the relationship between dermis and epidermis, which prevents the development of bullous cutaneous lesions.

The complete absence of hemidesmosomes results in an entity known as Herlitz's lethal junctional epidermolysis bullosa (H-JEB), which belongs to a genodermatosis group clinically characterized by extensive separation of the epidermis from all over the body surface. This alters the skin to an excessively fragile type to the action of friction and as a consequence, to the presence of generalized blisters, atrophic scars that could affect oral mucus, the genitourinary area and subsequently be associated with the loss of fingernails and toenails, anemia, delayed growth and even congenital absence of the skin [39]. These conditions lead to death in the perinatal period or within a few months of birth [29]. This pathology is inherited as an autosomic recessive disorder and although mutations could occur in any of the genes that encode each one of the three LM-5 chains, more than 80% of those that are responsible for the Herlitz variety occur in the gene for the β-chain

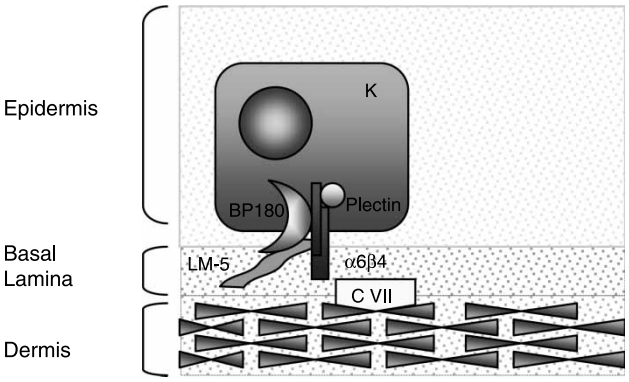

Figure 5. Hemidesmosome structure and protein composition. Their main components are observed, such as K, keratinocytes; BP180, CVII; α6β4, LM-5, (LM-332); plectin; BL. Plectin has recently been shown to bind directly to the cytoplasmic domain of β4 integrin. Modified from Jones et al. [37].

(*LAMB3*). There are two "hot points" with high frequency mutation of the *LAMB3* gene that correspond to C> T transitions [39]. There is also a non-lethal form of H-JEB that is generally associated with the presence of mutations that generate a change in the frameshift in different LM genes or that is due to the presence of mutations in the *COL17A1* gene and in the *LAMB3* gene. In these cases, LM-5 is not totally absent but expressed on a smaller scale with an absence of XVII collagen. This brings about the formation of blisters, primary hemidesmosomes and severe but non-lethal defects in the fingernails and toenails [40].

Genetic structure and regulation

Sixteen LM composed of different combinations of the five types of α-chains, three types of β-chains and three types of γ-chains have been described. The complexity of the regulation of the genetic expression of these molecules resides in the fact that each chain is encoded by different genes located on different chromosomes. The main characteristics of these genes and their product are described in detail in Table III [41].

A variety of factors that have an influence on the proliferation and differentiation *in vivo* and *in vitro* of the epithelial cell by means of the modulation of the expression of LM genes have been described. Multiple factors for growth, cytokines, kinase protein activators and retinoids are included among them [42].

Genetic regulation

Retinoic acid (RA) is the main biologically active form of vitamin A and has the capacity to influence the process of epithelial differentiation in a variety of specific stages of development. In monolayer cultures of embryonic carcinoma F9, which is considered very similar to embryonic cells, the administration of RA induces cell differentiation and simultaneously increases the levels of mRNA in the α1, β1 and γ1-chains [43]; simultaneously, there is a continuous increase in the expression of the retinoid nuclear receptor (RAR). Therefore, it has been suggested that it could influence the modulation of the LM expressions, if we keep in mind the fact that, in depleted cell lines for this gene (RAR), the addition of RA does not generate an expression of the LM. In an extensive analysis of the *LAMB1* promoter, it was shown that cis-acting elements responding to RA, through RAR as transcription factors [44,45].

On the other hand, within the cytokines, TGF-β is considered the most important mediator in stimulating the synthesis of ECM proteins. Some studies have shown an increase of at least three times the levels of mRNA for LM-1 (LM-111) in mouse liver and lungs in the presence of this cytokine. Nevertheless, those studies have not been reproducible in all of the tissues. An increase in the expression of α3A and γ2 chains (LM-5; LM-332) in different cell lines of keratinocytes and in adenocarcinoma has also been proven [46].

Recent studies have succeeded in identifying some specific functional domains in the genes that encode for these chains. These are DNA sequences to which transcription factors bind in response to external regulatory agents that, as has already been mentioned, may be tissue specific and be regulated during specific stages of development. The promoters of these genes have in common, the lack of boxes—TATA and CAAT—[42] and the presence of multiple regions that are rich in GC, an aspect that, in housekeeping genes, is characteristic of the promoter regions. Some of the main domains and factors involved in the transcription of these genes in eukaryote cells are presented in Table IV [42].

Clinically relevant genetic polymorphisms

For each one of the genes that encode for the chains of the LM, multiple genetic variants that could be classified as single nucleotide polymorphisms (SNPs), insertion or deletion of base pairs (In/Del), variable number of repetitions in sequences (VNTR) have been described. Nevertheless, the most frequent ones

Table III. LM genes and protein information [11].

Chain	Gene	Genomic location	Properties (Kb /no. exons)	mRNA (pb)	Protein (kDa)
α1	*LAMA1*	18p11.32	175.93/63	9512	337.2
α2	*LAMA2*	6q22–23	633.37/64	9649	342.8
α3	*LAMA3*	18q11.2	81.86/38	5433	189.3
α4	*LAMA4*	6q21	145.73/39	6297	202
α5	*LAMA5*	20q13.2–13.3	58.25/80	11426	178.2
β1	*LAMB1*	7q22	79.54/34	5831	198.1
β2	*LAMB2*	3p21.3	12.05/32	5808	196.1
β3	*LAMB3*	1q32	37.51/23	3971	129.6
γ1	*LAMC1*	1q31	122.17/28	7931	177.6
γ2	*LAMC2*	1q25–31	58.64/23	5175	131
γ3	*LAMC3*	9q31–34	82.94/28	5098	172.1

Table IV. Control elements in LM gene promoters: *LAMA3*, *LAMB1*, *LAMB2*, *LAMC1 and LAMC2* [8].

Gene	Control elements-enhancer	Location	Transcription factors
LAMA3	FAP1, AP-1, AP-2	− 314 t − 114	TGF*β*
LAMB1	RARE	− 477 t − 432	The RA-RARγ-RXR complex binds
LAMB2	TATA or CAAT boxes GC-rich regions	− 94 t 106	Insulin, TPA, thyroid hormone
LAMC1	KappaB consensus sequence. Bcn-1 element and GC boxes	− 550 t − 525	IL-1*β*, TGF*β*, Sp1, glucose
LAMC2	Cis-acting motifs like AP-1, Sp1 y GC boxes	− 2.5 t − 0.12	TPA, Sp1, TGF*β1*, HGF

FAP-1, fos activator protein 1 site; AP-1, activator protein 1; TGF*β*, transforming growth factor beta; RARE, retinoic acid-responsive element; RA, retinoic acid; RARγ, nuclear retinoid receptors gamma; TPA, phorbol ester; KappaB; consensus sequence to NF-kappaB; Bcn-1, GC rich-Bcn-1 motif; IL-1*β*, interleukin 1-beta; Sp1, transcription factor sp1; and HGF, hepatocyte growth factor (scatter factor).

are the SNPs whose change in the base pairs leads to a modification in the protein sequence (non-synonymous) or those that become localized in the promoter, where they exercise direct action on the rate of gene transcription.

Various studies of genetic association analyzed the different polymorphisms in the genes that encode for the LM and neuromuscular entities, bullous skin diseases and carcinoma. The relationship that has been revealed in different studies and that is congruent with biological plausibility suggests that genes are the essential candidates for the overall approach of these pathologies (Table V) [11,41].

LM and autoimmune diseases

LM are components of the BL, the structure that provides tissue integrity, besides, they are important for the proper structure formation and development of the tissue. It is not surprising that processes that interfere with wild type functions of LM produce human pathology, some of which characterize certain AIDs. We will examine the role of LM in autoimmunity focusing mainly in SLE and Sjögren's syndrome (SS).

Systemic lupus erythematosus

Murine lupus models were the first approach to determine the importance of LM in SLE. In 1993, Termaat et al. [58] described the presence of antibodies directed against DNA and histones in mice with diffused proliferative glomerulonephritis. However, they also observed antibodies that reacted against components of GBL and tubular BL, but in particular against the LM, which suggested that these could also induce the development of experimental lupus nephritis [58]. Later studies reported quantitative alterations in the expression of the mRNA for LM-1 (LM-111) and the presence of immunocomplexes at the mesangial and subepithelial level throughout the GBL as mechanisms involved in the development of glomerular disease [59,60]. These findings were corroborated in patients with SLE in whom antibodies, which had been purified from serum and their own urine, reacted against a commercial preparation of matrix produced by epithelial tumor containing LM as its major component. Additionally, the levels of these IgG antibodies against the β1 and β2-chains were correlated with the progress of the disease [61]. Moreover, the presence of lgG antibodies recognizing the α3- and γ2-chains of the LM-5 (LM-332) and LM-6 (LM-311) in the hemidesmosomes, dense lamina and anchoring proteins were reported in bullous SLE [62].

Genetic families' studies in SLE, have shown evidence of linkage to different regions on chromosome 1. Noteworthy, three of the genes that encode for the LM chains are found at this level (Table III). Moser et al. [63], carried out a genome-scan in 533 individuals belonging to 94 pedigrees containing 220 probands. They analyzed more than 300 microsatellite

Table V. LM genes polymorphism and their implication in disease [41].

GENE	SNPs	Non-synonymous SNPs	Disease (reference)
LAMA1	760	6	Neuromuscular diseases, Alzheimer disease, neoplasms [47]
LAMA2	528	3 W166X, V2587X	Muscular dystrophies, Walker–Warburg syndrome [48]
LAMA3	577	3 E281X, K1299X	Epidermolysis bullosa, pemphigoid bullous [49]
LAMA4	507	2	Carcinogenesis and metastasis of endocervical adenocarcinomas [50]
LAMA5	267	20	Muscular dystrophies [51]
LAMB1	230	2	Muscular dystrophies, carcinoma, teratocarcinoma [52]
LAMB2	8	1	Muscular dystrophies, Walker–Warburg syndrome [53]
LAMB3	162	9 1628insG, R635X, Q373X	Epidermolysis bullosa, lethal junctional epidermolysis bullosa [54]
LAMC1	496	5	Epidermolysis bullosa [55]
LAMC2	220	7	Epidermolysis bullosa [56]
LAMC3	363	2	Bladder transitional cell carcinoma [57]

Table VI. Maximized parametric analysis of potential human SLE susceptibility loci [63].

LOD score	Region	Marker	Ethnic group	Model
3.5	1q41	D1S3642	African–American	Dominant
3.45	1q23	FcγRIIA	All*	Recessive
3.37	1q23	FcγRIIA	African–American	Recessive
2.50	13q32	D13S779	All*	Recessive
2.49	20q13	D20S3481	All*	Recessive
2.21	14q11	D14S742	European–American	Dominant

* Includes the entire pedigree collection (All).

markers that spanned the 22 autosomes [63]. These authors provided evidence of linkage for 16 potential susceptibility markers, with only six *loci* presenting LOD values score for suggestive linkage (2.2–3.5) using the criteria defined by Lander and Kruglyak [64], including the 20q13 region where the gene that encodes for an isoform in the α-chain (*LAMA5*) is located (Table VI). In this same study, the analysis of 78 pairs of siblings who were affected by the disease showed linkage to 1q23 (FcγRIIA). A later and finest analysis reported the possibility that the *loci* located between 1q21 and 1q31 would link to SLE. This included the gene *LAMC1* (1q31), as one of the multiple genes that are incriminated with SLE [63].

More recently, a study was conducted involving 87 multi-case families with SLE, of European origin (Iceland, Switzerland, England, Norway, Italy and Greece) and on recently mixed populations, including Colombians [65]. After analyzing 62 microsatellites on chromosome 1 and later, carrying out a double point parametric analysis, six potential regions for linkage disclosing a LOD score >1.5 (1p36, 1p21, 1q23–24, 1q25, 1q31 and 1q43) were identified. Nevertheless, the only locus that showed significant linkage (LOD score = 3.79) in all of these populations was 1q31 (*LAMC1*).

The question that arises is how to relate the presence of autoantibodies against LM-1 (LM-111) and the hypothetical link with 1q31 which harbor *LAMC1* gene. Previous studies in diabetes [66], thyroiditis [67] and pemphigus [68] have shown that germinal mutations at the gene coding for autoantigens (i.e. insulin, thyroglobulin, desmoglein) are associated with such AIDs. In this sense, it is tempting to speculate that polymorphisms at *LAMC1* gene could be associated with SLE and the presence of anti-LM-1 (LM-111) antibodies. Besides LM1 (LM-111), there have been other laminins incriminated into the autoimmune response in SLE, thus those genes are biologically plausible candidates to be examined in this pathology as risk factors.

Sjögren's syndrome

SS is an autoimmune disease characterized by lymphocytic infiltration of the salivary and lachrymal glands. Disruption of the acinar and duct structures and significant changes in the expression and activation of the matrix metalloproteinases (MMPs) of ECM are both characteristics of this disease [69]. The MMPs are important factors in the remodeling of BL [69]. A recent study showed that LM-5 (LM-332), LM-6 (LM-311) and LM-10 (LM-311) are expressed in glandular BL and also that LM-1 (LM-111), LM-2 (LM-211) and LM-8 (LM-411) are mainly expressed in acinar BL, while LM-1 (LM-111) is the molecule that is considered essential for the homeostasis of the acinar cells [70].

In 1997, McArthur et al. [71], identified an increase in the expression of LM at the level of the salivary duct epithelium in SS patients in comparison with controls. However, at that time, the nature of the primary lesion and the chronology of the pathological changes were poorly understood. Alterations in the BL and possibly a diminution of cell polarity precede the periductal lymphocytic infiltration. Later studies corroborated these discoveries upon finding elevated levels of protein in biopsies of patients with SS and the presence of their mRNA in the acinar and duct epithelium of the salivary gland as compared with controls [72,73]. Besides, the fact that this over-expression was associated with a low degree of $CD4^+$ or $CD8^+$ lymphocytic infiltration suggesting that the alteration in the pattern of LM expression is an early and independent event, readily supports the idea that this glandular pathology is epithelial origin [72,73].

The expression of MMPs generates proteolysis that is local (acinar y ductal) and compromises the BL [69]. A recent study reported that increases in the expression of MMPs 2, 3 and 9 are associated with SS [74]; their presence positively correlates with dramatic changes in the structural organization of the BL. This aspect makes the gland vulnerable to lymphocytic infiltration and exposes the tissue to cytotoxicity. Nevertheless, the presence of BL disruption does not seem to be sufficient to favor leukocyte infiltration, since the presence of cytokines and chemokines influences over the generation of this process [73].

Acinar cell death is also promoted by detachment of the cells from their BL, a process known as anoikis [74]. This latter process does not require the presence of mononuclear cells. MMPs secreted by the acinar and ductal cells themselves are implicated and particularly imbalanced ratios of MMP-9/TIMP-1

and MMP-3/TIMP-1 have been observed in SS [75]. So far, no information is available concerning turnover of BL components in the labial salivary glands (LSG) of SS patients. Thus, the hypothesis that remodeling of BL molecules is altered in SS patients was investigated in two groups of patients, SS1 and SS2, with similar levels of remnant glandular tissue but with low or high interacinar fibrosis, respectively. The expression of the LM α1, α4, γ2-chains and nidogens were examined at the mRNA and protein levels. Increases in the amount of mRNA and protein levels of both the processed and unprocessed LM-γ2 chain were more pronounced in SS1 patients. Increases in the protein levels of LM-α1 and -α4 chains were observed in SS1, but not SS2 patients. Our results suggest that the BL of LSG from SS patients is actively being remodeled, whereby alterations are less evident in patients that have advanced morphological signs of the disease (SS2) [76].

Perspectives and conclusions

The LM are a growing family of matrix molecules highly incriminated in the organization, development and homeostasis of tissues. These trimers have a strong impact on the matrix to cell communication signals and vice versa. This is a determining factor in the early stages of embryogenesis and in the functioning of the tissues in post-natal stages. In the next few years, crucial advances in our understanding of the forms and functions of each one of the members of this family of proteins are envisioned, their genetic association with different pathologies including AIDs will be examined and the use of their measurement as a diagnostic tool will be considered in clinical practice.

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