

Tissue distribution of the laminin $\beta 1$ and $\beta 2$ chain during embryonic and fetal human development

Matthias Roediger · Nicolai Miosge ·
Nikolaus Gersdorff

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Abstract Laminins are the major glycoproteins present in all basement membranes. Previously, we showed that perlecan is present during human development. Although an overview of mRNA-expression of the laminin $\beta 1$ and $\beta 2$ chains in various developing fetal organs is already available, a systematic localization of the laminin $\beta 1$ and $\beta 2$ chains on the protein level during embryonic and fetal human development is missing. Therefore, we studied the immunohistochemical expression and tissue distribution of the laminin $\beta 1$ and $\beta 2$ chains in various developing embryonic and fetal human organs between gestational weeks 8 and 12. The laminin $\beta 1$ chain was ubiquitously expressed in the basement membrane zones of the brain, ganglia, blood vessels, liver, kidney, skin, pancreas, intestine, heart and skeletal system. Furthermore, the laminin $\beta 2$ chain was present in the basement membrane zones of the brain, ganglia, skin, heart and skeletal system. The findings of this study support and expand upon the theory that these two laminin chains are important during human development.

Keywords Laminin · Basement membrane · Tissue distribution · Human embryogenesis · Immunohistochemistry

Introduction

The formation and maintenance of normal epithelial organization requires a basement membrane (Ekblom

1989; Virtanen et al. 1995a, b). Basement membranes are thin, specialized structures surrounding and separating layers of cells from different lineages. Basement membranes first appear during the blastocyst stage, between the primitive endoderm and the inner cell mass (Timpl and Brown 1996). They are the earliest extracellular matrices (ECM) produced during embryogenesis (Graham and Lehtonen 1979). At this stage, all main basement membrane components are synthesized, including laminin, nidogen, perlecan and collagen type IV (Leivo et al. 1980). Although basement membranes at various body sites are similar on the ultrastructural level (Merker 1994), there is evidence for their organ-specific heterogeneity (Ljubimov et al. 1995; Hallmann et al. 2005; Roediger et al. 2009). Though the molecular basis for such heterogeneity is not yet fully defined, many studies have shown organ-specific expression of the main basement membrane components, such as laminins (Glukhova et al. 1993; Virtanen et al. 1995a, b; Otonkoski et al. 2008).

The laminin family of glycoproteins is a major constituent of the basement membrane (Timpl 1996). During metazoan embryogenesis, laminins are required for basement membrane assembly and cell polarization, and have subsequent effects on cell survival and tissue organization (Li et al. 2003). In addition to their role in the assembly and architectural integrity of the basement membrane, laminins interact with cells to influence proliferation, differentiation, adhesion, and migration processes. In mammals, there are at least 15 laminins, each an $\alpha_x\beta_y\gamma_z$ glycoprotein heterotrimer derived from five α , three β , and three γ subunits (Sasaki and Timpl 1999; Colognato and Yurchenco 2000; Libby et al. 2000). In 2005, a new heterotrimer identification system was introduced, using three Arabic numerals based on the α , β , and γ chain numbers (Aumailley et al. 2005). The earliest-expressed laminins during mammalian

M. Roediger · N. Miosge · N. Gersdorff (✉)
Department of Prosthodontics, Tissue Regeneration Work
Group, Georg-August-University Goettingen, Robert-Koch-Str.
40, 37075 Goettingen, Germany
e-mail: ngersdo@gwdg.de

embryogenesis are laminin-111 and laminin-511, which show widespread expression and are crucial during mammalian embryonic development (Li et al. 2003). These two laminins mostly overlap in developmental expression and function, but only laminin-111 appears to be essential during the periimplantation period (Smyth et al. 1999).

We have previously shown that perlecan is present during embryonic and fetal human development, particularly at those stages of human development when epithelial–mesenchymal interactions occur (Roediger et al. 2009). In this work, we studied the immunohistochemical expression and tissue distribution of the laminin $\beta 1$ and laminin $\beta 2$ chains in various developing embryonic and fetal human organs between gestational weeks (gw) 8 and 12. Up to now, distribution of the laminin $\beta 1$ chain during human embryogenesis has generally been examined during late stages of fetal development, i.e., from gw 12 onwards. During this later stage, there is evidence for expression in the kidney (Virtanen et al. 1995a), several parts of the nervous system (Jaakola et al. 1993), pancreas, heart and skin (Iivanainen et al. 1995). However, laminin $\beta 1$ chain expression in skeletal muscle (Wewer et al. 1997) and smooth muscle cells in the aorta and intestine (Glukhova et al. 1993) could only be found during gw 10. Laminin $\beta 2$ chain expression was detected in the choroid plexus, skin, heart and pancreas during gw 17–19 (Iivanainen et al. 1995) and was shown not to be expressed before gw 9 in the lens capsule of the eye (Byström et al. 2006).

Materials and methods

Tissue sources

Aborted human embryos and fetuses were obtained according to the regulations of the Ethics Committee of the Medical Faculty of the University of Goettingen, Germany. The cut-off point for the differentiation between embryos and fetuses has been defined as ranging from gw 8 to 9 (Moore 1982). We investigated three embryos of gestational week gw 8, three fetuses of gw 10, two fetuses of gw 11 and two fetuses of gw 12. The ages were determined according to Carnegie stages (O’Rahilly and Müller 1987). No malformations or abnormalities were observed in these specimens. The abortion procedure leads to the destruction of much of the embryonic tissue; our results are, therefore, limited to those tissues we were able to follow to completion.

Tissue processing

The abortion material was transported to the laboratory in a histidine-tryptophane-ketoglutarate solution at 4°C to

ensure good preservation of the tissues (Bretschneider 1980; Koelling et al. 2006) and were fixed in 3.7% paraformaldehyde in phosphate buffer, pH 7.2, at 4°C for 24 h. The tissues were then serially dehydrated in ethanol from 30 to 100% and embedded in paraffin according to standard protocols (Gersdorff et al. 2005). Serial sections of 5 μ m thickness were cut with a Reichert’s microtome. Every fifth section was stained with hematoxylin and eosin (HE) for topological orientation within the anatomical regions examined.

Antibodies

Rat monoclonal antibodies against the laminin $\beta 1$ chain were purchased from Chemicon International (Temecula, USA; catalogue number: MAB1928). An affinity purified rabbit anti-mouse antiserum specific for laminin $\beta 2IV$ was used to detect the laminin $\beta 2$ chain and has been shown not to cross-react with the $\beta 1$ chain (Sasaki et al. 2002). The secondary antibodies used for the light microscopic immunostaining were purchased from Dakopats (Hamburg, Germany).

Immunohistochemistry

Immunoperoxidase staining was performed on paraffin-embedded tissue sections as follows: Tissues were deparaffinized, rehydrated and rinsed for 10 min in phosphate buffered saline (PBS), pH 7.2. Endogenous peroxidase was inhibited with a solution of 3% H_2O_2 in methanol for 45 min in the dark (Koelling et al. 2006). The sections were pre-treated for 5 min with 10 μ g/ml protease XXIV (Sigma Deisenhofen, Germany). The antibodies against the laminin $\beta 1$ and $\beta 2$ chains were used at a 1:100 dilution in PBS/BSA 1% and incubated for 1 h at room temperature. The tissues were rinsed in PBS for 10 min following each of the steps. The secondary antibody was applied at a 1:50 dilution in PBS/BSA. A standard peroxidase-antiperoxidase procedure followed, applying a peroxidase-coupled goat-anti-rabbit antibody (Dako, Hamburg, Germany) at a dilution of 1:150 in PBS for 30 min at room temperature. The sections were counterstained with hematoxylin. Negative controls omitted the primary antibody.

Results

A list of our results regarding the tissue distribution of the laminin $\beta 1$ chain is given in Table 1 and Fig. 1. Comparative findings regarding the tissue distribution of the laminin $\beta 2$ chain are shown in Table 2 and Fig. 2. Results for the developing human eye are mentioned in text below and shown in Fig. 3.

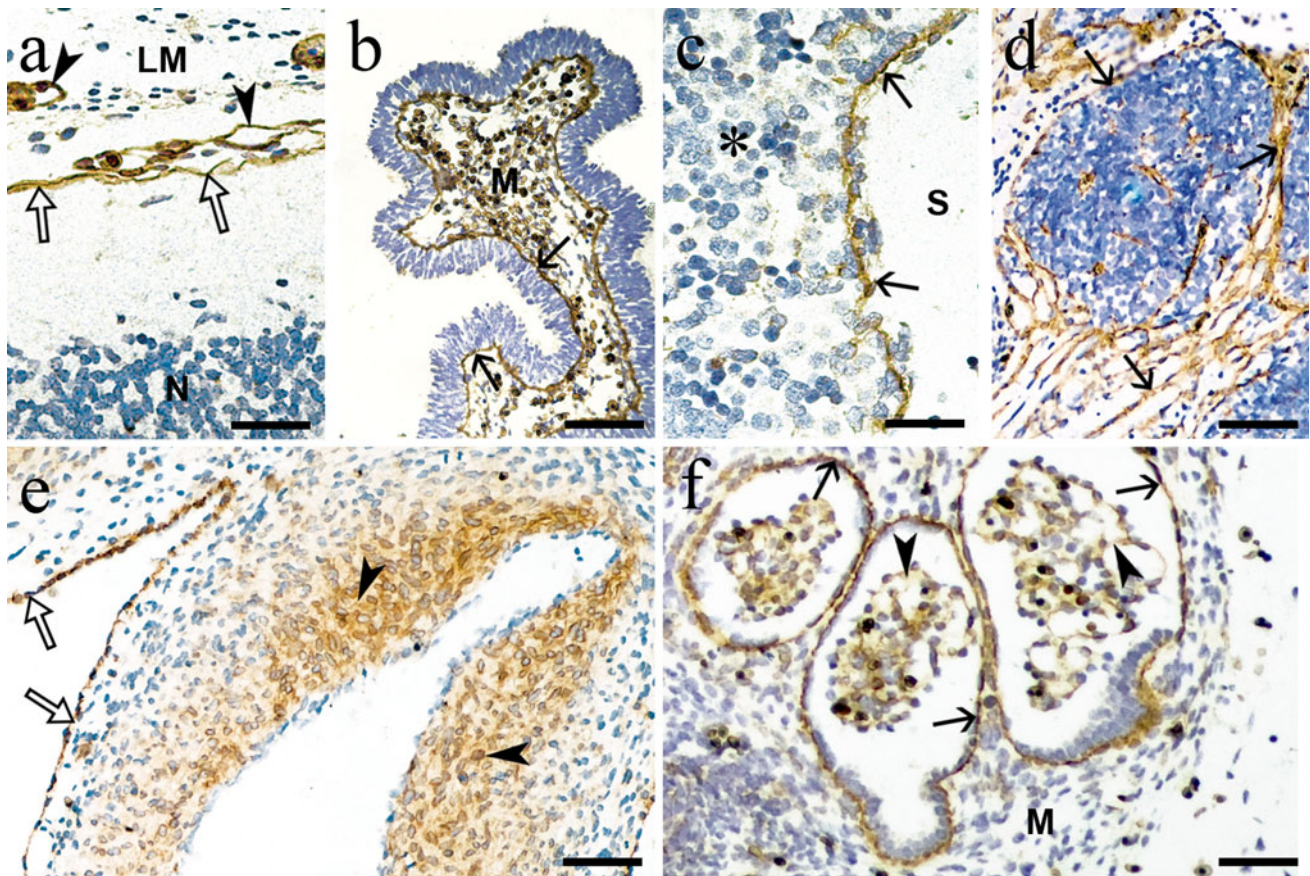


Fig. 1 Localization of the laminin $\beta 1$ chain during gw 8 and 9 in human embryogenesis. **a** Immunostaining for laminin $\beta 1$ chain in BMZs of neuroectoderm (*open arrows*) and capillaries (*arrowheads*). Loose mesenchyme cells (*LM*) and neuronal cells (*N*) showed no staining for the laminin $\beta 1$ chain. **b** BMZs (*arrows*) and mesenchymal cells (*M*) of the choroid plexus exhibited staining for the laminin $\beta 1$ chain. **c** Localization of the laminin $\beta 1$ chain in BMZs of a sinusoid (*S*) of developing liver (*arrows*). Hepatocytes (*asterisk*) were negative

for the laminin $\beta 1$ staining at gw 8. **d** Immunostaining for laminin $\beta 1$ chain in the endoneurium of spinal ganglia (*arrows*). **e** The laminin $\beta 1$ chain in the ECM of cardiomyocytes (*arrowheads*) and in BMZs of pericardium. **f** Detection of the laminin $\beta 1$ chain in Bowman's capsule (*arrows*) and in glomerular basement membranes (*arrowheads*) of the developing kidney. Mesenchymal cells (*M*) showed no staining for the laminin $\beta 1$ chain. Bars 15 μm in **a**, **b**, **c**, **d**, **e**, and **f**

Neuronal system

The choroid plexus consists of many capillaries and is the part of the ventricular system where cerebrospinal fluid is produced. The invagination of the choroid plexus in the developing telencephalon starts at gw 5 (Sadler 2005). We found the laminin $\beta 1$ and laminin $\beta 2$ chains in basement membrane zones (BMZs) and mesenchymal cells of choroid plexus at gw 8 and 9. BMZs of the neuroectoderm and BMZs of capillaries stained positive for both laminin chains from gw 8, whereas no staining was detected for either laminin chain in neuroectodermal cells.

The laminin $\beta 1$ and $\beta 2$ chain expression was found in the endoneurium of peripheral ganglia and BMZs of capillaries from gw 8 onwards. Neuronal cells were negative for the laminin $\beta 1$ and laminin $\beta 2$ chains at all stages examined.

Blood vessels

The differentiation of angioblasts into endothelial cells begins in the visceral mesoderm at gw 3 (O’Rahilly and Müller 1996). Endothelial BMZs of arteries and veins, as well as BMZs of capillaries, between gw 8 and 12 stained positive for the laminin $\beta 1$ chain.

Liver

The development of the liver is initiated by the budding of endodermal cells from the distal end of the foregut (O’Rahilly and Müller 1996). The laminin $\beta 1$ chain was detected in BMZs from sinusoids from gw 8 to 12. Hepatocytes did not express the laminin $\beta 1$ chain before gw 10. The presence of the laminin $\beta 1$ chain was detected at gw 12.

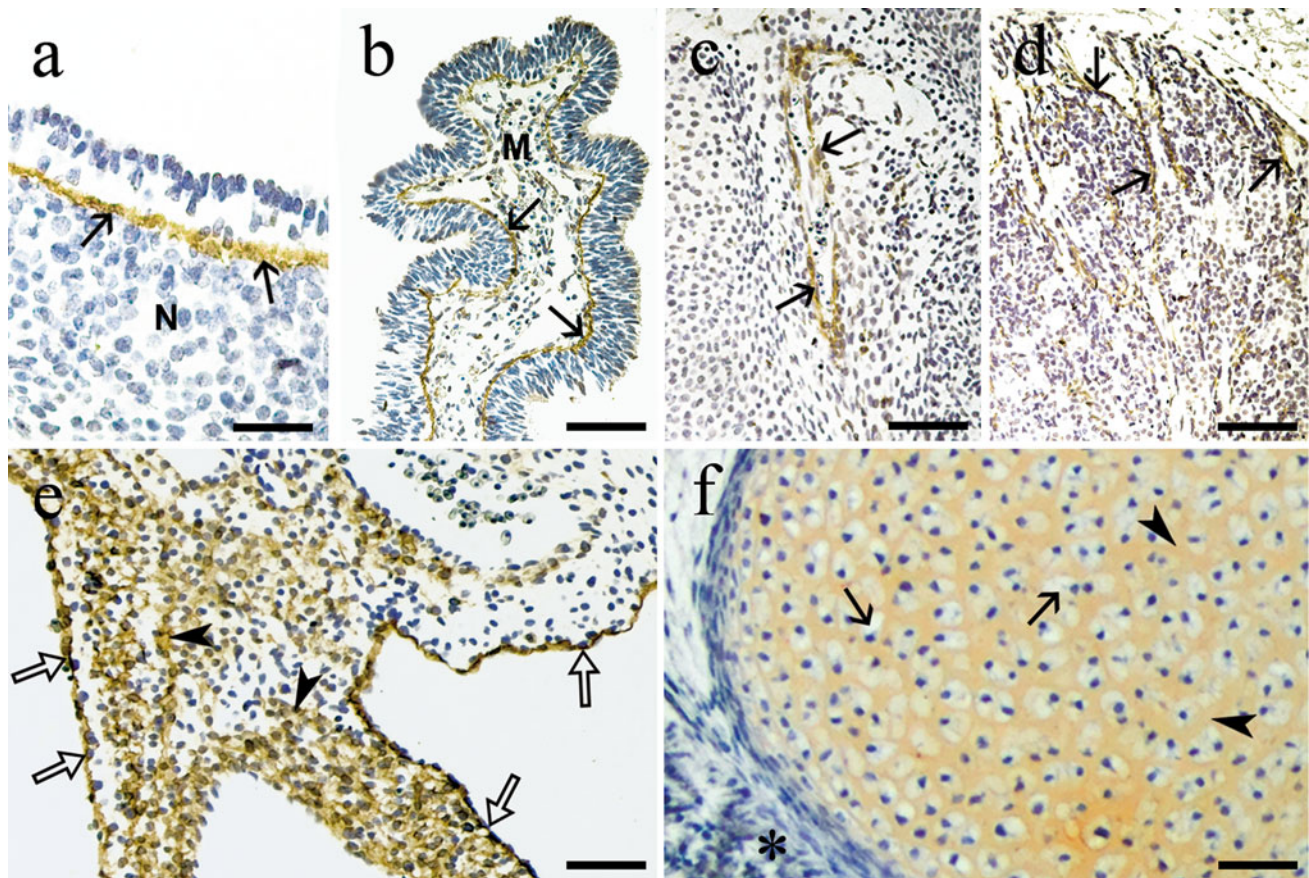


Fig. 2 Localization of the laminin $\beta 2$ chain during gw 8 and 9 in human embryogenesis. **a** BMZs of neuroectoderm (arrows) were positive for immunostaining of the laminin $\beta 2$ chain, whereas neuroectodermal cells (N) showed no staining. **b** BMZs (arrows) of the choroid plexus exhibited staining for the laminin $\beta 2$ chain, whereas mesenchymal cells (M) showed only weak staining. **c** Localization of the laminin $\beta 2$ chain in the BMZ of a capillary of neuronal tissue (arrows). **d** Immunostaining for the laminin $\beta 2$ chain

in the endoneurium of spinal ganglia (arrows). **e** The laminin $\beta 2$ chain in the ECM of cardiomyocytes (arrowheads) and in BMZs of perian and endocardium (open arrows). **f** The interterritorial matrix (arrowheads) of chondrocytes showed positive staining for the laminin $\beta 2$ chain, whereas the proliferating chondrocytes themselves (arrows) exhibited no staining. Skeletal muscle cells (asterisk) were negative for the laminin $\beta 2$ chain. Bars 15 μm in **a**, **b**, **c**, **d**, **e**, and **f**

Kidney

During kidney development, three renal systems evolve: the pronephros, the mesonephros and the metanephros (Saxen and Sariola 1987). The Bowman's capsule and BMZs of the glomeruli and tubules stained positive for the laminin $\beta 1$ chain at all developmental stages examined, whereas mesenchymal cells exhibited no expression of the laminin $\beta 1$ chain.

Skin

Skin development starts from a separation of the ectodermal and mesodermal compartments. The epidermis derives from the ectoderm, whereas the dermis derives from the mesoderm (Smith and Holbrook 1986). In BMZs of dermal-epidermal junctions and capillaries, the laminin $\beta 1$ chain was expressed from gw 8 onwards, and positive

staining for the laminin $\beta 2$ chain could be shown during gw 11. Cells of the loose mesenchyme were negative for the laminin $\beta 1$ and $\beta 2$ chain staining at all developmental stages examined.

Pancreas

BMZs of the developing exocrine gland were positive for the laminin $\beta 1$ chain from gw 8 onwards. Furthermore, BMZs of glandular capillaries were positive for the laminin $\beta 1$ chain staining, whereas epithelial cells exhibited no staining for the laminin $\beta 1$ chain.

Intestine

The early foregut forms by gw 4. The musculature and connective tissues of the gastro-intestinal tract derive from the surrounding mesenchyme (O'Rahilly and Müller

Table 1 Light microscopic immunostaining for the laminin $\beta 1$ chain in human specimens from gw 8 to 12

Developing organ	Gestational week			
	8/9	10	11	12
Brain				
BMZ of neuroectoderm	+	+	+	∅
Neuroectodermal cells	–	–	–	∅
BMZ of capillaries	+	+	+	∅
BMZ of choroid plexus	+	∅	∅	∅
Mesenchyme of choroid plexus	+	∅	∅	∅
Ganglia				
Neuronal cells	–	∅	∅	–
Endoneurium	+	∅	∅	+
BMZ of capillaries	+	∅	∅	+
Blood vessels				
BMZ of endothelium	+	+	+	+
Liver				
Hepatocytes	–	+	∅	+
BMZ of sinusoids	+	+	∅	+
BMZ of mesothelium	–	∅	∅	–
Kidney				
BMZ of glomeruli	+	∅	+	+
BMZ of tubules	+	∅	+	+
Bowman’s capsule	+	∅	+	+
Mesenchyme	–	∅	–	–
Skin				
Epidermis	–	–	–	–
Dermal-epidermal BMZ	+	+	+	+
Dermis	–	–	–	–
BMZ of capillaries	+	+	+	+
Mesenchyme	–	–	–	–
Pancreas				
Glands	–	–	–	–
BMZ of glands	+	+	+	+
BMZ of capillaries	+	+	+	+
Intestine				
Epithelium	–	–	–	–
BMZ of epithelium	+	+	+	+
Mesenchyme	+	+	+	+
BMZ of capillaries	+	+	+	+
Heart				
Cardiomyocytes	–	∅	–	–
ECM of cardiomyocytes	+	∅	+	+
BMZ of endo-/pericardium	+	∅	+	+
BMZ of capillaries	+	∅	+	+
Skeletal system				
Cartilage	–	+	+	+
Bone	∅	∅	+	∅
BMZ of skeletal muscle cells	∅	+	+	+

(+) positive reaction; (–) negative reaction; ∅ tissues not available

Table 2 Light microscopic immunostaining for the laminin $\beta 2$ chain in human specimens from gw 8 to 11 (tissues of other gestational weeks were not available)

Developing organ	Gestational week	
	8/9	11
Brain		
BMZ of neuroectoderm	+	∅
Neuroectodermal cells	–	∅
BMZ of capillaries	+	∅
BMZ of choroid plexus	+	∅
Mesenchyme of choroid plexus	+	∅
Ganglia		
Neuronal cells	–	∅
Endoneurium	+	∅
BMZ of capillaries	+	∅
Skin		
Epidermis	∅	–
Dermal-epidermal BMZ	∅	+
Dermis	∅	–
BMZ of capillaries	∅	+
Mesenchyme	∅	–
Heart		
Cardiomyocytes	–	∅
ECM of cardiomyocytes	+	∅
BMZ of endo-/pericardium	+	∅
BMZ of capillaries	+	∅
Skeletal system		
Cartilage	+	∅
Bone	∅	∅
BMZ of skeletal muscle cells	–	∅

(+) positive reaction; (–) negative reaction; ∅ tissues not available

1996). In the developing intestine, the laminin $\beta 1$ chain was detected in BMZs of capillaries and in the mesenchyme from gw 8 onwards. The laminin $\beta 1$ chain was absent in epithelial cells of the intestine at all stages investigated.

Heart

The early heart anlage consists of two compartments separated from each other by the cell-free, homogeneous cardiac jelly (CJ): the endocardial tube and the developing myocardial layer, both already present at gw 4. The CJ also surrounds individual myocytes (Wenink 1976). The laminin $\beta 1$ chain was first detected at gw 8 in BMZs of the endo- and the pericardium, as well as BMZs of capillaries, and was present until gw 12. Developing cardiomyocytes were negative for the laminin $\beta 1$ chain

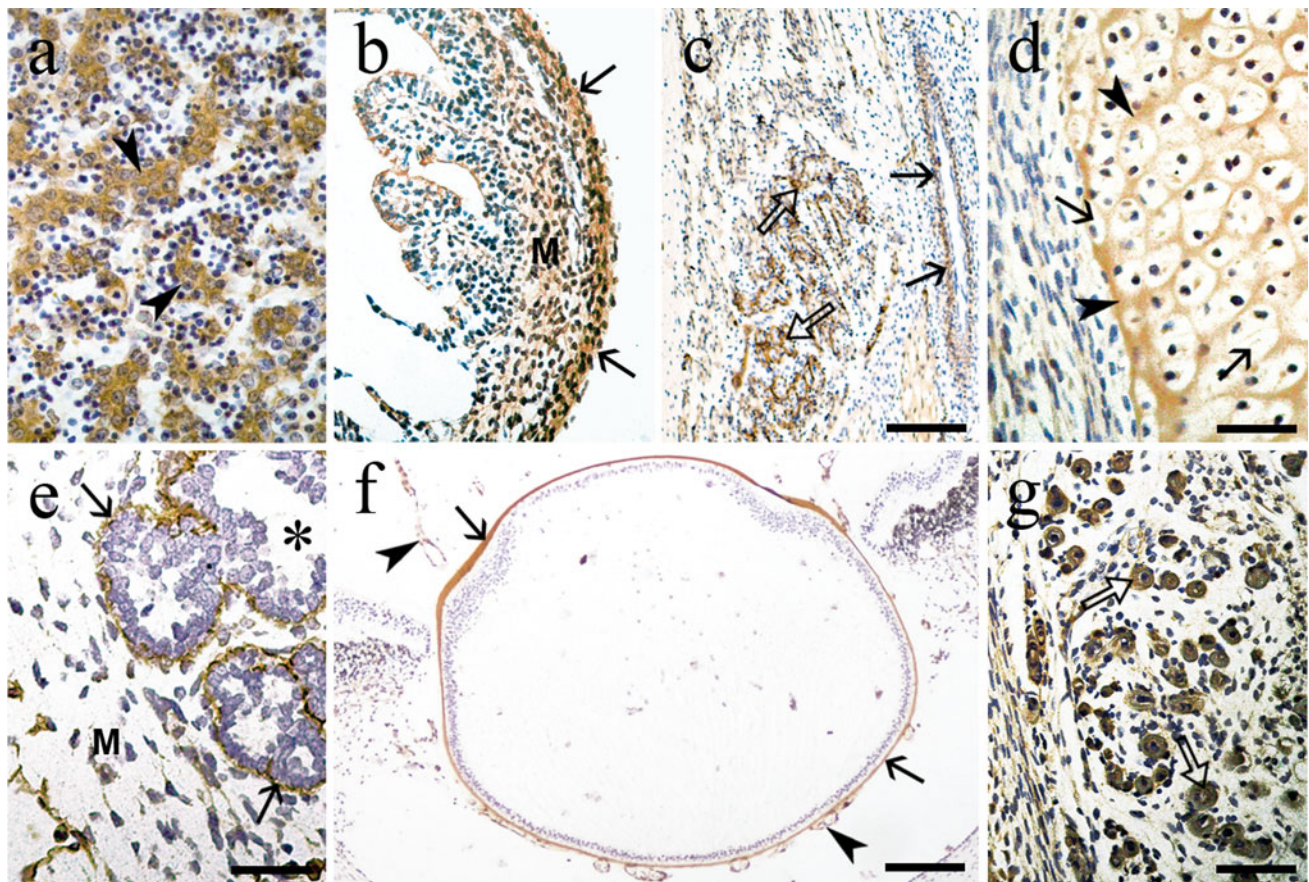


Fig. 3 Localization of the laminin $\beta 1$ chain in various organs during human embryogenesis. **a** At gw 10, hepatocytes of developing liver revealed distinct staining for the laminin $\beta 1$ chain (arrowheads). **b** The laminin $\beta 1$ chain was detected in mesenchymal cells (*M*, arrows) of the intestine at gw 12. **c** Positive staining for the laminin $\beta 1$ chain was seen in BMZs of skeletal muscle cells (open arrows) and in BMZs of capillaries (arrows) at gw 12. **d** Staining for the laminin $\beta 1$ chain in the pericellular and interterritorial matrix (arrowheads) of rib cartilage anlagen at gw 12. Chondrocytes (arrows) revealed no specific staining

for the laminin $\beta 1$ chain. **e** At gw 8, BMZs of glands of the developing pancreas exhibited positive staining for the laminin $\beta 1$ chain (arrows). The pancreatic gland itself (asterisk), and mesenchymal cells (*M*), were negative for the laminin $\beta 1$ chain. **f** Detection of the laminin $\beta 1$ chain in the lens capsule of the eye (arrows) and BMZs of capillaries (arrowheads). **g** BMZs of transversal sections of skeletal muscle cells showed positive staining for the laminin $\beta 1$ chain (open arrows). Bars 15 μm in **a**, **b**, **d**, **e**, and **g**; 60 μm in **c** and **f**

staining, but the ECM of the cardiomyocytes revealed positive staining.

Additionally, the expression of the laminin $\beta 2$ chain during gw 8 and 9 had a similar pattern as the distribution of the laminin $\beta 1$ chain during the same period.

Skeletal system

The laminin $\beta 1$ chain is present in developing bone. In cartilage, we found the laminin $\beta 1$ chain from gw 10 onwards, whereas the detection of the laminin $\beta 2$ chain was limited to gw 8 and 9, another difference between the embryonic distribution of these two laminin chains. BMZs of the skeletal muscle cells were positive for staining of the laminin $\beta 1$ chain from gw 10 to 12, whereas the laminin $\beta 2$ chain was not detected.

Eye

The laminin $\beta 1$ chain was detected in the lens capsule of the developing eye from gw 10 to 12. The laminin $\beta 2$ chain was only detected in the lens capsule during gw 10.

Discussion

Laminin is the first extracellular matrix protein to appear during embryonic development, first detectable in the 16-cell (morula) embryo (Leivo et al. 1980). From the blastocyst stage onwards, laminin or its subunits are required for development, maintenance of cellular polarity and compaction of the cells (Timpl et al. 1983; Smyth et al. 1999).

An overview of mRNA-expression of the laminin $\beta 1$ and $\beta 2$ chains in various developing fetal organs (gw 17–19) has been provided by Iivanainen et al. (1995). In organs like the eye, choroid plexus, kidney, pancreas and skin, both chains showed similar expression patterns. We identified the laminin $\beta 1$ and $\beta 2$ chain proteins in the endocardium of the heart and in the choroid plexus. Additionally, laminin $\beta 1$ chain mRNA was detected in the dermis of the skin and endothelial cells of blood vessels (Iivanainen et al. 1995). We found that BMZs of these tissues contain the laminin $\beta 1$ chain protein. These findings support the idea that the structural components of the subepithelial basement membrane are produced both by the epithelial cells and by stromal fibroblasts of the upper dermis (Iivanainen et al. 1995).

Localization of laminin $\beta 1$ chain mRNA to the glomeruli of the kidney could not be demonstrated, but we found positive staining for the protein in the relevant BMZs. Miner (1998) highlighted the important role of the laminin chains $\beta 1$ and $\beta 2$ during the development of the kidney. In the maturing glomeruli of wild type mice, the laminin $\beta 2$ chain is gradually replaced by the laminin $\beta 1$ (Noakes et al. 1995). This is in agreement with our results, which show the presence of the laminin $\beta 1$ chain in BMZs of glomeruli and tubuli in the developing kidney from gw 8 to 12 during human development.

We found the laminin $\beta 1$ chain in the lens capsule of the eye between gw 10 and 12, and the laminin $\beta 2$ chain at gw 10, as did Byström et al. (2006) up to gw 20. Furthermore, another study demonstrated that laminin $\beta 1$ is essential for BM integrity in the zebrafish eye (Lee and Gross 2007).

We have previously shown that perlecan is present during embryonic and fetal human development in BMZs of blood vessels and capillaries in various organs (Roediger et al. 2009). Now, we present evidence for a similar localization of the laminin $\beta 1$ chain from embryonic gw 8 onwards in BMZs of endothelial cells of blood vessels. The laminin $\beta 1$ chain has been described in human smooth muscle cells of fetal developing vasculature and intestine up to gw 22. Based on these results, an important role for laminins in the maintenance of differentiated smooth muscle cells has been postulated (Glukhova et al. 1993). Additionally, we found positive staining for the laminin $\beta 1$ chain in BMZs of capillaries and in the mesenchyme from gw 8 to 12, demonstrating the presence of this protein in the developing embryonic and fetal gut. Another study showed the omnipresent localization of the laminin $\beta 1$ chain in all BMZs of human adult gastric mucosa (Virtanen et al. 1995b).

In skeletal muscle cells, we found the laminin $\beta 1$ chain in BMZs between gw 10 and 12, whereas the presence of the laminin $\beta 2$ chain could not be shown before gw 15 (Wewer et al. 1997). This indicates that the laminin $\beta 2$

chain is only present in later stages of skeletal muscle development.

Previous studies demonstrated the involvement of laminin fragments in the development of cartilage. In human fetal cartilage (gw 17 and 24), a strong pericellular immunohistochemical reaction for laminin-111 was shown (Dürr et al. 1996). In embryo chick sternum and mouse limb bud, laminin $\beta 1$ and $\beta 2$ chains are present in the cytoplasm of chondrocytes (Lee et al. 1997). We found laminin $\beta 1$ present in cartilage from gw 10 onwards, but not during gw 8 and 9. This suggests that the laminin $\beta 1$ chain does not play a role in human cartilage development until the fetal stage. According to the results of our study, the laminin $\beta 2$ chain could only be detected during gw 8 and 9, indicating a laminin β switch in which laminin $\beta 2$ is eventually replaced by laminin $\beta 1$ during cartilage development, as has been demonstrated in the glomeruli of the kidney (Noakes et al. 1995).

In our current work, laminin $\beta 1$ and $\beta 2$ chains were detected in various neuronal tissues. The first laminin subunits detectable within the human nervous system are $\beta 1$ and $\beta 2$ chains, present in BMZs of Schwann cells at gw 11, and in the perineurium at gw 17 (Jaakola et al. 1993). Based on a study of the development of the rat central nervous system, it has been postulated that laminin $\beta 1$ has an influence on rat nervous system development (Hunter et al. 1992).

Taken together, our data demonstrate the ubiquitous presence of the laminin $\beta 1$ chain during human embryonic and fetal development from gw 8 to 12. The laminin $\beta 2$ chain was not as widely distributed during these developmental stages. In some organs, such as kidney or cartilage, a chain switch from the laminin $\beta 2$ chain to the $\beta 1$ chain seems to be a common developmental pattern.

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