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# Gene Section
## Review

# COL16A1 (collagen, type XVI, alpha 1)

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## Identity

**Other names:** 447AA

**HGNC (Hugo):** COL16A1

**Location:** 1p35.2

## DNA/RNA

### Description

In 1992 the cDNA sequence of COL16A1 has been discovered in a screening for collagen-like sequences in cDNA banks of a human fibroblast cell line and human placenta tissue.
Two laboratories published independently the human COL16A1 cDNA sequence (Pan et al., 1992; Yamaguchi et al., 1992).
The coding sequence of authentic collagen type XVI comprises of 1604 amino acids including a 21 amino acid signal peptide, whereas the recombinant version of collagen type XVI contains 1597 amino acids (Kassner et al., 2004).
The nucleotide sequences published by Pan et al. and Yamaguchi et al. were completed by Kassner et al. with respect to a missing codon for one amino acid (Kassner et al., 2004).
Two predicted imperfections in the collagenous region could not be confirmed (unpublished data).

### Transcription

The cDNA of 5,4 kb comprises a 4809 bp coding sequence, framed by non-translated parts, including a 425 bp 3'-non-coding sequence which contains polyadenylating signals. COL16A1 has been localized to chromosome 1, 1p35-p34 (Pan et al., 1992).
No splice variants have been described up to now. COL16A1 gene expression and transcription varies in various phases of cell growth in cultured skin fibroblasts.
Gene expression was increased in stationary phases (G0/G1) of cell growth when cell proliferation was inhibited by serum deprivation or suspension arrest (Tajima et al., 2000).
Transcription activity of the COL16A1 gene appears to be mechanosensitive. It is downregulated in HCS2/8 human chondrosarcoma cells after application of continuous hydrostatic pressure (Sironen et al., 2002).
Recently, COL16A1 is described to act as a Smad-signalling specific target gene for BMP-4/BMP-6 in hepatocellular carcinoma (Maegdefrau and Bosserhoff, 2012).

### Pseudogene

No pseudogenes are described up to now.

## Protein

### Description

Collagen type XVI, by structural analogy a member of the FACIT - (fibril-associated collagens with interrupted triple helices) family of collagens, contains 10 collagenous (COL) domains interspersed with 11 non-collagenous (NC) regions (figure 1A-C).

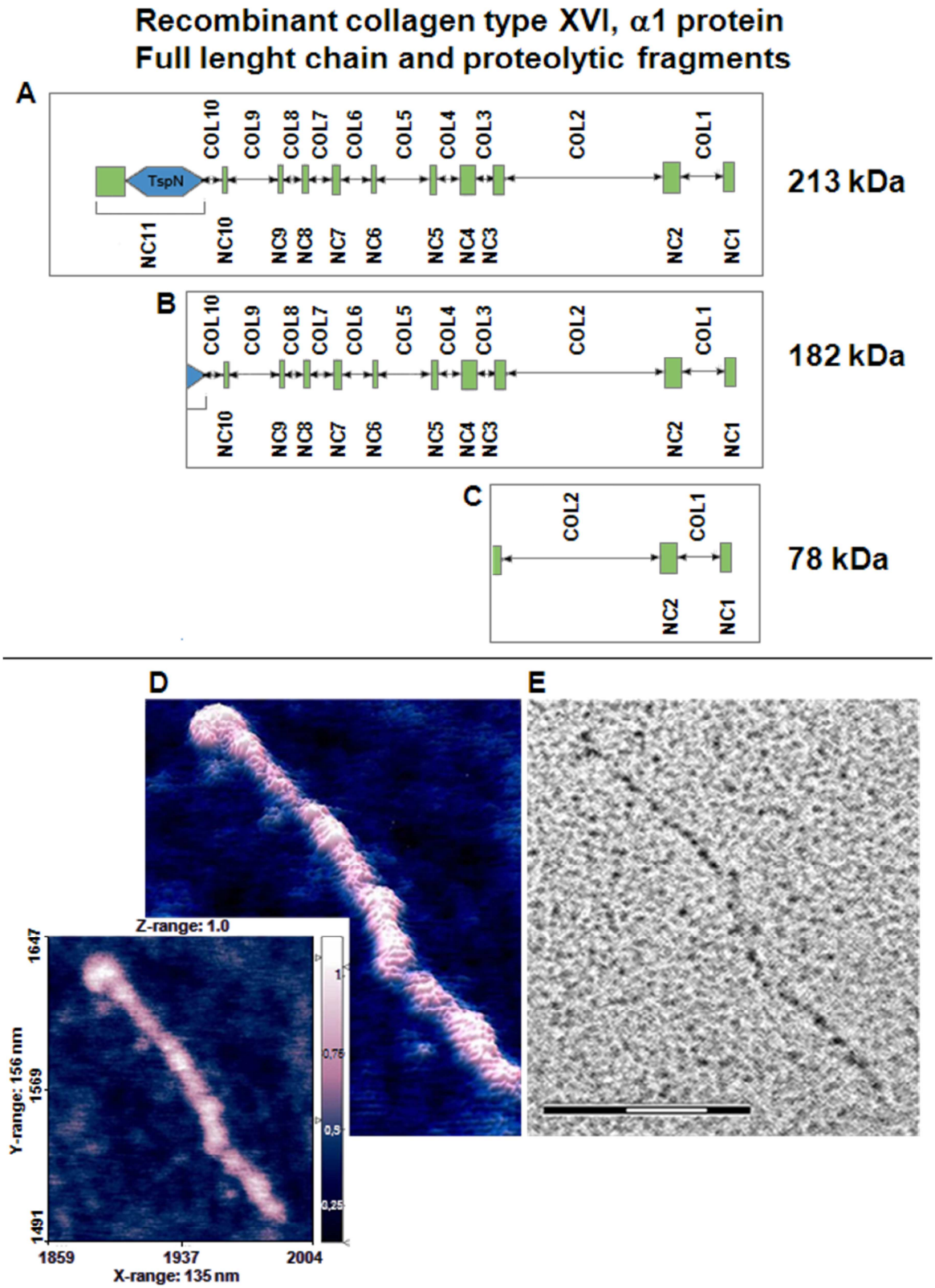


**Figure 1. Collagen type XVI, domain and molecular structure.** Collagen type XVI affinity-purified from culture medium of over expressing HEK 293 EBNA cells elutes in full-length chains and proteolytically processed fragments with following molecular weight as (213 kDa) (A), (182 kDa) (B) and (78 kDa) (C). One alpha 1 chain of intact collagen XVI consists of 10 collagenous domains (COL1-COL10) and 11 non-collagenous domains (NC1-NC11). Atomic Force Microscopy (AFM) of affinity-purified recombinant full-length collagen type XVI trimers allows measurement of molecular size (D). Rotary shadowed TEM image of purified recombinant full-length collagen type XVI trimers corroborates the AFM data (E). Length of intact collagen XVI comes to about 240 nm. COL= collagenous domains, NC= non-collagenous domains.

It is a homotrimeric molecule of about 210 kDa for each native α1 chain. 32 cysteine residues, which are almost all located in the non-collagenous domains at the junction to the preceding collagenous regions, contribute to a high thermal stability of the homotrimer in form of disulfide bonds (Pan et al., 1992; Yamaguchi et al., 1992). The prominent non-collagenous NC11 domain consists mainly of a 200-residue motif referred to as proline-arginine-rich protein (PARP) in several other collagen types or as tsp-1 in thrombospondin (figure 1A). It has been recombinantly expressed and used for generation of specific anti-NC11 antibodies (Tillet et al., 1995). 24% of the total number of proline residues and 48% of the total number of lysine residues were hydroxylated in recombinant collagen type XVI.

Because only lysine and proline in the Y position of X-Y-Gly amino acid triplets and additionally some lysine residues in the Y position of X-Y-Ser and X-Y-Ala in collagens are subject to hydroxylation, the amino acid sequence of authentic human collagen type XVI would imply that 54% of the available prolines and a maximum of 92% of the available lysines could potentially be hydroxylated in recombinant collagen type XVI.

Two of the three potential N-glycosylation sites reside in the N-terminal NC11 region and are glycosylated.

The third has been assigned to the NC1 domain whereas here, no evidence has been found for the attachment of a glycosaminoglycan chain (Kassner et al., 2004).

Atomic force images of individual trimeric molecules exhibited a total length of 168 ± 3 nm including the N-terminal NC11 globular domains and the flexible threadlike tail comprising all collagenous regions plus the remaining non-collagenous domains.

The height of the NC11 domain constituted 0,94 ± 0.06 nm and the radius at half height ($r_{0.5h}$) was calculated as 9,48 ± 0,47 nm. The threadlike section of the remaining molecule C-terminal of the NC11 domain appeared to be a thin flat structure with a height between 0,5 and 0,7 nm.

Notably, at a distance of 94.8 ± 4.6 nm from the NC11 terminus the molecular measurements increased either in height or diameter.

The extension of this section contributed with 73,1 ± 1,6 nm to the total length of the protein (figure 1D).

Rotary shadowing images of purified recombinant collagen type XVI exhibited extended rod-like molecules with a globular domain at one end, probably constituting the large N-terminal NC11 domain (figure 1E).

The shape of the molecules revealed highly flexible regions, in some molecules even two or more kinks. The length of the molecules varied between 100-240 nm, with the majority being close to 150 nm.

The N-terminal half of human fibrillin-1/-2 binds dose-dependent to collagen type XVI at low salt concentrations of 50-100 mM NaCl, while interaction between collagen type XVI and the C-terminal half of fibrillin-1/-2 under these conditions were considerably lower.

These results indicate that monomeric fibrillin-1/-2 can interact with collagen type XVI with low affinity. Both, fibrillin-1 and fibrillin-2 did not interact with the recombinant NC11 domain. Soluble recombinant fibronectin interacted strongly with collagen type XVI at 150 mM NaCl with half maximal binding at ~12 µg/ml (~55 nM fibronectin), indicating that fibronectin can bind to collagen XVI with high affinity (Kassner et al., 2004).

Collagen XVI co-localizes with α2 integrin at the dermal epidermal junction (DEJ) (figure 2 A-C) and with α1 integrin and around fat cells in subdermal layers (figure 2 D-F). Cells bearing the integrins α1β1 and α2β1 attach and spread on recombinant collagen type XVI. Collagen type XVI induces the recruitment of these integrins into focal adhesion plaques, a principal step in integrin signaling. In cell-free binding assays, collagen type XVI is more avidly bound by α1β1 integrin than by α2β1 integrin. Both integrins interact with collagen type XVI via the A-domain of their α-subunits. A tryptic collagen type XVI fragment comprising the collagenous domains 1-3 is recognized by α1β1 integrin. Electron microscopy of complexes of α1β1 integrin with this tryptic collagen XVI fragment or with full-length collagen type XVI revealed a unique α1β1 integrin binding site within collagen type XVI located in the COL 1-3 domains (Eble et al., 2006).

## Expression

Collagen type XVI is expressed in various cells and tissues. It is synthezised by dermal fibroblasts, smooth muscle cells (Grässel et al., 1996), dermal dendrocytes and dendritic cells in the skin (Akagi et al., 2002), articular and costal chondrocytes (Kassner et al., 2003), endometrial stromal cells (Tierney et al., 2003), basal dermal and oral keratinocytes (Grässel et al., 1999), bone marrow derived mesenchymal stem cells (Grässel et al., 2009), neurons from the dorsal root ganglion (Hubert et al., 2007), glioblastoma/astrocytoma cells (Senner et al., 2008) and intestinal myofibroblasts (Ratzinger et al., 2010).

Collagen type XVI is further expressed in the limbal stem/progenitor niche which comprises clusters of cells in the basal epithelium.

There it is associated with the corneal-limbal transition zone (Schlötzer-Schrehardt et al., 2007).

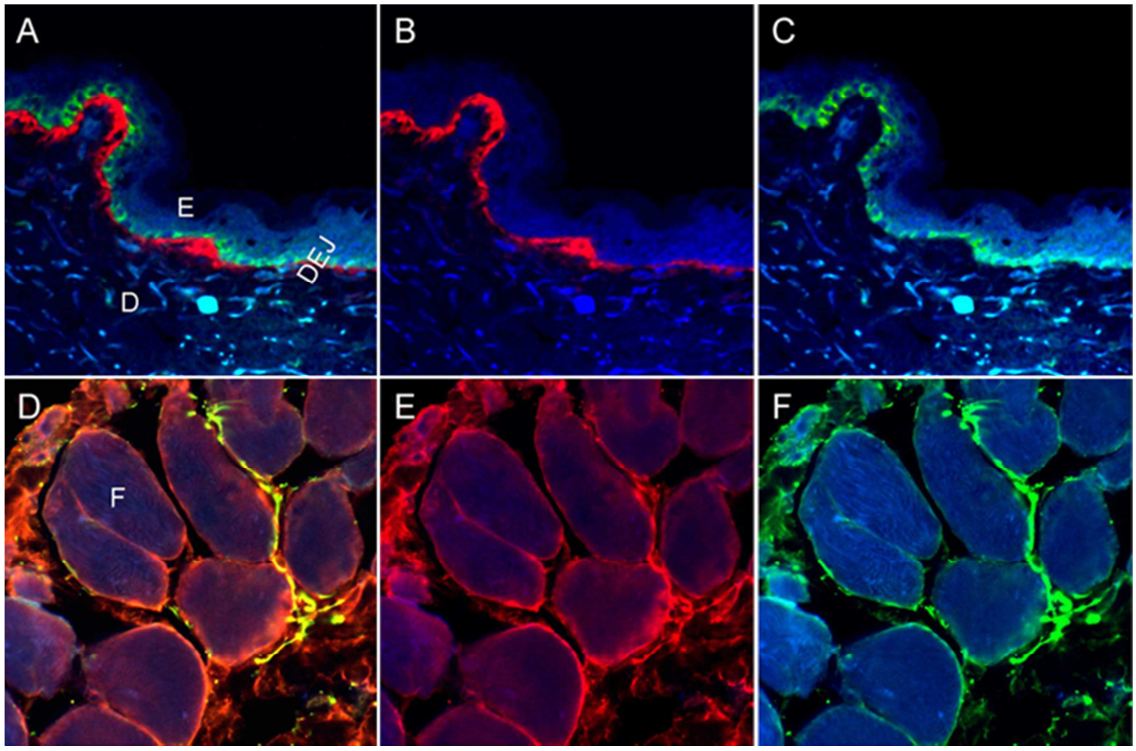


**Figure 2. Distribution of collagen XVI and integrins α1β1 and α2β1 in adult murine skin.** Cryosections from murine skin were stained with purified anti-collagen XVI-antibodies (red fluorescence, A, B, D, E), and with mAb JA221 directed against the integrin α2 subunit (green fluorescence, A, C) and with mAb AGF-1 directed against the integrin α1 subunit (green fluorescence, D, F), Panels A and D show combined staining for collagen XVI and the integrin subunits. The same sections are shown either in panel B, E stained for collagen XVI together with DAPI, or in panel C, F stained for integrin subunits and DAPI. E= epidermis, F= fatty tissue, D= dermis, DEJ= dermal epidermal junction zone. All pictures were taken at 400 x magnification.

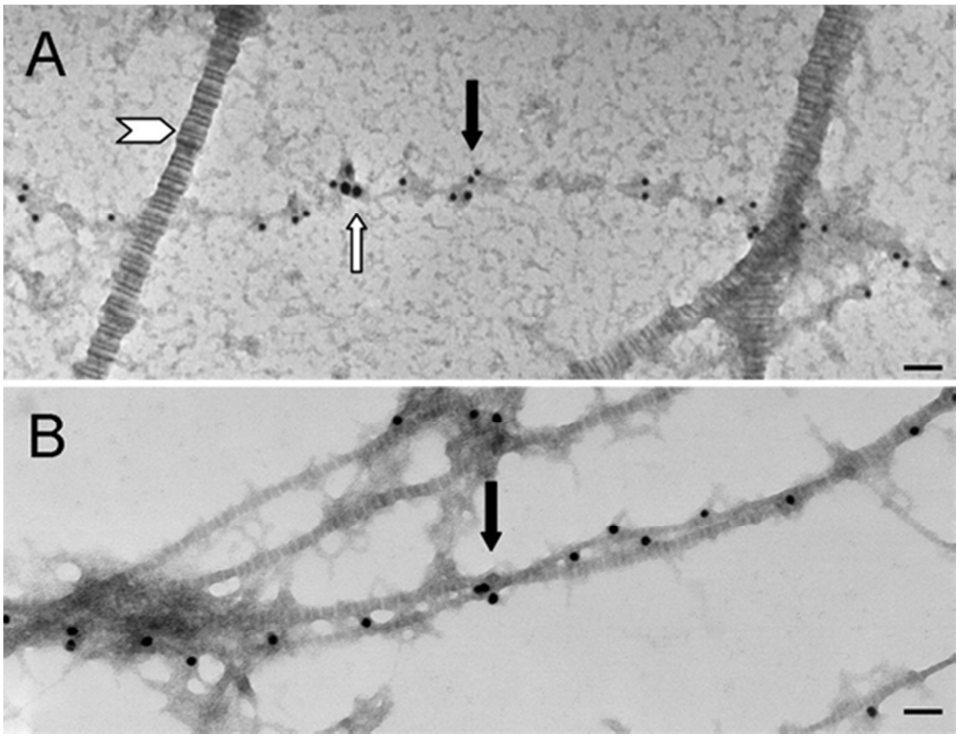


**Figure 3. Ultrastructural localization of collagen XVI in fibrillar extracts from skin and cartilage by immunogold electron microscopy.** Double labeling of collagen XVI (18 nm gold particles, light arrow) and fibrillin-1 (12 nm gold particles, dark arrow) demonstrate co-localization on "bead on the string" microfibrils with collagen XVI bound at one distinct bead of the microfibrils. The large D-periodically banded collagen I fibrils lack collagen XVI labeling (light arrowhead). Bar= 0,12 µm. (A). In cartilage a special subpopulation of thin D-periodically banded cartilage fibrils were labeled with collagen XVI (black arrow, 18 nm gold particles), other fibril populations lack collagen XVI association, Bar= 0,09 µm. (B).

During early mouse development, collagen type XVI occurs in many tissues and is co-distributed with the major fibrillar collagens. In particular, it is strongly expressed in differentiating chondrocytes and dermal fibroblasts, smooth muscle cells of the heart and dorsal root neural fibers, whereas in adult mice no signal appears in brain tissue. Additional expression is found in the cortical areas of the kidney and ovaries (Lai and Chu, 1996). In adults it is found in skin, cartilage, gastrointestinal tract and glioma tissues.

### Localisation

Extracellular matrix of tissues. For skin and cartilage tissue its suprastructure is known. It is associated to the fibrillin containing microfibrillar apparatus in the dermal-epidermal junction zone in skin and to collagen II containing D-banded cartilage fibrils in costal cartilage (Grässel et al., 1999; Kassner et al., 2003). It is depositred pericellular around fibroblasts and smooth muscle cells (Grässel et al., 1996) and in the territorial region of chondrocytes (Kassner et al., 2003).

### Function

Morphogenesis and assembly of distinct suprastructures in different tissues, i.e. microfibrillar apparatus in the dermis and fibrillar networks in various connective tissues (figure 3A, B). Presumably, it is an adaptor protein such as collagen type IX and connects and organizes large fibrillar networks and thus regulates integrity and stability of ECM (Eble et al., 2006; Grässel et al., 1999; Kassner et al., 2003). It is a substrate for adhesion and invasion of tumor cells, i.e. glioblastomas (Senner et al., 2008) and regeneration of connective tissues after neural injury (Hubert et al., 2007). In addition, it induces invasiveness of glioblastoma by altering the cell-matrix interaction (Bauer et al., 2011) and proliferative activity of oral squamous cell carcinoma by altering the cell cycle activity of the tumor cells (Ratzinger et al., 2011). Notably, COL16A1 is a Smad-signalling specific target gene for BMP-4/-6 in hepatocellular carcinoma where these BMPs are involved in the process of carcinogenesis (Maegdefrau and Bosserhoff, 2012).

### Homology

Based on conserved structural features with other FACIT-collagens, namely: collagens type IX, type XII, type XIV, type XIX, type XX, type XXI and type XXII.
These structural features are:
1. The presence of two highly conserved cysteine residues separated by four amino acids at the NC1-junctions and the existence of two G-X-Y triplet imperfections within the COL2 domain.
2. A succession of triple-helical domains connected by short non-collagenous domains and the presence of a large N-terminal domain that always exhibits a TSPN subdomain next to the collagenous domain. 3. Besides from these common criteria, the FACITs display remarkable divergence in the size and composition of their N-terminal domains and in the number of their collagenous domains (Ricard-Blum and Ruggiero, 2005).

## Mutations

**Note**
There are no reports about mutations in the COL16A1 gene published as yet.

### Germinal

None yet described.

### Somatic

None yet described.

## Implicated in

### Glioblastoma tumorigenesis

**Note**
The progression of glioblastoma growth is characterized by diffuse invasion of tumor cells into the brain tissue. COL16A1 was upregulated on mRNA level in glioblastoma tissues compared to normal cortex (figure 4). Collagen type XVI protein was detected in glioblastoma tissue and was secreted by glioblastoma cell lines. A siRNA mediated knockdown of collagen type XVI resulted in decreased cell adhesion of glioblastoma cell lines whereas adhesion was augmented on culture surfaces coated with recombinant collagen type XVI. However, the migration potential of glioblastoma cells on collagen type XVI remained unaffected. Collagen type XVI appears to play a supportive role for tumour specific remodelling of extracellular matrix indicated through de novo expression by glioblastoma cells (Senner et al., 2008).
Novel data suggest that in glioblastoma tissue collagen XVI may impair the cell-cell interaction in favour of enhancement of invasion.
The modification of the β1-integrin activation pattern through collagen XVI might be a molecular mechanism to further augment the invasive phenotype of glioma cells (Bauer et al., 2011).

**Disease**
Gliomas are the most frequent intrinsic brain tumors and comprise astrocytic gliomas (grades II, III, IV) including fibrillar astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and glioblastoma (WHO grade IV).
They are characterized by diffuse invasion of tumour cells into the brain parenchyma.
The fatal outcome of this disease results from single-tumour cells that have already invaded distant brain regions at the time of diagnosis.

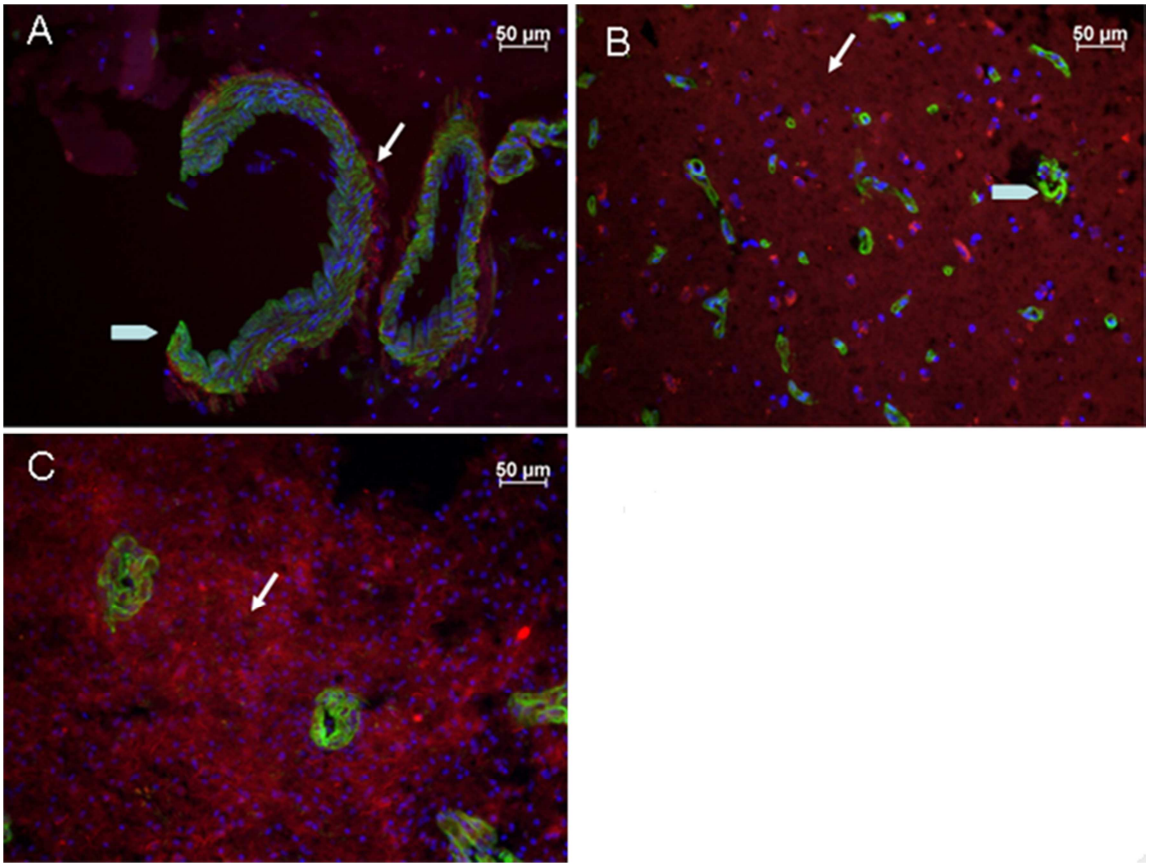


**Figure 4. Immunohistochemical staining of collagen type XVI and collagen type IV in brain sections.** Immunofluorescence staining on cryo-sections for collagen XVI (red, white arrows) and collagen IV (green, light blue arrow heads) reveals an expression of collagen XVI around blood vessels, however not in the parenchyma of normal brain (A), whereas in glioblastoma (B) and pilocystic astrocytoma (C) collagen XVI is highly expressed throughout the tumour tissue.

Glioblastoma behave highly invasive which cause the high morbidity and mortality rates of these tumours (Claes et al., 2007; Louis et al., 2007).

**Prognosis**

The 5-year survival rate of glioblastoma (WHO grade IV) is 3%.

## *Oral squamous cell carcinoma tumorigenesis*

**Note**

There is still a lack of reliable prognostic tools for oral squamous cell carcinoma (OSCC).

Initial, early stages of the tumor are hard to identify. COL16A1 expression is upregulated in dysplastic stages of OSCC compared to normal oral epithelium where it is restricted to the dermal-epidermal junction (figure 5).

Moreover, in protein lysates from OSCC tissues more collagen type XVI was detected by immunoblotting compared to lysates from normal oral tissue.

Overexpression of collagen type XVI in an OSCC cell line (PCI13) led to an upregulation of kindlin-1 and an increased interaction of kindlin-1 with beta1-integrin.

Beta1-integrin activity was enhanced in collagen type XVI overexpressing OSCC cells and an earlier S-phase and G2/M-phase entry six hours after synchronisation was observed compared to control cells leading to a markedly higher proliferation activity.

Blocking beta1-integrin induced a decrease of the proliferative activity of the collagen XVI overexpressing cells (Ratzinger et al., 2011).

In summary, collagen type XVI overexpression leads to early S-phase entry in OSCC cells due to enhanced interaction of kindlin-1/beta1-integrin and subsequent beta1-integrin activation.

**Disease**

Head and neck cancer is the sixth leading cancer by incidence worldwide (Rousseau and Badoual, 2011) and affects more than 500000 people each year. Oral squamous cell carcinoma represents 95% of all head and neck cancer forms and within the past ten years its incidence has increased more than 50%. Despite multimodal therapies including excision of malignant tissue and a combination of radio- and chemotherapy the 5-year survival rate is still only 53%.

A high rate of patients remains with a poor response to therapy and high frequencies of relapses (Bettendorf et al., 2004). Moreover, frequent lymph node metastasis involving migration and invasion of aberrant cells from the primary neoplasm to distant sites results in poor prognosis (Bray et al., 2002; Parkin et al., 2005).

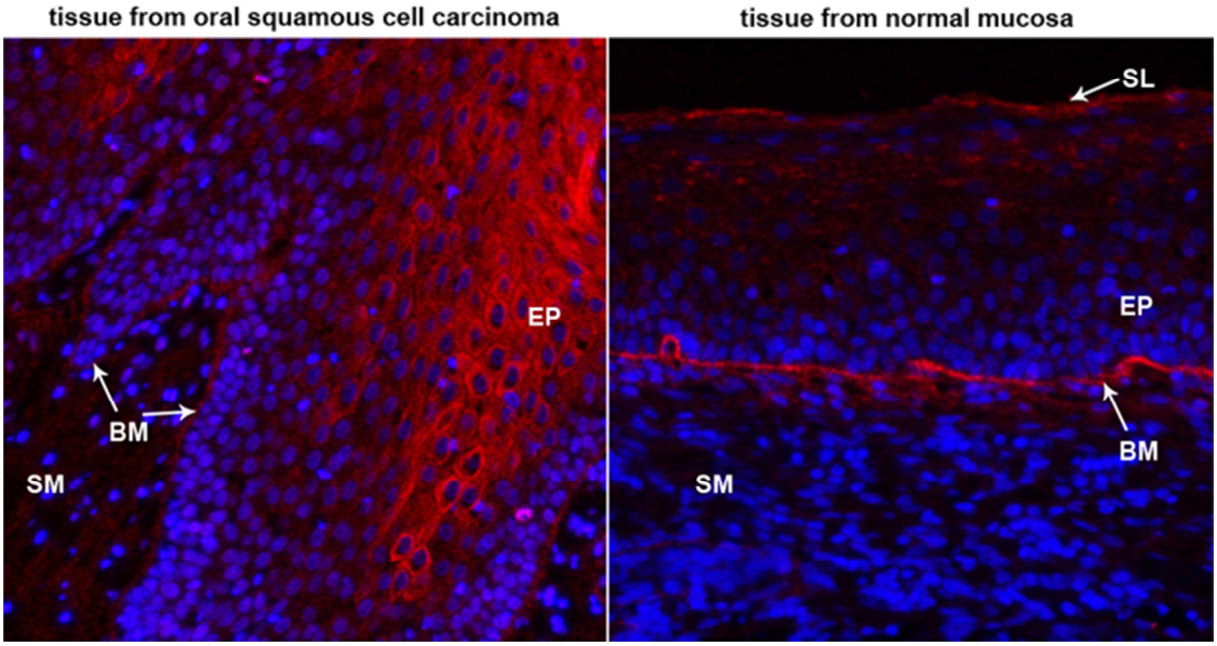


**Figure 5. Immunohistochemical staining of collagen type XVI in dysplastic areas of tissue from oral squamous cell carcinoma.** Immunofluorescence staining on paraffin-sections for collagen type XVI (red) reveals a strong and diffuse expression of collagen type XVI throughout the oral epithelium in contrast to normal oral epithelium where collagen type XVI location is restricted to the dermal-epidermal junction. BM= basal membrane, EP= oral epithelium, SL= surface layer, SM= submucosa.

**Prognosis**

The 5-year survival rate of head and neck squamous cell carcinoma is 40-50%.

## *Crohn's disease*

**Note**

Collagen type XVI is produced by myofibroblasts in the normal intestine and its synthesis is increased in the inflamed bowel wall (figure 6).

Collagen type XVI promotes cell spreading, formation and maturation of focal adhesion contacts. Myofibroblasts develop increased numbers of focal adhesion contacts on collagen type XVI with increased recruitment of α1 integrin into the focal adhesions at the tip of the cells. Focal adhesions on myofibroblasts from inflamed colon tissue also display an increase in length on collagen type XVI compared to collagen type I.

As a result, larger forces can be transmitted which then promote and augment contraction of the ECM and ultimately result in elevated stricture formation. Increased cell spreading on collagen type XVI presumably adds to the maintenance of cells in the inflamed intestinal regions and thus promotes fibrotic responses of the tissue and prolongs further disturbances of the delicate homeostasis between cells and surrounding ECM (Ratzinger et al., 2010).

**Disease**

Crohn's disease is characterized by chronic inflammation of the gastrointestinal tract, accompanied by other systemic abnormalities. Inflammatory lesions progress to intestinal fibrotic processes.

A pathologically overshooting healing response to inflammation-induced disintegration of mucosal tissue leads to excessive tissue repair.

An altered cyto-architecture of the bowel wall with disruption of the muscularis mucosa, thickening of the muscularis propria, and deposition of collagens contributes to the inflammation process (Burke et al., 2007).

Fibrillar and non-fibrillar collagens are up-regulated in CD (type I, II, IV, V, VI) (Graham et al., 1988; Matthes et al., 1992; Pucilowska et al., 2000; Stallmach et al., 1992).

Mesenchymal cells like fibroblasts, myofibroblasts and smooth-muscle cells are the main producers of extracellular matrix components and play an important part in tissue growth and development (Powell et al., 1999; Simon-Assmann et al., 1995).

Myofibroblasts are considered as central player in tissue repair contributing to fibrosis, stricture formation and stenosis by reconstituting a collagen-rich extracellular matrix (ECM) and promoting wound closure by contraction (Pucilowska et al., 2000; Tomasek et al., 2002).

Myofibroblasts motility, their ability to contract wounds and the production of ECM is altered in chronic inflammation.

Normal wound healing would terminate the contractile and synthesizing activity of myofibroblasts by apoptotic reduction of the cell number (Desmoulière et al., 1995).

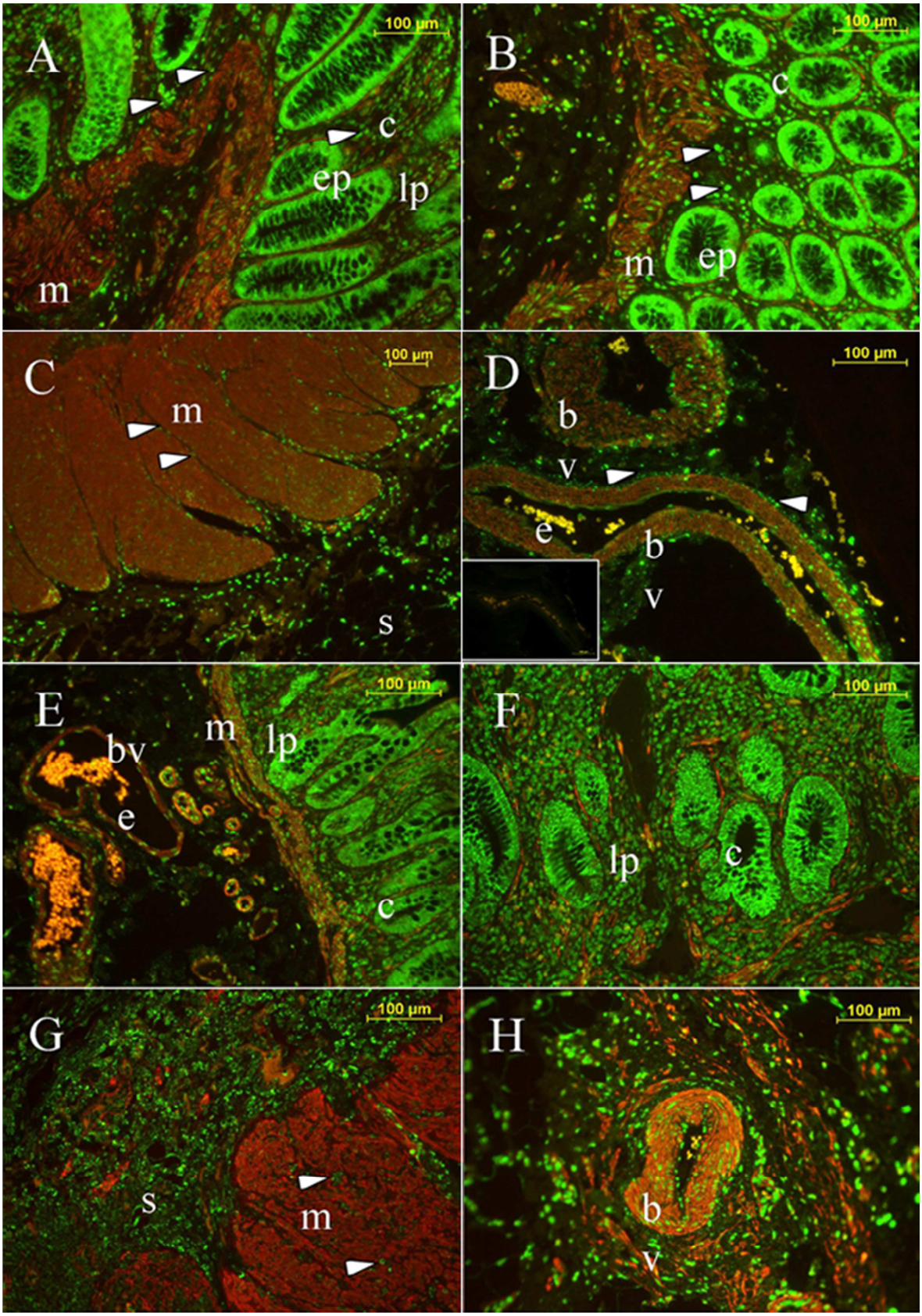


**Figure 6. Morphological distribution of collagen type XVI in healthy and diseased intestine.** Morphological distribution of collagen XVI (green fluorescence) and a-smooth muscle actin (red fluorescence) is demonstrated for the bowel wall of healthy tissue (A-D) and CD tissue (E-H). Arrow heads indicate positive staining for collagen XVI. A negative control is displayed as inlet in D. c: crypts, m: muscle layer, s: submucosa, bv: blood vessel, e: erythrocytes, ep: epithelial cells, lp: lamina propria.

## Neuronal development and regeneration

**Note**

In the nervous system, low collagen type XVI expression was reported in the brain, however, in spinal root fibres high gene expression levels were detected during development (Lai et al., 1996). A SAGE banks analysis showed an induction of Col16a1 gene expression during development and after nerve injury in dorsal root ganglia (DRG) of mice which contain the cell bodies of neurons (Méchaly et al., 2006). Their axons transmit sensory information from the periphery to the central nervous system. During development and regeneration, neurites require extracellular matrix for growth and guidance (Hari et al., 2004), however, the composition of the ECM is yet unknown. In cell culture, satellite cells express collagen type XVI indicating secretion and deposition by neuronal and glia cells. Collagen type XVI participates in final steps of DRG structural and functional maturation. So far, collagen type XVI is the only FACIT collagen, whose expression is regulated by nerve injury, taking presumably part in remodelling events like inflammation, cell proliferation, and neuronal death (Hubert et al., 2007).

## Fibrotic skin diseases

**Note**

In skin, COL16A1 transcripts were detected in cultured dermal fibroblasts and keratinocytes (Pan et al., 1992). Gene expression in fibroblasts varied according to the horizontal layers in skin. Fibroblasts explanted from the upper dermis displayed higher COL16A1 gene expression than those from the middle and lower dermis. In cultured skin fibroblasts an increase of COL16A1 mRNA level was observed in stationary phases of the cell cycle (non-adherent and confluent phases) (Tajima et al., 2000). In localized scleroderma and in systemic scleroderma COL16A1 gene expression was upregulated 2,3 fold and 3,6 fold, respectively, compared with keloid and normal controls (Akagi et al., 1999).

**Disease**

Systemic and localized scleroderma are characterized by systemic and localized deposition of highly overproduced collagens in the skin. This collagen accumulation is a result of overproduction of collagens type I, II, and VI (Graves et al., 1983; Krieg et al., 1985).

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