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# The role of Collagen type VI in fibrosis

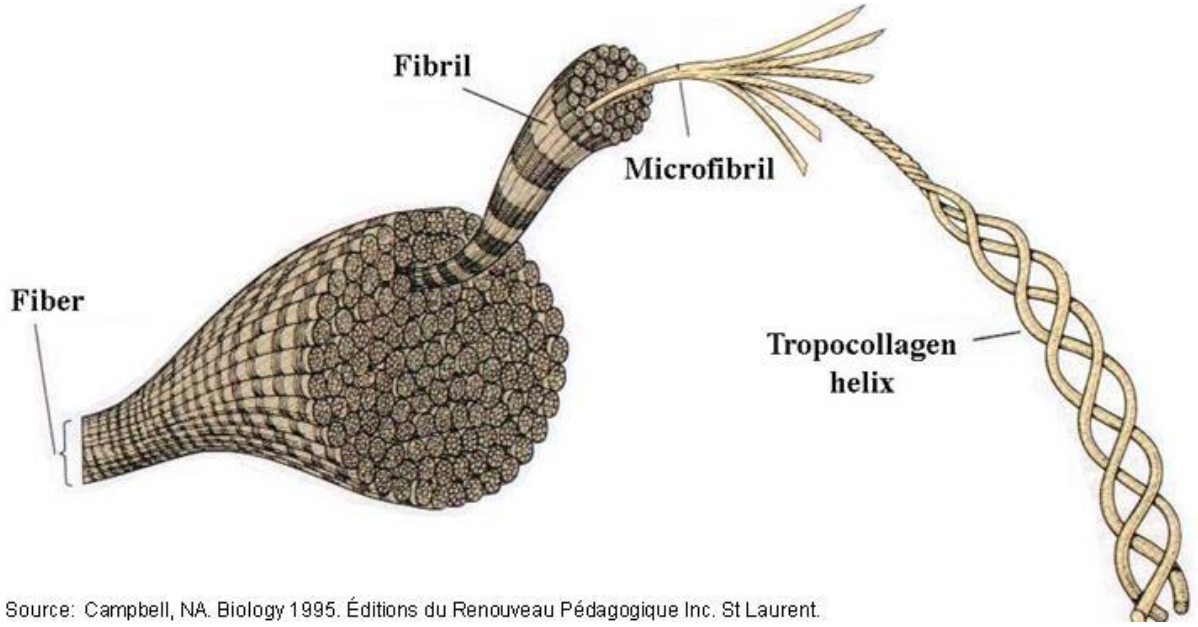


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**Table of contents**

**Abstract**

In this review, collagen type VI structure and function are described and its role in fibrosis. Collagen type VI is an extracellular matrix (ECM) component. This protein forms a microfibrillar network in most connective tissues, where it is mostly found. Type VI collagen is produced mainly by fibroblasts, but also by macrophages. The structure of collagen type VI is complex. Collagen VI consist of three α chains, and recently three novel α chains are added. The assembly of this collagen type is a complex process. The three chains, α1, α2 and α3, form a triple helical monomer followed by assembly into disulfide bonded antiparallel dimers. These dimers align to form tetramers that are also stabilized by the disulfide bonds. In the last step, the tetramers are secreted into the ECM forming long molecular chains, known as microfibrils. The function of type VI collagen is not been identified clearly. Studies have shown that collagen VI interacts with several extracellular matrix proteins. Also is indicated that collagen VI anchors large interstitial structures and it has a critical role in integrity of tissues. Collagen VI is expressed in many tissues especially is the muscles. Mutations of the collagen VI genes cause two myopathies, Bethlem myopathy and Ullrich congenital muscular dystrophy. Collagen type VI has an important role in the remodeling of extra cellular matrix and also in several tissues fibrosis. At present, it is known that collagen VI has a role in liver, lung, cardiac and renal fibrosis. It is showed that collagen type VI can be used as a biomarker for liver fibrosis, a non-invasive method. Future studies are required for determination of the role of collagen VI in fibrosis of other tissues and for understanding the mechanism behind this.

**1. Introduction**

Collagen is one of the most abundant proteins in the human organism. It is a unique triple-helix protein molecule, along with proteoglycan's, laminin, fibronectin, elastin and several cells form the major part of the extra cellular matrix (ECM). The ECM is composed of these elements that ensure the tissue architecture, but have also a pivotal role in the biological functions of several different organs (Divoux & Clement, 2011). Collagen is mainly produced by fibroblasts. Until now, a total of 28 different types of collagen are known (Myllyharju & Kivirikko, 2004) (Veit et al., 2006). These different types differ in structure, tissue distribution and affinity to the other components of ECM. The types I, II, III, IV and V are the most common types in the human body. Type I, III and VI collagens are iso-types that are mostly associated with an organ's fibrotic depots (Divoux & Clement, 2011). Parts of the body that consist largely of collagen are skin, bones, tendons, teeth and cartilage (Jöbsis, 1999). Collagen is responsible for the tensile strength, maintenance of integrity and elasticity of the connective tissue. The main function of collagen consists of forming a connective tissue structure that contains mainly of collagen type I, II and III (Myllyharju & Kivirikko, 2004). Collagen is composed of three polypeptide chains, wound around each other. These polypeptide chains consist of repeats of a pattern Glycine-X-Y (amino acid at the X position and proline at the Y position). The three helixes are connected by disulfide bonds to the hydroxyl groups. These are needed to form a stable and total structure.

After damage at the human body, a reaction is initiated consisting of inflammation, proliferation and wound healing. In all these reactions collagen has an important role (Veit et al., 2006). The key steps in wound healing and regeneration are actively orchestrated by the ECM. During wound healing, the holes in the tissue are filled with collagen produced by fibroblasts. Epithelial tissue may heal by the mechanism of regeneration, mainly by collagen type III, but dermal tissue and wound repair must be obtained by the formation of collagen connective tissue scar (Veit et al., 2006). This scar tissue consist mainly collagen type I, which ensures the tissue will restore and that an acceptable strength and functionality is achieved. Repair of damages tissues is an essential biological process. Restoring of a tissue begins with a regenerative phase, in which cells that are injured are replaced by cells of the same type. If the damage remains, this initial phase is followed with fibrosis accumulation in which connective tissue replaces the normal parenchymal tissue (Divoux & Clement, 2011).

The process of fibrosis is mostly characterized by the modification of both the amount and composition of the components of ECM. In the pancreas, kidney, lung and liver, accumulation of fibrosis destroys cellular processes and seems to damages the organ function (Divoux & Clement, 2011).Collagen type I has an important role in fibrosis, but little is known about the role of collagen VI. Collagen VI filaments are ubiquitous. It is a major structural component of microfibrils that is first isolated in 1976 (Chung, Rhodes, & Miller, 1976). Collagen type VI is present in all connective tissues that consists of collagen type I and III fibers and in cartilage. Studies showed that collagen type VI interacts with several other ECM components (Myllyharju & Kivirikko, 2004). It seems that collagen type VI has a role in the process of fibrosis. But it is not clear what the exact role of collagen type VI is in fibrosis.

In this review the structure and function of collagen type VI will be first described. Thereafter in chapter 3 and 4 the cells producing collagen type VI and tissues that contain collagen type VI will be discussed. Chapter 5 will describe short the myopathies of collagen type VI. Also an overview of monitoring collagen type VI and the role of collagen type VI in fibrosis will be given. In the last chapter the effect of absence of collagen VI in the cardiac will be discussed. The aim of this review is to get insight into the role of collagen type VI in fibrosis.

## 2. Structure and function of collagen type VI

This will describe chapter the structure of collagen type VI. Also the function of type VI collagen that is up to now known will be discussed. Collagen type VI was originally discovered in extracts of pepsin aortic intima (Chung et al., 1976).

### *2.1 Structure*

Collagen type VI is a member of the collagen family that consist more than 20 different types (Jöbsis, 1999). Collagen type VI forms a microfibrillar network in the ECM of all connective tissues, also in skeletal muscle collagen type VI. Collagen type VI consists of three different genetically polypeptide chains, described more than 20 years ago; α1 (VI) encoded by COL6A1, α2 (VI) encoded by COL6A2 and α3(VI) encoded by COL6A3, most probably in the ratio of 1:1:1 (Weil et al., 1988). Collagen chain α1 and α2 are encoded on chromosome 21q and collagen chain α3 on chromosome 2q. The peptide chains consist of non-collagenous and collagenous segments (Engel et al., 1985).The α1, α2, and α3 chains have molecular masses about 140, 140, and 260 kilo Dalton, respectively. Collagen type VI is characterized by a short triple helical region with a large N-terminal and C-terminal globular domains (Baldock, Sherratt, Shuttleworth, & Kielty, 2003). The N-terminal and C-terminal globular domains are greater than 70% of the mass. The N-terminal has a width of about 9.4 nm and a length of 13.9 nm and the C-terminal has a width of about 8nm and a length of 11.8 nm (Baldock et al., 2003). In the short triple helical region every third amino acid is a glycine, Gly-X-Y, enabling the tight bends of the peptides to form an α helix.

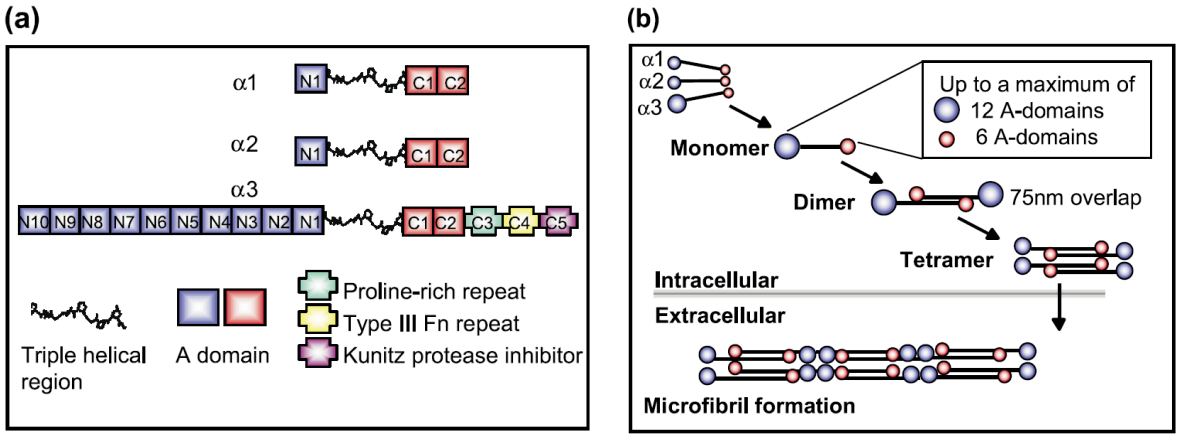


Figure 1. Domain organization and assembly of the three α chains of collagen VI. (a) The organization of domains in the α1, α2 and α3 chains of collagen type VI. Blue and red rectangles represent N and C-terminal von Willebrand Factor A domains, respectively. The green, yellow and purple represent the proline-rich region, Fibronectin type III repeat and Kunitz protease inhibitor domain, respectively. The molecular structure in black is the collagenous region. (b) The assembly of collagen type VI microfibrils of the three α chains. Monomers, dimers and tetramers formation occurs intracellular, while microfibril formation occurs extracellular. (Baldock et al., 2003)

The N-terminal and C-terminal globular domains are composed of several subdomains with homology to the von Willebrand factor A domain (non-collagenous), fibronectin III domain, the Kunitz protease inhibitor domain and other recognized protein motifs. The α1 (VI) and α2 (VI) peptides consist of one N-terminal von Willebrand factor A domain and two C-terminal von Willebrand factor A domains.

The α3 (VI) peptide is larger, it consists of ten N-terminal von Willebrand factor A domain(N10-N1) and two C-terminal von Willebrand factor A domains (Figure 1). In addition, the α3 collagen VI chain has three C-terminal subdomains. These subdomains are not found in the α1 and α2 chains (Lamande, Morgelin, Adams, Selan, & Allen, 2006) . The three C-terminal subdomains are one fibronectin type III domain, one Kunitz type protease inhibitor domain and a unique domain with similarities to salivary gland proteins (Myllyharju & Kivirikko, 2004). So, the α1 and α2 collagen type VI chains are the smallest and the α3 chain is the largest.

However, the assembly of collagen type VI is a complex process, some main details have been described (Chu et al., 1987). Unlike the other collagens, collagen type VI undergoes intracellular polymerization to assembly and it is secreted as a tetramer. The three peptides mentioned above, are associated intracellular into a collagen VI heterotrimeric monomer (triple-helical monomers). These collagen VI monomers align into antiparallel, overlapping dimers, held by disulfide bonds. Dimers form tetramers, before excretion, by covalent association with their end. Dimers and tetramers stabilization take place by disulfide bonds formed between cysteine residues, that are presented in the triple helix of all three chains (α1, α2 and α3 collagen VI chains) (Chu et al., 1897). Tetramers aggregate into microfibrils, extracellular, in an end-to-end association by interaction of the N-terminal and C-terminal globular domains with each other and with the short triple helical domains (Figure 2). The beading of microfibrils is the final stage of collagen type VI that occurs outside the cell (Lamande et al., 2006).

Collagen type VI assembly is unique within its three chains. Studies have showed that initial association of the three chains into a collagen VI triple helical heterotrimer is a precondition for further intracellular assembly, stabilization and for the secretion (Lamande et al., 1998). The non-collagenous domains play a central role in the assembly steps of collagen VI (Ball, Baldock, Kielty, & Shuttleworth, 2001). In the absence of α3 chain, the α1 and α2 collagen VI chains do not form stable secreted assemblies. There is no triple-helical collagen VI produced in the absence of α3 collagen VI chain. The mechanism of the unassembled collagen type VI was not determined. The α3 collagen VI chain is essential for the composition of stable collagen type VI molecules (Lamande et al., 1998).

Lamande et al. provides fundamental new information about the protein domains that are involved in intracellular collagen type VI assembly and the extracellular microfibril formation (Lamande et al., 2006). The α3 subdomains are involved in intracellular and extracellular assembly production and expression of the α3 chain cDNAs that contains C-terminal truncations. Processing of the C-terminal domain of the α3 collagen type VI chain is not essential for microfibril formation, only the C1 subdomain is essential. The formation of dimers and tetramers of collagen VI proceed normally when the α3 C2-C5 subdomains are absent. This shows that these subdomains are not directly involved in any of the intracellular collagen type VI processes. However, data showed that α3 C5 subdomain is critical for extracellular microfibril formation, but the cleavage of this subdomain is not essential for the microfibril formation (Lamande et al., 2006). Another study showed that the α3 N-terminal N5 subdomain of the α3 collagen VI is critical for the microfibril formation (Paulsson et al., 1987). It plays a critical role in the interactions between the tetramers of collagen VI that leads to the formation of microfibrillar network. This is because the α3 N5 subdomain is exposed at both ends of the tetramers (Fitzgerald et al., 2001). The critical role of α3 N5 subdomain identifies a functional role for a specific A domain in the assembly of collagen type VI (Fitzgerald et al., 2001).

Cells that expressed α3 collagen type VI chains in absence of the N5 subdomain were severely affected in their ability to form tetramer assemblies and failed to contribute a collagen VI matrix. This indicates that α3 N5 subdomain is important for stable extracellular association of tetramers, forming the collagen VI microfibrils (Fitzgerald et al., 2001). It is possible that the two, C5 and N5 subdomains of α3 chain drive interactions in the microfibril formation. Other subdomains may be available to participate in interactions with variety proteins of ECM (Fitzgerald et al., 2001).

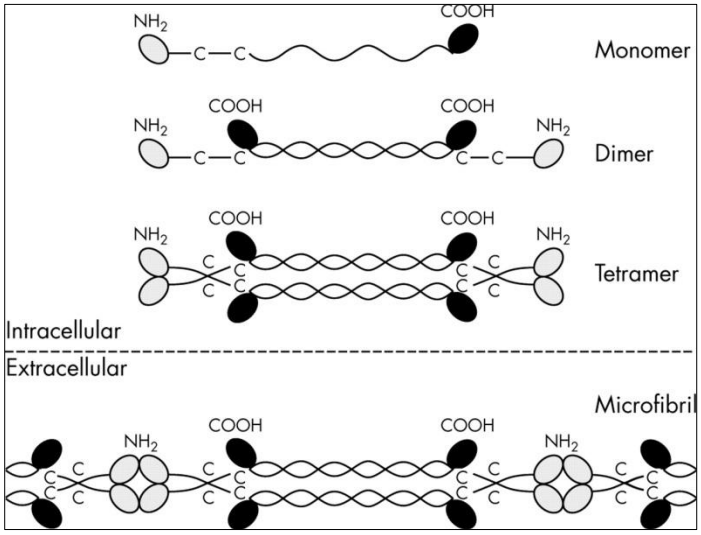


Figure 2. Schematic model of type VI collagen assembly. Modified from Furthmayr et al and Zhang et al. (Lampe & Bushby, 2005)

In addition to the well-known chains of collagen type VI, new chains of collagen type VI are recently discovered. A study of February 2008 showed a high homology of three novel collagen type VI chains with α chain (Gara et al., 2008). The authors describe in this study three novel collagen VI chains, α4, α5 and α6 (Gara et al., 2008). Each chain is composed of seven von Willebrand factor A domains followed by two C-terminal von Willebrand factor A domains and a unique domain (Gara et al., 2008). Collagen type VI α4, α5 and α6 are found on the human chromosome 3 (Gara et al., 2008). The three chains of collagen type VI previously known contain a relatively short collagenous domain (Gara et al., 2008). The three novel chains have a similar size as collagen type VI α3 chain (Gara et al., 2008). The sequences and the found domain structures of the novel proteins show that they represent new collagen type VI chains. This probably occurs as the consequence a gene duplication of the known collagen type VI α3 chain followed by other duplications. The size of the new α collagen type VI chains implies that they could replace the α3 chain, because it seems to have an identical size compared with each other. The new chains probably form α1α2α4, α1α2α5 or α1α2α6 heterotrimers (Gara et al., 2008). However, data presented that only the α4 collagen type VI chain encompassing the N6 to C2 domains are able to co-assemble with α1 collagen VI and α2 collagen VI chains (Fitzgerald, Rich, Zhou, & Hansen, 2008).

The similarities in the organization of the domains and triple helix length strongly indicate that these three novel collagen chains belong to the collagen type VI subfamily. The study of Fitzgerald et al., showed the identification of three novel collagen type VI genes on human chromosome 3 (Fitzgerald

et al., 2008). The three new genes are COL6A4, COL6A5 and COL6A6 and encode the α4, α5 and α6 collagen type VI. This study showed that the new chains contains a 336-amino acid triple helix accompanied by seven N-terminal von Willebrand factor A-like domains and two (the α4 and α6 chains) or three (the α5 chain) C-terminal von Willebrand factor A-like domains. Here, the authors did not report that the domains are von Willebrand factor A domains but they seems to be von Willebrand factor A domains. COL6A5 mRNA expression is restricted to a few tissues in humans, in contrast COL6A6 mRNA is expressed widely in fetal and adult tissues (Gara et al., 2008). The α4 chain collagen type VI contains all the elements that are needed for trimerization with α1 and α2 chain collagen type VI. But the gene COL6A4 is being split by a chromosome break and thus is not coding for a protein (Fitzgerald et al., 2008).

The α3, α4, α5 and α6 collagen VI chains have the same interruption in the pattern Gly-X-Y repeat in the triple helix. This is not present in the α1 and α2 collagen VI chains. Also α3 chains and the three novel chains contain a single cysteine at amino acid 50 of the triple helix and the α1 and α2 chains have a helix cysteine at position 89. Cysteine residues are crucial for forming disulfide bonds and stabilizing collagen type VI assembly intermediates (Odermatt, Risteli, van Delden, & Timpl, 1983). This is an essential difference between the chains. The expression of these three novel chains will be described in chapter 4.

The discovery of the three novel collagen type VI chains doubles the size of the collagen VI subfamily. The study of Gara et al. describes three novel collagen type VI chains that have the potential to replace the α3 chain of collagen VI. Thereby the novel chains can increase the structural and functional alterability of collagen type VI (Gara et al., 2008). The identification and initial biological characterization of these three novel collagen type VI chains give implications for the etiology caused by collagen type VI (Gara et al., 2008).

*2.2 Function*

Extracellular matrix components are thought to be important for morphogenesis of virtually all tissues (Jöbsis, 1999). Collagen type VI interacts with several components of ECM (Jöbsis, 1999). However, the precise role of collagen VI is not clearly understood. Also the exact role of collagen type VI during ECM development and remodeling has not been identified. Collagen type VI could serve a role in regulation of proliferation and differentiation by connecting matrix components to cells. Several studies suggest such a role (Aumailley et al., 1989). Collagen type VI has cell adhesion properties and protein binding activities of the ECM. Collagen type VI may play an essential role in the interconnection between the cell and the structural scaffolding of the ECM. It has been shown that matrix components and membrane proteins interact with collagen type VI. This includes various proteoglycans, several collagens, heparin, hyaluronan and several integrin's. This interaction may provide a scaffold for cell migration or anchor cells to the structural components of the ECM (Lamande et al., 2006). Collagen VI is basically important to maintain regular structural functions. It undergoes an elaborate assembly process in the cell before it is secreted in the ECM (Alexopoulos et al., 2009). Several studies indicate that collagen type VI functions are to anchor the basement membrane to the pericellular matrix in muscle (Fitzgerald et al., 2008). Other studies suggest that collagen VI has a role in cell signaling and cell migration (Jimenez-Mallebrera et al., 2005).

Collagen type VI forms beaded filaments with a complex domain structure. This structure is known to interact with ECM and cell surface receptors to anchor interstitial structures and cells of the nearby tissues (Richard-Blum et al., 2000). Collagen type VI has a stimulatory effect on mesenchymal cell growth and it inhibits apoptosis. Several proteins interacts to collagen type VI; decorin, NG2, perlecan, mac-2, MBP2, fibulin-2, fibronectin, collagen type IV and integrin's. Integrin's are a family of trans membrane proteins with cell signaling and regulatory properties. Integrin's link the cytoskeleton to the ECM. Interaction of integrin's with matrix components, also collagen type VI, are critical in triggering metabolic processes in myogenic differentiation. Interaction of collagen type VI with integrin α1β1 and α2β1 moderates attachment and migration of cells. And the interaction of collagen type VI and integrin α3β1 seems to have a role in fibroblast migration, development and matrix architecture of the cornea. However, the cell binding to collagen type VI by integrin receptors is complex and seems to be cell type dependent (Tulla et al., 2001). Alternative splicing events of COL6A3 mRNA leading to variation of the amount of N-terminal von Willebrand factor A modules in the α3 (VI) peptide, occur in a tissue specific manner, and might be able to modulate cell adhesion and interaction with other components of the extracellular matrix.

It is known that collagen type VI has a critical tissue-specific role in muscle. Collagen VI is also important in maintaining the integrity of tissues such as lung, skin and blood vessels (Kielty & Grant, 2002). It is also important in tissue structure. Collagen VI provides structural integrity and key matrix signals for regulation.

Also is demonstrated that collagen type VI is an essential basal lamina component involved in the regulation of epithelial cell behavior. The data of Groulx et al. indicate that collagen type VI plays a crucial role in the modulation of epithelial cell migration (Groulx et al., 2011). Collagen type VI affects the production, organization and deposition of fibronectin. It regulates epithelial cell-fibronectin interactions (Groulx et al., 2011). Thus collagen VI is a basement membrane. This collagen seems to play a critical role in anchoring and organizing the fibrillar type I and III collagen network (Alexopoulos et al., 2009). Because collagen type VI has unique structural features and the known functions may have a role in matrix homeostasis and remodeling (Oono et al., 1993). But the exact role of collagen type VI in many tissues in which it is expressed remains to be studied.

## 3. Cells producing collagen type VI

Collagen type VI has a complex structure. The detailed function of collagen type VI is not identified. This chapter describes the cells that are able to synthesize type VI collagen.

### *3.1 Fibroblasts*

Collagen type VI is a form of collagen. Collagen is produced by activated fibroblasts, also collagen type VI. Fibroblasts are the most important cells of connective tissues (Jimenez-Mallebrera et al., 2006). Type collagen VI is found in intra- and extracellular fibroblast and smooth muscle cell cultures (von der Mark et al., 1984). A study showed that fibroblast and smooth muscle cells produce collagen type VI (von der Mark et al., 1984). Fibroblasts synthesize the ECM and collagen. This plays a critical role in wound healing. The α1, α2 and α3 collagen type VI chains mRNA are present in human skin fibroblast cultures (Olsen et al., 1989). They are commonly present is corneal fibroblasts, in fetal skin and in fetal skin fibroblasts (Olsen et al., 1989). In general, collagen type VI is produced by fibroblasts.

### *3.2 Macrophages*

Macrophages are the first phagocytes activated in the cellular immune system; they have a function in both innate and adaptive immunity (Burke & Lewis, 2002). Macrophages are cells produced by monocytes in tissues. Inside the tissue, monocytes can differentiate into macrophages. The differentiation into macrophages is related to tissue injury and repair. The main effect of these cells on the ECM is considered in nature as destructive, because macrophages secrete metalloproteinase (protease enzyme) and macrophages ingest foreign components as part of the remodeling process that is involved in wound healing (Schnoor et al., 2008). Macrophages neutralize the stimulus of inflammation (Burke & Lewis, 2002). In general, activated macrophages are degradative in nature, destabilize and destroy the ECM and break down tissues. Though, macrophages can also be active in other ways, this depends on the stimulus of the cell are exposed to the macrophages (Burke & Lewis, 2002). It has been showed that activated macrophages play pivotal roles in liver injury and repair (Duffield et al, 2005).

For a long time, it was believed that macrophages not produce collagens, the major structural proteins of the ECM. A study of Weitkamp et al., demonstrated that macrophages synthesize and secrete collagen type VIII in vitro (Weitkamp et al., 1999). In the study of Schnoor et al., they report that monocytes and macrophages express virtually almost all collagen that are known and collagen-related mRNAs. The macrophages are derived of monocytes from human blood. They also reported that macrophages secrete collagen type VI protein abundantly; it depends on their mode of activation, cell density and stage of differentiation. Collagen type VI is here induced by TGF-β1 and anti-inflammatory interleukins.

Collagen type VI secreted by macrophages is not present in fibrillar form. Explanation for this data is that macrophages express biglycan and decorin; they are both needed to incorporate collagen type VI into the ECM, at very low levels (Reinboth et al., 2006). These are proteins required for collagen type VI processing and filament formation. So, the virtual reduce of biglycan and decorin levels may explain why macrophages not incorporate collagen type VI into ECM in fibrillar form (Schnoor et al., 2008).

The primary function of collagen type VI, secreted by macrophages, is modulation of cell-cell and cell-matrix interactions. The study of Schnoor et al. suggests that the production of collagen VI is a marker for a nondestructive, matrix-conserving and probably for a tissue-stabilizing macrophage phenotype. This is suggested because activated and deactivated macrophages exhibit reduced proteolytic activity, added to their anti-inflammatory phenotype. It adds a new dimension to macrophage functional heterogeneity. This data implies that the role of macrophages is more complex in the remodeling and repair of injured tissue than thought. The findings of this study may also apply to tissues which are macrophage rich, where fibrosis occurs or to macrophage-containing tumors. It could deeply influence pathophysiological and physiological conditions in vivo (Schnoor et al., 2008).

## 4. Collagen type VI containing tissues

In the previous chapter the structure, function and cells that produce collagen type VI are reviewed. In this chapter the tissues where collagen type VI is distributed will be described. Also the expression of the three novel chains will be discussed.

### *4.1 Collagen VI distribution in tissues*

Collagen type VI is the major collagen type produced by intestinal epithelial cells. It is subsequently secreted and contributed at the base of epithelial cells (Groulx et al., 2011). Collagen type VI is expressed in all ECMs (Bruns et al., 1986). It is widely distributed in connective tissues, such as tendons, skin, placenta, adipose tissues, large blood vessels and in some specialized region (Engel et al., 1985) (Groulx et al., 2011). Most of the collagen is localized in human skin (van der Rest & Garrone, 1991). In human normal skin, collagen type VI is localized throughout the dermis and pronounced reactivity nearby basement membranes (Betz et al., 1993). Collagen VI is also expressed throughout several sort of interstitial matrices and it is found near the basement membranes of tissues where it functions as an anchoring meshwork. It is not typically a constituent of cartilage or of basement membranes. Collage VI has a wide occurrence in connective tissue especially of large vessels, skin, kidney, skin, lung, muscle and liver (von der Mark et al., 1984). Collagen VI is a component of microfibrillar structures of the human body (von der Mark et al., 1984).

### *4.2 Expression of α4, α5 and α6 collagen type VI chains*

Recently, the expressions of the three novel chains are described. These findings are found in mouse. The expressions of the three novel chains are weaker than α1, α2 and α3 chains. In contrast to the α3 chain of collagen type VI, the novel chains show a highly differential, limited and frequent complementary expression (Gara et al., 2011). The α3 chain collagen VI in mouse is widely distributed in the skin. It is also present in other tissues. All three novel chains are expressed in the bronchi. The expression of α4 chain is showed effectively in the intestinal smooth muscle, around the follicles in ovary and in testis of a mouse. The α5 chain is expressed in perimysium and at the neuromuscular junctions in skeletal muscle, in the kidney glomerulus, in skin and also in the ovary and testis. The α6 chain is most abundant in the perimysium and endomysium of skeletal muscle and in myocardium. It is also localized to the reticular lamina of muscular fibers. The novel chains were not detected in lung, liver, spleen, pancreas and brain. It is found that the novel chains can replace the α3 collagen VI chain. So the results were compared with the α3 chain expression and were highly differential and restricted. The novel chains seem to be closely related with basement membrane structures in many tissues (Gara et al., 2011).

Previous studies showed the novel α5 and α6 chains expression in human (Fitzgerald et al., 2008). Sabetelli et al. detected these two chains in human dermis. Expression of α6 chain was found in human articular cartilage, skeletal and cardiac muscle, kidney, blood vessels and lung. Alpha 6 chains were found in pancreas and spleen in low levels (Sabatelli et al., 2011). The difference of the novel chains expression between human and mouse may be the loss of a functional α4 collagen VI chain gene in humans (Fitzgerald et al., 2008).

**5. Myopathies of collagen type VI**

In this chapter a short overview will be described of the myopathies of collagen type VI. Collagen type VI provides structural and mechanical stability to tissues. It is an essential component of skeletal muscle ECM. Collagen VI plays a critical role in muscle. Over the years the etiological definition of collagen type VI myopathies has evolved.

What is known about the medical side of collagen type VI? Collagen type VI myopathies are caused by mutations in the genes that encode for collagen VI. Two major skeletal muscle disorders are linked to this type of collagen (Allamand et al., 2011). Mutations in any of α1, α2, and α3 collagen type VI chains leads to this two type of congenital myopathies. It causes the relatively mild Bethlem myopathy (BM) and the more severe Ullrich congenital muscular dystrophy (UCMD, probably the most common type of congenital muscular dystrophy) (Bonneman, 2011). These two disorders, under-recognized for a long time, have important improvement made in understanding its molecular pathogenesis. The mutations are resulted in formation of abnormal collagen type VI. Also downstream effects occur, such as increased apoptosis of muscle cells.

The both myopathies are recognized as the extreme end of a continuous clinical spectrum, UCMD at the severe endpoint and BM at the other end (milder form) (Allamand et al., 2011). UCMD and BM are unique among the hereditary disorders in that these myopathies are hybrid myopathies with clinical features imputable to muscle and connective tissue. There are several clinical phenotypes of the collagen VI myopathies. For example, UCMD phenotypes are orthopedic deformities, muscle weakness and BM phenotypes are milder, and they are characterized by contractures of finger flexors, elbow, wrist and ankles (de Visser et al., 2004).

Dominant and recessive autosomal mutations are possible for all clinical collagen type VI-related myopathies. BM is dominantly inherited and the more severe UCMD showed that it is dominant and recessive inherited (Bonneman, 2011). Different diagnoses are considered for the myopathies, depending on the age of the patient and the clinical features. A lot of research is done in these myopathies (Allamand et al., 2011). Studies indicate that myopathies of collagen VI are due to a mitochondrial dysfunction (Irwin et al., 2003). At this moment no curative treatment is known for these myopathies. Most of the patients rely on supportive treatment of symptoms. The past years of research in neuromuscular disorders has showed that collagen VI myopathies are an important set of disorders. It is hoped to see the development of safe and efficient treatments for these myopathies in the following ten years. In this review no further details of the myopathies will be discussed.

## 6. Collagen type VI involved in fibrosis

Collagen type VI is a component of the ECM (a glycoprotein) that has a microfibrillar structure. Collagen type VI is found in the wound area and appeared to increase during wound healing (Betz et al., 1993). It is thought that collagen VI serves as an anchoring component between collagen type I and III fibrils and basement membranes. In this chapter the role of type VI collagen in fibrosis is reviewed.

### *6.1 Wound healing*

The healing of a wound is a highly regulated process. During wound healing collagen type I and III are expressed in a time-dependent fashion in humans (Oono et al., 1993). The scar tissue consists mainly of collagen type I. This will ensure that the involved tissue will be restored. Also type VI collagen mRNA is expressed during the early phase wound healing. The α1 and α3 collagen VI chains were increased during wound healing, it was not increased in smooth muscle cells. It has been reported that the α3 chain of collagen type VI binds to collagen type I, generally associated with each other (Bonaldo et al, 1990). Also is known that collagen VI has important cell-attachment properties. Collagen type VI expression could be localized to endothelial cells of newly formed vessels and to fibroblast-like cells. These cells seem to play an important role in the synthesis of collagen VI during wound healing (Oono et al., 1993). Collagen type VI is reported in many pathological conditions, like fibrosis. Fibrosis is a formation of fibrous tissue as a reactive or reparative process (Khan et al., 2009). Collagen type VI may stimulate the proliferation of cells, leading to fibrosis of the tissues that are affected in after damage (Schuppan, Ruhlmann, & Hahn, 1985) (Shahin et al., 1992). Betz et al. showed that collagen type VI was detectable after a post-infliction interval of at least 3 days. It showed also a strong positive reaction with fibroblasts in the wound area. In this study collagen type I and VI appeared to be constant after a wound after 6-7 days (Betz et al., 1993).

### *6.2 Lung fibrosis*

Type VI collagen expression is increased in lung fibrosis (Specks et al., 1995). Fibrosis of the pulmonary is characterized by disturbances of ECM protein deposition. This is caused by fibroblast activation and proliferation. Collagen type VI is located in vascular and bronchial walls in the interstitial space of the normal human lung. In the study of Specks et al. collagen VI was increased in lung fibrosis. MRNA of collagen type VI is expressed by fibroblasts, mostly like myofibroblast (Specks et al., 1995). In this study, they suggest that the expression of collagen VI may be an early phenomenon of lung fibrosis. Data showed no difference between the expression of α1 and α3 chains of collagen VI. To identify the potential various deposition patterns in forms of fibrosis, coexpression of collagen VI with type I and III collagen was determined. Coexpression with collagen type III was observed in all various forms of fibrosis and in the earliest fibroblasts. This indicates that collagen type VI is up regulated in the early phases in lung fibrosis. Collagen VI deposition is clearly prior to type I collagen. These data may suggest that type VI collagen as a contributory role in complex mechanisms of disorganized matrix protein leading to pulmonary fibrosis (Specks et al., 1995).

*6.3 Renal fibrosis*

Renal fibrosis is the common pathway for almost all forms of kidney disease in the end stage of the renal failure (Groma, 1998). Data showed that type VI collagen has a universal nature and participates in fibrotic lesions that develop in several injuries of the renal. Collagen type VI is absent in the renal bowman's capsule, tubules and media layer. But in renal fibrotic injury areas, collagen type VI was strongly expressed. Deposition of type VI collagen is increased in renal fibrotic lesions (Groma, 1998). Further examination is needed for this finding.

*6.4 Arthrofibrosis*

Arthrofibrosis is a complication after trauma of the knee and surgery. It is characterized by the proliferation of massive connective tissue, a disordered deposition of matrix proteins (Zeichen et al., 1999). This is caused by activation of fibroblasts. In the pathogenesis arthrofibrosis, collagen type VI expression is increased. Collagen type VI was found in arthrofibrotic tissue. The study of Zeichen et al. suggest that dysregulation of type VI collagen synthesis could be an essential contributing factor that can lead to arthrofibrosis. The detailed aetiopathology of arthrofibrosis is not yet identified. Because the known functions of collagen type VI, it may play an essential role in matrix homeostasis. It functions as an anchoring element between fibers of collagen and as a cell binding organization (Zeichen, van Griensven, Lobenhoffer, & Bosch, 2000).

*6.5 Liver fibrosis*

Collagen type VI is a minor but an important matrix component in the liver. Chronic excessive alcohol intake may cause hepatic fibrosis and cirrhosis (Bolarin & Azinge, 2007). Hepatic fibrosis or cirrhosis development is increased due production, deposition and reduced degradation of hepatic ECM elements, especially collagens, including collagen type VI (Lieber, 1994). Type VI collagen is highly up-regulated in liver fibrosis. An acute and a chronic injury model in rats were determined, to study the process of liver fibrosis (Takahara et al., 1995). After 2 days of acute injury, accumulation of collagen VI was seen. This indicates that collagen VI expression, with other connective tissue elements is activated in the early phases of fibrosis (Takahara et al., 1995). Collagen VI accumulation may concur to the deformed architecture and functional impairment of hepatic fibrosis (Takahara et al., 1995). A rational therapeutic approach for liver fibrosis is a targeted blockade of the receptors of collagen VI (Stickel et al., 2001). Collagen type VI was significant elevated in patients that has chronic active hepatitis, liver cirrhosis, hepatic cellular carcinoma and chronic persistent hepatitis. The combined determination of collagen type IV, type VI and other markers of connective tissue metabolism showed that it may be predict progressive hepatic fibrosis (Ji et al., 1997).

*6.5.1 Schistosomiasis*

This disease leads to pre-sinusoidal hepatic fibrosis (Shahin et al., 1992).In mice with schistosomal liver fibrosis, dynamic changes occurs in the expression of collagen type VI (Shi et al., 1999). The expression of collagen type VI, mainly α1 chain of collagen VI was significantly increased in the liver of the mice in the early phase of fibrosis (Shi et al., 1999). Collagen VI may be important for evaluation of the intensity of schistosomal liver fibrosis (Shi et al., 1999).

*6.6 Adipose tissue fibrosis*

Adipocytes, fat cells that are embedded in a unique ECM. Its function is to provide mechanical help and to take part in signaling processes. In the diabetic state, component of the ECM are up regulated in adipose tissue. Diabetic is associated with increased adipose tissue fibrosis (Spencer et al., 2010). Collagen type VI is an ECM component that highly is enriched in adipose tissue in diabetic state. The absence of type collagen VI has improvements in the body energy homeostasis. This is associated expansion of individual fat cells. Collagens are up regulated in adipose tissue when metabolic changes occur (obesity) (Spencer et al., 2010).

Humans with obesity have a high level expression of collagen type VI (Spencer et al., 2010). The absence of collagen VI in adipose tissue improves the metabolic phenotype in mice (Khan et al., 2009). Also inflammation in adipose tissue is reduced in lack of collagen VI in mice. Collagen type VI and other ECM components are important in the modulation of adipocyte physiology (Khan et al., 2009). Type VI collagen has an essential role in the fibrotic constituent of obesity. It affects directly the fat cells expansion (Khan et al., 2009).

*6.7 Cardiac fibrosis*

Collagen type VI appears to play a major role in cardiac fibrosis (Mollnau, Munkel, & Schaper, 1995). In normal myocardium of human, collagen VI was located in endomysium and perimysium. Collagen VI is a minor type in the heart of humans. Recent studies suggested that non-fibrillar collagen type VI is also deposited during wound healing and has a role in myofibroblast differentiation (Shamhart & Meszaros, 2010). Myofibroblasts are cells that have ultra-structural features intermediate between fibroblasts and smooth muscle cells (Skalli et al., 1989). They express α-smooth muscle actin, allows for organization of stress fibers and stabilization of the wound. The failing of myocardium had an extension of the extracellular space and type VI collagen was abundant (Mollnau et al., 1995). In hearts that has progressed far of failure areas of replacement of fibrosis, collagen VI amounts were increased. It is obvious that type VI collagen has an essential role in the fibrosis process in a failing heart (Mollnau et al., 1995). Fibroblasts of cardiac are the major ECM producers in the cardiac. They are triggered to alter ECM composition from the acute myocardial infarct to chronic conditions (Shamhart & Meszaros, 2010). It has an important role in the wound healing process (Naugle et al., 2006). The study of Naugle et al. showed that collagen VI induces cardiac myofibroblast differentiation in vitro (Naugle et al., 2006). This can lead to implications for post infarction remodeling. Cardiac fibroblasts are the major non-contractile cells that are located in the myocardium and in the primary regulators of secretion of ECM (Grotendorst, Rahmanie, & Duncan, 2004). They are mainly responsible for forming the infarct area. Proliferation and differentiation of cardiac fibroblast into myofibroblast can cause to over-abundant production of ECM and if the myofibroblasts remain in the damaged area for a long period, cardiac fibrosis results (Naugle et al., 2006). In turn, ECM that is produced can potentially activate the fibroblast of cardiac via several mechanisms. The over-abundant production of ECM appears by patients who have experimental myocardial infarction and during heart failure, this leads often to cardiac function loss (Capasso et al., 1990). The activation of cardiac fibroblasts has a critical role in wound healing and repair of tissues (Cleutjens et al., 1995). Myofibroblasts are characterized with the organization of α-smooth muscle actin into stress fibers. This was most evident on the collagen type VI substrate (Naugle et al., 2006). Myofibroblasts were at highest in the infarcted myocardium.

Collagen type VI has an effect on the differentiation of myofibroblasts, but a little effect in the cardiac fibroblast proliferation, found in in vitro and in vivo model (Naugle et al., 2006). In this study was showed that collagen type I and III stimulate cardiac myofibroblast proliferation, whereas collagen VI plays a potentially new role in cardiac remodeling through alleviation of the differentiation of myofibroblast (Naugle et al., 2006). The mechanism of this finding has not been at present established (Naugle et al., 2006).

*6.7.1 Alpha 3 integrin in fibrosis*

As follow a study showed that α3 integrin blockade attenuate cardiac myofibroblast differentiation (Bryant et al., 2009). The aim of the study was to determine the patterns of expression of collagen VI and myofibroblast to get insight into whether collagen VI induces the differentiation of myofibroblast in vivo via specific matrix-receptor interactions (Bryant et al., 2009). Collagen type VI is elevated in the myocardial infarct. Collagen VI interacts with the α3 integrin receptor in cardiac fibroblasts (Bryant et al., 2009). Receptors of α3 integrin are important mediators of ECM signaling in fibroblasts and myocytes. Results confirmed that the α3 integrin interacts with collagen VI in vitro and the blockade of α3 integrin can inhibit the differentiation of cardiac fibroblasts (Bryant et al., 2009). These data indicate a potential role of collagen VI in stimulating in vivo myofibroblast differentiation. Pathways that are involved in the mediation of α3 integrin with collagen VI are the SMAD 2/3 pathway induced by TGFβ and ROCK/LIMK pathway induced by mechanical stress (Shamhart & Meszaros, 2010).Collagen type VI stimulate potently myofibroblast differentiation (Shamhart & Meszaros, 2010). Collagen VI deposition is increased in myocardial infarction and myofibroblast is enhanced. Alpha 3 integrin plays a key role in collagen type VI –induced myofibroblast differentiation (Shamhart & Meszaros, 2010). Cell-matrix interactions are an essential and critical subject of remodeling and repair of tissues (Bryant et al., 2009). Data of Bryant et al. showed a role for collagen VI in cardiac remodeling (Figure 3). It is suggesting that the initial phase of myocardial infarction involves integrin receptors up-regulation, which in the end leads to fibrosis.

The progression of fibrosis of the myocardium in patients with hypertrophic cardiomyopathy has impact on both diastolic and systolic function of the left ventricle. Increased collagen type VI is correlated with cardiac dysfunction (Kitamura et al., 2001) (Kawahara et al., 1990). In the reparative process following left ventricle type I and III collagens were detected, and also type VI collagen in fine fibrillary pattern in fibrous tissue. It was also found around the adipocytes. Probably collagen VI plays an important role in wound healing. In conclusion, collagen VI deposition may play a role in the control of function and phenotypic distribution of the cardiac fibroblasts and myofibroblasts in myocardial infarct remodeling through interactions of collagen VI with α3 integrin receptors (Bryant et al., 2009).

*6.7.2 Matrix metalloproteinases*

Collagen has a role in the interactions between enzymes that the ECM remodeling controls. This included matrix metalloproteinases (MMPs) and their inhibitors (Veidal et al., 2011). MMPs are the regulators of ECM degradation during the remodeling. In fibrosis both collagen VI and matrix metalloproteinases are significantly increased (Veidal et al., 2011).The degradation of old matrix that allows deposition of new matrix is a key element to cardiac remodeling. All collagens are degraded by these MMPs, but collagen type VI does not interact with MMP, and seems to be resistant for degradation by MMPs.

Type VI collagen is resistant to degradation by metalloproteinases (Okada et al., 1990).In conclusion, type VI collagen may represent a more stable form of collagen in comparison with the other collagens that are involved to breakdown by MMPs.

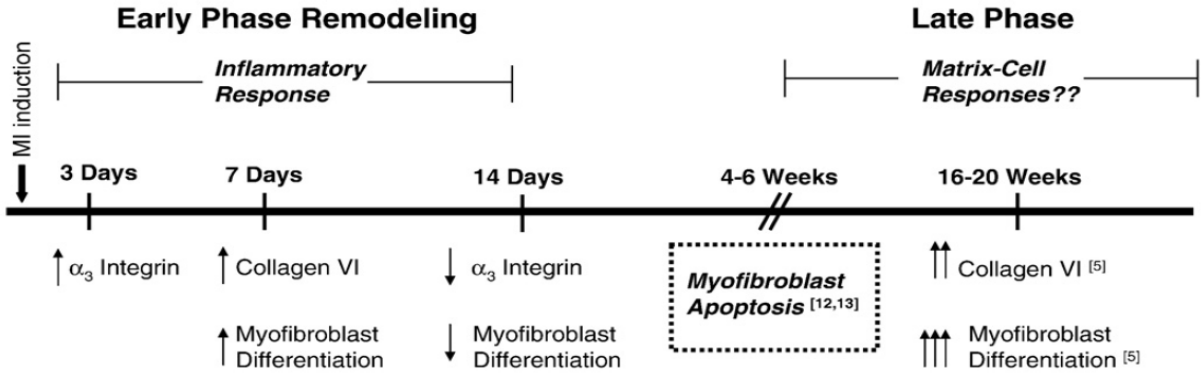


Figure 3 Timeline of collagen VI, α3 integrin, and myofibroblast differentiation during early and late phases of post-myocardial infarction remodeling. Results of the study are showed in this figure. This model propose that there is an appearance of myofibroblasts in early and late phase remodeling, due to inflammatory reactions.(Bryant et al., 2009)

*6.8 Muscle fibrosis*

Type VI collagen has a critical role in the keeping of the skeletal muscle functional integrity (Sabatelli et al., 2012). The α5 and α6 chains of collagen VI are identified in humans. The α6 chain deposition was up-regulated in fibrotic areas of the muscle (Duchenne muscular dystrophy-related), but α5 was undetectable. Alpha 6 chain seems to be involved in ECM remodeling during fibrosis of the muscle. Results showed that α6 chain-producing cells were positive for α-smooth muscle actin that indicates that it may be myofibroblasts. Myofibroblasts play a major role in fibrosis. The results indicate that α6 chain is producing mainly myofibroblasts (Sabatelli et al., 2012). Also α3 chain of collagen VI was found with α6 chain in fibrotic areas. It seems that these two chains are assembled and have a role remodeling of the ECM. General was found that collagen type VI was increased in fibrotic muscle, in particular α6 chain of collagen VI (Sabatelli et al., 2012).

Collagen type VI has certainly an important role in several tissues fibrosis. Further studies are needed to confirm the findings described and to determine the role in other tissues.

**7. Monitoring of collagen type VI**

There are many methods to detect collagen. In this chapter collagen VI as marker will be discussed. Collagen type VI can be detected by a modified immunochemical method (Fraser et al., 2006).To determine the localization of collagen VI, antibodies can be used. In addition the expression can be studied by molecular hybridization techniques (Takahara et al., 1995). Collagen type VI immunohistochemical localization provides information that is useful for an applicable age estimation of human skin wounds in the forensic field (Betz et al., 1993). It may be regard as an extracellular marker of the proliferation of connective tissue (Zeichen et al., 1999). Collagen type VI is also a molecular marker for pericellular matrix (Fraser et al., 2006).

In the previous chapter, the hepatic fibrosis in alcoholic liver disease is described. This heralds often progression to cirrhosis and therefore noninvasive parameters are needed for the early diagnosis and follow-up of patients. Collagen type VI appears to be a sensitive marker for indication of fibrotic transformation in alcoholics (Stickel et al., 2001). This can be a useful method, because liver biopsy with subsequent histologic determination is considered the most exact method to assess hepatic fibrosis. Here may occur sampling errors. This is a high risk, therefore noninvasive test are required to obtain information of the fibrotic transformation (Stickel et al., 2001). Collagen type VI is suggested to be a useful cell type-specific marker (Hessle & Engvall, 1984). Because collagen VI is present in the ECM of cultured fibroblasts and in trace amounts in cultured sarcoma cells, but not in cultured epithelial or endothelial cells (Hessle & Engvall, 1984).

Determination of the importance of serum markers of fibrosis as prognostic and diagnostic parameters would be of great interest for the early stages of chronic liver disorders, during follow-up and in order to monitor a therapy. Collagen type VI is a presumptive marker of the activation of mesenchymal cells, and is suggested to be markers of early remodeling of the architecture in hepatic fibrosis (Bissell et al., 1990). The serum level of collagen type VI is found elevated in patients with alcoholic cirrhosis (Shahin et al., 1992).

Serum collagen VI levels can be measured using a sandwich ELISA technique. Here an antibody binds to collagen type VI and a second antibody detects this. Serum levels collagen VI is significant elevated in alcoholic liver disease patients compared to controls. Data of Stickel et al., showed a two to threefold elevated serum levels of collagen type VI in alcoholic liver disease, also in the early stage (Stickel et al., 2001). It seems as if collagen VI levels are raised, it may indicate an early process in hepatic connective tissue alteration. Collagen type VI was also elevated in liver damage irrespective of the cause. In these patients alcoholic cirrhosis had already developed in whom a malfunction of collagen metabolism was expected (Stickel et al., 2001).

The collagen VI serum marker represents fibrolysis, and appears to be an important marker of early fibrotic transformation. Serum collagen VI can be used as an indicator in the early phase for altered connective tissue turnover in alcoholic liver disease, where fibrosis is absent. This finding could be of particular value to detect patients whom fibrotic transformation is threatening but still preventable (Stickel et al., 2001).

Another study focused also on non-invasive methods for the assessment of liver fibrosis (Veidal et al., 2011). Recently a novel ELISA has been determined, an assay enabling assessment of MMP degraded collagen type VI. This method allows quantification of collagen VI degradation that can be relevant for several pathologies. This ELISA detects a fragment of collagen VI generated by 2 types of MMP, MMP-2 and MMP-9. Veidal et al. were able to develop this method in two preclinical rat models of liver fibrosis (bile duct ligation, BDL and carbon tetrachloride, CCL4) The marker was highly associated with fibrosis of the liver. This suggests that collagen VI turnover may have a central role in fibrosis (Veidal et al., 2011). MMPs have an important role in the degradation of extracellular macromolecules, included collagens. During fibrosis, levels of MMPs increase. MMP-2 and MMP-9 seemed highly regulated in fibrous tissue (Hemmann, Graf, Roderfeld, & Roeb, 2007) (Kirimlioglu, Kirimlioglu, & Yilmaz, 2008). Collagen type VI could be used as a liver fibrosis biomarker (Veidal et al., 2011). The main findings of Veidal et al. were the developing of a technically robust assay with monoclonal antibodies that were highly specific for the collagen VI-MMP fragment and the levels of collagen VI-MMP were assessed in two different liver fibrosis models (BDL and CCL4). In these two models levels of collagen VI-MMP in liver fibrosis were significant increased (Veidal et al., 2011). Thus, collagen VI-MMP is an early marker for fibrosis and it may be a good biomarker.

The data described in this chapter indicate that fibrosis of liver may be a high collagen turnover disorder with increased collagen formation and degradation (Veidal et al., 2011). The developing of an assay using a specific monoclonal antibody for detecting collagen VI-MMP is determined. Also was demonstrated that collagen VI may be used as a marker in liver fibrosis. This indicates that there is a high potential for the application of non-invasive biomarkers in ECM-related disorders.

**8. Modulation of collagen type VI in order to inhibit fibrosis**

In this chapter, a study will be discussed about the absence of collagen type VI after myocardial infarction. The ECM plays an essential role in the remodeling of cardiac and wound repair after a myocardial infarction. Patients, who survive a myocardial infarction, show a development of cardiac fibrosis. This concurs to the decline in the function of cardiac and may be lead to cardiac failure. Collagen type VI deposition is increased after myocardial infarction. The study of Luther et al. showed that absence of collagen type VI paradoxically improves cardiac function, remodeling and structure. This appears after a myocardial infarction (Luther et al., 2012).

In the chapter of fibrosis was demonstrated that collagen type VI induces myofibroblast differentiation in vitro (Naugle et al., 2006). Previous was reported that collagen type VI deposition increases in myocardial infarction in vivo (Veidal et al., 2011). The deposition of collagen type VI is enhanced in vivo after myocardial infarction. The specific role for collagen type VI in this section was not determined.

The objective of the study of Luther et al. was to determine whether absence of collagen VI in an in vivo model of myocardial infarction wound healing would alter the function and remodeling of cardiac after the injury (in days to weeks) (Luther et al., 2012). In this study mice were used for the determination of the deletion of type VI collagen. This study demonstrated a reduced collagen volume and decreased long-term myocyte/nonmyocyte apoptosis in absence of collagen VI. Results showed that the reductions in chronic myocyte apoptosis and fibrosis are critical processes leading to long-term remodeling improvement. The data showed a significant improvement of remodeling after myocardial infarction in the lack of collagen type VI. Also the data of this study indicate that less myocyte apoptosis takes place in the knock-out model after 14 days. This support the concept that wound healing occurs and it is completed (Luther et al., 2012).

The results of Luther et al. showed that deletion of collagen type VI in the determined knock-out model plays a critical protective role after myocardial infarction. It limits the infarct size, aberrant remodeling, chronic apoptosis and fibrosis that eventually lead to conservation of cardiac function (Luther et al., 2012). This is conflicting because this deletion of collagen type VI is a model of the disease Bethlem Myopathy (Luther et al, 2012). Previous studies of skin and tendon are suggesting that the deletion of collagen type VI has an effect on fibrillar collagen network organization (Alexopoulos et al., 2009). This could be create a more advantageous biomechanically environment for the healing of a wound after myocardial infarction.

In conclusion, the deletion of collagen type VI provides a beneficial effect on cardiac function and remodeling after myocardial infarction.

**9. Discussion and perspectives**

This review gave insight into the structure, function and the role in fibrosis of collagen type VI. Collagen type VI is one of the 28 different types of the collagen family. It forms a microfibrillar network in the ECM of all connective tissues. Collagen type VI consists of three polypeptide chains, and recently three novel chains of collagen VI are discovered (Gara et al., 2008). Thus, type VI collagen consists totally of six chains. One of the novel chains, α4 chain, is not found in human (Gara et al., 2011). This is because α4 chain gene function is lost in humans by a chromosome break (Fitzgerald et al., 2008). Expression of the three chains, α1, α2 and α3, are almost known. Also the expression of the three novel chains is determined. The expressions of the novel chains in mouse in comparison with α3 collagen VI chain demonstrate a differential and restricted expression in tissues (Gara et al., 2011). More studies are required to confirm these findings.

It is known that collagen VI serves as a major cell-binding structure and it may has an important role in the homeostasis of matrix (Aumailley et al., 1989). The detailed function of collagen VI is not identified. Type VI collagen is important to maintain regular structural functions. This type of collagen has a critical tissue-specific role in muscle. It is also essential in maintaining the integrity of several tissues (Baldock et al., 2003). Fibroblasts and macrophages produce type VI collagen (Schnoor et al., 2008). The production of collagen VI by macrophages is not immediately obvious. This study was done in vitro, and whether macrophages secrete collagen VI in vivo the distribution of this collagen type in regenerating tissue must be identified. To clarify the implications that macrophage produced collagen VI for activity of macrophage and for tissue integrity, additional investigations are required (Schnoor et al., 2008).

The medical part of collagen VI diseases is mostly understood. Mutations of collagen VI lead to myopathies. Collagen VI plays a critical role in muscles. The related myopathies are a unique part of muscle disorders (Bonnemann, 2011). The past decade, studies of neuromuscular diseases showed myopathies of type VI collagen as an important set of disorders. In the future treatment will be developed for the myopathies of collagen type VI (Bonnemann, 2011) (Allamand et al., 2011).

After damage, a phase wound healing takes place. This plays a role in the forming of fibrosis. Fibrosis is a complex process and the formation is driven by several factors (Oono et al., 1993). In general, results showed that collagen type VI has an essential role in fibrosis, but mostly associated with other ECM components. Several studies have showed that collagen VI has a role in lung, liver, renal, and adipose tissue fibrosis (Takahara et al., 1995). Results of two studies showed that collagen VI induces cardiac fibroblasts into myofibroblasts differentiation (Mollnau, Munkel, & Schaper, 1995) (Naugle et al., 2006). The studies of fibrosis and collagen VI suggest a potential link between collagen VI and the myofibroblast differentiation process (Mollnau, Munkel, & Schaper, 1995). Collagen type VI is a potent inducer of cardiac myofibroblast differentiation and is a key component of ECM of post-myocardial infarct (Naugle et al., 2006). There are several possibilities that can explain the mechanisms of the cardiac fibrosis, but the mechanisms are not yet clarified. Further investigation is required, also more information on the usefulness of collagen VI-MMP is needed (Veidal et al., 2011). Several studies showed that collagen VI and MMPs levels are high during liver fibrosis (Veidal et al., 2011). The results of collagen VI-MMP is a strong evident for a high potential biomarker. Biochemical markers that consist of protein fragments (collagen VI) from pathologic tissue remodeling could be useful for prognostic and diagnostic targets.

Taken together, the absence of collagen VI can be positive for wound healing, but absence of collagen VI is related to myopathies (Luther et al., 2012). The study of Luther et al. showed that deletion of collagen VI improves paradoxically remodeling after myocardial infarct. Previous studies showed that the absence of type VI collagen has an effect of the organization of fibrillar collagen network (Keene, Engvall, & Glanville, 1988) (Izu et al., 2011). This could be create a more advantageous biomechanically setting for wound healing after myocardial infarct. These findings are a basis for the development of therapies based on collagen to reduce disadvantageous remodeling after myocardial infarction. Although the mechanisms are not well identified, what the effect is on the myopathies (Luther et al., 2012).

In this review, the structure and function of the collagen type VI, the tissues where type collagen VI is expressed, collagen VI as marker and the role of collagen VI in fibrosis are described. In conclusion, collagen type VI has an important role in fibrosis associated with other ECM proteins. In addition, collagen type VI may probably be used as a biomarker to detect fibrosis. Future larger studies are necessary for a better understanding of the risks and the benefits associated with collagen VI and fibrosis.

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