ABSTRACT
Collagen VI represents a remarkable extracellular matrix molecule, and in the past few years, studies of this molecule have revealed its involvement in a wide range of tissues and pathological conditions. In addition to its complex multi-step pathway of biosynthesis and assembly that leads to the formation of a characteristic and distinctive network of beaded microfilaments in the extracellular matrix, collagen VI exerts several key roles in different tissues. These range from unique biomechanical roles to cytoprotective functions in different cells, including myofibers, chondrocytes, neurons, fibroblasts and cardiomyocytes. Indeed, collagen VI has been shown to exert a surprisingly broad range of cytoprotective effects, which include counteracting apoptosis and oxidative damage, favoring tumor growth and progression, regulating autophagy and cell differentiation, and even contributing to the maintenance of stemness. In this Cell Science at a Glance article and the accompanying poster, we present the current knowledge of collagen VI, and in particular, discuss its relevance in stemness and in preserving the mechanical properties of tissues, as well as its links with human disorders.

KEY WORDS: Collagen, Extracellular matrix, Skeletal muscle

Introduction
Collagen VI (ColVI) is an unusual member of the collagen family and has been studied in the past few years within the context of a remarkably wide range of tissues. It is encoded by six different genes (COL6A1, COL6A2, COL6A3, COL6A4, COL6A5 and COL6A6), and the distinctive feature of this protein is its unique supramolecular assembly, which is driven by a multi-step process that leads to the formation of the characteristic beaded microfilaments network in the extracellular matrix (ECM). ColVI exerts different roles in the tissues where it is expressed, spanning from mechanical roles, which are typical of collagen components of the ECM, to more specific cytoprotective functions; these include inhibition of apoptosis and oxidative damage, the promotion of tumor growth and progression, the regulation of cell differentiation and of the autophagic machinery, and maintenance of cell stemness.
ColVI-null (Col6a1−/−) mice, in which a targeted inactivation of the Col6a1 gene prevents the assembly and secretion of the entire ColVI protein, have largely helped to unveil many of these roles in vivo, thereby shedding new light on the relevance of this matrix component, but also of the ECM in general, in regulating a number of key cellular pathways. Several human disorders have been linked to altered expression or mutations of the genes encoding ColVI, emphasizing the importance of this protein for tissue homeostasis.

In this Cell Science at a Glance article and accompanying poster, we will summarize the current knowledge of ColVI. We will first focus on the multi-step assembly process, before moving on to the description of the distribution and expression pattern. We will discuss in detail the tissue-specific functions that have been revealed by studies in Col6a1−/− mice and in the related human disorders. We will close by highlighting how the study of this collagen has stimulated research at intersections of different areas and fields of biomedical research.

Collagen VI structure and assembly

Collagens represent a prominent component of the ECM and are often described as a superfamily, which is divided into subtypes depending on the supramolecular assemblies (Myllyharju and Kivirikko, 2004). Among the 28 identified members of the collagen superfamily, ColVI displays distinctive molecular properties that make it one-of-a-kind among all collagens.

Three genetically distinct ColVI chains were originally identified and named α1(VI), α2(VI) and α3(VI), respectively encoded by the COL6A1, COL6A2 and COL6A3 genes in humans. More recently, genomic database mining has led to the identification of three additional genes encoding ColVI chains. Owing to the sequence homology and shared domain structure with COL6A1, COL6A2 and COL6A3 genes, respectively (Fitzgerald et al., 2008; Gara et al., 2008). Several alternatively spliced variants that involve some of the vWF-A modules have also been reported for the α3(VI) and α2(VI) chains. For example, in the α3(VI) chain, the domains N10, N9 and N7 are subjected to alternative splicing in mouse tissues, and transcript variants lacking one or more of these N-terminal domains, a large part of the N3 domain or the entire N5 domain have also been found in mouse tissue and human cells (Doliana et al., 1990; Dziadek et al., 2002). Conversely, alternative splicing of the human α2(VI) transcript was found to generate three different protein variants, referred to as α2C2, α2C2a and α2C2a (Saïta et al., 1990) (see poster).

Box 1. Collagen VI chain structure

The COL6A1 and COL6A2 genes are organized in a head-to-tail fashion on chromosome 21q22.3, whereas the COL6A3 gene maps to chromosome 2q37 (Lampe and Bushby, 2005). COL6A4, COL6A5 and COL6A6 are located in tandem on chromosome 3q21. All ColVI chains contain a relatively short triple-helix domain of 335–336 amino acid residues, which are flanked by large N- and C-terminal globular regions that share similarity with the von Willebrand factor type A (vWF-A) module. The α1(VI) and α2(VI) chains are approximately 130–150 kDa in size and contain one N-terminal and two C-terminal vWF-A modules (N1, and C1 and C2, respectively) (Bonald et al., 1989). Conversely, the α3(VI), α4(VI), α5(VI) and α6(VI) are much larger, ranging from approximately 220 kDa to over 300 kDa. Although they share structural similarity at the N-terminal end, which comprises up to seven (α4, α5 and α6) or up to ten N-terminal vWF-A modules (α3), at the C-terminus they display two C-terminal vWF-A modules (C1 and C2), followed by unique regions (C3–C5). The C3 domain comprises a proline-rich sequence that in the α6(VI) chain also represents the C-terminal end. In the α3(VI) chain, C4 is a fibronectin-type III domain, and C5 is a Kunitz-like domain (Bonald et al., 1990). The murine α4(VI) chain carries a short stretch of 17 amino acid residues at the C-terminal end (C4) that is similar to a partial Kunitz domain. The C-terminus of α5(VI) contains a third vWF-A domain (C4), followed by another unique domain (C5) (Bonald et al., 1989, 1990; Bonald and Colombatti, 1989; Fitzgerald et al., 2008; Gara et al., 2008). Several alternatively spliced variants that involve some of the vWF-A modules have also been reported for the α3(VI) and α2(VI) chains. For example, in the α3(VI) chain, the domains N10, N9 and N7 are subjected to alternative splicing in mouse tissues, and transcript variants lacking one or more of these N-terminal domains, a large part of the N3 domain or the entire N5 domain have also been found in mouse tissue and human cells (Doliana et al., 1990; Dziadek et al., 2002). Conversely, alternative splicing of the human α2(VI) transcript was found to generate three different protein variants, referred to as α2C2, α2C2a and α2C2a (Saïta et al., 1990) (see poster).

Collagen VI functions and tissue distribution

Given its complex structure and variety of domains, ColVI is able to bind to different components of the ECM, thus bridging cells to the surrounding connective tissue and organizing the three-dimensional tissue architecture of skeletal muscles, tendons, bone and cartilage.

By binding to collagen IV and perlecan in the basal lamina, ColVI allows the establishment of a proper link between muscle cells and ECM (Kuo et al., 1997). Interactions with other collagens have also been reported, including collagen type I (Bonald et al., 1990), type II (Bidanset et al., 1992) and type XIV (Brown et al., 1994). Some ECM interacting molecules, such as biglycan and WARP, are thought to play a role in stabilizing and regulating ColVI secretion and assembly in the extracellular space (Hansen et al., 2012), whereas absence of ColVI has been reported to affect fibronectin deposition (Sabatelli et al., 2001). Interactions between ColVI and microfibril-associated MAGP1 glycoprotein (Finnis and Gibson, 1997), matrilin-1 (Wiberg et al., 2001), fibrillin-2 (Sasaki et al., 1995), lumican (Takahashi et al., 1993), heparin, hyaluronan (Specks et al., 1992) and the small leucine-rich-repeat proteoglycan decorin (Bidanset et al., 1992) have also been demonstrated. ColVI large tetramers that are also stabilized by disulfide bonds (≥2000 kDa). These tetramers are finally secreted and, in the extracellular space, they associate end-to-end through non-covalent bonds to form the characteristic beaded microfilaments with a beaded repeat of 105 nm, as revealed with electron microscopy (Furthmayr et al., 1983; Knupp et al., 2006; Bernardi and Bonald, 2008) (see poster).
also interacts with several membrane receptors that are involved in intracellular signaling pathways, depending on the tissue of expression (see poster and below).

**Skeletal muscle**

ColVI is one of the major components of muscle ECM and, thus, is involved in building the basement membrane of myofiber endomysium (Bönne mann, 2011). Interstitial fibroblasts are the major cell type responsible for its deposition, whereas myogenic cells, which contain factors that can influence ColVI secretion, do not express it (Braghetta et al., 2008; Zhou et al., 2008). The crucial role of ColVI in skeletal muscle is emphasized by the fact that mutations in the genes encoding ColVI chains have a causative role in several forms of inherited human muscle diseases, including Bethlem myopathy, Ulrich congenital muscular dystrophy (UCMD) and myosclerosis myopathy (Jöb siss et al., 1996; Camacho Vanegas et al., 2001; Merlini et al., 2008). Interestingly, complete ablation of ColVI in Col6a1−/− mice leads to an early-onset myopathic phenotype that is characterized by structural and functional defects of the diaphragm and other skeletal muscles (Bonald o et al., 1998). Initial studies in Col6a1−/− mice have also revealed a cytoprotective role for ColVI, as ablation of the gene triggered spontaneous apoptosis in muscle fibers that was associated with a latent mitochondrial dysfunction and organelle alterations (Irwin et al., 2003). More recent studies have demonstrated that the occurrence of dysfunctional organelles in Col6a1−/− muscle is due to defects in the regulation of the autophagic flux (Grumati et al., 2010). Lack of ColVI causes an impaired regulation of the autophagic flux, a defect that is accompanied by lower levels of Beclin 1 and BNIP3, which are key effectors in the initiation of autophagy, and by the persistent activation of the Akt–mTOR pathway under fasting conditions. Notably, analysis of muscle biopsies of UCMD and Bethlem myopathy individuals revealed a marked decrease in the protein levels of Beclin 1 and BNIP3, thereby confirming a defect in autophagy regulation in the presence of mutated ColVI (Grumati et al., 2010). ColVI has also been shown to be a key component of the niche of adult muscle stem cells (or satellite cells) and to be involved in the proper regulation of muscle stiffness; this is in agreement with the impaired self-renewal capabilities of satellite cells and defective muscle regeneration in Col6a1−/− mice (Urciuolo et al., 2013). Despite the dramatic impact of ColVI ablation on muscle fibers and on specific cell-surface pathways, such as apoptosis and autophagy, the specific cell receptors accounting for these effects and thus mediating ColVI signals in muscle, remain unknown (Irwin et al., 2003; Grumati et al., 2010). Earlier in vitro studies identified several cell surface receptors that are capable of binding to ColVI – including the α1β1, α2β1, α3β1, α10β1 and αvβ3 integrins (Doane et al., 1992; Pfaff et al., 1993; Tulla et al., 2001), as well as the chondroitin sulfate proteoglycan-4 (CSPG4; also known as NG2) (Marcelino and McDevitt, 1995; Doane et al., 1998; Petriti et al., 2005) – but it remains to be elucidated how ColVI extracellular signals are transduced within muscle fibers.

**Nervous system**

Different studies have shown that ColVI is expressed in the central and peripheral nervous system. ColVI deposition in the brain was initially found in meningeal cells (Sievers et al., 1994). More recently, Cheng and co-workers have highlighted a link between ColVI expression and Alzheimer’s disease by analyzing hippocampal Col6a1 expression in wild-type mice and in transgenic mice expressing a mutant form of human amyloid precursor protein (APP) that is associated with familial Alzheimer’s disease, as well as in human control subjects and those affected by Alzheimer’s disease (Cheng et al., 2009). The authors found that both the mRNA and protein levels of Col6a1 were higher in the samples affected by the Alzheimer’s disease mutation, in particular in the granule cells of the dentate gyrus. Neuronal cultures derived from Col6a1−/− mice display increased apoptosis compared with wild-type cultures when they are treated with Aβ-peptides, which are involved in the etiology of Alzheimer’s disease, pointing to a neuroprotective role for ColVI against Aβ-peptide toxicity (Cheng et al., 2009). An anti-apoptotic role for ColVI in the nervous system has also been suggested owing to the effects of ultraviolet (UV) irradiation on cultured neurons. In that study, addition of ColVI to the culture medium rescued UV-induced apoptosis and limited dendrite shrinkage, and ColVI was found to mediate this protection by acting through the Akt and JNK pathways (Cheng et al., 2011). These observations provided new insights into the function of ColVI in the central nervous system and also provided new perspectives for the potential role of this ECM component in regulating neuronal survival processes. Interestingly, even though its pathogenic role has not been clearly demonstrated yet, a recent study has described a disease-segregating mutation in the Col6a2 gene in a consanguineous family affected by progressive myoclonus epilepsy (Karkheiran et al., 2013).

In the peripheral nervous system, ColVI is abundantly expressed by Schwann cells and is present in the connective tissue of the endo-, peri- and epineurium (Braghetta et al., 1996; Chen et al., 2014a). It has been shown previously that ColVI has a role in regulating Schwann cell differentiation because it is expressed by immature Schwann cells in a neuregulin-dependent manner when they start differentiating into myelinating cells (Vitale et al., 2001). Our recent study has provided evidence for the role of ColVI in maintaining proper peripheral nervous system myelination and function in the sciatic nerves of wild-type and Col6a1−/− mice (Chen et al., 2014a). In that study, we showed that hypermyelination in the absence of ColVI results in altered Remak bundles (fibers responsible for sensory transmission), deficits in motor and sensory functions, and in decreased nerve conduction velocities. ColVI deficiency in peripheral nerves was accompanied by higher phosphorylation levels of focal adhesion kinase (FAK), Akt, extracellular-signal-regulated kinase (ERK) and p38 MAP kinases – all of which are known signaling pathways involved in axon myelination – whereas phosphorylation of e-Jun N-terminal kinase (JNK) decreased in Col6a1−/− sciatic nerves (Chen et al., 2014a). We also reported an important function for ColVI in peripheral nerve regeneration, which, moreover, points to this ECM molecule having a crucial role in macrophage recruitment and polarization. Indeed, we demonstrated that injury-induced nerve regeneration is impaired in ColVI-null mice owing to a failure in recruiting polarized macrophages to the injury site (Chen et al., 2014b). This is in agreement with previous studies that describe the regulated expression and secretion of ColVI from macrophages (Schnoor et al., 2008).

**Adipose tissue**

ColVI is also an abundant component of the ECM of white adipose tissue (Divoux and Clemen t, 2011). Its role has been assessed in the obese adipose tissue, where lack of ColVI results in a loose and disorganized tissue, and in adipocyte hypertrophy (Khan et al., 2009). Interestingly, lack of ColVI in the ECM surrounding adipocytes leads to the inhibition of JNK-mediated apoptotic...
signaling that is typically observed in obesity and to increased insulin sensitivity; this is owing to a higher number of adipocyte membrane caveolae, where insulin receptors reside, consistent with enhanced Akt activation upon insulin stimulation (Khan et al., 2009). Within the adipose tissue, a novel role for the cleaved C5 domain of the α3(VI) chain has also been revealed (Aigner et al., 2002). Indeed, it has been shown that the resulting peptide, which has been named endotrophin (ETP), is capable of promoting the growth of breast cancer cells that is triggered by the interaction of adipocytes with tumor and stromal cells (Park and Scherer, 2012; see Box 2). Expression analysis of distinct cellular populations in the adipose tissue demonstrates that ColVI is also produced by cells of the stromal vascular fraction (McCulloch et al., 2015), which represent the major source of adipose-derived stem cells. Interestingly, transplantation of human adipose-derived stem cells has recently been tested in Col6a1−/− mice and demonstrated their potential for therapeutic application in ColVI-related muscular dystrophies (Alexeev et al., 2014).

Bone and cartilage

ColVI is also a component of the ECM of articular cartilage and fetal bone. In the adult cartilage, ColVI is mainly concentrated in the pericellular matrix (PCM), where it is involved in the attachment and integrity of chondrocytes (Wu et al., 1987). In the fetal bone, ColVI is present in discrete fibrils and becomes restricted to the margins of bone cells and the bone surface during development (Keene et al., 1991). Studies performed using Col6a1−/− mice revealed an accelerated development of osteoarthritic joint degeneration, as well as a delayed secondary ossification process and reduced bone mineral density (Alexopoulou et al., 2009; Christensen et al., 2012). Despite a structurally intact PCM in the absence of ColVI, the alterations found in the cartilage were mostly linked to the mechanical properties of the PCM, resulting in decreased stiffness (Alexopoulou et al., 2009). This defect, in turn, increases the extent of chondrocyte swelling and osmosis-induced signaling through transient receptor potential cation channel subfamily V member 4 (TRPV4), which responds to a variety of physical signals at the cell surface (Zelenksi et al., 2015). These findings highlight the importance of ColVI in the transmission of mechanical and osmotic stresses from the ECM to the PCM, and thus to the chondrocytes, thereby identifying the importance of the PCM in transducing mechanical and physico-chemical signals (Zelenksi et al., 2015). In a different context, the use of soluble ColVI has been shown to be an important stimulus for the proliferation of both adult and osteoarthritic chondrocytes. This observation suggests that ColVI can be used for the expansion of chondrocytes, such as in autologous chondrocyte transplantation or in tissue-engineering applications (Smeriglio et al., 2015). With regard to bone, Col6a1−/− mice display abnormalities in the morphology of the knee trabecular bone structure, as revealed by the lower bone volume and connective tissue density, the reduced trabecular number and thickness, and the higher structure model index (a quantitative measure of the trabecular shape) and trabecular separation compared with those of wild-type mice (Christensen et al., 2012). Similar findings have been demonstrated in the femora of Col6a1−/− mice, which contain osteoblasts with distorted shapes and disorganized arrangement of the surrounding collagens (Izu et al., 2012). Interestingly, a reduced amount of ColVI is reported in the ECM of human osteoporotic bones (Bailey et al., 1993).

Skin

It is well known that ColVI is abundantly expressed by skin fibroblasts, and indeed, human skin biopsies and in vitro primary skin fibroblast cultures have been widely used to characterize ColVI defects in Bethlem myopathy and UCMD individuals (Lamandé et al., 1999, 2002; Sasaki et al., 2000; Zhang et al., 2002; Guandalini et al., 2009; Martoni et al., 2009). Not surprisingly, several skin abnormalities, such as keloids or ‘cigarette paper’ scars, dry skin, striae rubrae and follicular keratosis, have been described in individuals with mutations in the COL6A3, COL6A2 or COL6A3 genes (Pepe et al., 2002; Lettmann et al., 2014). A recent study also describes some COL6A6 variants that are likely to be pathogenic, but functional studies are still required to confirm their role in disease (Hunter et al., 2015). Although ColVI is absent in the epidermis, it shows a broad distribution in the dermis, including associated vasculature and nerve fibers, hair follicles and hypodermis; it is particularly abundant in the basement membrane at the epidermal-dermal junction (Keene et al., 1988; Gara et al., 2011). In contrast to the broader distribution of the α1(VI), α2(VI) and α3(VI) chains in skin, α5(VI) is found to be localized in the papillary dermis, whereas α6(VI) is found around the blood vessels (Sabatelli et al., 2011). It has been reported that variants of COL6A5 are associated with atopic dermatitis (Söderhäll et al., 2007); however, work in Col6a1−/− mice has not revealed any overt skin or wound healing defect, apart from a decrease in tensile strength (Lettmann et al., 2014). In a very recent study, we have demonstrated the involvement of ColVI in hair growth and maturation. Interestingly, although lack of ColVI delays hair growth under physiological conditions, wound-induced hair regrowth is remarkably enhanced in Col6a1−/− mice, a process that has been shown to involve the activation of the Wnt/β-catenin signaling pathway (Chen et al., 2015).

Box 2. Collagen VI in cancer

The deposition of ColVI is altered in pathological conditions, and it has been shown that the different ColVI chains are abundantly expressed in a variety of cancers in both animal tumor models and human cancer biopsies (Chen et al., 2013). High amounts of ETP are also deposited in tumor tissues (Park and Scherer, 2012). The enhanced ColVI expression favors tumor development and progression through various mechanisms. On the one hand, ColVI directly acts on cancer cells, where it binds to NG2, activating the Akt–GSK-3β–β-catenin–TGF–TEF pathway (Iyengar et al., 2005) and the phosphoinositide 3-kinase (PI3K) pathway (Cattaruzza et al., 2013), or induces epithelial–mesenchymal transition (Park and Scherer, 2012), thus promoting tumor growth and metastasis. On the other hand, ColVI is an important pro-tumorigenic factor acting on the tumor microenvironment, where it promotes tumor inflammation and angiogenesis by targeting macrophages and endothelial cells, respectively (Park and Scherer, 2012; Chen et al., 2013). Further evidence indicates that ColVI is a key factor for the response to cancer chemotherapy. It has been shown that COL6A3 is the most upregulated gene in oesalpinx-resista and cisplatin-resistant ovarian cancer cells (Sherman-Baust et al., 2003; Varma et al., 2005), and addition of ColVI promotes in vitro resistance in cisplatin-sensitive cells (Sherman-Baust, et al., 2003). In vivo findings show that COL6A3 levels are enhanced in response to cisplatin exposure in tumor cells, and inhibition of ETP confers cisplatin sensitivity to mammary tumors (Park et al., 2013). In addition, a growing body of evidence shows that ColVI is a potential biomarker for cancer diagnosis. ColVI levels in the sera of individuals with melanoma or pancreatic cancer are dramatically increased when compared with those of healthy controls (Burchardt et al., 2003; Makawita et al., 2011; Kang et al., 2014). Collectively, these findings point to ColVI as an ECM molecule that promotes tumor growth.
Other tissues
ColVI is additionally expressed by many other tissues, where it exerts a range of functions. For instance, in the heart, ColVI is secreted by interstitial fibroblasts, and although it has been reported to be overexpressed in the infarcted myocardium, studies in Col6a1−/− mice led to the paradoxical finding that lack of ColVI in fact improves cardiac function, structure and remodeling after myocardial infarction (Luther et al., 2012). In tendons, the strong mechanical properties are largely provided by uniaxially grouped collagen fibrils. Here, ColVI is localized to the peri-cellular region surrounding tendon fibroblasts and has been suggested to have a role in the establishment of the extracellular microdomains, where fibril intermediates are assembled (Izu et al., 2011). Col6a1−/− mice display disrupted microdomains and abnormal fibrillogenesis, accompanied by a decrease in maximum load and stiffness, thus clearly indicating that ColVI contributes to the maintenance of the mechanical properties of tendons (Izu et al., 2011). Furthermore, in the lung, ColVI is a component of the basement membrane and provides elasticity and mechanical support (Bober et al., 2010). An independent study has shown that a failure to secrete ColVI in annexin-A2-null (AnnA2−/−) mice is associated with an altered basement membrane structure and a decrease in cell–ECM interactions in the lung, which affects pulmonary elasticity and leads to reduced exercise tolerance (Dassah et al., 2014). Further information about the distribution of ColVI in tissues has been provided by studies that used specific antibodies against the different ColVI chains; those analyses show a differential and restricted expression of α4(VI), α5(VI) and α6(VI) chains compared with that of α3(VI). For example, α4(VI) expression is restricted to the intestinal basement membrane and a decrease in cell–ECM interactions in the lung, which affects pulmonary elasticity and leads to reduced exercise tolerance (Dassah et al., 2014). Further information about the distribution of ColVI in tissues has been provided by studies that used specific antibodies against the different ColVI chains; those analyses show a differential and restricted expression of α4(VI), α5(VI) and α6(VI) chains compared with that of α3(VI). For example, α4(VI) expression is restricted to the intestinal basement membrane and a decrease in cell–ECM interactions in the lung, which affects pulmonary elasticity and leads to reduced exercise tolerance (Dassah et al., 2014).

Conclusions and perspectives
Although the majority of the studies concerning ColVI have focused on skeletal muscles, owing to its causative link with Bethlem myopathy and UCMD, the interest in ColVI has expanded into a wide range of tissues and contexts, as we have underscored in this review. Further mechanistic studies, as well as the detailed characterization of the tissue-specific defects displayed by ColVI-null mice and comparison of these with other animal models (Telfer et al., 2010), will help us to understand in more detail the molecular basis of the different roles played by this major ECM component in various tissues under physiological and pathological conditions. We expect that, in the near future, further insights into the functions of this distinctive ECM molecule will lead to its application as a biological cue for tissue-engineering scaffolds, and perhaps even provide the basis to decipher the orphan mutations of COL6 genes in other diseases besides inherited muscle disorders.

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Competing interests
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