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Review

Collagens in the developing and diseased nervous system

T. Hubert[a], S. Grimal[a,b], P. Carroll[a] and A. Fichard-Carroll[a,b,*]

[a] INSERM U-583, Institut des Neurosciences de Montpellier, Hôpital Saint-Eloi, 80 rue Augustin Fliche, 34 091 Montpellier Cedex 5 (France), Fax: +33 4 99 63 60 20, e-mail: agnes.fichard@univ-montp2.fr
[b] University Montpellier II, F34091, Montpellier (France)

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Abstract. Collagens are extracellular proteins characterized by a structure in triple helices. There are 28 collagen types which differ in size, structure and function. Their architectural and functional roles in connective tissues have been widely assessed. In the nervous system, collagens are rare in the vicinity of the neuronal soma, occupying mostly a "marginal" position, such as the meninges, the basement membranes and the sensory end organs. In neural development, however, where various ECM molecules are known to be determinant, recent studies indicate that collagens are no exception, participating in axonal guidance, synaptogenesis and Schwann cell differentiation. Insights on collagens function in the brain have also been derived from neural pathophysiological conditions. This review summarizes the significant advances which underscore the function and importance of collagens in the nervous system.

Keywords. Collagens, neuron, nervous system, Knobloch syndrome, Alzheimer disease, axonal guidance, neuromuscular junction, Schwann cell differentiation.

Introduction

The existence of an extracellular matrix (ECM) in the brain has been the subject of a long historical controversy. It is now well established that the extracellular space, which occupies around 20% of the adult brain volume, contains several extracellular matrix components such as hyaluronan, chondroitin sulphate, aggrecan and tenascin [1, 2] which are in close contact with some neurons, forming the so-called perineuronal net [3, 4, 5]. Although collagens are cardinal components of extracellular matrices, they are rarely present in the mature nervous system. Only recently was it shown that a few of them are expressed by neurons [6–9]. Instead, collagens are principally found in a marginal position in the mature nervous system in three locations, the connective tissues associated with the nervous system, the basement membranes between the nervous system, and other tissues (muscular, endothelial) and the sensory end organs.

However, in the last decade it has become apparent that collagens play active roles during the development of the nervous system. They participate in axon guidance and synaptogenesis [10], in the terminal differentiation of myelinating Schwann cells [11] and in the establishment of the architecture of the brain [12]. Moreover, recent studies have implicated collagens, particularly those located in the basement membranes, in several pathophysiological processes. These emerging and converging data, which invite us to consider collagens as fundamental elements in the developing and diseased nervous system, will be presented here.

* Corresponding author.

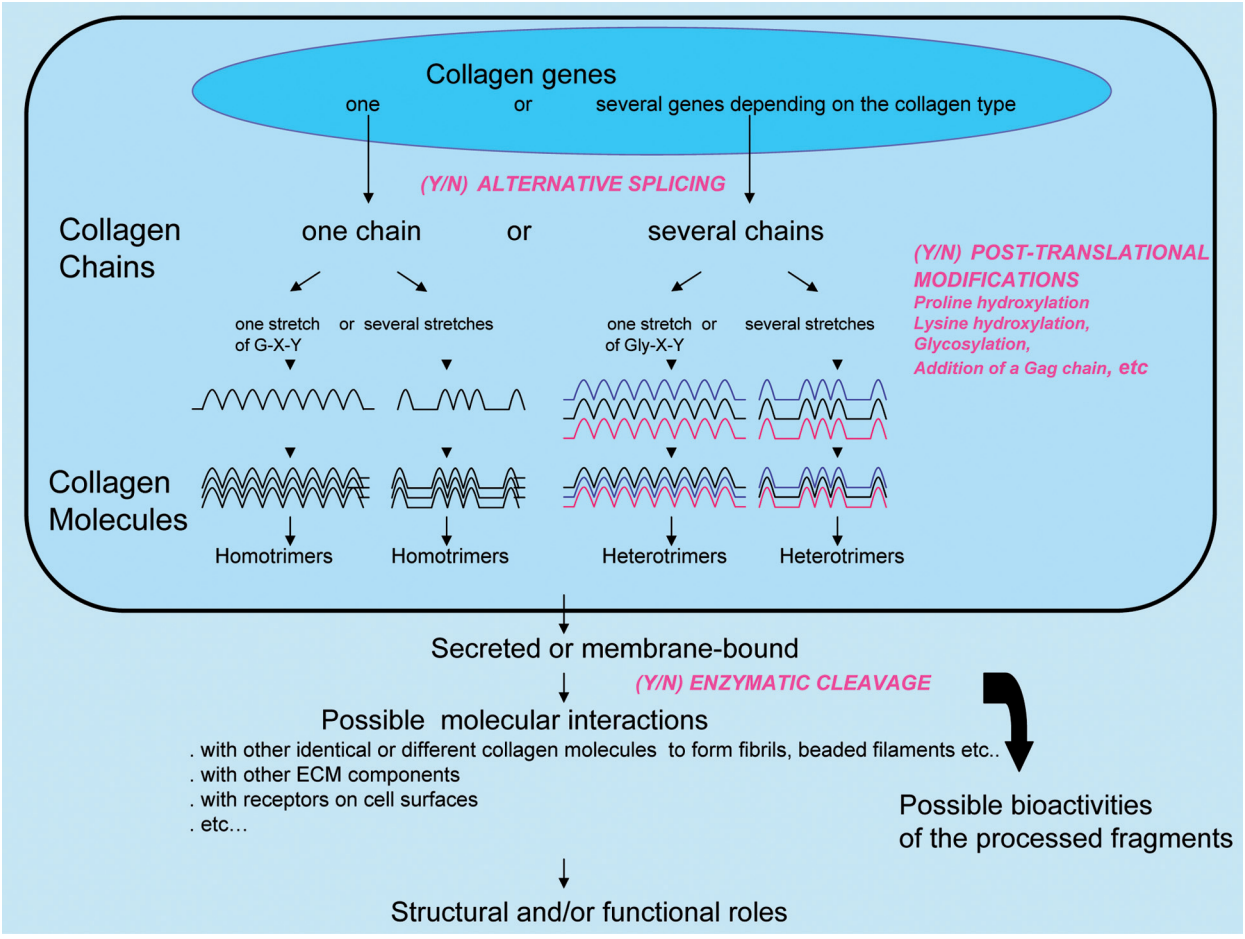

Figure 1. For a given collagen type, there can be one or several genes coding for one or several alpha chains. (As an example, there are two genes for collagen I noted COL1A1 and COL1A2, which code for two alpha chains. However for collagen XVIII, there is a single gene, noted COL18A1). The alpha chains can be composed of a unique stretch of repetitions of Gly-X-Y triplets which will allow the formation of the triple helix structure (this is the case for collagen I, II, III, V, XI, XXIV and XXVII) or the chain can comprise several stretches of triplets interrupted by non collagenous sequences (collagen XVIII is composed of 10 collagenous domains flanked by non collagenous domains). Then, the α chains assemble into trimers, (collagen I alpha chains can form two defined stoechiometries, the heterotrimer [α1(I)]2α2(I) or the homotrimer [α1(I)]3, but collagen XVIII can only form homotrimers [α1(XVIII)]3). However, as for other collagens, there exist spliced variants of collagen XVIII. There are two promoters in the COL18A1 gene and three variants of the molecule are produced). It should also be noted that hybrid molecules composed by the association of different types of collagens can also exist (collagen V/XI trimers). Collagen molecules undergo several post-translational modifications, some of them being unique to collagens, like the hydroxylation of some proline and lysine residues, and further glycosylation of these hydroxylated lysine residues. These modifications occur before triple helix formation but the trimer can be further glycosylated (As an example, collagen XVIII carries heparan sulphate glycosaminoglycan chains). After the biosynthesis process, collagen molecules can be either bound to the cell membrane (collagens XIII, XVII, XXIII, XXV) or secreted. Further enzymatic modifications can occur extracellularly (such as the N and C propeptide cleavage of fibrillar collagens, the oxidation of lysil residues on fibrillar collagen molecules which will allow cross-linking between molecules and thus fibril formation or the C-terminal cleavage of collagen XVIII which will generate the endostatin fragment). For a defined collagen type, the number of alpha chains, the possibility of alternatively spliced variants, their different possible stoechiometries, the intracellular and extracellular enzymatic modifications should be taken into account. (y/n): Yes or no; depending on the collagen chain or the collagen type, various modifications can occur.

Structure of collagens

Twenty-nine collagens numbered I to XXIX have been reported in the literature. However, the molecule formerly named collagen XXIX actually corresponds to a new variant of collagen VI [13, 14]. Their common characteristics include the following: 1) they are transmembrane or extracellular molecules, 2) they are formed by three chains named α chains. For a defined type of collagen, one or several α chains can exist and they can assemble into homo or heterotrimers (Fig. 1). This implies that, for a defined collagen type, various isoforms with distinct functions can exist, 3) they form a triple helical structure which is determined by a repetition of Gly-X-Y triplets in the primary sequence of each α chain. It has to be noted that X and Y could represent any amino-acid but X is often a proline and Y a 4- hydroxyproline. 4-hydrox-

yproline residues are critical for the stability of the triple helix. Some of the collagens have a unique stretch of Gly-X-Y while others have several which are interrupted by non-collagenous (NC) sequences. Structural heterogeneities among the various collagen types is even broader and include the existence of alternatively spliced variants for some α chains, the possible formation of hybrid molecules resulting from the assembly of α chains from different collagen types and the addition of covalently linked glycosaminoglycan (Gag) chains to some of them. Collagen molecules can assemble to form several suprastructures and, based principally on this criterion, seven different subfamilies have been delineated. The quantitatively major one comprises collagens that are able to aggregate to form fibrils. This sub-family encompasses collagen I, II, III, V, XI, XXIV and XXVII. The diameter and length of the fibrils vary depending on the tissue but can reach respectively 500 nanometres and a few millimetres [15]. To these fibrils, other collagens can be associated, and are thus called the Fibril-associated collagens with interrupted triple helices (FACITS), among which are found collagens IX, XII, XIV, XVI, XIX, XX, XXI, XXII and XXVI. Collagens forming networks include collagens IV, VIII and X. Collagen VI forms beaded filaments and collagen VII forms anchoring fibrils between the basal lamina and the dermis. Collagens XV and XVIII release an anti-angiogenic non collagenous fragment called endostatin. Collagens XIII, XVII, XXIII and XXV are transmembrane proteins. One should also note that collagen domains can be found in several other molecules like C1q, gliomedin etc. [16].

There is thus a vast variety of structural differences between collagens and, as a consequence, in the molecular partners to which they can bind and in their structural and physiological roles in tissues. It is indeed now well-documented that, beyond their contribution to the architecture of tissues, this group is multifunctional, being involved in a wide variety of biological processes ranging from dorso-ventral patterning in the embryo [17] to tumorigenesis [18].

Occurrence of collagens in the nervous system

As already mentioned, in the mature nervous system collagens are expressed in the layers of connective tissue that surround the central (CNS) and peripheral (PNS) nervous systems, in basement membranes and in sensory end organs. Concerning the connective tissues associated with the nervous system, the neural tissue in the CNS is protected by the meninges which, from the outer to the inner part, comprise the dura mater and the leptomeninges (arachnoid and pia mater) [19]. The pia is separated from the neural tissue proper by a basal lamina along which are tightly apposed astrocyte processes forming the glia limitans. A dense network of collagen fibres is observed in the dura mater [20] but collagen fibres are also present in the leptomeninges, particularly at the spinal level [21]. These fibres likely contain collagen I [22] but the presence of collagen II transcripts in the dura mater in human has also been reported [23] and, to our knowledge, the exact composition of the fibres in the meninges has not yet been determined. In any case, these fibres, which are the canonical example of collagens, are absent from the brain itself and this it is probably the reason why the roles of collagens in the nervous system have been generally underestimated. Inhibition of fibril formation in the brain could be the consequence of interactions between the astrocytes and the meninges. Indeed, *in vitro*, astrocytes are able to secrete fibrillar collagen but *in vivo* their collagen synthesis is suppressed [24]. Two mechanisms are suspected to be involved: first, a secretion by the meninges of an unknown diffusible inhibitory factor and, second, an inhibitory autocrine loop on astrocytes involving Epidermal Growth Factor [25]. Following injury, inhibition of astrocytic collagen synthesis could be attenuated, resulting in a glial scar. In the PNS, nerves are ensheathed in three layers which are designated from the outer part to the inner part, the epineurium, the perineurium and the endoneurium. Collagen fibres are present in these sheaths forming a wavy pattern in the epineurium which protects the nerve from external stress [21]. Collagens XII and XIV are also detected in these layers, which is consistent with the fact that these collagens occur preferentially in tissue where collagens I fibres are present [26].

Basement membranes (BM) are thin specialized extracellular matrices located at interfaces between tissues. In nervous tissues, they are present, for instance, at the neuromuscular junction [27] or between the nervous and the vascular systems. In the latter case, the basement membrane participates in the neurovascular unit which forms the blood-brain barrier or the blood-nerve barrier and which maintains neuronal homeostasis [28, 29]. The composition of the BM includes collagen IV, quantitatively the most abundant protein, as well as laminins, perlecan, nidogen and other components that are heterogeneously distributed. There are six collagen IV α chains which can assemble into three different combinations, [α1(IV)]2 α2(IV), [α5(IV)]2 α6(IV) and α3(IV) α4(IV) α5(IV). In the nervous system, all isoforms are present but in distinct locations [30]. [α1(IV)]2 α2(IV) and [α5(IV)]2 α6(IV) are present in the pia mater basement membrane. [α1(IV)]2 α2(IV) is located in the basement membrane

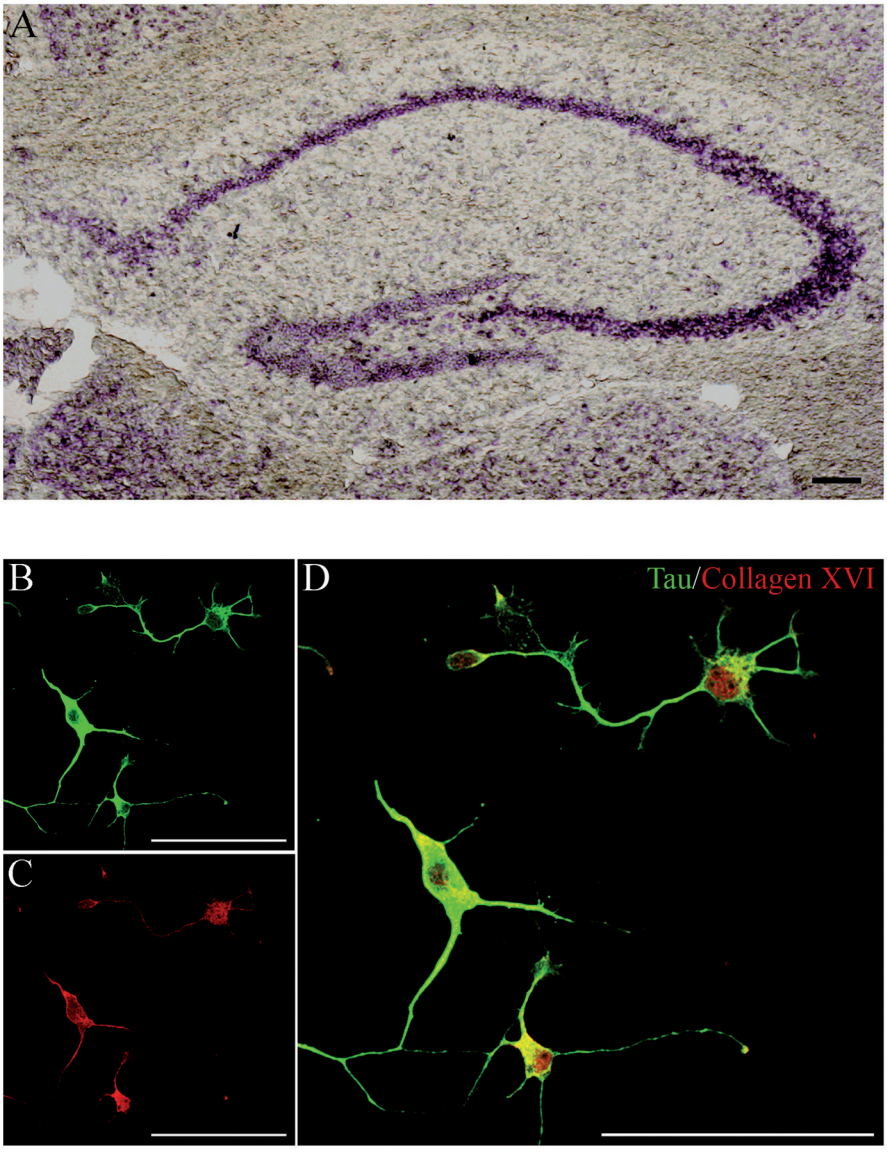

Figure 2. (*A*) Expression of collagen XVI in the adult mouse hippocampus is revealed by in situ hybridization. (*B, C, D*) Collagen XVI protein is expressed in the neuronal cell body, along neurites and also at the growth cone in cultures of mouse hippocampal neuron cultures at E18. (*B*) Labelling with anti- Tau, (Sigma) in green. Tau is a marker of neurons, (*C*) Labelling with anti-collagen XVI, (generous gift of S. Grassel) in red, (*D*) Merged image.

around capillaries and the α3(IV) α4(IV) α5(IV) heterotrimer is found in the subependymal basement membrane in the choroid plexus. This latter isoform is also present in the renal glomeruli and could thus be involved in the degree of permeability of basement membranes. These heterogeneities in the distribution of the different isoforms in the basement membranes probably reflect functional specificity. Among the other collagen family members, collagens XV and XVIII are also frequently detected in basement membranes. Noticeably, although it is expressed around most capillaries, collagen XV is absent from those forming the blood brain barrier [31].

It has to be remembered that sensory end organs such as inner ear hair cells, skin receptors, muscle spindles, etc. are surrounded by collagens [32, 33] but the discussion of collagens in these structures is beyond the scope of this review.

In the nervous system proper, the extracellular matrix in the adult can form a perineuronal net which surrounds certain neurons. This net is thought to have a major role in activity-dependent plasticity and to be involved in neuroprotection [34–37]. It is composed mainly of hyaluronan, chondroitin sulphate, aggrecan and tenascin [3–5] but is devoid of collagens. Independently of the perineuronal net, two

studies have shown that collagens can be found in the nervous system proper. Indeed, collagen XVII is detected at membranes of neuronal cell bodies and at the proximal axon in several neuronal locations in the CNS [38]. Collagen XVI is found apposed to neuronal cell bodies in the sensory ganglia and CNS expression was also noticed (Fig. 2). Collagen XIII is expressed in the developing mouse nervous system and promotes neurite outgrowth *in vitro* [6]. For both collagens XVI and XIII *in vitro* expression by neurons has been demonstrated. Apart from acting as a permissive substrate for neuronal growth and migration, collagen XIII could be involved in angiogenesis in the brain. Indeed, transgenic mice expressing a truncated form of collagen XIII display reduced microvascularization in the brain [39]. However, endothelial cells of capillaries and large blood vessels lack collagen XIII. Knowing that neurons can secrete collagen XIII, it is tempting to speculate that neurons could control the pattern of vascularization through collagen XIII. Moreover, considering that collagen XIII strongly binds to fibronectin [40] and that fibronectin has a powerful angiogenic activity on CNS endothelial cells [41], it would be interesting to evaluate the combined action of the couple collagen XIII/fibronectin on brain angiogenesis.

Altogether the occurrence of collagens in the mature nervous system appears limited, however, if the developmental and the pathophysiological states are taken into consideration, most of the collagens are expressed in association with the nervous system (Table 1). Little or no nervous system expression was noticed for collagen X [42], collagen XX, [43] collagen XXII [44] collagen XXIV, [45], collagen XXVI, [46] and collagen XXIX [47]. In the following, we present what is known about the influence of collagens on neural development and neuronal pathologies.

Collagens in neuronal development

Axonal growth and guidance. In search of their targets, developing axons extend on suitable extracellular substrates which can support their growth. Collagen I is generally considered as such a favourable substrate [48, 49]. Several ECM molecules also provide cues to orient axonal growth and to allow accurate patterning. This is the case for collagen XVIII which was shown to be involved in motor axon pathfinding in the zebrafish [50]. In this model, collagen XVIII is modified by a lysyl hydroxylase (LH3, diwanka) and, once secreted in the ECM, it subsequently becomes a suitable substrate for motoneuron growth cone migration. Lysyl hydroxylases 1, 2 and 3 (LH1, LH2, LH3) catalyze the hydroxylation of lysine residues in collagens which enable carbohydrate unit attachment, and LH3 possesses a glucosyltransferase and a galactosyltransferase activity. Glycosylated collagen XVIII secreted by the myotome allows selective adhesion of motoneuron axons. In mice, *null* targeted mutation of LH3 leads to an early embryonic lethal phenotype due to abnormal biosynthesis of collagen IV and subsequent disrupted basement membranes [51]. Thus, the role of LH3 mediated glycosylation of collagen XVIII in mammalian neuronal development could not be determined. More sophisticated transgenic mouse models should allow the resolution of this question.

Another key step in the development of the nervous system is the projection of axons to their final destination targets. In the zebrafish, a mutation on the *dragnet* gene, which encodes the α5 chain of collagen (IV) results in inappropriate targeting of retinal axons onto the tectum [52]. A similar phenotype is observed in zebrafish mutants, in which heparan sulphate proteoglycans are degraded by heparitinase. The authors of the study suggest that perturbed deposition of collagen IV along the tectum in *dragnet* mutants could lead to abnormal anchoring of HSPG in the extracellular matrix and subsequently to mispatterning of neuronal projections. In humans, mutations of the α5 chain of collagen (IV) lead to Alport syndrome, which is characterized by kidney and hearing disorders and to some extent to ocular and neurological deficits [53, 54]. As is the case for collagen XVIII in motor axonal pathfinding, the involvement of collagen IV in axonal targeting reported in the zebrafish has to be further investigated in mammals.

It was also suggested that collagen IX could act through its chondroitin sulphate chains as a repellent molecule for growing axons. Collagen IX is expressed by the posterior sclerotome of the somite and thus could participate in the segmentation of the peripheral nervous system [55]. However, no deficiency in the PNS segmentation was observed in COL9A1 *null* mice [56, 57].

Thus, growing evidence suggests that collagens are important molecular components of the growth cone guidance and axon targeting mechanisms [10].

Formation of the neuromuscular junction. The neuromuscular junction is undoubtedly the most studied synapse. The synaptic cleft at the neuromuscular junction contains a dense basement membrane which differs molecularly from the extrasynaptic basal lamina covering the myofibrils. Much work has been devoted to the understanding of how synaptogenesis is achieved during development [58]. One molecule of the extracellular matrix, agrin, has been shown to be a

Table 1. Expression and roles of the collagens present in the nervous system.

Collagen type (known supramolecular assembly) *Gene*	**Expression and/or role in the nervous system**	**References**
Collagen I and III (fibril-forming) *COL1A1,COL1A2,COL3A1*	Expressed in the meninges.	[22]
	Neurological defects associated with osteogenesis imperfecta.	[98–102]
Collagen II (fibril-forming) *COL2A1*	Present in the developing mouse brain of 9.5- to 14.5-day fetuses.	[77, 23]
	Expression in hippocampus and thalamus.	[135]
	Expressed by Schwann cells	[69]
Collagen IV (sheet forming) *COL4A1,COL4A2, COL4A3, COL4A4, COL4A5, COL4A6*	Involved in the development of the neuromuscular junction.	[60]
	Mutations in COL4A1 are associated with intracerebral hemorrhages and porencephaly.	[81–84]
	Injection of collagen IV antibody improves axonal regeneration following injury in the CNS.	[132]
	Associated with axonal regrowth in the injured spinal cord.	[130]
	Present in the basement membranes in the pia mater in the subendothelial basement membranes and in the subependymal basement membrane in the choroid plexus.	[30]
	Present in fractone, in relation with stem cell niche.	[75–76]
Collagen V (fibril-forming) *COL5A1; COL5A2, COL5A3, COL5A4*	Expressed in the PNS by Schwann cells.	[68]
	Inhibits axonal outgrowth.	
	Required for Schwann cell myelination.	[11]
Collagen VI (beaded filaments) *COL6A1, COL6A2, COL6A3, COL6A4, COL6A5,COL6A6*	Marker of Schwann cell differentiation.	[70, 136]
Collagen VII (anchoring fibril) *COL7A1*	Expressed in the pituitary.	[137]
Collagen VIII (hexagonal networks) *COL8A1, COL8A2*	Present in the meninges.	[138, 139]
	Upregulated during repair processes in the mouse brain. Expressed by astrocytes in culture.	[140]
Collagen IX (FACIT) *COL9A1, COL9A2, COL9A3*	Expressed in the meninges (chick).	[141]
	Potentially involved in the peripheral nervous system segmentation by inhibitory effects on axonal outgrowth.	[55]
Collagen XI (fibril-forming) *COL11A1, COL11A2*	Expressed in the frontal and occipital lobe of the brain during human development.	[78]
Collagen XII (FACIT) *COL12A1*	Present in the meninges during development.	[142]
Collagen XIII (transmembrane domain) *COL13A1*	Strongly expressed in CNS and PNS during development. Expressed by neurons in culture.	[6]
	Promotes *in vitro* axonal growth.	
	Absence in human fetal tissue (15–19 gestational week).	[143]
Collagen XIV (FACIT) *COL14A1*	Present in nerve during development (chick).	[26]
Collagen XV *COL15A1*	Expressed in peripheral nerves.	[31]
	Present in most capillaries but absent from those forming the blood-brain barrier.	
Collagen XVI (FACIT like) *COL16A1*	Low expression in the brain in the adult.	[144]
	Expression in the spinal nerves during development and up-regulated in the dorsal root ganglia following injury. Secreted by neurons in culture.	[8]

Table 1 *(Continued)*

Collagen type (known supramolecular assembly) *Gene*	**Expression and/or role in the nervous system**	**References**
Collagen XVII (transmembrane domain) *COL17A1*	Detected in the soma and proximal axons of human CNS neurons.	[9, 38]
Collagen XVIII *COL18A1*	Mutations responsible of Knobloch syndrome characterized by neural tube closure defects.	[12, 88]
	Present in the choroid plexus and in the pial and endothelial basement membranes. Absence leads to hydrocephalus.	[95] [121, 122]
	Accumulation in amyloid plaques in Alzheimer's disease.	[50]
	Together with myotomal diwanka (lh3) glycosyltransferase, collagen XVIII is involved in motor axon patterning in the zebrafish.	
Collagen XIX (FACIT) *COL19A1*	Expressed in the cerebral cortex and hippocampus of the newborn brain.	[145]
Collagen XXI (FACIT) *COL21A1*	Low level in the brain.	[146]
Collagen XXIII (transmembrane domain) *COL23A1*	Brain and dura mater expression. Released form in the brain.	[147, 148]
Collagen XXV (transmembrane domain) *COL25A1*	Collagen-like Alzheimer amyloid plaque component (CLAC).	[7]
Colllagen XXVII (fibril forming) *COL27A1*	Gene first identified as a brain-derived cDNA. Little expression in the brain.	[149] [150]
Collagen XXVIII *COL28A1*	Strong expression in the developing peripheral nervous system. Detected in the developing and mature sciatic nerve at the basal lamina of certain Schwann cells	[71]

fundamental organizer of this synapse [59]. However, recent data indicate that several other organizers are needed, such as FGFs, beta-2 laminin and also collagen IV [60]. These organizers act sequentially, and two different roles for collagen IV at different developmental time points have been defined. Indeed, collagen α2(IV) chains are involved in the differentiation of motor nerve terminals being implicated in the clustering of the neurotransmitter vesicles, while collagen α3(IV) and α6(IV) chains, are essential in the adult to maintain the structure of the synapse. Interestingly, for all three chains, the synaptic organizer activity lies within the non collagenous NC1 domain. The exact intracellular pathways induced by these collagens remain to be determined.

In *C. elegans*, collagen XVIII (CLE-1) has also been shown to be involved in neuromuscular synaptogenesis [61]. Collagen XVIII is localized near but not strictly at the synapse. However, loss-of-function mutants exhibit defects in synaptic organization and transmission. The underlying mechanism has not been unravelled.

Schwann cell differentiation. Glial cells are more numerous than neurons in the human nervous system. In the CNS, this population is composed of oligodendrocytes essential for myelination of nerve fibres, astrocytes, which apart from their supportive role for neurons are now acknowledged as regulators of synaptic transmission [62], and the microglia which have an immune function. In the PNS, the glial population comprises the satellite cells present in the ganglia and the Schwann cells around axons. There are few reports associating collagens with glial cells in the CNS except for their expression in gliomas [63]. However, in the PNS, collagens have been shown to be involved in Schwann cell development. All nerve fibres in the PNS are wrapped by Schwann cells which are, in turn, surrounded by a basal lamina. Nerve fibres can be either myelinated or unmyelinated and thus ensheathed by either myelinating or unmyelinating Schwann cells. During development, Schwann cells originate from the neural crest and evolve, through a process depending on neuregulin signalling via NRG1-III, either towards a non-myelinating or a myelinating fate [64, 65], (Fig. 3). Together with

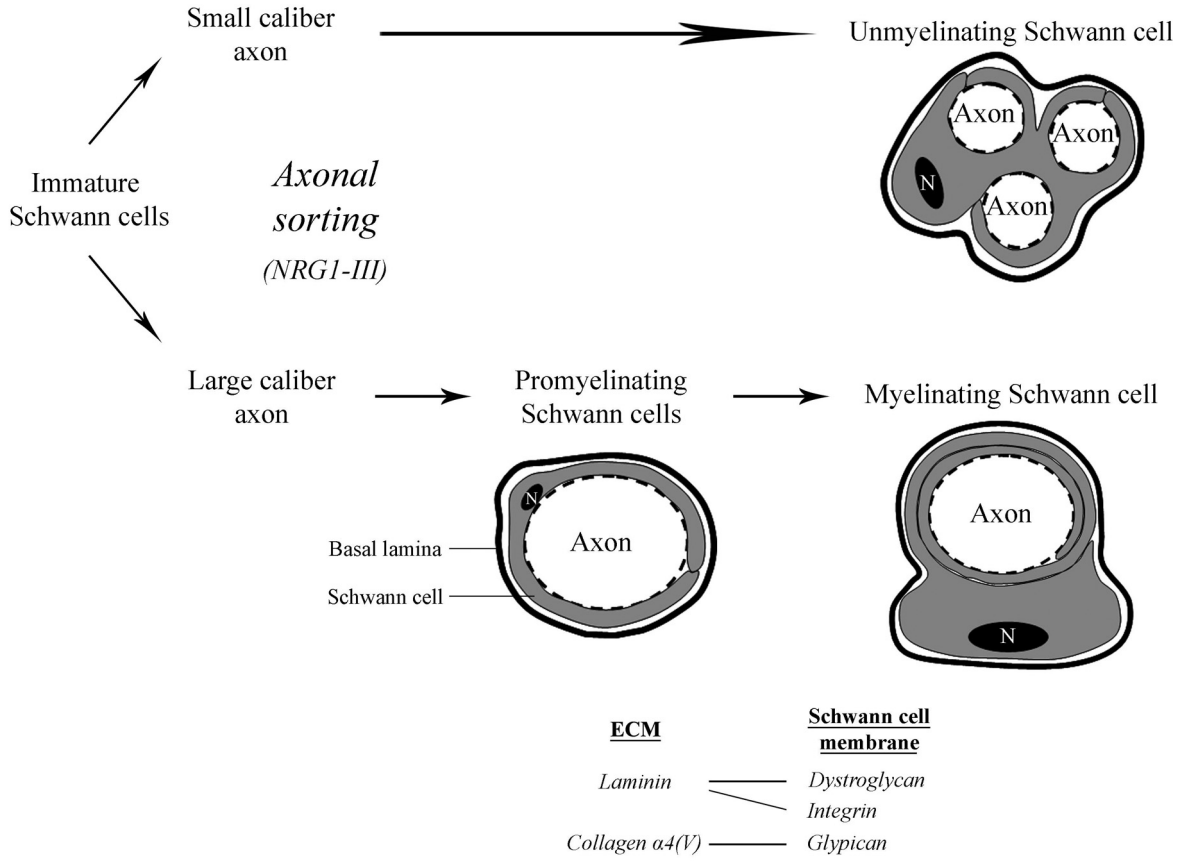

Figure 3. Schwann cell precursors can differentiate into myelinating or non myelinating Schwann cells depending on the threshold levels of NRG1 type III expressed by axons. Through their interactions with integrins and dystroglycan, laminins present in the basal lamina (bold line) surrounding Schwann cells regulate myelination [151] and stabilize the myelin sheath [152]. Collagen α4(V) binding to glypican could participate to the end differentiation of Schwann cells.

neuregulins, laminins present in the basal lamina through their interaction with integrins and dystroglycan have been shown to be determinant for Schwann cell differentiation and myelination [66] while collagen V is particularly associated with myelination. Collagen V is a fibrillar collagen present in minor quantities in tissues and, for which, four α chains are known [67]. The collagen α4(V) chain, which associates into heterotrimers with α1(V) chains, is strongly expressed by Schwann cells during development at the timepoint where myelination occurs [68]. In their noncollagenous N-terminal domain, α4(V) chains contain a site of high affinity for glypican, a lipid anchored cell surface proteoglycan which is expressed on Schwann cell membranes. When glypican expression is suppressed in culture by siRNA transfection, the adhesion of Schwann cells to collagen V is perturbed as is myelin formation, through mechanisms that are still to be elucidated [11]. Together with laminin/integrins and laminin/dystroglycan interactions, α4(V)chain/glypican association could thus be crucial in the terminal differentiation of Schwann cells. Interestingly, three other collagens, collagens II, VI and XXVIII, are linked to Schwann cell differentiation. Collagen II is expressed by immature Schwann cells as well as by both unmyelinated and myelinated mature Schwann cells [69]. Transcription of COL6A1 by Schwann cell precursors was suggested to evolve in the time course of their differentiation, being under the influence of neuregulins first, and then depending on other unknown signals [70]. The physiological significance of this change, however, is not known. Recently, collagen XXVIII was shown to be expressed in the basement membrane surrounding certain Schwann cells [71]. These studies raise more questions than answers and more work is needed to determine the exact roles of these three collagens in the physiology of Schwann cells.

Although not strictly viewed as a collagen, we shall also consider here the role of gliomedin, a transmembrane protein harbouring a collagenous domain.

Proteolytic shedding of gliomedin generates trimers which bind to heparan sulphate proteoglycan. They are detected at nodes of Ranvier and through interactions with cell adhesion molecules (namely neurofascin and NrCam), they provoke the clustering of sodium channels, which is necessary for proper saltatory conduction [72, 73].

Collagen and neural stem cells. Interestingly, collagen IV could also be involved in neurogenesis during development as well as in the adult. Indeed, collagen IV was shown to promote neuronal differentiation from progenitor cells *in vitro* [74]. Moreover, collagen IV together with collagen I is found in fractone, an extracellular matrix structure which is present in the lateral wall of the ventricules. This location is one of the main neural stem cell niches in the adult brain. Fractones are in direct contact with neuronal progenitors and, by binding growth factors such as FGFs, could be involved in regulating adult neurogenesis [75, 76].

Collagens present during brain development without any associated function. Collagens II and XI, which are well known for being key components of cartilage matrix, are also present in the brain during development [77, 78]. The specific localization of collagen II in the neural tube suggests that it could be involved in neuroblast differentiation. No more is known about this, but since recent data argue for the possible transdifferentiation of adult mesenchymal cells into neural cells [79, 80], knowing if there is a specific cell type secreting collagen II during brain development might be a relevant issue.

Neurological disorders associated with collagen mutations

Perinatal haemorrhages and porencephaly. Apart from its previously described role in the establishment and maintenance of the neuromuscular junction, collagen IV also plays a role in the CNS. In COL4A1 mutant mice, the basement membranes around blood vessels are particularly affected, leading to perinatal haemorrhages [81]. A similar phenotype is observed in humans, where COL4A1 mutations have been reported [82, 83, 84]. These are principally mutations of one of the conserved glycine residues present in the repeating Gly-X-Y sequence. As observed for α5(IV) chain glycine substitutions [85], data on α1(IV) mutations converge to indicate that triple helix formation is defective and that, in most cases, abnormal molecules are retained in the cytoplasm or, if secreted, could rapidly be degraded. In this respect the absence of secreted molecules due to missense mutations on glycine residues in humans could mimic the phenotype of the targeted disrupted gene in mice. A correlation between the severity of the phenotype in COL4A1 point mutation carriers and the nature of the substituting residue and its position in the chain must still be investigated. Moreover, even among carriers of the same mutation, clinical expression of the disease varies [86] but, in some cases, perinatal vascular accidents leading to porencephaly (cavity filled with cerebrospinal fluid in the cerebral hemispheres) have been reported. Depending on the location of the cysts, porencephaly can induce severe phenotypes such as hemiplegia, epilepsy, mental retardation. Recurrent intracerebral haemorrhages could also be observed later in life. Although not much is known about how these factors are involved in the regulation of angiogenesis, one should mention that three anti-angiogenic fragments called arresten, canstatin and tumstatin are derived from collagen IV [87, 88]. Interestingly, canstatin has been shown to have an inhibitory property with regard to tumour growth in an animal model of ocular cancer with brain metastasis [89]. In addition to angiogenesis defects, neuronal ectopia is observed in mice lacking both the α1 and α2 isoforms of collagen IV due to the disruption of the pial basement membrane [90].

Knobloch syndrome. Mutations in COL18A1 cause Knobloch Syndrome. This syndrome is an autosomal recessive disorder [12] mainly characterized by severe eye defects including high grade myopia, vitroretinal degeneration, retinal detachment, abnormal eye vasculature and CNS malformations in the occipital regions resulting in encephalocele (neural tube closure defect). High variability in the clinical phenotype is observed [91]. Heterotopia and pachygyria (thicker convolutions of the cerebral cortex) were noted in some cases suggesting abnormal neuronal migration [92].

Although there is only one collagen XVIII α chain, three different isoforms which differ in their N-terminus can be generated from the COL18A1 gene. Proteolytic cleavage of its C-terminal generates a 20 kDa peptide called endostatin [87] which has a powerful anti-angiogenic property and collagen XVIII/endostatin is now viewed as one of the elements regulating angiogenesis [93]. Another proteolytic fragment of collagen XVIII located in the N-terminal domain of the molecule contains a frizzled motif which could act by inhibiting Wnt signalling [94]. Collagen XVIII null mutant mice are not a completely appropriate model for the understanding of the Knobloch syndrome in the brain. Indeed, if these mice present hydrocephaly, a symptom coherent

with the ventricular dilatation observed in Knobloch patients [95], they never exhibit encephalocele. Hydrocephaly observed in collagen XVIII *null* mice results from the broadening of the choroid plexus basement membrane which thus probably affects cerebral spinal fluid production. Interestingly this phenotype was observed only in mice with a specific genetic background, suggesting that additional factors contribute to the emergence of the pathology. This could also be relevant to the difference in the encephalocele phenotype in mice and men. Since Wnt signalling is known to intervene in neural tube closure [96], it is tempting to suggest that the encephalocele could result from the loss of interaction between the N-terminal frizzled motif of collagen XVIII and Wnt signalling molecules. This hypothesis, however, must be tested, but the specific neurological defects observed in Knobloch syndrome might not be simply related to defective angiogenesis. Indeed, the eye but not the brain vasculature is affected by the lack of collagen XVIII in the mutant mice [97] and the pial and cerebral blood vessel basement membranes appear normal. Further studies are needed to determine the exact role of collagen XVIII in basement membrane and to understand why the eye and the brain are particularly affected by its mutation.

Osteogenesis imperfecta. Osteogenenesis imperfecta (OI) is characterized by bone fragility resulting from autosomal dominant mutations on the COL1A1 and COL1A2 genes. Several studies reported alterations in the CNS including hydrocephaly, underdevelopment of the cerebellum and microvascular defects [98–101]. At the cellular level, presence of nests of neuroblasts and lissencephaly indicate that neuronal migration could be impaired [102]. Although these data could suggest that collagen I is directly involved in neuron migration, two other plausible hypotheses might explain this phenotype [102]. First, particularly in severe forms of OI, fragility of the skull could result in *in utero* trauma. The scarring process taking place following this injury could impair the migration of neurons. Second, modification of the vasculature noticed in OI, which is consistent with the presence of collagen I in the vessel walls, could also indirectly affect neuronal migration. Indeed, during development migrating neuroblasts are guided towards and close to the blood vessels [103]. Analysis of mouse models of OI could potentially help to discriminate between these hypotheses.

Collagens in neural pathologies

Tumour and Peripheral neuropathy. Altered secretion of various collagen types has been reported in several pathological processes such as diabetes, which can lead to peripheral neuropathy [104], or tumours. These include both PNS tumours such as Schwannomas, neurofibroma and malignant peripheral nerve sheath tumours [105, 106] and CNS tumours like gliomas, medulloblastomas and fibrous tumours of the meninges [107, 108]. This appears consistent with the known roles of collagens in key steps (adhesion, motility, and angiogenesis) of tumour progression that also occur in non neuronal tissue [109, 110] and it will not be further discussed here.

Alzheimer's disease. Collagens have recently been implicated in Alzheimer's disease (AD). The pathological hallmarks of AD are intraneuronal tau-rich neurofibrillary lesions and extracellular senile plaques [111]. These plaques contain high amounts of amyloid beta peptide (Aβ) generated by proteolysis of a transmembrane protein called amyloid precursor protein (APP). Several proteolytic variants can be generated by APP proteolysis, among which the Aβ 1–42 variant, which is more hydrophobic and amyloidogenic. Aβ monomers can assemble into oligomers and could form protofibrillar and fibrillar aggregates that are found in the senile plaques. Whether Aβ deposition and fibrillization is a cause or a consequence of the disease is still in debate [112]. Aβ can interact with various components present at the neural membrane or in the senile plaque [113, 114]. In attempts to identify new molecular constituents in the aggregates, a collagenous component called CLAC, collagenous Alzheimer amyloid plaque component, (also called AMY) was discovered [7, 115]. CLAC was shown to be synthesized by neurons and to represent the furin cleaved extracellular domain of the transmembrane collagen XXV [7]. Both the furin cleaved secreted (sCLAC/sCollagenXXV) and the membrane tethered (pCLAC/pCollagenXXV) forms can bind to Aβ deposits. *In vitro*, two binding sites for Aβ were identified on CLAC, one in the collagenous domain 1 and one in the non collagenous 2 domain [116, 117]. It was shown that CLAC could favour the resistance of Aβ aggregates to protease [118] and two studies converge to show that CLAC reduces Aβ fibril growth [117, 119]. Interestingly, collagen IV was also shown to prevent Aβ protein fibril formation [120]. Endostatin/collagen XVIII secreted by neurons has also been detected in amyloid plaques [121, 122]. Recombinant insoluble collagen XVIII/endostatin has been shown to form fibrils with a cross B-sheet structure that resembles amyloid fibrils and endostatin/collagen

XVIII aggregates also appear toxic to neuronal cells *in vitro* [123, 124]. It should be noted that, apart from these collagens, two other proteins with collagenous domains, namely C1q [125] and scavenger receptor type A [126] can bind to Aβ amyloid. Whether the triple helical structure is a key feature in this binding, however, remains to be elucidated. Apart from the classical senile plaque, amyloid deposits can also occur in the cerebral vasculature. Vascular amyloidosis can result from pathological states other than AD such as stroke and seizures and are grouped under the term cerebral amyloid angiopathy (CAA) [127]. The molecular constituents of these amyloid plaques differ from those observed in classical senile plaques and this also holds true for collagens. Indeed, CLAC is not found in CAA but collagen XVIII/endostatin is found both in CAA and senile plaques [121, 122]. More studies are needed to evaluate what roles the above collagens might play in senile plaque formation *in vivo*, and if they could be involved in the diagnosis and the therapeutic issues of this disease.

Collagens in nerve injury and nerve repair

Collagen I is an adhesive substrate for many types of neurons. As a biomaterial, collagens have been widely used to guide nerves in the regeneration processes that follow traumatism in the PNS [128]. These collagen based nerve conduits are now designed to release neurotrophic factors in order not only to guide the axons but also to favour their growth. However, following injuries, deposition of collagens could be an indirect cause of axonal regeneration impairment in the CNS. Indeed, response to traumatic damage in the CNS includes the formation of a scar by inflammatory cells and astrocytes which react by overexpressing molecules such as chondroitin sulphate proteoglycan (CSPG). CSPG as well as myelin debris found at the site of injury constitute an unfavourable environment for axonal regrowth [129]. Some of these inhibitory molecules could potentially bind to collagens (collagen IV but also to collagens I, III and V and in some cases VIII) that are also secreted at the site of injury [49]. Thus, although collagens cannot be considered strictly responsible for regeneration failure, they could, through their interaction with axonal growth inhibitory molecules, indirectly prevent or favour axonal growth [130, 131]. They could thus represent a target for therapeutic intervention. As an example, injection of collagen IV antibody was shown to improve regeneration after a mechanical transsection of postcommissural fornix in the adult rat [132]. Formation of a collagenous scar also occurs in the PNS and could attenuate nerve repair [133]. Peripheral nerve injuries induce profound changes that include morphological rearrangements, apoptosis of neurons, proliferation and activation of glial cells in the sensory ganglia where the soma of sensory neurons is located. We have shown that secretion of collagen XVI in close apposition to sensory neuron cell bodies is strongly increased following axotomy of the sciatic nerve [8]. What signals regulate these changes and what are their consequences in terms of regeneration and neuropathic disorders remains to be elucidated. Taking into account all the above considerations, it is evident that we need to understand precisely the balance between beneficial and detrimental effects of the different types of collagens in the injured nerve.

Concluding remarks

Even if the nervous system proper (i.e excluding meninges and protective layers of the nerves) does not contain collagen fibres, increasing evidence indicates that collagens are critical elements of its integrity. From the data described above, it is apparent that collagens are particularly involved in the establishment of the architecture of the brain and that they are linked to the development of various neurological diseases. Particularly crucial roles have been determined for collagens IV and XVIII, which are localized in basement membranes. However, other collagen players have been identified but much work remains to be done to fully elucidate their functions.

Future directions in the work should include the following:

1) The repertoire of the expression of collagens in the brain must still be completed. Owing to the complexity of the anatomy of the brain and to the multiplicity of the various collagen isoforms and to the different functions that they can subserve, this work, although tedious, could be helpful to understand the roles of collagens.

2) More mechanistic work must still to be done to understand the function of collagens in the brain. Collagen XVIII for instance has been shown to be involved in neural tube closure, but the underlying mechanism must still be unraveled. In general, for all collagens involved in development and pathogenesis in the nervous system, not much is known about their interactions with other ECM molecules, cell surface receptors and downstream signalling pathways.

3) The roles of the genetic context and of the environment have to be further explored. It is clear from all of the studies so far that the phenotypes resulting from collagen mutations in mice and men also depend on the broader genetic context. We previously noted that hydrocephaly in collagen XVIII

mutant mice is observed only in mice with a specific genetic background [95]. Another study on ocular dysgenesis caused by COL4A1 mutation also strengthens the idea that the genetic context modifies the severity of the phenotype [134]. Moreover, environmental stressors can accentuate the phenotype. Carriers of COL4A1 mutations are more prone to intracerebral haemorrhages after trauma or anticoagulant therapy. It was shown in COL4A1 null mice that caesarean delivery prevents cerebral hemorrhage [83]. The genetic and environmental influences thus can affect the observed phenotype and should be taken in account both in fundamental research as well as in clinical practice.

The family of collagens has a huge structural diversity and complexity. In connective tissues, our knowledge of its role has evolved from purely structural to bioactive functions. As the family expands, more of these molecules are being found to be associated with nervous tissue and their diversity of function is just beginning to be explored.

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