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Review

The cochlear matrisome: Importance in hearing and deafness

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ABSTRACT

The extracellular matrix (ECM) consists in a complex meshwork of collagens, glycoproteins, and proteoglycans, which serves a scaffolding function and provides viscoelastic properties to the tissues. ECM acts as a biomechanical support, and actively participates in cell signaling to induce tissular changes in response to environmental forces and soluble cues. Given the remarkable complexity of the inner ear architecture, its exquisite structure-function relationship, and the importance of vibration-induced stimulation of its sensory cells, ECM is instrumental to hearing. Many factors of the matrisome are involved in cochlea development, function and maintenance, as evidenced by the variety of ECM proteins associated with hereditary deafness. This review describes the structural and functional ECM components in the auditory organ and how they are modulated over time and following injury.

Introduction

The extracellular matrix (ECM) is a three-dimensional network of macromolecules surrounding cells in all tissues. Fibrous proteins such as collagens confer tensile strength and structural properties to the ECM, while glycosaminoglycans (GAGs), such as hyaluronic acid (HA), provide viscosity and resistance to compression thanks to their capacity to retain water. With the exception of HA, all GAGs are covalently bound to core proteins to form proteoglycans (PGs). ECM also comprises adhesive glycoproteins, such as laminins and fibronectin, which connect ECM molecules with one another but also to cell surface proteins or secreted factors [1].

Typically, ECM underlying epithelia or endothelia is composed of a thin layer of specialized ECM called the basement membrane, whose primary functions include cell anchorage and protection by forming a physical barrier with other tissue compartments [2]. Interstitial matrix is a looser form of ECM found below the basement membrane or surrounding cells in connective tissues. These ECM types differ in composition, collagen organization and functional properties and they are produced by different cell types. ECM heterogeneity also exists across tissues as some constituents are tissue specific.

ECM has long been considered a non-cellular compartment offering passive structural support and viscoelastic properties to the tissue it bathes. However, it is now recognized as a biologically active compartment playing key roles in the fate and behavior of cells and tissues. Indeed, ECM directly takes part in cell signaling as collagens, laminins, HA and PGs have all been shown to interact with cell surface receptors, such as integrins [3,4]. The activation of downstream effectors can mediate changes in cellular cytoskeleton to regulate cell shape, adhesion, or migration. In addition, some signaling pathways activated following ECM-cell interaction modulate gene expression to control cell proliferation, differentiation, or inflammatory and stress responses [5–7]. Moreover, ECM forms a lattice whose local density and composition may either act as a reservoir for ions and secreted factors or influence their diffusion rates, thus creating concentration gradients for growth factors and morphogens. Recently, its enrichment in extracellular vesicles (EVs), which are a category of lipid-bilayer structures encapsulating a multitude of compounds such as bioactive lipids, nucleic acid, and proteins, highlighted a new action mode for ECM-cell communication [8,9].

Accumulating knowledge of ECM structures and functions has profoundly modified our view of this extracellular compartment. As such, the set of proteins involved in ECM and its cellular interactions, namely the matrisome [10,11], comprises four classes: the core matrisome, including the structural elements, the ECM-affiliated proteins, containing proteins structurally or functionally associated with ECM-proteins, secreted factors and ECM-modulators involved in ECM remodeling. Indeed, the ECM constantly changes through the synthesis and degradation of its components as well as proteolytic events that regulate the activity of these components. ECM is thus a highly dynamic structure that undergoes temporal and spatial variations, conferring essential and irreplaceable roles in many biological processes, including development and tissue repair [5,6].

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Abbreviations

ARHL	age-related hearing loss
BLB	blood-labyrinth-barrier
BM	basilar membrane
CI	cochlear implant
CNS	central nervous system
CSPG	chondroitin sulfate proteoglycan
CVG	cochleovestibular ganglion
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
EV	extracellular vesicles
GAG	glycosaminoglycan
HA	hyaluronic acid
HSPG	heparan sulfate proteoglycan
LMW-HA	low molecular weight hyaluronic acid
MET	mechanoelectrical transduction
NIHL	noise-induced hearing loss
OC	organ of Corti
OWM	oval window membrane
PNN	perineuronal nets
RA	retinoic acid
RWM	round window membrane
SGN	spiral ganglion neurons
SSM	striated sheet matrix
SV	stria vascularis
TM	tectorial membrane

The hearing sense relies on the intricate interplay of cellular structures and ECM within the coiled-shape cochlea. Indeed, sound detection by the mechanosensory cells, called hair cells, crucially depends on two cochlear membranes that are exclusively made of highly specialized ECM, the basilar and tectorial membranes (BM and TM, respectively). Following sound wave transmission through the outer and middle ears, pressure waves propagate in the fluids filling the cochlear canals and induce BM vibration (Fig. 1). As the TM is coupled to BM and lies above the organ of Corti (OC), this membrane transmits sound-induced vibrations to the hair cells by inducing the deflection of their mechanosensory organelles, the stereocilia. Upon bending of these apical projections, mechanoelectrical transduction (MET) channels open, and potassium entry leads to hair cell depolarization, triggering neurotransmitter release and signal transmission to the auditory neurons of the spiral ganglion.

Both cochlear matrices contribute to the remarkable sensitivity and selectivity of the mammalian hearing function, as their vibrational properties associated with structural changes along the longitudinal axis of the cochlea ensure frequency discrimination and the ability of humans to hear a broad range of frequencies (20 Hz to 20 kHz) [12]. In this regard, BM structural anisotropy plays a key role in the mechanical decomposition of the sound wave: the base perceives high-frequency sounds, whereas low-frequency sounds are perceived at the apex. From this frequency tuning arises the cochlear tonotopic map that differs from species to species (Fig. 1).

Mutations in ECM genes, expressed in these membranes as well as in other cochlear structures, have been identified to cause syndromic and non-syndromic deafness of various severity [13], further emphasizing the crucial role of matrisome in hearing, and the importance of a tight regulation of ECM composition, organization and turnover to ensure homeostasis. Like any other ECM, cochlear matrices undergo continuous changes through synthesis and degradation of their components and can be remodeled in response to physiological or pathological changes. Therefore, substantial modifications occur during development, aging, and following injuries such as noise or ototoxic drug exposure and cochlear implantation. This review aims to shed light on the instrumental function of cochlear ECM in hearing and its contribution to human deafness.

The cochlear ECM: structure, function, and dysfunction

In the adult cochlea, ECM is widely present and significantly contributes to the hearing organ architecture, since decellularization treatment does not affect its global structure [14,15]. Each cochlear compartment hosts extensive ECM (Fig. 2A). Although some similarities exist across different compartments, specific ECM composition and organization actively participates in their crucial function (Fig. 2B). As such, mutations in ECM genes have been identified as deafness-causing and they will be discussed as cochlear structures and their ECM components are described below.

Basilar membrane

The BM is the resonant matrix lying underneath the OC that plays a crucial role in hearing. Its sound-induced vibrations are responsible for hair cell stimulation and its structural properties are essential for sound-frequency decoding. The BM shows structural anisotropy, which refers to directional variations. Indeed, its width increases (126 μm-418 μm in humans), and its thickness decreases from base to apex, and varies radially as well [16]. These features create a stiffness gradient (stiff at the base, more compliant at the apex) that participates in building the tonotopic map of the cochlea (Fig. 1). In humans, the BM is a heterogenous matrix composed of four layers: (1) the basement membrane layer, (2) the BM "proper" layer, (3) a layer of collagen IV and (4) the tympanic covering layer constituted of type IV collagen, laminin heterotrimers and fibronectin [16].

Like all cochlear basement membranes, the BM basement membrane layer comprises type IV collagen, heparan sulfate proteoglycans (HSPGs), nidogen-1 and laminin β2 [17,18]. Together with the other subepithelial basement membranes lining the cochlear duct (Fig. 2A, dark blue), the ECM structure forms a continuum that is suggested to provide a barrier function to control fluid transport [19]. This compartmentation is a prerequisite to hearing function as it guarantees the proper ionic composition of endolymph, which is required for hair cell depolarization. Two HSPGs (perlecan and agrin), and the glycoprotein Tenascin-C (TnC) have been specifically identified in the BM basement membrane [17,18,20]. Interestingly, mutations in TnC are responsible for non-syndromic autosomal dominant deafness DFNA56 in humans (Table 1). Although the exact function of TnC needs to be determined in the BM, the progressive hearing loss in DFNA56 patients is thought to result from disrupted ionic homeostasis [21]. Alternatively, due to its ability to be induced by mechanical stress and to take part in signaling as a Damage-Associated Molecular Pattern (DAMP) [22], TnC could also play a role in cochlear inflammation and tissue repair following damage [23].

The BM "proper" layer has been studied in animals and biochemical studies revealed that collagen represents 32 % of all components in the guinea pig BM [24]. Collagens are essentially type II and to a lesser extent type XI [16]. Collagen is organized in aggregated and arranged bundles that connect the ECM of adjacent compartments, the spiral limbus and the spiral ligament. Disturbance in their composition or organization can cause deafness (see Table 1 and explanations below). Chondroitin sulfate proteoglycans (CSPGs), notably decorin, have been identified as colocalizing with type II collagen, and fibronectin is present in the ground substance [25]. A couple of years ago, Emilin-1 and Emilin-2 have been reported to localize in the BM [26], and the latter

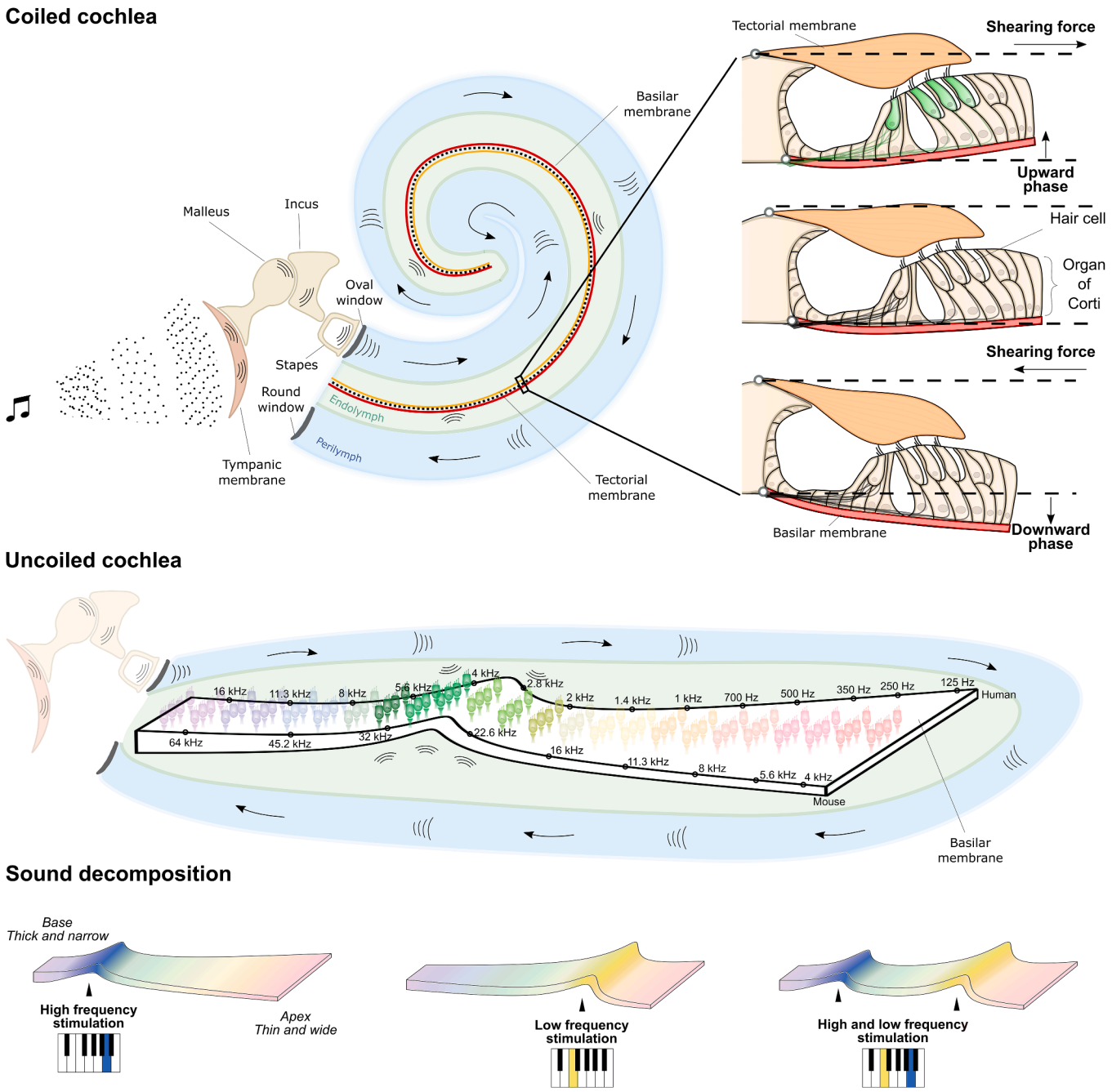

Fig. 1. Hearing process, sound decomposition and tonotopic map of the cochlea – Sound waves travel in the air and induce vibrations of the tympanic membrane. Ossicles of the middle ear are then set in motion and the vibrations are transmitted to the cochlear fluids. Due to changes along the apical-basal axis of the cochlea, including gradients of stiffness in the tectorial and basilar membranes, the mechanical properties are affected, allowing for a mechanical decomposition of the sound wave into pure frequencies. The maximum amplitude of this wave defines the most sensitive region to the specific tone stimulus; this gives rise to the tonotopic map. The base of the cochlea is sensitive to high frequencies, while the apex perceives low frequencies. Complex sounds are mechanically decomposed, according to the Fourier transform, into pure frequencies that are simultaneously perceived at different locations in the cochlea.

has recently been identified as a major organizer of collagen fibers that is critical to ensure normal cochlear biomechanics and proper hearing. Indeed, a recent study assessed the hearing function of Emilin-2 depleted mice and demonstrated increased thresholds for click and pure tone auditory brainstem responses (ABR), as well as distortion product otoacoustic emissions (DPOAE). They performed measurements of BM displacement using a laser-diode interferometer through the round window and recorded cochlear microphonics and compound action potentials. The authors identified defects in frequency tuning and suggested that the BM of Emilin-2 depleted mice might be unevenly stiff and overall more compliant than normal [27]. This example suggests that defects in the BM ECM are likely to disturb the biomechanical properties of this membrane and impair hearing.

Tectorial membrane

The TM is an acellular gel-like structure that contacts the mechanosensory stereocilia of the hair cell. This membrane's movement, coupled with BM vibrations, induces stereocilia deflection and hair cell stimulation. This highly specialized membrane, mostly composed of

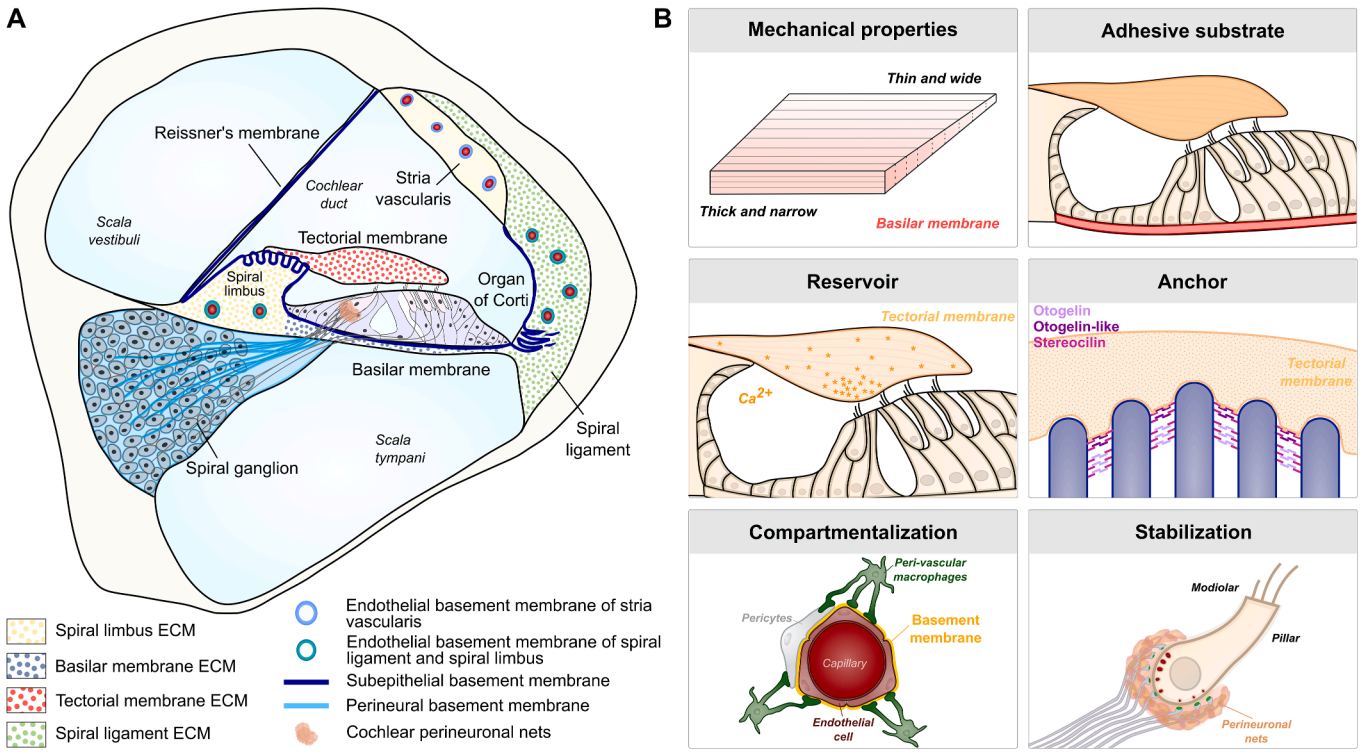

Fig. 2. Cochlear matrisome and its associated functions – **A.** Schematic section of the cochlea representing its extracellular matrix across the different compartments. Basement membranes (shades of blue) are thin specialized layers of ECM that self-assemble underneath epithelial cells, around vessels or neurons. 1. Subepithelial basement membranes run along the spiral limbus (underneath the interdental cells), the basilar membrane (below the sensory epithelium), the spiral ligament (below root cells and their processes) and Reissner's membrane; 2. The endothelial (or perivascular) basement membranes surround capillaries in spiral limbus, spiral ligament and stria vascularis; 3. The perineural basement membrane is found around myelinated nerve fibers and in spiral ganglion. Cochlear PNNs are specialized ECM lying at the interface of the inner hair cells and neurons – **B.** Diversity of functions ensured by the cochlear extracellular matrix. The cochlear ECM fulfils a broad range of functions critical for hearing function. ECM provides biomechanical properties to the cochlea and serves as an adhesive substrate for cells. ECM is also a reservoir for ions and small molecules. Some structures, including stereocilia, are anchored into the ECM while other structures are physically insulated, or stabilized by the ECM meshwork, such as blood vessels and synapses respectively.

water (97 %), collagens and unique glycoproteins [28], is an atypical matrix crucial to sound detection. Collagen fibers are embedded in a laminated collagenase-resistant matrix, named striated sheet matrix (SSM), which is composed of two alternating filament types, interconnected by staggered bridges [29].

The TM derives its tensile strength from a dense network of well-organized collagen fibers. Type II collagen is the main component, but together with types V, IX and XI [24,30,31], they account for 40-50 % of the total protein content in the TM [24,32]. The collagen fibrils are radially oriented, with a slight slope toward the apex, the angle increasing from base to apex [33]. This longitudinal variation along the cochlea is likely to be part of several anisotropic changes in TM structure that contribute to the tonotopic sensitivity of the cochlea. Mutations in genes encoding TM collagens are responsible for syndromic hearing losses, such as Stickler syndrome, in which multiple connective tissues are affected (Table 1). Clinical signs and phenotypes overlap, they often include ocular, orofacial, skeletal and auditory defects. The hearing deficits associated with type II, IX and XI collagenopathies are commonly attributed to TM structure defects, although these collagens are not restricted to this cochlear region (Table 1). Mice models mutated for type IX or type XI collagens suffer from TM abnormalities and hearing impairments with average thresholds respectively 30 dB and 40 dB higher compared to wildtype animals [34,35]. Mutants for type IX collagen show disorganized collagen fibers and a loss of type II collagens, emphasizing the role of type IX collagens in maintaining TM structural integrity [34]. Similarly, mutant mice for type XI collagen also display disorganized collagen fibers, with a reduced density of radial fibers, which appear twice more spaced than those of wildtype animals [35,36]. The ratio of radial to longitudinal shear impedance is reduced in Col11a2 KO and this results in a loss of TM mechanical anisotropy [36]. The broad diversity in mutation type and location within collagen genes probably explains the wide phenotypic spectrum of the syndromes, as well as the variability in the onset and severity of hearing loss.

α-tectorin (TECTA), β-tectorin (TECTB), and Carcinoembryonic antigen-related cell adhesion molecule 16 (CEACAM16) are three ECM glycoproteins that are required for TM development and/or the establishment of the SSM [37–39], since they may form, altogether, the SSM filaments and their crosslinks. Mice models in which one of these proteins was invalidated display no SSM [37–39]. Interestingly, mutations in TECTA and CEACAM16 have been identified to cause non-syndromic hearing loss in humans. TECTA mutations are responsible for DFNA8, DFNA12, DFNB21, whereas CEACAM16 mutations induce DFNA4B and DFNB113 (Table 1). Although no mutations in TECTB have been identified in humans, mouse studies demonstrate hearing impairments upon TECTA, TECTB and CEACAM16 deficiency [38–40]. Invalidation of TECTA and TECTB leads to important hearing phenotypes due to TM defects, which include TM detachment in TECTA mutants [37], and alterations in frequency-dependent TM mechanical properties for TECTA and TECTB [41]. Longitudinal changes in TM mechanical properties are critical for traveling waves propagation and amplification, such alterations can subsequently affect hearing sensitivity and frequency selectivity [42]. On the contrary, despite abnormalities in the TM structure very early in life, hearing of CEACAM16 null mice is slightly affected in young mice but clearly impaired at 12 months of age, as shown by ABR and DPOAE recordings [43]. CEACAM16 is therefore crucial for SSM organization, and it prevents accelerated age-related TM degradation [39,43].

Table 1
ECM-related genes involved in human sensorineural hearing loss.

Protein	Cochlear localization	Gene	Associated syndrome or non-syndromic deafness	Onset	Severity in human	Stable or progressive in human	Causes identified or suggested	Human mutations inducing hearing loss (non-exhaustive)	Mice model with hearing studies (non-exhaustive)
Cell adhesion molecule 16	Expression starts postnatally. Expressed in the TM (limbal and marginal zone)	**CEACAM16**	DFNA4B	Post-lingual	Moderate to profound	Progressive	Defects in TM organization	[89–91]	[39,57]
		CEACAM16	DFNB113	Post-lingual / Late onset	Mild to moderate	Progressive	Accelerated age-related degradation of the TM	[92,93]	[43]
Cochlin	Spiral limbus Spiral ligament	**COCH**	DFNA9	Depends on variants. ±40-50 years old	Mild to profound	Progressive	Dominant-negative pathogenic variants Involved in protection against pathogens Involved in structural and ionic homeostasis	[94–100]	[101]
		COCH	DFNB110	Congenital or post-lingual	Mild to profound	ND	Loss of function variants	[102,103]	[63]
Type II collagen (alpha-1 chain)	BM, TM, Spiral limbus, Spiral ligament	**COL2A1**	Type I Stickler syndrome	Childhood	Mild	Might be slightly progressive		[104,105]	
Type IV collagen	All basement membranes	**COL4A3**	Alport syndrome	Variable from late childhood / early adolescence	ND	Progressive	Alteration of cochlear basement membranes	[73]	[75–77,106]
		COL4A4	Alport syndrome		ND			[73]	
		COL4A5	Alport syndrome		ND			[74]	
		COL4A6	DFNX6	Congenital	Severe	Stable	Cochlear malformation	[107]	[108]
Type IX collagen (alpha-1, alpha-2, alpha-3 chains)	TM	**COL9A1**	Type IV Stickler syndrome	Childhood	Moderate to severe	Slightly progressive		[109–111]	[34]
		COL9A2	Type V Stickler syndrome	Congenital or childhood	Mild to moderate	ND		[111–113]	
		COL9A3	Type VI Stickler syndrome	Early	Moderate to profound	Progressive		[111,114–117]	
Type XI collagen (alpha-1, alpha-2 chains)	BM, TM, Spiral limbus, Spiral ligament	**COL11A1**	Type II Stickler syndrome Marshall syndrome	Childhood	Mild to profound	May be progressive during childhood	Impaired structure and function of BM and TM	[105,118–122]	
		COL11A1	Fibrochondrogenesis 1	Early	Mild to moderate	ND		[123]	
		COL11A1	DFNA37	Post-lingual	Mild to moderate	Progressive	TM structural defects (hypothesis)	[124]	
		COL11A2	Type III Stickler syndrome Autosomal dominant otospondylomegaepiphyseal dysplasia / Heterozygous OSMED / Weissenbacher-Zweymuller syndrome	Birth / Childhood	Mild to Severe	No or slight progression during childhood	Impaired structure and function of BM and TM	[125–127]	[36]
		COL11A2	Homozygous otospondylomegaepiphyseal dysplasia	Birth / Childhood	Moderate	Stable		[126,128,129]	
		COL11A2	DFNA13	Congenital	Moderate to severe	Stable	Loss of collagen fibrils organization; TM abnormalities	[35,130,131]	[35]
		COL11A2	DFNB53	Congenital / Pre-lingual	Severe	Stable or progressive	Loss of collagen fibrils organization; TM abnormalities	[132,133]	

(*continued on next page*)

Table 1 (*continued*)

Protein	Cochlear localization	Gene	Associated syndrome or non-syndromic deafness	Onset	Severity in human	Stable or progressive in human	Causes identified or suggested	Human mutations inducing hearing loss (non-exhaustive)	Mice model with hearing studies (non-exhaustive)
Hyaluronan synthase 1	Transmembrane protein Spiral limbus, OC, Spiral ganglion, SV	**HAS1**		Late onset	Moderate to profound	Progressive		[134]	[134]
Hyaluronidase 2	ND	**Hyal2**	Usually, conductive, sensorineural reported in one case. Associated with cleft lip and palate syndrome and cor triatriatum sinister (heart anomaly)	Pre-lingual	Severe to profound	ND		[135]	[135]
Otoancorin	TM (limbal zone)	**OTOA**	DFNB22	Pre-lingual	Moderate to profound	ND	Defect in limbal attachment of the TM inducing defects in IHC stimulation	[44,136–138]	[45]
Otogelin	TM TM-stereocilia attachment crown	**OTOG**	DFNB18B	Congenital / Pre-lingual	Mild to moderate	Stable (progressive in mice)	Slight defects in TM organization Defects in horizontal top links Defects in TM-attachment crowns	[139–141]	[49–52,142,143]
Otogelin like	TM TM-stereocilia attachment crown	**OTOGL**	DFNB84B	Congenital to post-lingual	Mild to moderate	Stable (progressive in mice)	Slight defects in TM organization Defects in horizontal top links Defects in TM-attachment crowns	[140,144–148]	[49]
Stereocilin	TM-stereocilia attachment crown	**STRC**	DFNB16	Congenital to post-lingual	Mild to moderate	Stable (progressive in mice)	Defects in horizontal top links Defects in TM-attachment crowns	[46,149]	[47–49]
Tectorin A	TM	**TECTA**	DFNA8/DFNA12	Pre-lingual	Mid to severe	Stable, but it might be mutation-dependent	Defects in TM organization	[150–152]	[37,40,153–155]
		TECTA	DFNB21	Pre-lingual	Moderate to profound	Stable, but it might be mutation-dependent	Defects in TM organization	[156–158]	
Tenascin-C	BM	**TNC**	DFNA56	Post-lingual	Mild to severe	Progressive	BM defaults: disturbance in ionic homeostasis, tissue repair mechanisms	[21]	

BM: Basilar membrane
IHC: Inner hair cell
ND: Not determined
OC: Organ of Corti
PG: proteoglycan
SV: Stria vascularis
TM: Tectorial membrane

Other glycoproteins associated with genetic hearing loss are present in the TM. For instance, Otoancorin is an inner-ear specific glycoprotein, associated with the DFNB22 locus (Table 1), that is expressed during development at the interface between the spiral limbus and the TM and its expression persists during adulthood [44,45]. Otoancorin is required to ensure the adhesion of the TM with the spiral limbus, as the acellular membrane is detached from the limbal attachment zone in KO mice [45]. Various functional tests demonstrate that the sound amplification process, mediated by outer hair cells, is not affected in these mice. However, the elevation of compound action potential thresholds in KO mice suggests that the transmission of the mechanical response to inner hair cells is impaired in these animals and that inner hair cells' excitation fails, despite a close to normal cochlear amplification. This study highlights the role of the limbal attachment zone of the TM in inner hair cell stimulation [45]. In addition, a study demonstrates that traveling waves velocities are altered in Otoancorin KO mice, due to the abolishment in frequency-dependent stiffening of the TM [41].

Otogelin, otogelin-like and stereocilin are present between outer hair cell stereocilia to ensure their cohesion, and between the TM and the tallest outer hair cell stereocilia to allow their mechanical coupling [46–49]. Mutations in those genes are responsible for deafness in mice and non-syndromic hearing loss in humans (DFNB18B, DFNB84B and DFNB16 respectively). Inappropriate anchorage of outer hair cells' stereocilia in TM likely affects the amplification forces necessary to transmit sound information to the principal sound decoders, the inner hair cells [37]. Unlike stereocilin, otogelin and otogelin-like proteins are also expressed within the TM [49,50]. To our knowledge, little is known about their exact role of this localization, and the TM structure is only slightly impaired upon otogelin loss, suggesting that otogelin is not required for its formation but may be involved in the stabilization of TM fibers [51,52].

Besides its mechanical role, a new function for the TM has recently been described. It appears to be a reservoir for Ca^{2+}, especially in the TM regions close to the hair cells and the spiral limbus attachment zone [53]. This local enrichment in Ca^{2+} is probably mediated by its ability to bind TM components, such as TECTA and otogelin, via their calcium-binding domain [53]. Ca^{2+} takes part in several processes that are instrumental to hearing sensitivity. As such, Ca^{2+} is known to regulate synaptic transmission [54]. However, due to its localization, the pool of Ca^{2+} in the TM is more likely to participate in modulating MET channels activity. Indeed, Ca^{2+} has been shown to be required for tip links integrity [55], to determine the number of MET channels opened at rest, and to contribute to fast and slow adaptation processes [55]. Moreover, Ca^{2+} storage guarantees sustained capacity to respond to sound, as Ca^{2+} concentration, hair cell function and hearing sensitivity are transiently reduced following prolonged noise stimulation [53,56].

Ubiquitous and specific components of the TM matrix are thus crucial to TM integrity. The organization of collagens, TM anchorage to the limbus and to the outer hair cell stereocilia, as well as Ca^{2+} storage, are exquisitely important to the hearing function.

Spiral limbus and spiral ligament

The spiral limbus and the spiral ligament are located on either side of the OC, respectively on the modiolar and strial sides (Fig. 2A). Their basement membranes are part of the subepithelial basement membrane that surrounds the cochlear canal and limits the endolymph compartment [17]. As such, its composition resembles all cochlear basement membranes [17]. Interdental cells, located on top of the spiral limbus where TM is anchored, participate in some TM protein synthesis and release [39,40,57]. Some resident cochlear macrophages are present in the spiral ligament, but both the spiral limbus and spiral ligament mainly house ECM-producing fibrocytes [58]. In the spiral ligament, fibrocytes are involved in ion recycling to maintain the endocochlear potential [59]. The matrix that bathes all these cell types mainly comprises randomly oriented individual fibrils of collagens. Collagens, mainly type II, represent 16 % and 12 % of ECM protein content in the spiral limbus and ligament, and they are associated with decorin [24,25]. Type XI collagen is also present in both structures [24], and type V collagen has been detected in the connective tissues of the spiral limbus [60]. Aggrecan has been observed in the ECM of the spiral limbus, and around fibrocytes V in the spiral ligament [61]. Cochlin has been reported to be the most abundant ECM protein after collagen in the inner ear, and this glycoprotein is highly expressed in the spiral limbus and ligament [62–64]. Cochlin is associated with hereditary deafness DFNA4 and DFNB110 and its function has been extensively reviewed recently [65]. Cochlin maintains ECM structure by binding collagen fibers or other ECM components, ensuring ion homeostasis, and providing support to withstand shear stress [66,67].

The spiral limbus and ligament are also involved in the cochlear blood supply. They host capillaries that are surrounded by an endothelial basement membrane sharing common components with regular cochlear basement membranes: type IV collagen, HSPGs, such as perlecan and agrin, and glycoproteins, including nidogen-1, laminin β2 [17,18]. This basement membrane participates in the embedment of pericytes, which also contribute to the blood-labyrinth-barrier (BLB), a physical structure that controls and limits the diffusion of blood-borne compounds. By releasing inflammatory cytokines within the extracellular space upon danger signals, both macrophages and fibrocytes can modulate the BLB permeability [68].

Thus, in these two structures, the subepithelial and endothelial basement membranes participate in the compartmentation by forming physical barriers, to respectively ensure the control of endolymph composition and the efficiency of the BLB. Conversely, the interstitial ECM is quite loose, which facilitates the transmission of molecular signals, such as inflammatory molecules released following noise exposure or infection, and ion diffusion or recycling.

Stria vascularis

The stria vascularis (SV) is a secretory epithelium composed of three layers of cells (marginal, intermediate, and basal) responsible for the ionic composition of the endolymph. Although a subepithelial basement membrane is detected at embryonic stages in mice, it was shown to be lost postnatally following marginal cell interdigitation with the basal and intermediate cells [69], and type IV collagen as well as other basement membrane proteins are not detected underneath the marginal epithelial cells beyond this stage [19,70,71]. As the name suggests, SV is highly vascularized, and an endothelial basement membrane covers all its capillaries. Although ECM components around these strial capillaries are also found around vessels of the spiral ligament (type IV collagen, laminins, nidogen, perlecan and agrin) [17], it differs by its reduced amount of sulfated GAGs [72], the presence of α-dystroglycan [18], and its structural organization [17]. This basement membrane also participates in the establishment of the BLB. Interestingly, Alport syndrome - a hereditary kidney disease associated with hearing loss - is a basement membrane-related disease induced by mutations in COL4A3, COL4A4 and COL4A5 genes [73,74]. Studies of a murine model of Alport syndrome reveal a thinner subepithelial basement membrane running from the spiral limbus to the spiral prominence, but a thicker endothelial basement membrane in SV capillaries [75]. Alteration of BLB induces hypoxic conditions and the SV of Alport mice is in an inflammatory state and associated with oxidative stress [76]. Although the hearing function is not affected in Alport mice [75], inflammation and strial dysfunction could explain their susceptibility to noise [77]. Thus, integrity of basement membranes, including the endothelial ones seems instrumental to hearing.

Spiral ganglion neurons

Perineural basement membrane was identified twenty years ago

surrounding cochlear myelinated nerve fibers from the spiral ganglion to the habenula perforate, where neurons enter the sensory epithelium [78]. Like all cochlear basement membranes, it comprises type IV collagen, laminins, nidogen-1 and HSPGs (agrin and perlecan) [17,78]. Unfortunately, they have been poorly described since then, and their role remains to be determined in the cochlea.

A recent investigation provides evidence of a distinct neuron-related specialized ECM within the cochlea, subsequently referred as cochlear perineuronal nets (PNNs) [61]. PNNs have first been observed in the central nervous system (CNS) at the end of the nineteenth century by Golgi and Ramón y Cajal, although the latter initially misidentified them as staining artifacts [79]. They are extracellular nets surrounding CNS neurons' somata, dendrites, and proximal axons, mainly fast-spiking parvalbumin-expressing interneurons [80]. PNNs are essentially composed of (1) CSPGs, such as aggrecan, versican, brevican, and neurocan, associated with (2) a hyaluronan-based skeleton, (3) HA-linker proteins, such as HAPLN1 and HAPLN4, and (4) tenascin-R [81]. In the CNS, they have been associated with multiple functions, including synaptic plasticity, stabilization of synaptic contacts, neuroprotection, learning and memory [80,81]. In the cochlea, ECM with a similar composition is present at the basal pole of sensory inner hair cells, forming a basket-like structure that encloses the synaptic region of those cells [61]. These cochlear PNNs only differ from CNS PNNs by a change in the predominant CSPG component, which is brevican instead of aggrecan. Brevican-null mice suffer from a mild hearing impairment due to the loss of cochlear PNNs, since none of the CSPGs or HA-linker proteins were found below the inner hair cells. Further analysis revealed that PNNs disruption was associated with defects in synaptic coupling [61], as presynaptic machinery in inner hair cells was not always in close apposition to the postsynaptic domain of spiral ganglion neurons (SGNs). Thus, cochlear PNNs are likely to be involved in the functioning of synapses, at least by ensuring spatial coupling.

Oval and round window membranes

The oval and round window membranes (OWM and RWM, respectively) close the two openings of the middle ear to the cochlea. The OWM receives sound-induced vibrations from the stapes and transmits it to cochlear fluids, while the RWM vibrates with opposite phase to serve as an outlet for fluid displacement. By separating the air-filled middle ear from the perilymph-filled cochlea and by allowing the motion of the cochlear fluids, both membranes are critical for sound energy propagation and cochlea functioning. Whereas precise ultrastructural studies of the OWM are still lacking, the RWM has received more attention due to its significant interest as a local delivery route for therapeutic compounds, helping circumvent BLB restrictions. Human RWM is a ~70 μm semipermeable three-layer structure constituted of two epithelial layers flanking a thick connective tissue layer. A basement membrane lies basally to epithelial cells and separate them from the connective tissue [82,83]. These ECM compartments likely contribute to the overall barrier function of the membrane that prevent perilymphatic fluid leaking into the middle ear. The connective tissue is composed of fibroblasts, nerve fibers, blood and lymphatic vessels, as well as collagen and elastic fibers [83]. Fiber types and density form a gradient throughout the connective tissue. Coarse collagen fibers are loosely arranged near the middle ear epithelium and there is a progressive increase in the number of collagen and elastic fibers towards the inner ear epithelium, where both radial and longitudinal bundles of collagen fibers are seen [83]. This connective tissue is thought to guarantee the viscoelastic properties of the RWM and its efficiency to decompress acoustic energy. In the elderly, the arrangement is looser, elastic fibers are thicker and the ground substance increases [83]. These age-related changes in the connective tissue suggest a decrease in compliance that could impair RWM function. Pathologies associated with OWM and RWM cause conductive or mixed hearing loss that can arise from developmental abnormalities, leading to the partial or total absence of oval and round windows caused by stenosis or atresia [84]. Acquired OWM and RWM-related pathologies correspond to membrane rupture that are induced by surgical lesions, or otological diseases, including otosclerosis, otitis media and middle ear damage [85,86].

Apart from the ECM-related genes associated with deafness in humans, described above, years of hearing research have highlighted other matrisome genes responsible for hearing impairment in mice. Among them, some are involved in structuring cochlear ECM, such as TECTB and laminins [38,87], while others interact with ECM molecules, such as the collagen receptor DDR1 [88]. It is likely that, in the coming years, multiple other ECM-related genes will be identified as new deafness-causing genes, either on their own or in combination with other genes. Overall, the diversity in ECM composition and structural organization provides each cochlear compartment its own properties and ensures a large variety of functions that are instrumental to the hearing function.

The cochlear ECM: a dynamic structure

Cochlear matrisome undergoes dynamic changes over time or following stress and environmental insults. Indeed, by ensuring the coupling with cells, it allows tissues to respond to mechanical forces, and also actively participates in driving morphological changes. ECM also takes part in multiple processes via the modulation of signaling pathways to ensure the transduction of chemical and mechanical cues through ECM-cell receptors and their subsequent pathways (Fig. 3). Thus, ECM changes are crucial for the cells to thrive in their environment and adapt to external stress. In the cochlea, ECM remodeling occurs during development, aging and following injuries.

Development

Shaping the inner ear: ECM takes part in mechanical processes and regulates signaling pathways

Inner ear development begins with the thickening of a non-neural ectoderm region to form the otic placode. This region gives rise to most of the cells composing the inner ear. After this otic induction and thickening period, the otic placode invaginates, forming a pit that will progressively deepen and close to form the otic vesicle. Several studies have shown that ECM disruption at this critical stage impairs its invagination [159–161]. Degradation of ECM components such as CSPGs, HSPGs and HA leads to wider otic pit opening and drastically reduces its folding. Laminins are also involved in this process, potentially through interactions with the β1 integrin subunit. Indeed, targeting β1 integrin subunit resulted in a milder effect and was unable to fully recapitulate the phenotype, suggesting the involvement of additional receptors [161].

The developing inner ear is instructed for positional identity throughout otic vesicle formation and growth. Retinoic acid (RA), FGF8 and BMP specify the anterior-posterior axis while Wnt and Shh define the dorso-ventral axis of the inner ear. As demonstrated in other organs, ECM properties control the establishment of concentration gradients and the ability of factors to diffuse. For instance, type IV collagens interaction with BMP4 [162] and HSPGs binding to Shh [163] allow the local enrichment of morphogens. ECM components also actively modulate signaling pathways by acting as co-factors, as it has been demonstrated with heparan sulfate and FGFR activation by FGF [164]. In turn, morphogens and growth factors can affect organogenesis, at least partially, by driving local ECM remodeling. In cultured human fetal palate mesenchymal cells, RA controls the expression level and the activity of fibronectin, TnC and Matrix Metalloproteinase (MMP) 2 [165]. Therefore, the RA gradient in the cochlea could directly modulate ECM composition along the anterior-posterior axis and lead to spatial discrepancies in the biomechanical properties or cell signaling.

To further develop into a ventral cochlea and a dorsal vestibule, the otic vesicle continues to grow axially and undergoes morphological

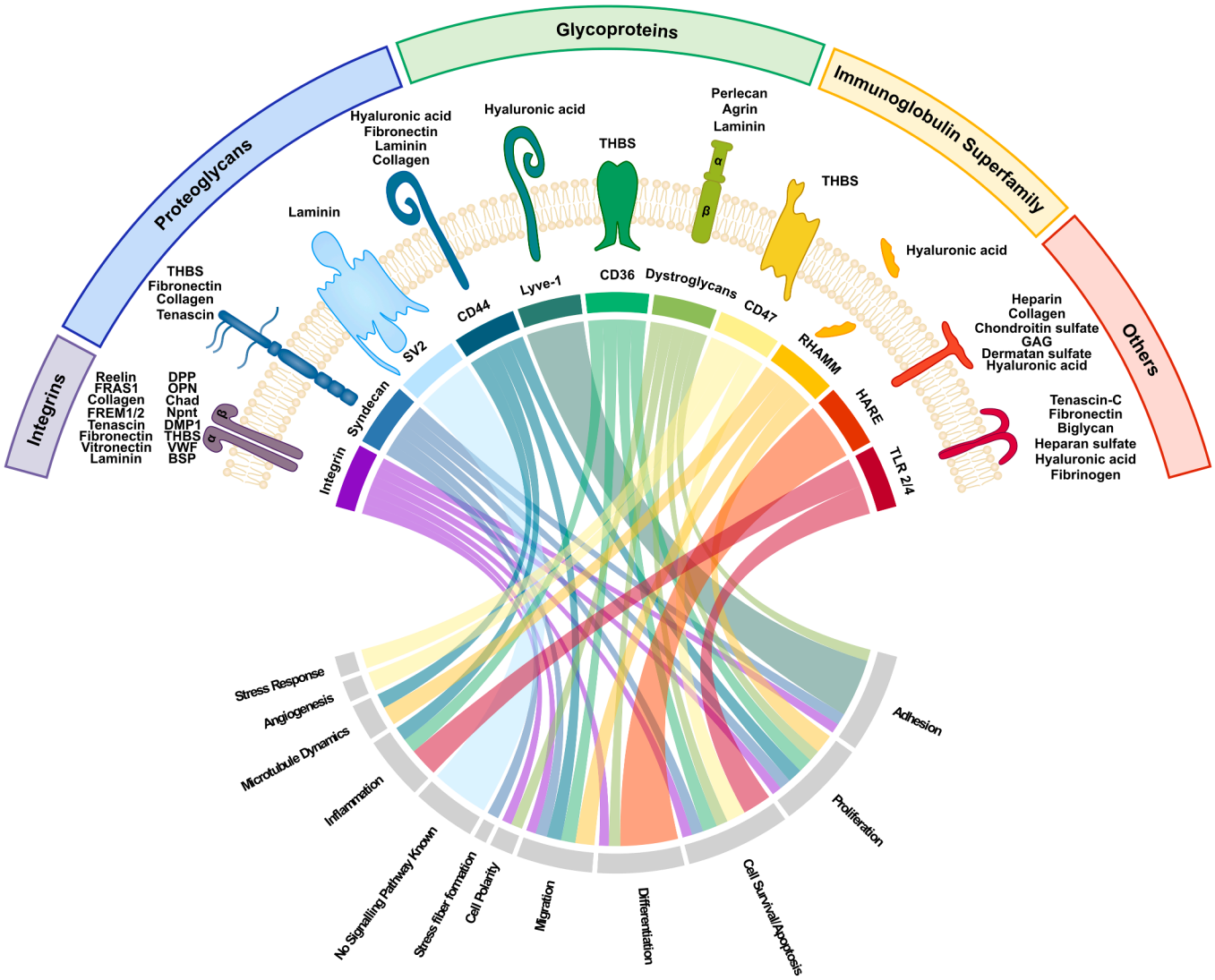

Fig. 3. Cell-ECM receptors transduce extracellular cues – ECM affects cellular functions through ECM-receptors leading to the conversion of mechanical and chemical cues into a large range of cellular response and biological processes.

changes resulting in the coiled structure dedicated to hearing and the semi-circular canals responsible for balance. Interestingly, studies conducted on vestibular morphogenesis indicate that ECM gene expression greatly varies along the development of epithelial projections, the transient structures that will further give rise to the semicircular canals [166]. Amongst others, versican, HAS3 and chondroitin synthase 1 are transiently upregulated and this boost in ECM production is a driver for projection outgrowth. HA is important for this morphogenetic process, as its disruption by hyaluronidases leads to epithelial projection collapse and failure to fuse [166,167]. With molecular weights up to $\sim 10 \times 10^4$ kDa [168], HA is the largest polysaccharide produced by vertebrate cells. Composed of D-glucuronic acid and N-actelyl-D-glucosamine, HA is highly negatively charged, and this anionic feature allows for HA exquisite capacity of water retention. Interestingly, it has recently been shown that the hydraulic pressure generated by HA synthesis, rather than its associated signaling, is required to shape the vestibular canals [169]. While some CSPGs located at the evagination site before any sign of epithelium deformation may participate in initiating their outgrowth, some HSPGs could act in concert with HA to form the viscous gel filling the projection core and drive epithelial projection outgrowth [170]. Further investigations would be necessary to decipher whether similar ECM-powered morphogenesis also applies to the cochlea and determine whether matrisome components participate in forming its coiled and hollowed shape.

Cochlear cell differentiation: importance of cell-ECM interactions

Expression changes of collagens, fibronectin, decorin and their integrin receptors were recently suggested to promote otic neurosensory cell derivation from human induced-pluripotent stem cells [171]. Although the evidence is only correlative, ECM signaling to integrin receptors is well-known, in many tissues, to govern cell differentiation (Fig. 3). Hence, it would not be surprising that ECM-cell interactions play an active role in this early stage of cochlear development.

In the otic vesicle, the pro-neurosensory domain is the source of both neurons and sensory epithelial cells. Neuroblasts delaminate from this region and migrate short distances to form the cochleovestibular ganglion (CVG). These cells display transcriptomic features that classify them as intermediates between otic vesicle cells and neurons. This transitional state is characterized by expression changes recalling an epithelial-to-mesenchymal transition (EMT) [172,173]. Repression of epithelial genes such as EPCAM and E-Cadherin is accompanied with N-Cadherin and vimentin upregulation. In cancer cell lines, switching from E- to N-Cadherin during EMT allows cell migration and is associated with the upregulation of MMP-2 and MMP-9 [174] that degrade ECM components, including collagens IV and fibronectin [175]. As holes in the basement membrane have been observed surrounding neuroblasts

while they delaminate [172], we could hypothesize that a similar process occurs to favor MMP-mediated ECM breakdown and cell progression. The migrating neuroblasts will finally settle and coalesce to form the CVG, suggesting that a controlled balance between cell-ECM and cell-cell interactions must be required through the process.

Changes in integrin signaling are also crucial for sensory epithelium formation. Although Itga3 and Itga6 are initially expressed throughout the cochlear epithelium, they are later restricted to the non-sensory and prosensory domains, respectively [176]. Itga3 has been shown to decrease cell adhesion and increase proliferation, and its inhibition by miR-183 is necessary to specify the non-proliferating zone of the sensory epithelium [177]. Thus, downregulation of Itga3 in the prosensory domain is required for cell cycle exit, defining the onset of sensory cell differentiation. On the other hand, Itga6 upregulation could directly contribute to hair cell formation. It was shown, together with β1 and β3 subunits, to potentiate the differentiation of OC-2 otic progenitor cell line into cells expressing the hair cell marker Myo7a [178]. Thus, changes in integrin expression allow cells to differentially sense and respond to ECM cues during cochlea development.

The ability of ECM to promote otic cell differentiation encouraged researchers to take advantage of the decellularized murine cochlea as a support for cell culture. They successfully differentiated human mesenchymal stem cells into Myo7a-positive cells, demonstrating that spontaneous differentiation into auditory hair cells can occur on a cochlear substrate, and confirming that differentiation cues remain in the matrix despite the absence of cells [179].

Cochlear innervation: ECM for neuronal guidance and trophic support

Two types of SGNs innervate the sensory cells of the OC: type I neurons account for 90-95 % of afferent neurons and innervate inner hair cells; the rest corresponds to type II neurons innervating outer hair cells. Numerous *in vitro* studies showed that ECM guidance cues can be sufficient for neurite outgrowth and pathfinding. In the cochlea, laminin substrates are favorable to SGNs, whereas fibronectin, and to a lesser extent TnC, exert an inhibitory influence on neurite outgrowth, regardless of the neuron type [20,180,181]. Neurons also tend to grow in the same direction as collagen fibers [182]. Interestingly, cultured type I neurons preferentially grow on cell adhesion molecule (CAM) L1 stripes, whereas type II neuronal outgrowth is not affected by this molecule [183]. This differential response to guidance cues is consistent with the cochlear expression pattern since CAM L1 is enriched in the region surrounding inner hair cells [184], which will be specifically targeted by type I SGNs. Whether ECM proteins would be independent mechanical guidance cues required to channel neurites or if they could be part of wider signaling pathways remains unclear. Innervation of hair cells is also controlled by the release of secreted factors, including neurotrophins and Brain-derived neurotrophic factor (BDNF). The core matrisome likely contributes to their diffusion and concentration gradients, by building the ECM network. Furthermore, some ECM modulators, usually involved in ECM degradation, may directly control the activity of these factors. As such, BDNF, which is essential to SGN survival and neurite extension towards the OC [185], may be activated by MMPs through the proteolytic cleavage of its inactive form, pro-BDNF [186,187].

Maturation of the sensory organ: modeling and remodeling the ECM

In mice, during the early postnatal stages, the cochlea still undergoes important processes required for functional maturation. Indeed, mice are born deaf and start hearing within the second postnatal week. During these two weeks, changes in laminin composition [188], collagen expression [189] and collagen fiber organization [190] have been reported in the BM. The fibers are progressively thicker, aligned and compacted, and BM ECM reaches its final organization by P20, providing the mechanical basis for frequency tuning and allowing for the definitive tonotopic map [190]. Although the TM starts to develop at embryonic stages, it acquires its singular architecture and final organization around P12-P14. TECTA and TECTB are no longer expressed at this stage, but tectorin proteins are present in the TM, and have contributed to its formation. A recent study suggests that the TM develops at the surface of the epithelium following a 3D bioprinting model, in which ECM components are released by TM underlying cells in successive layers, and retained by GPI-anchored TECTA to prevent their diffusion into the cochlear duct [40].The multilayered ECM-based TM detaches from the underlying OC (between P2 and P7), suggesting changes in cell-ECM interactions, thus allowing the TM to correctly set up and to later play its crucial role in auditory transduction [191]. While TECTA allows TM growth by recruiting glycoproteins and contributing to collagen fibril organization, it is insufficient to establish the unique features of the SSM. The appearance of the highly organized SSM coincides with CEACAM16 expression, around P12-P14, suggesting it could drive the organization of the SSM prior to hearing onset.

In addition, OC maturation relies on postnatal ECM remodeling and signaling to reduce cell adhesion and modify cell shapes. Supporting cells are subjected to partial EMT and reorganize within the sensory epithelium [192], creating new extracellular spaces crucial to cochlear fluid homeostasis and hair cell capacity to respond to sound. Finally, ECM proteins are also involved in the functional maturation of cochlear innervation after birth. Thrombospondin (TSP) 1 and TSP2, two secreted ECM proteins produced by supporting cells, participate in synapse formation, as their loss affects the number of cochlear synapses and hearing function [193]. Their expression at postnatal stages seems to be required for the maturation of the pre-synaptic machinery at the base of inner hair cells. Brevican, another ECM component of cochlear PNN, ensures synaptic coupling [61] and function. This PNN property is thought to relate to ECM capacity to limit membrane diffusion of the synaptic elements or to induce their clustering through bridging. The period of appearance of cochlear PNNs has not been determined, but they likely form at postnatal stages to consolidate synapses after maturation, as shown in CNS, where PNN formation coincides with the closure of the critical period [80]. Besides neurotransmission, cochlear ECM could also impact the propagation speed of the acoustic signal. Abnormal glycosylation patterns of alpha-dystroglycan were shown to correlate with myelin defects at the peripheral SGN terminals, both in mice and humans [194]. Although alpha-dystroglycan plays a role in laminin deposition in most cochlear basement membranes and is likely to be required for cochlear homeostasis [195], the increased latency of signal propagation through SGN fibers could contribute to the hearing impairments reported in Muscular Dystrophy patients suffering alpha-dystroglycanopathies [194]. Altogether, these studies demonstrate that ECM proteins are involved in synapse consolidation and cochlear nerve myelination and are thus actively contributing to the faithful and efficient transmission of sound.

Aging

During aging, changes in ECM composition and mechanical properties are common in various organs, including the skin, the brain, and the ovaries [196–198], and these non-cellular deteriorations are likely to contribute to cellular degeneration. Therefore, it is not surprising to observe ECM modifications in the aging cochlea [190,199,200]. Studies in mice and gerbils report a vascular degeneration in the SV, with a thickening of the basement membrane of strial capillaries, certainly due to an increase in laminin deposition [195,201,202]. This age-related thickening of strial capillaries basement membrane was also detected in humans [203]. In addition, aging gerbil cochleae exhibit a dystroglycan decrease, especially in perineural and SV basement membranes [195]. This feature could be associated with neuron demyelination and disruption of the BLB, both of which are susceptible to participate in presbycusis. A recent study has questioned the predominant role of SV in presbycusis by demonstrating, through histological analysis of human cochleae, that SV atrophy is a poor predictor of hearing decline [204]. Although this report indicates that hair cell death precedes measurable

signs of SV degeneration, it does not imply that SV function is normal and that BLB permeability or endocochlear potential are maintained.

Age-related hearing loss (ARHL) can result from a fibrocyte pathology causing the loss of type II collagen fibers in the lateral wall [205]. Although the cause is not understood, it raises the hypothesis that gene mutations could increase presbycusis susceptibility through the direct or indirect deregulation of ECM-related genes. Moreover, RNAseq data point out ECM organization as one of the main deregulated pathways [206] between 6-weeks and 1-year-old mice. Whether ECM changes trigger ARHL or whether it is a consequence of hearing dysfunction remains to be determined. Notably, MMP2 gene has been specifically linked to ARHL in humans [207], underpinning the importance of ECM-modulators in hearing. In addition, the TM undergoes age-related progressive degeneration, in which the TM becomes thinner, holed, with missing collagen fibers and a reduction in non-collagenous TM components [208]. This degradation occurs from apex to base and eventually results in the detachment of the TM from the spiral limbus. Degeneration seems to be at least partially associated with tectorin loss with aging [208]. Despite tectorins are detected at the protein level long after their synthesis have stopped [209,210], their progressive loss coincides with TM degeneration [208]. Loss of CEACAM16, the SSM organizer, was shown to accelerate this age-related degeneration [43], and TM mechanical properties were shown to be impaired, as a result of a reduced stiffness and a reduced viscosity of the TM in adult CEACAM16-null mice [211]. Finally, a recent study revealed the role of a miRNA on BM thickening and ARHL by controlling the expression of some core matrisome genes, such as laminins and type IV collagens [212]. Thus, the aging cochlea displays modifications in ECM composition that can exacerbate or cause ARHL, by affecting cell signaling or cochlear mechanical properties.

Cochlear damage

As a susceptible organ, the cochlea can suffer from various environmental insults, including noise or ototoxic drug exposure. While hair cell death has been extensively studied, acquired forms of hearing loss also result from defects in the SV, affecting ion homeostasis or blood supply, and from SGN degeneration. More recently, the auditory synapses have emerged as the most vulnerable elements of the cochlea (reviewed in [213]). The loss of presynaptic ribbons in inner hair cells, or the presence of orphan ribbons that are no longer coupled to postsynaptic terminals, is the first cochlear damage evidenced upon ageing and can also be observed immediately after drug or noise exposure [214–216]. In the absence of hair cell death, synaptic disruption does not lead to the elevation of the hearing threshold, however the amplitude of the auditory nerve response is reduced. This is not benign as it affects perceptual hearing capacities, such as discriminating speech in a noisy background. Synaptic loss is also correlated with long term consequences on SGN survival and it was shown to aggravate ARHL [215,217]. Despite variable efficiency across species, strains and age, synaptic regeneration occurs in mammals and the restoration of hair cell and SGN communication improves the hearing function [218–221].

Currently, cochlear implantation is the recommended therapeutic intervention to restore hearing in patients with severe to profound hearing loss who show no improvement with classical hearing aids [222]. However, cochlear injury and progressive hearing loss were also attributed to implant insertion. The pathophysiological mechanisms responsible for cochlear damage depend on the nature, intensity and duration of the insult, however oxidative stress, inflammation, and apoptosis are common features. ECM is markedly modified upon damage and during tissue repair. Whether matrisome components are degraded [223–225], or whether ECM deposition is excessive [226], abnormal ECM remodeling in the cochlea affects tissue integrity and function.

Noise-induced hearing loss

ECM components may be damaged and degraded upon mechanical and oxidative stress, which both occur upon intense acoustic stimulation. A recent proteomic screen, performed in the mouse cochlea confirms the reduction of various collagen proteins immediately after noise exposure [224]. Therefore, noise trauma is associated with ECM breakdown that would result in structural and signaling changes for the cells comprising the tissue. In turn, traumatized cochlear cells respond to stress by modulating the expression of ECM genes, such as collagens, laminins, integrins and MMPs, to restore ECM homeostasis [223,225,227,228]. These expression changes may be very rapid, as soon as 2 h following noise exposure, and the identity of the upregulated ECM components varies along the cochlear compartment [225,227] and most likely according to cell types [229].

Following acoustic overstimulation, ECM replenishment favors cellular attachment and protection and thus contributes to tissue repair. However, the induction of non-structural glycoproteins, such as TnC and Thrombospondins also provides signaling cues that may exert positive and negative effects on hearing recovery [227,228,230]. While TnC, an important driver of innate immunity in the brain [231], could potentiate the damage by promoting inflammation and subsequent neurodegeneration, TSP1 and TSP2 are rather beneficial to the cochlea as they are required to improve auditory synapse restoration and protect against noise-induced hearing loss (NIHL) [230].

Similarly, expression changes of ECM remodelers can either serve protective functions or potentiate noise-induced cochlear damage. In this line, alterations in HA-metabolic enzyme levels and HA degradation into low-molecular-weight forms (LMW-HA) could contribute to cochlear inflammation and aggravate hearing decline after noise trauma [223]. LMW-HA is thought to act by interacting with TLR4 and mediate the upregulation of IL-1β and TNF-α pro-inflammatory cytokines. In contrast, ECM remodeling by MMP7 plays a protective role against noise since genetic ablation in mice exacerbates NIHL [225]. Similarly, when administered twice daily for a week, the use of a broad MMP inhibitor Doxycycline aggravates hearing threshold shifts and hair cell loss following acoustic trauma [225]. However, a shorter administration of the same inhibitor, one day before noise exposure, exerts an opposite effect as it ameliorates hearing recovery. Hence, the upregulation of several MMPs upon noise exposure (MMP1, -2, -3, -7, -9, -10, -13 and -14) [225,232,233] could serve time-dependent functions according to their respective expression kinetics, cochlear location, targets and depending on the presence of Tissue Inhibitor of Metalloproteinase and A Disintegrin And Metalloproteinase regulating their activity.

In the cortex, PNN are disrupted upon traumatic brain injury or stroke, and this may improve axonal or neuritic growth and reactivate neural plasticity [234]. If cochlear PNN behave similarly, noise overexposure could degrade this specialized ECM compartment to enhance the regeneration of auditory synapses, thereby contributing to hearing recovery. Interestingly, PNN properties may also be regulated by glutamate receptor activation and excitotoxic injury, which extensively occurs during acoustic trauma. In the cerebral cortex, kainic acid treatment induces post-translational modification changes to PNN components, resulting in a switch from 4-O sulfation to 6-O sulfation that is more permissive to axonal growth and guidance [235]. It is tempting to speculate that following acoustic overstimulation, and subsequent glutamate overload around the auditory synapse, sulfation pattern changes in cochlear PNN could facilitate the restoration of synaptic contacts. Future studies are thus needed on cochlear PNNs to increase our understanding of its role in synapse plasticity and regeneration after hyperactivity-driven damage.

Ototoxic drugs

Aminoglycosides and cisplatin are widely used in clinics to fight bacterial infections and cancer [236,237], respectively. Their therapeutic efficacy makes them vital despite their well-known adverse effects on the cochlea. By predominantly affecting the sensory hair cells,

these ototoxic drugs cause permanent hearing loss, but they also have been associated with synaptopathies [214,238].

Aminoglycoside treatment of cultured cochleae results in the upregulation of MMP2 and MMP9 proteins [239]. Although the impact of these MMPs was not demonstrated, their induction following drug treatment could lead to ECM breakdown in cochlear basement membranes and cell-ECM interaction changes that contribute to hair cell death. In addition, a detrimental effect on the cochlea could also result from junction loosening in the secretory epithelium and subsequent disruption of the BLB [232]. Alternatively, MMP2 and MMP9 upregulation could be part of a stress response destined to protect against aminoglycoside-induced hearing loss. Indeed, both enzymes catalyze the cleavage of pro-BDNF into its active form [187], and BDNF is an essential factor required to prevent sensory hair cells and SGNs death, including in the case of cisplatin treatment [240–242].

Whether MMPs are upregulated upon cisplatin administration is unknown, however ECM alteration is obvious in the damaged sensory epithelium [243]. Cell-ECM contact loss and epithelial cell disorganization in cisplatin treated cochlear explants was suggested to induce anoïkis-like programmed cell death of hair cells [243], a form of apoptosis associated with cell detachment from basement membranes. *In vivo*, the implication of this extrinsic apoptotic pathway in cisplatin-induced hair cell death and hearing loss remains nonetheless uncertain [244,245].

Interestingly, EVs fulfill a broad range of functions and are key structural and functional components of the ECM [246]. EVs can carry and interact with ECM proteins and regulate matrix properties. In turn, ECM controls EV diffusion and uptake by target cells [8,9]. Their tropism and signaling properties are thought to depend on cell-matrix adhesion molecules. For instance, the set of integrin receptor subunits present could dictate target cell identity and behavior. Although hair cell-derived EVs have been evidenced in human perilymph, their function remains uncertain [247]. Interestingly, exosomes, corresponding to small-size EVs, have been shown to mediate the protective effects of HSP70 through TLR4 against neomycin-induced hair cell death in the utricle [248]. Similarly, the use of exosomes derived from bone marrow-mesenchymal stem cells (MSC) shows protective effects against ototoxic cisplatin treatment *in vitro* and *in vivo* in the cochlea [249,250]. Whether a similar process occurs upon noise is unknown, but the therapeutic potential of EVs delivery to cochlear cells after noise-induced damage has been supported by a recent *in vivo* study. Indeed, local application of human MSC-derived EVs significantly reduced NIHL in rodents, possibly through immunomodulatory effect and release of trophic factor BDNF [251].

Upon hair cell death, the sensory epithelium reorganizes to seal the reticular lamina, restoring a barrier function to prevent leakage of cochlear fluids. The healing process and scar formation depend on non-sensory cells that undergo shape changes and movements to remodel the epithelium. In aminoglycoside-damaged cochlea, this step is associated with the transient disappearance of laminins from the basement membrane, combined with Ecad reduction and PSA-NCAM induction in epithelial cells [252]. Hence, cells undergo EMT to acquire the migration properties of mesenchymal cells and ECM remodeling is required to allow spatial reorganization of the damaged cochlea.

Cochlear implant-induced fibrosis

Clinical management for severe hearing loss relies on the use of cochlear implants (CI) that electrically stimulate the SGNs forming the auditory nerve. The benefit of CI varies and remains largely unpredictable as it depends on many aspects of surgery, device type and cochlear health of the recipient [253,254]. In patients with residual hearing, mainly for low-frequency sounds, CI may worsen the outcome and lead to progressive hearing loss after surgery. Indeed, implanted cochleae mount inflammatory and fibrotic responses, caused by the acute trauma resulting from the electrode insertion and by the presence of the implant, which elicits a foreign body response and chronic inflammation (reviewed in [255]). In human and animal models of CI, excessive ECM accumulation in fibrotic niches is evidenced around the electrode array and new bone formation occurs in severe cases. The fibrous tissue formed around the CI is likely to reduce its performance [256] but also affects cochlear micromechanics as the BM was shown to be stiffer following CI implantation in guinea pigs [257]. Inflammatory and fibrotic cascades are also thought to induce hair cell and SGN degeneration [258,259], but evidence from human studies is scarce [260].

Cochlear implantation rapidly induces pro-inflammatory cytokines IL-1β and TNF-α and upregulates the pro-fibrotic factor TGF-β1 [261]. Leukocyte infiltration and macrophage activation are evidenced in the damaged cochlea together with the recruitment of myofibroblasts [262–264]. Involved in wound healing, these cells synthesize ECM components in large amounts. Collagen fibers are formed in the scala tympani, an area normally devoid of cells but in which fibrous tissue builds up following CI. ECM deposition and remodeling during CI-induced fibrosis is highlighted by gene expression increase for collagens, integrins, mediators of ECM cross-linking (Lox, TSP2) and ECM remodelers (including MMP2, MMP3, MMP9, MMP13 and TIMP1, TIMP2) in the cochlea [261,263]. Accumulation and stiffening of ECM probably exacerbates cochlear inflammation and fibrosis, as mechanical and chemical signals provided by the fibrotic tissue perpetuates pro-inflammatory cytokines and TGFβ1 production [265,266]. Hence ECM could play a crucial role in cochlear damage progression and acoustic hearing decline after CI implantation.

Residual hearing preservation in CI patients is thus a new challenge and many strategies dedicated to mitigating cochlear damage, inflammation and fibrosis are being explored. Besides amelioration of surgical techniques and electrode characteristics that reduce the insertion trauma, biomaterial modification and anti-inflammatory treatments are tested to modulate the foreign body response (reviewed in [253–255]). Noteworthy, ECM core proteins HA and laminins have been tested in hydrogels or coated on the implant [267,268]. A beneficial outcome on hearing and SGN survival was reported for laminin-coated electrodes in guinea pig [268]. This protection might relate to reduced mechanical stress during surgery but could also be linked to improved SGN neurite regrowth and pathfinding [269]. The use of EVs in CI patients has also been investigated and provide clues about the potential of EVs treatments in alleviating cochlear damage [270].

Finally, strategies to predict cochlear health and CI outcome are warranted. The recent identification of a genetic variant of MMP9 as a predictor of post-implantation performance in prelingual deaf children holds significant promise in clinical practice [271]. Moreover, preoperative plasma levels of MMP9 and its proteolytic target BDNF could serve as a predictive biomarker to classify good and poor performers with CI [272].

Concluding remarks and future perspectives

Although sidelined for a long time, cochlear matrisome has recently re-drawn researchers' attention. Indeed, cochlear ECM plays a prominent biomechanical role in guaranteeing efficient and frequency-dependent sound detection, and its remodeling is inherent to both pathological and non-pathological biological processes. Despite growing interest, cochlear matrisome remains to be further explored mechanistically, to fill the gaps between cochlear ECM components, cell signaling pathways and ECM remodeling in hearing. Thus, in the coming years, the challenge will be to elucidate these interactions to fully discover how ECM orchestrates cellular responses, and finally link the cells and the cellular pathways to the surroundings in which they evolve. To do so, a better understanding of cochlear matrisome is needed and will require setting up new analytical tools and combining omics approaches such as single-cell RNAseq with proteomics of ECM-enriched samples, to identify the ECM changes that occur as well as the cells responsible for those changes. Tremendous progress has been made in the past years, and despite remaining challenges [273], they will soon allow for a better

profiling of cochlear ECM, and highlight its huge potential as a reservoir of therapeutic targets.

Emerging questions in cochlear ECM biology

- Cochlear organoids are currently grown on synthetic or tumor-derived ECM substrate. How could biomechanical and biochemical cues be modulated to better mimic *in vivo* processes and facilitate cochlear development *in vitro*? Would enrichment in cochlear ECM-proteins promote hair cell differentiation?
- ECM-modulators are not only affected by transcriptional changes but often activated and inhibited through extensive post-translational modifications (PTM) or proteolytic cleavages. What transcriptional changes, PTM or cleavages affect ECM proteins following cochlear insults? Do they persist over time or change along with recovery? How do cells sense and subsequently react to changes in ECM following injuries? What are the proteins interacting with cochlear ECM?
- In cancer, researchers identified some disease-specific proteoforms, arising mainly from PTM or proteolytic cleavages. Could the cochlear matrisome also display disease-specific variations in ECM protein structure? Is the diversity of proteoform expanded in pathological cochlea?
- As ECM is largely modulated with aging and following cochlear damage, what are the ECM proteins involved and the subsequent deregulated pathways?
- ECM-modulators have been extensively studied in cancer and ECM seems to represent a large reservoir of therapeutic targets. Could specific regulators of ECM components be locally delivered to prevent or limit cochlear damages?

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Data availability

No data was used for the research described in the article.

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