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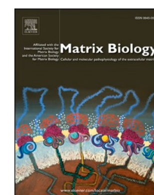

Role of extracellular space and matrix remodeling in cardiac amyloidosis

Francesca Lavatelli [a,b,1], Loredana Marchese [c,1], Palma Patrizia Mangione [a,b], Sara Raimondi [a], Diana Canetti [d], Guglielmo Verona [d], Lucia Venneri [d], Eloisa Arbustini [b], Laura Obici [e], Alessandra Corazza [f], Vittorio Bellotti [a,b,*], Sofia Giorgetti [a,b,**]

[a] Department of Molecular Medicine, Università degli Studi di Pavia, Pavia, Italy
[b] Research Area, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[c] Department of Pathology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[d] National Amyloidosis Centre, University College London, London, UK
[e] SS Malattie Rare, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[f] Dipartimento di Area Medica (DAME), University of Udine, Udine, Italy

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ABSTRACT

The hallmark of amyloid diseases is deposition of misfolded proteins as amyloid fibrils in the interstitium of target organs. Amyloid deposits surround cells, distorting the micro and macro-architecture of the extracellular space and profoundly changing the physical and molecular properties of this compartment. In the heart, extracellular matrix (ECM) remodeling has a profound impact on the mechanical properties of this target organ and on the physiology and metabolism of resident cells. This review critically summarizes the available knowledge on ECM alterations in cardiac amyloidosis, with the goal of providing an overview on how biochemical, biophysical and anatomical modifications are interrelated, and how ECM remodeling participates in the pathophysiology of this unique type of cardiopathy.

Introduction. The heart: an engine conjugating rhythm and strength

The heart is a restless engine that throughout our life provides the blood flow perfusing tissues with nutrients and oxygen. This extraordinary engine conjugates a sophisticated mechanism of electrical pacing with an effective bioenergetic apparatus, to provide adenosine triphosphate (ATP) and guanosine triphosphate for contraction and myofibril stability. The energetic physiology of the heart is dynamically regulated according to workload and substrate availability, and critically depends on the integrity of vasculature, perfusion and diffusion of molecules and oxygen to cells through the extracellular space. Heart cells are in fact embedded within a complex extracellular matrix (ECM) microenvironment, which plays a fundamental role in cardiac physiology and homeostasis [1,2]. Besides being a structural scaffold, the cardiac ECM mediates force transmission and participates in signaling and tissue metabolism. Alteration of the ECM is a major contributor to the pathophysiology of cardiomyopathies and heart failure [3].

Some cardiac diseases indeed primarily target the extracellular compartment. A major example is cardiac amyloidosis (CA), in which interstitial accumulation of misfolded proteins as amyloid fibrils is the signature pathological event, leading to progressive organ damage [4–6]. More than 40 distinct human amyloidoses are known to date, classified based on the amyloid-forming protein [7]. About ten distinct forms of amyloidosis can affect the heart and cardiovascular system, although many of them target also other organs [6–9]; the two most prevalent types are light chain amyloidosis (AL), due to deposition of monoclonal immunoglobulin light chains (LCs), and transthyretin

Abbreviations: ECM, extracellular matrix; ATP, adenosine triphosphate; CA, cardiac amyloidosis; CMCs, cardiomyocytes; MMPs, matrix metalloproteases; TIMPS, tissue inhibitors of metallo proteases; PGs, proteoglycans; GAGs, glycosaminoglycans; HSPG, heparan sulfate PGs; LCs, light chain; AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; HFpEF, heart failure with preserved ejection fraction; AEFEMP1, EGF containing fibulin extracellular matrix protein 1; EGF, epidermal growth factor; MRI, magnetic resonance imaging; SAP, serum amyloid P; β2m, β2-microglobulin; SAA, serum amyloid A; Cryo-EM, cryo electron microscopy; ECV, extracellular volume.

* Corresponding author at:Research Area, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy.
** Corresponding authors at: Molecular Medicine Department, University of Pavia, 27100 Pavia, Italy.
E-mail addresses: vittorio.bellotti@unipv.it (V. Bellotti), sofia.giorgetti@unipv.it (S. Giorgetti).
[1] Equal contribution.

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amyloidosis (ATTR), either due to wild-type (ATTRwt) or to misfolding-prone transthyretin variants (ATTRv) [10–13]. The overall estimated prevalence of amyloid diseases has been profoundly redefined in recent years, thanks to improved imaging and pathological evidence [14,15]. Once considered rare, deposition of amyloid in the heart is in fact turning out to be a common and often unrecognized phenomenon especially in the ageing population, being histologically detectable in up to one fifth of elderly individuals [15,16]. Given the significant morbidity associated with CA, the overall medical and socioeconomic impact is likely destined to grow further in the ageing societies.

Amyloid fibril accumulation profoundly subverts the architecture, composition and functional properties of the ECM. Conversely, specific biochemical and biophysical features of the cardiac extracellular space itself, such as cyclic mechanical forces during contraction and relaxation, collagen and negatively charged proteoglycans (PGs) and active proteases may create a favorable environment to nest amyloidogenesis of predisposed proteins [17,18]. Amyloid accumulation is paralleled by dysfunction of parenchymal cells, to which matrix alteration likely contributes through interwoven mechanisms (Fig. 1). This review critically summarizes the available knowledge on ECM alterations in CA, with the goals to provide an overview of how damage of extracellular space is a crucial contributor to the pathophysiology of this unique type of cardiomyopathy and to point out substantial open issues that still await to be defined.

The cardiac ECM: a dynamic environment that participates in heart physiology and pathology

The cardiac ECM is a molecular network that embeds cells, participates in contraction by providing a proper viscoelastic module and regulates diffusion of molecules and metabolites. Its composition changes during life, in response to specific stimuli and in distinct pathological settings, thus influencing the properties of the myocardium [3, 19–24]. Its production depends on multiple cell types, primarily myofibroblasts but also endothelial and smooth muscle cells, cardiomyocytes (CMCs) and macrophages. The ECM is also ground for signaling cascades by anchoring growth factors and cytokines, and contains a complex system of proteases, such as matrix metalloproteases (MMPs), serine-proteases or ADAM metalloproteinases, and of their modulators (e.g. Tissue Inhibitors of Metallo Proteases, TIMPs). To ensure physiological maintenance and repair of the cardiac ECM, in response to aging and fibrous proteins damage, some of these proteases are constantly active. Their activation mechanism is remarkable: for example, MMP9 is activated by post-translational modifications, such as oxidation or cysteinylation, associated with aging or oxidative stress [25]. This is an efficient mechanism to face the problem of protein damage, since the same modifications that affect the structure and function of ECM proteins also activate the processes that renew the ECM proteome. Protease activity, in turn, generates matrix-derived biologically active peptides, i.e. matrikines [26].

The normal ECM is a hierarchically organized space, whose major structural components are fibrillar collagens (especially type I and type III), elastin, PGs and glycosaminoglycans (GAGs), fibronectin and other glycoproteins [22]. Close to the plasma membrane, the matrix specializes in the basal lamina, which contains distinctive molecules, such as laminins, non-fibrillar type IV collagen and specific PGs. While most matrisome proteins, PGs and GAGs are expressed in different organs, their relative abundance varies from tissue to tissue. The peculiarity of the heart is reflected in the composition of its ECM, both in terms of proteins [27] and glycans [28–30]. Matrix composition modulates myocardial stiffness, which, in turn, profoundly influences resident cells. Thanks to transmembrane proteins working as mechano-transductors, such as integrins, the extracellular space conveys signals to the intercellular environment and modulates intracellular expression pathways. Other features, including shear forces, pressure and composition of interstitial fluids are determinant for tissue homeostasis by influencing transcapillary exchange, electromechanical impulse transduction and protein function [31,32].

After birth, the cardiac ECM maturates with progressive increase in stiffness [20] and further undergoes qualitative and quantitative changes during chronological ageing. One of the hallmarks of ECM ageing is increased fibrillar collagen deposition and cross-linking [33–35]. Numerous additional matrisome proteins accumulate in the senescent heart of humans and mice, among which collagen VI, vitronectin and lactadherin [36]. The composition in PGs and GAGs is also affected [33,34]: an example is the progressive increase in heparan sulfate PGs (HSPG) in ventricles and vessels [18,37–39]. The genesis of these alterations is multifactorial, but an important contribution is provided by age-dependent variations in the degradative activity of several ECM proteases and enzymes [36,40].

Extracellular matrix remodeling is also an inherent pathophysiological component of most cardiac diseases [19,23]. In early disease stages, ECM changes allow the organ to adapt to pathological stimuli, but eventually become detrimental and end up participating in the pathogenesis of heart failure [3]. Activation of a matrix-synthetic program, such as in chronic pressure overload, results in interstitial fibrosis, thus increasing stiffness and leading to diastolic abnormalities [3]. Tissue scars and fibrotic branches can perturb the myocardial excitation-contraction coupling and interfere with impulse propagation, predisposing to conduction anomalies and rhythm disturbances. Deposition of adventitial matrix in vessels may perturb perfusion and nutrient exchange from blood. Pathological remodeling also affects extracellular, pericellular and cell surface PGs, which have an important role as disease modulators and as potential treatment targets [29,41,42]. Importantly, these changes also influence the physiology of resident cells, through deranged signaling and trophic pathways.

The interstitium is a primary target in cardiac amyloidosis

Cardiac amyloidosis is unique for etiology but shares paradigmatic features with other heart diseases in which the interstitium is a key pathogenic target. This condition should be suspected in the presence of manifestations consistent with heart failure with preserved ejection fraction (HFpEF), electrocardiographic abnormalities such as low voltages, or suggestive imaging findings (e.g. increased wall thickness at echocardiography). In most CA cases, the heart is involved in the context of a systemic form, in which multiple organs can be affected by fibril deposition from amyloid precursors produced in distant sites and transported through the bloodstream (e.g. immunoglobulin LCs from bone marrow plasma cells in AL amyloidosis; transthyretin from liver in ATTR).

Histologically, amyloid deposits are evident as amorphous material surrounding cells, altering their topological relationship and expanding the extracellular space. The green birefringence under cross-polarized light after Congo red staining is pathognomonic and is the histological hallmark for diagnosis. The amyloid distribution pattern can vary, ranging from diffuse pericellular infiltrates to scattered deposits or nodular agglomerates [43–45]. Macroscopically, fibril deposition translates into thickening of the cardiac walls, predominantly affecting the ventricles.

The increased stiffness and reduced compliance of amyloid-laden tissue alter diastolic filling, leading to clinical manifestations of restrictive cardiomyopathy. However, systolic function is also affected in patients, as shown by the impaired global longitudinal strain (GLS), a robust marker of myocardial contractility [46]. Amyloid cardiopathy can evolve into overt heart failure, typically without affecting the ejection fraction until advanced stages, and more than two-thirds of deaths are due to cardiovascular events [47]. The peculiar pathophysiology of HFpEF in CA is also consistent with a prominent early damage of the heart's elastic module due to derangement of the elastic fibers organization [48,49]; in fact, stiffness not only reduces the diastolic ventricular expansion, but also decreases the entropic contribution of

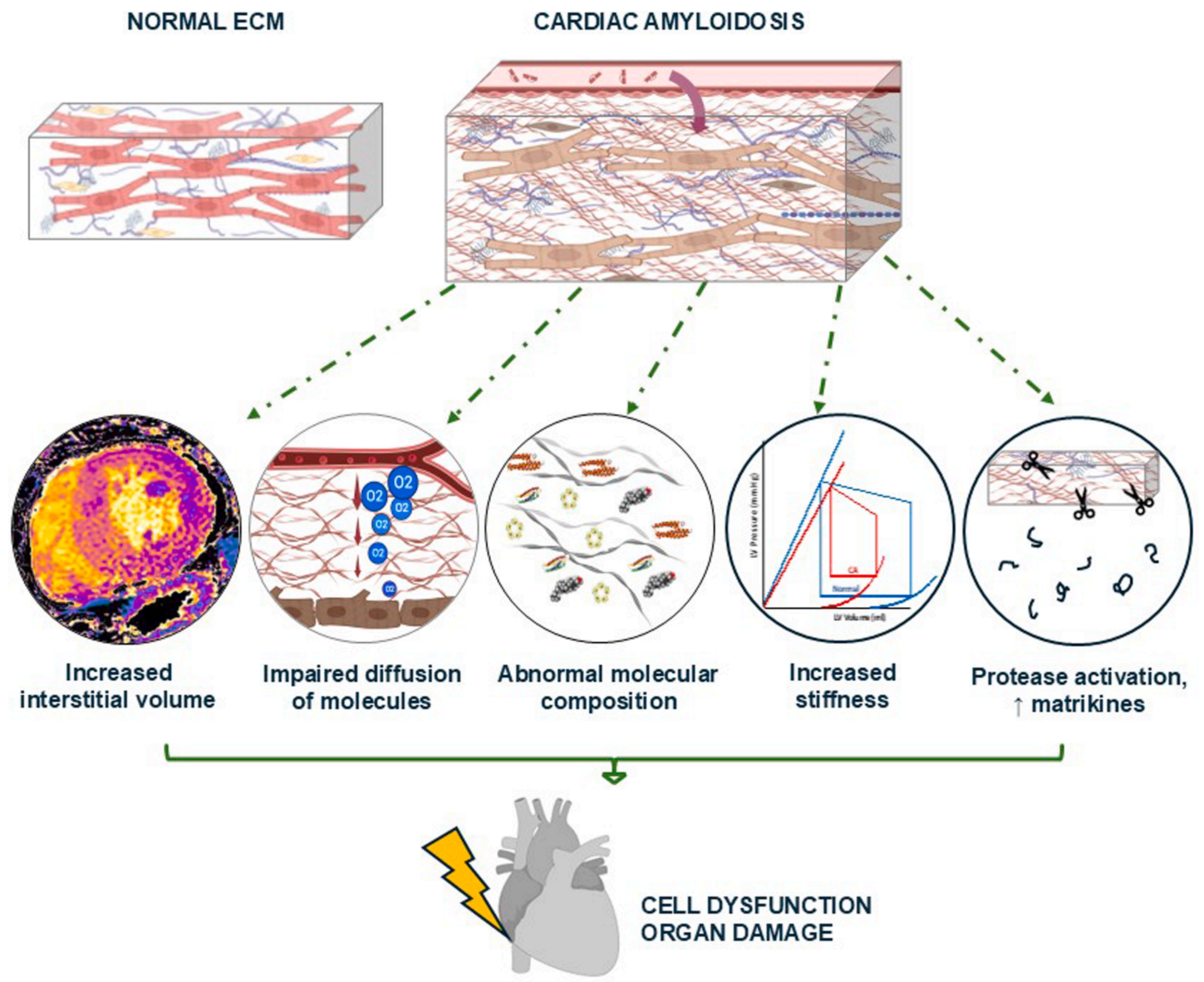

Fig. 1. Multifactorial contribution of extracellular space derangement to heart dysfunction in cardiac amyloidosis.

elastin to the subsequent systolic contraction [50,51].

Amyloid infiltration is not limited to ventricles but can also affect atria, valves, and vessels. Atrial involvement leads to increased stiffness and progressive loss of function, with a significant contribution to clinical severity and prognosis [52–54]. Amyloid deposition can affect tissue vascularization through at least two mechanisms, i.e. by infiltration of the vessel walls and by modification of the fractal space-filling properties of the vascular tree [55]. Fibril accumulation in microvessels or in vasa vasorum and in the adventitial matrix of coronary arteries can in fact lead to vascularization defects and, rarely, to overt ischemic events [56,57]. Some amyloid types, namely AEFEMP1 (caused by EGF containing fibulin extracellular matrix protein 1) [58] and AMed (by Medin) [59] have the vascular system as main target.

With the increasing frequency of ATTRwt diagnosis thanks to the novel imaging-based criteria, the epidemiology of CA has been profoundly redefined [6]. Cardiac amyloidosis likely represents a significantly underrecognized cause of heart failure but remains a diagnostic challenge, due to nonspecific manifestations that overlap with other cardiomyopathies. A panel of first line and advanced imaging approaches, used in conjunction with circulating biomarkers, are currently available for assessing non-invasively the presence and severity of CA [6,60,61]. Besides echocardiography, which can raise the suspicion and help evaluate the disease course, the imaging portfolio has been more recently expanded by cardiac scintigraphy with bone-avid tracers (^{99m}Tc-DPD; ^{99m}Tc-HDP; ^{99m}Tc-PYP) [62–64] and by cardiac magnetic resonance imaging (MRI) [65–67]. Scintigraphy has deeply impacted on the diagnostic pathway, especially for ATTRwt, being determinant for increasing the recognition of this form [6,68]. A unique role in the evaluation of the extracellular space, however, is played by cardiac MRI with contrast administration, which allows quantitative volumetric evaluation [4,66,69,70].

With the only exception of ATTR CA patients with positive cardiac scintigraphy and absence of monoclonal components, histological demonstration of amyloid deposits in an endomyocardial biopsy or in a surrogate site (most often subcutaneous abdominal fat) is required for confirming the diagnosis and for disease classification. Amyloid typing, i.e. identification of the amyloid-forming protein, is mandatory for choosing appropriate therapies in each patient. This is a critical endeavor that involves direct characterization of tissue amyloid through antibody-based methods or mass spectrometry, search for monoclonal components, cardiac imaging and genetic testing [14]. Timely diagnosis of AL CA is especially crucial, as this is the most aggressive form that requires prompt initiation of specific anti-plasma cell treatments. The therapeutic portfolio for AL and ATTR CA has recently witnessed the approval of new classes of disease-specific compounds, with a profound impact on prognosis and quality of life [71]. Initiation of appropriate therapy can halt or slow down fibril accumulation, preventing disease progression and allowing functional amelioration.

The mechanisms behind the onset of CA remain elusive. Amyloid deposition likely derives from the concurrence of multiple factors, including the intrinsic misfolding propensity of the amyloid precursor (due to specific sequence, destabilizing mutations and/or post-translational modifications), its concentration, and the interplay with tissue protective or permissive factors [72]. The imbalance between extracellular proteostasis and increased proteotoxic stress eventually results in the accumulation of stable, protease resistant fibrils that cannot be removed by the organism. The relation between amyloid load and cardiac damage, however, is not univocal and varies across amyloidosis forms [73,74]. In fact, in organs concomitantly affected by amyloid deposits, prefibrillar aggregates can also play an important additive role, through direct proteotoxicity on resident cells [72,75–80]. Toxicity is especially pronounced for amyloidogenic LCs, which were shown to cause oxidative stress, mitochondrial dysfunction, impaired proteostasis with lysosomal defects [75–80] and altered production of specific ECM components [80,81]. Structural identification of the pathogenic conformers is far from being defined, but biophysical analyses on model proteins showed that it is possible to differentiate between toxic and non-toxic oligomeric conformations, and that hydrophobicity of the aggregates might represent a critical pathogenic feature [82]. This may subtend the ability of aggregates to interact with cellular membranes or to recruit cellular proteins through hydrophobic interactions. *In vitro* and *ex vivo* studies suggest that fibrils themselves can exert toxic effects on resident cells, being important contributors to damage and functional impairment [83–85]. While activation of an overt inflammatory response is generally not a hallmark of tissue amyloidosis, exposure of cultured CMCs to amyloid aggregates was shown to induce changes associated with initiation of an innate immune response, suggesting immunologic mechanisms of action for fibril toxicity [83]. A recent scanning transmission electron microscopy (STEM)-based tomography reconstruction of *ex vivo* cardiac AL deposits shows that randomly-arranged amyloid fibrils, besides disrupting the ordered tissue architecture, also interact with the surfaces of resident CMCs, in some cases deforming the plasma membrane [85].

The tissue specificity of the proteotoxic effect, which parallels the organ distribution of amyloid deposits, suggests that mature amyloid deposits and prefibrillar aggregates act as obligatory partners, concurring to determine the overall damage with distinct pathogenetic mechanisms [72,78,85]. Understanding how proteotoxicity is related to ECM derangement, and how the amyloid-laden interstitium affects resident cells are necessary steps to enlighten the still elusive molecular bases of CA.

Extracellular matrix remodeling in cardiac amyloidosis has unique features

Whether caused by amyloid accumulation or by oligomers bioactivity, modification of the extracellular space properties in CA is unique for quantitative and qualitative features at structural, mechanical and electrical levels [20,86]. Amyloid fibrils can in fact be considered anomalous fibrous proteins that are interlocked with physiological fibrous matrix proteins and alter the properties of the ECM in an unconventional manner. Furthermore, amyloid has a "sponge effect" by absorbing a plethora of molecules that are not standard ECM components and whose function once deposited is unknown. Clinical proteomics studies of human affected tissues have provided important information on the identity of amyloid-associated proteins [87–90]. In first place, they include serum-derived species with distinct nature and function, such as apolipoproteins (mainly ApoE, ApoAIV, ApoAI), the pentraxin serum amyloid P (SAP), which may protect fibrils from digestion, and several components of the complement system [87,89]. It is unclear, however, how much of the original function of these out of place proteins is retained, or which novel properties are acquired in tissues. The amyloid proteome also includes serpins and chaperones, such as clusterin, which may play a role in inhibiting the early phases of aggregation but may also stabilize fibrils once they are formed. Additionally, amyloid is enriched in calcium and other metals ions [64,91], and in lipids, most notably cholesterol [92]. Whether recent structural evidence supports the direct interaction of some types of cardiac fibrils with calcium [91], little is known about the mechanisms through which most of the other molecules interact with amyloid in the heart. The individual properties of the protein precursor can determine specific properties of the fibrils, such as surface electrostatics (Fig. 2), in their interactions with soluble molecules and fibrous proteins. Large negatively charged regions (Fig. 2A) and negatively and positively charged neighbouring regions (Fig. 2B) are observed in AL and ATTR fibrils and can influence the interactions with charged molecules that elude detection in structural studies but likely decorate the amyloid fibrils and influence their interaction with the environment. GAGs are a well-known example of such interactors.

Alterations also involve intrinsic components of the extracellular matrix, such as matrisome proteins, proteoglycans and GAGs, enzymes and constituents of the basal lamina (Table 1) [87,89,93]. The most

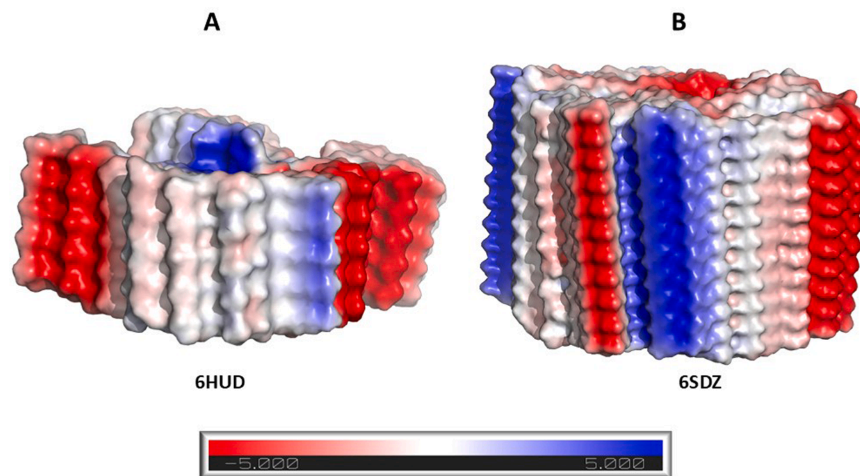

Fig. 2. Examples of molecular structure of cardiac amyloid fibrils from a patient affected by AL amyloidosis (λ light chain, IGLV6–57 germline) (A) and from one patient with ATTR amyloidosis (Val30Met TTR variant) (B), represented as surfaces. Structures were previously resolved using cryo-electron microscopy and deposited in PDB archive; accession numbers are, respectively, 6HUD [188] and 6SDZ [189]. The electrostatic potential is visualized on the fibrillar surface and calculated using the APBS software [190]. The potentials are on a |−5, 5| red-white-blue colour map in units of kT/e).

prominent and consistent changes in affected myocardium include the increase in specific collagens (COL1A1, COL1A2, COL6A1 and COL6A2), glycoproteins (vitronectin, mucin-19), and PGs (mainly heparan sulphate-containing PGs and proteoglycan 4) [18,88,89,92]. Fibrosis, in hearts affected by CA, could contribute to extracellular volume expansion [94] and may be partly related to the activation of a matrix remodeling program. Of note, the HSPG changes in diseased tissues may not be limited to a quantitative aspect; amyloid-associated HSPG were indeed reported to possess a distinctive glycan structure compared to unaffected organs [95].

An open issue concerns the water content in amyloid deposits and its exchange within the extracellular matrix. Up to five different types of water interactions with Abeta fibrils have been described, ranging from tightly bound to free water constrained in the interfibrillar space and slowly exchanging with bulk water [96]. The water content of the matrix can determine the degree of hydration of negatively charged GAGs [97], which favors gel formation and provides more resistance to mechanical forces, and may be related to the efficiency of hydrolytic matrix remodeling by proteases. Additionally, the entropic role of water in fibril nucleation cannot be neglected, modulating also the aggregation kinetics and possibly contributing to the existence of polymorphisms [98].

Several lines of evidence show that the intrinsic proteolytic activity of the ECM is intensified in amyloid-affected organs, independently from cell-mediated inflammation. In tissues and purified amyloid material, the activity typical of human neutrophil proteases, elastase and cathepsins was found to be remarkably increased, suggesting an association between fibrils and proteolytic enzymes [99–104]. Activation of a matrix-remodeling program is also suggested by the increase in MMPs and TIMPs (MMP-9, MMP-2, TIMP-1) both in affected tissues and in blood, especially in patients with AL cardiomyopathy [105,106]. The mechanism by which amyloid deposits can stimulate proteolysis is unknown, although at least two properties could be implicated, i.e. a response of the host tissue, mediated by release of toxic radicals, and intrinsic activation of plasminogen upon interaction with amyloid fibrils that mimic fibrin aggregates. Matrix remodeling in amyloidosis may thus imply a complex interplay of molecular mechanisms, which are still far from being defined and are not evidenced by the current diagnostic techniques.

From an architectural point of view, amyloid profoundly disturbs the topological relation between cells and surrounding elements. Alterations become more evident after tissue decellularization, which exposes a thickened and qualitatively damaged matrix [107]. The average distance between cells and capillaries increases [108], with a longer path to be covered by nutrients, gases and other molecules from or to the bloodstream, and by signaling molecules between cells. This may profoundly impact the energetics of the heart, which relies on an active oxidative metabolism to support its continuous contraction. In addition, amyloid fibrils are themselves endowed of remarkable biophysical properties [109], which include bending rigidity and elevate stiffness, high resistance to breakage and tensile strength, comparable to those of silk or steel [110], and a periodic sequence of hydrophobic and charged patches (Fig. 2). These notions suggest that interstitial amyloid, although fibrils are not aligned and form a complex 3D arrangement, may significantly alter the mechanical and viscoelastic properties of the tissue. Given the fact that wall stiffness modulates ventricular compliance, diastolic filling and cell physiology, the mechanical contribution of amyloid fibrils may be significant in determining heart dysfunction, CMC response and release of natriuretic peptides [111].

Amyloid deposits may also influence the electrical properties of the myocardium, contributing to the abnormalities that are common in CA, including conduction system disease (reflected by atrio-ventricular block), arrhythmias, and QRS voltage aberrations. Changes in the conductive properties of the matrix could modify the local and global electric resistance within the heart; in fact, it was recently postulated that the insulating properties of amyloid, possibly combined with interstitial edema, could be responsible for the low voltages commonly observed in CA [86].

A chicken and egg situation: challenges in defining causes and consequences of amyloid deposition

Picturing the extracellular space as a passive target of amyloid deposition does not capture the complex interplay between ECM and amyloid, which are in fact linked by a reciprocal relationship (Fig. 3). A major lingering question is whether amyloid can accumulate in a normal heart at some point during life or if pro-amyloidogenic ECM remodeling is a prerequisite to nest fibrillogenesis. Growing evidence indeed shows that specific ECM components such as collagen and HSPGs, consistently increased in amyloid-positive tissues, can modulate protein misfolding and promote fibrillogenesis [88,112–115]. In fact, whether the peculiar amyloid-associated nano-environment precedes or follows amyloid deposition, resulting from entrapment of ECM molecules within the fibrillar mesh or being due to the tissue response to protein misfolding, is currently undefined. The ECM remodeling described above may promote further protein aggregation through multiple mechanisms, such as by increasing crowding or by modifying hydration and creating an

Table 1

Extracellular matrix components deranged in tissues with extracerebral systemic amyloidoses. Bold: documented in the heart. ↑: co-localized with amyloid deposits or increased in amyloid tissues compared with unaffected controls; ↓: decreased in amyloid tissues compared with unaffected controls. ** documented also in experimental models (mice). Abbreviations: LMD-MS: Laser Microdissection-Mass Spectrometry; MudPIT: Multidimensional Protein Identification Technology; IHC: Immunohistochemistry; EM: Electron Microscopy; H: Heart; K: Kidney; SFA: Subcutaneous Fat; ST: Soft Tissues; L: Liver; GI: Gastrointestinal tract; SG: Salivary Glands; CT: carpal tunnel.

	Molecule	Gene	Technique	Correlation with presence of amyloid in tissues*	Amyloidosis type	TISSUE (human)	References	Notes
EXTRA CELLULAR Proteins	**Collagen I α1**	Col1a1	Proteomics	↑	AL, ATTR, AA, other	H, SFA, K, ST, other	[87–89,93]	
	Collagen I α2**	Col1a2	Proteomics, Transcriptomics	↑	AL, ATTR, AA, other	H, SFA, K, ST, other	[80,87,89,93, 142]	
	Collagen III α1	Col3a1	LMD-MS	↑	AL, ATTR	H	[87,93]	
	Collagen IV α2 **	Col4a2	Proteomics, IHC	↑ or ↓	ATTR, AL, AA, other	K, SFA, H, other	[88,89,136,191]	↓ in SFA in ATTR [88]
	Collagen VI α1	Col6a1	Proteomics	↑	AL, ATTR, AA, other	SFA, H, other	[87–89,93,138]	
	Collagen VI α2	Col6a2	Proteomics	↑	AL, ATTR, AA, other	SFA, H, other	[87–89,138]	
	Collagen VI α3	Col6a3	Proteomics	↑	AL, ATTR, AA, other	SFA, H, ST, other	[88,89,93,138]	
	Collagen XII α1	Col12a1	MudPIT	↑	AL	SFA	[88]	
	Collagen XVI α1**	Col16a1	Transcriptomics	↑	AL	H	[142]	
	Collagen XXVII α1**	Col27a1	Transcriptomics	↑	AL	H	[142]	
	Fibronectin**	Fn1	Proteomics, IHC, Transcriptomics	↑ or ↓	ATTR, AL, AA	SFA, K, H, other	[80,88,142, 191–194]	↓ in SFA in ATTR and AA [88]
	Vitronectin	Vtn	Proteomics	↑	AL, ATTR, AA, other	H, SFA, K, other	[87–89,93,195]	
	Cartilage intermediate layer protein 1	Cilp1	LMD-MS	↑	ATTR	H	[87,93]	
	Mucin 19	Muc19	LMD-MS	↑	AL	H	[87]	
	Fibulin-1	Fbln1	Proteomics	↑	ATTR	CT	[93]	
	Fibulin-4	Fbln4	IHC	↑	AKer	Skin	[196]	
	Lumican	Lum	MudPIT	↓	AL, ATTR, AA	SFA	[88]	
	Mimecan	Ogn	MudPIT	↓	AL, ATTR, AA	SFA	[88]	
	Periostin	Postn	MudPIT	↓	AL, ATTR, AA	SFA	[88]	
	Coiled-Coil Domain Containing protein 80	Ccdc80	Proteomics	↑	AL, ATTR	SFA	[88,197]	
	Cartilage oligomeric matrix protein	Comp	Proteomics	↑	ATTR	CT	[93]	
	Asporin	Aspn	MudPIT	↓	AL	SFA	[88]	
	Fibrillin-1	Fbn1	Proteomics	↑	AL, AA	K	[89,93]	
PGs	Heparan sulfate proteoglycans **	–	Proteomics, histology	↑	AL, ATTR, AA, other	H, K, SFA, ST, other	[18,59,81,92, 112,118,194, 198]	
	Biglycan	Bgn	Proteomics, EM	↑ or ↓	AL, AA, ATTR	SFA, K, SGs, other	[88,199,200]	↓ in SFA in all forms [88]
	Proteoglycan 4	Prg4	LMD-MS	↑	AL	H	[87]	
	Chondroitin sulfate proteoglycans **	–	IHC	↑	ATTR	GI	[201]	
Enzymes	MMP-1	Mmp1	IHC	↑	AL, AA, other	K, L, other	[83,202,203]	
	MMP-2**	Mmp2	IHC, ELISA	↑	AL, AA, ATTR	H, K	[104,106,202, 204–206]	
	MMP-3**	Mmp3	IHC, Transcriptomics	↑	AL, AA other	H, ST	[83,142,202, 207]	
	MMP-9**	Mmp9	IHC, ELISA	↑	ATTR, AL	H, K, SG	[105,106,200, 201,204,206, 208]	
	MMP-12**	Mmp12	Transcriptomics	↑	AL	H	[142]	
	MMP-19**	Mmp19	Transcriptomics	↑	AL	H	[142]	
	TIMP-1**	Timp1	IHC, ELISA, Transcriptomics	↑	AL	H, L, other	[105,106,142, 202]	
	TIMP-2	Timp2	IHC, ELISA	↑	AL	H, L, other	[105,106,202]	
	TIMP-3	Timp3	LMD-MS	↑	AL, ATTR	H	[87,93]	
	Procollagen C-proteinase enhancer-1	Pcpe-1	IHC	↑	Aβ2-m	Joints	[209]	
	Procollagen C-endopeptidase enhancer 2	Pcolce2	LMD-MS	↑	ATTR	H, CT	[87,93]	
	HTRA1	Htra1	MudPIT	↑		SFA	[88]	
	ADAMTS2**	Adamts2	Transcriptomics	↑	AL	H	[142]	
BASAL LAMINA	Nidogen-2	Nid2	MudPIT	↓	AL, ATTR, AA	SFA	[88]	
	HSPG 2	Hspg2	MudPIT	↑	AL, AA	SFA	[88]	

(continued on next page)

Table 1 (*continued*)

Molecule	Gene	Technique	Correlation with presence of amyloid in tissues*	Amyloidosis type	TISSUE (human)	References	Notes
Basement membrane-specific HSPG core protein	PGBM	Proteomics	↑	AL, ATTR, AA, other	K, SFA, other	[89]	
FIBULIN 1 isoform C	FBLN1-isoC*	LMD-MS	↑	ATTR	H	[87]	
FIBULIN 1 isoform D	FBLN1-isoD*	LMD-MS	↑	ATTR	H	[87]	
DECORIN	DCN	LMD-MS, EM	↑	AA, ATTR	H, K	[87,199]	
PROLARGIN	PRELP	Proteomics	↑ or ↓	AL, ATTR, AA	H, SFA	[87,88]	↓ in SFA in AL and AA [88]
LAMININ n.o.s.	–	IHC	↑	ATTR	H	[191]	
LAMININ α4	LAMA4	MudPIT	↓	AL, ATTR, AA	SFA	[88]	
LAMININ β1 **	LAMB1	MudPIT, IHC	↑ or ↓	AL, ATTR, AA	SFA	[88,136]	↓ in SFA in ATTR and AA [88]
LAMININ β2 **	LAMB2	MudPIT, IHC	↑ or ↓	AL, ATTR, AA	SFA	[88,136]	↓ in SFA in all forms [88]
LAMININ γ1	LAMC1	MudPIT	↓	AL, ATTR, AA	SFA	[88]	

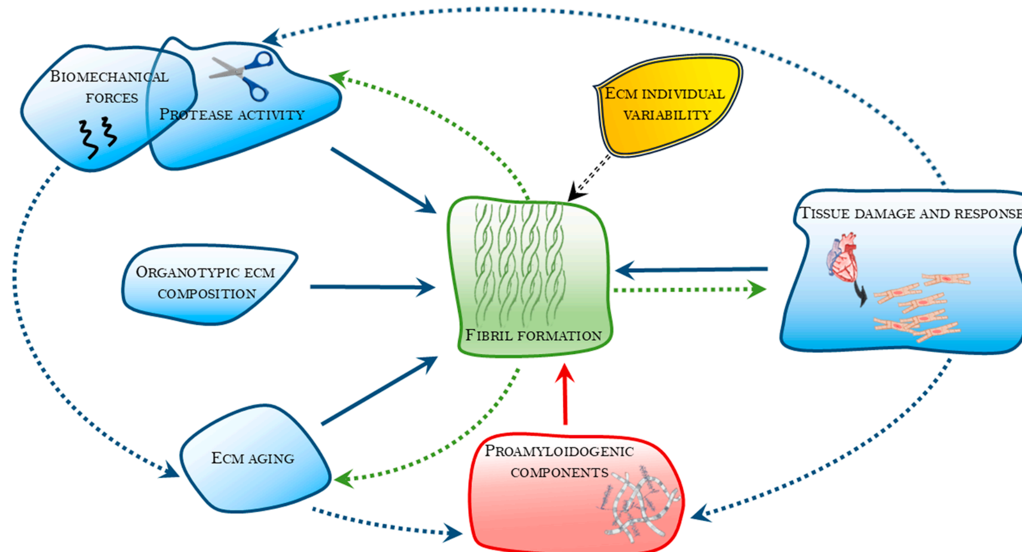

Fig. 3. Tissue damage and ECM alterations in cardiac amyloidosis. Several factors may lead to amyloid deposition in cardiac ECM: known components (red), possible modulators (blue) and several interconnections among them (dotted arrows). Open questions remain about the role of individual variability in ECM and what changes in ECM precede or follow amyloid deposition.

aggregation-permissive setting, in which confinement of amyloid precursors leads to supersaturation and aggregation. Additionally, the absorption of mechanical forces by matrix components may be altered.

Collagen and proteoglycans have been extensively studied for their ability to bind amyloid precursors and favor structural conversion [18,113,114,116–118]. Negatively charged HSPGs can interact with amyloidogenic proteins, among which β2-microglobulin (β2-m) [119–121], serum amyloid A (SAA) [118,122], TTR [18], LCs [115,123–125] and ApoAI [126,127], thus promoting the formation of β-sheet-rich secondary structures and possibly initiating amyloidogenesis. A special role is certainly played by complex carbohydrates, both conjugated and non-conjugated to a protein scaffold. These molecules may stabilize oligomers and nascent fibrils by binding to accessible basic residues in the misfolded conformation (Fig. 3), thereby creating a high local concentration of oppositely charged species and favoring a sort of polymerization [114,120]. In the case of SAA, interaction with HSPG also promotes dissociation from high-density lipoproteins, generating a lipid free form of the protein which is more prone to amyloidogenesis than the lipid-bound counterpart [122]. Once fibrils are formed, proteolgycans can protect them from proteolytic degradation and mediate their interaction with cells [128,129]. In the case of immunoglobulin LCs, heparan sulphate facilitates the acquisition of transient amyloidogenic conformations, whereas chondroitin sulphate kinetically traps partially unfolded intermediates, inhibiting further fibril elongation [123].

Other ECM molecules, particularly collagen [92,130,131] and laminins [132–135] can influence amyloidogenesis. Distinct collagen types, such as type IV [136], I [116,137] and VI [138], were shown to bind amyloid precursors, playing an active role in aggregation. Electrostatic effects concentrate the amyloidogenic species on the surface of these polymeric proteins, where misfolding and nucleation can occur [116]. It has been hypothesized that collagen might modulate amyloid catabolism by inhibiting fibril phagocytosis, possibly acting as a 'don't eat me' signal that contributes to the accumulation of deposits [139]. The increase in microfilament collagen VI is especially attractive, since it is observed in multiple tissues and various amyloid types (Table 1). AFM has previously highlighted the intimate interaction between collagen

fibers and amyloid fibrils [120] and recently molecular details of such interaction have been dissected through cryo-EM [138]. A synergy between amyloid and collagen was also postulated to contribute to aortic valves calcification. Aortic valves, in fact, are fibrous structures that often contain amyloid fibrils; these, in turn, could promote calcification through fibril-assisted nucleation of hydroxyapatite onto the collagen matrix [140].

Investigating physio-pathological events occurring in the extracellular space *in vivo* is however challenging, due to the paucity of non-invasive biomarkers and experimental models compared to those established for cells. The finding that incubation of cultured cardiac fibroblasts with prefibrillar amyloidogenic light chains alters the production and processing of ECM components [80,81] suggests that target cells may contribute to pro-amyloidogenic remodeling of the matrix. A breakthrough in this regard, however, will be represented by mouse models recently developed for ATTR and, lately, for cardiac AL amyloidosis [141,142]. In the AL model, in particular, amyloid deposition in the heart of mice transgenic for a human amyloidogenic LC is obtained after injection of amyloid seeds [142]. Transcriptomic analysis of cardiac tissue from amyloid-positive mice, compared to amyloid-negative transgenic animals, shows that major changes affect the ECM compartment, with tens of differentially expressed genes encoding for endoproteases (MMPs, ADAMs and extracellular cathepsins) and their inhibitors (TIMPs), as well as ECM-related proteins, such as collagens, fibronectin, laminin and adhesion molecules. These findings are consistent with ECM remodeling, early fibrotic processes and immune cell infiltration and powerfully suggest that, at least in mice, the process of amyloidogenesis translates into a profound response of resident cells that may further become concausal in the progression of the disease.

Another important player in the pathogenesis of CA is aging [143]. Amyloid deposition occurs in adulthood and the prevalence of this condition increases in the elderly, even in individuals who carry inherited pathogenic mutations in amyloid precursors [143]. It may be likely that aging-related modifications in the composition and proteolytic activity within the extracellular space may modulate the onset of CA [33,34,40,144,145]. The report that sulphated HSPG increase in the aging cardiovascular system [18,38] supports the speculation that the environment can become progressively pro-amyloidogenic later in life. Variations in protease activity may also have disease-modulating effects [33,146]. The cardiac EMC is subject to mechanical stress throughout life and undergoes proteolytic remodeling necessary for adapting to stimuli and for rejuvenating the challenged molecular apparatus. Proteases, in general, are important players in the dynamics of amyloid formation and degradation. Matrix metalloproteases and cathepsins, among others, can degrade amyloid fibrils [100,103,104,147]; nevertheless it has been known for at least 50 years that certain proteases can also selectively cleave native proteins inducing amyloidogenesis [148]. More recently, we contributed to characterize how specific proteolytic enzymes can induce TTR amyloidogenesis. The concept highlighted by our data is the dependence of proteolytic cleavage from forces that destabilize specific protein segments, thus reducing the protection from proteolysis [17,149]. A vast literature on protein dynamics upon exposure to mechanical forces exists [150]. We have hypothesized that the biomechanical forces specifically present in ATTRwt target organs have a crucial pathogenetic role. The heart, a site where mechanical forces are particularly important, is affected by ATTRwt deposition later in life; however, cardiomyopathy can be preceded by many years by ATTRwt-related carpal tunnel syndrome and by amyloid accumulation in the spine and ligamentum flavum [151]. Due to the anatomical and functional complexity of these deposition sites, calculation of organ-specific mechanical forces is not an easy task. Frictional forces are especially relevant in relation to carpal tunnel and are influenced by several variables as well as by gender [152]. Increase in frictional forces and local pressure can generate conditions favoring unfolding; nevertheless, the effective intensity of these forces may be further modulated by modifications of the microenvironment due to inflammation, edema or fibrosis. Better knowledge of the forces operating in different anatomic sites is crucial for understanding the organ-specific deposition of amyloid, a process in which ECM composition and architecture play a central role [153,154].

Overall, solving the complex amyloid-predicting equation that considers both tissue factors and intrinsic protein amyloidogenicity is a challenging task. The distinct TTR variants represent a natural model that helps solve this chicken and egg dilemma, showing that the kinetics of fibrillogenesis or degradation *in vitro* are alternative processes, modulated by specific mutations and by several environmental elements, such as seeds and GAGs [155]. Defining the events that shift this equilibrium *in vivo* is the key to understanding what causes tissue amyloidogenesis and what can be done to counteract the process.

From the outside in: role of matrix alterations in cardiomyocyte damage

Cardiomyocyte damage in CA is most likely a multifactorial process, in which proteotoxicity of soluble precursors aggravates the distress caused by interstitial amyloid infiltration. However, while the toxicity of prefibrillar species has been shown for most amyloidogenic proteins in cell cultures or in small animal models [75,76,79,156,157], we still lack direct evidence of toxic oligomers in rodent models or even in patients.

It is plausible that ECM derangement provides a substantial contribution to cell damage in CA. Several mechanisms could play a role in this regard, including stiffness-related cellular stimulation, increased active matrikines following protease activation, altered paracrine signaling through the expanded extracellular space, impaired diffusion of metabolites and O_2, and specific biological activity of amyloid-associated molecules. The metabolic consequences of ECM expansion may be relevant. Although the heart can use most energetic substrates, >95 % of ATP produced under normoxia conditions derives from oxidative phosphorylation [158,159]. Metabolic remodeling was documented in neurons of Alzheimer's disease patients, with a shift towards aerobic glycolysis and depression of fatty acids β−oxidation and Krebs cycle, thus displaying molecular signatures consistent with what observed in chronic hypoxia [160–162]. Study of amyloid-laden tissues has opened the perspective that the increased distance between cells and capillaries can have a profound metabolic effect by impairing the O_2 pressure gradient and causing actual hypoxia [108]. Cellular hypoxia may be a general mechanism through which amyloid causes tissue damage, especially relevant in organs with the highest O_2 consumption, such as the heart. Considering the role of metabolism in regulating CMC growth, survival and autophagy [158], parenchymal hypoxia may exacerbate proteotoxicity and worsen tissue damage. Importantly, matrix expansion may differently affect the diffusion gradients of nutrients with distinct biochemical properties, such as hydrophilic glucose or hydrophobic fatty acids, thus modifying the availability of energetic substrates and posing additional constraints to CMC metabolism. Further investigation on the metabolic consequences of ECM remodeling may be pivotal for understanding the bases of cell and tissue damage in CA.

Perspectives: the extracellular space as a target for advanced molecular imaging and therapy in cardiac amyloidosis

Assessing the interstitium in CA is challenging and routine clinical methods such as echocardiography lack the specificity, sensitivity and accuracy to measure changes over time. Evaluating diastolic function has long been the only way to estimate interstitial damage, but the landscape of opportunities is being profoundly transformed by new *in vivo* imaging approaches. In contrast to the widely used cardiac biomarkers, which provide information on cell damage, extracellular space visualization opens a window on fibril deposition and its direct consequences. Cardiac MRI assessment focused on extracellular space is a milestone that will deeply help understand the disease pathophysiology

[64,163]. Imaging amyloid is critical to improve disease detection, risk stratification and treatment monitoring, and various new radionuclide tracers are being clinically evaluated [64,164]. While the binding mechanisms between fibrils and probes have long been poorly defined, deeper understanding of the structure of cardiac AL and ATTR amyloid fibrils is opening new perspectives and has recently allowed proposing a molecular mechanism to explain the preferential association of ^{99m}Tc-labeled bone-seeking tracers to cardiac ATTR fibrils. These, in fact, chelate to surface-bound Ca^{2+} in amyloid, coordinated by pairs of acidic residues exposed on the TTR-derived fibril surface [91]. In the future, targeted *in vivo* imaging of molecules involved in the mechanisms of ECM remodeling, such as specific matrisome proteins and proteases [24,54] may represent an additional way for further understanding the physiopathological mechanisms, which are not captured by current diagnostic methods. A step in this direction is represented by polybasic pattern-recognition peptides that bind hypersulfated heparan sulfate and amyloid fibrils, such as ^{124}I-Evuzamitide, which were shown to be promising novel radiotracers to detect and quantify cardiac deposits in patients [165].

Interestingly, ATTRwt and AL CA were recently found to have a distinct serum biomarker profile compared to other forms of HFpEF, characterized by up-regulation of proteoglycans and cell-adhesion pathways; the proteoglycan decorin and lysosomal hydrolase alpha-L-iduronidase were proposed as potential new screening tools for ATTRwt cardiomyopathy [166].

Defining the clinical impact of interstitial alterations may be of utmost relevance for patient management and drug evaluation. In AL and ATTR CA, extracellular volume (ECV) fraction has relevant prognostic value [167–169], and MRI-measured ECV changes independently predict the outcome in AL patients [170,171]. Combined evaluation of ECV and longitudinal strain shows that both parameters associate with outcomes but correlate minimally, possibly reflecting distinct domains of cardiac damage [172]. Since both the involvement of the interstitium and CMC injury are crucial elements in CA, combining these two levels of clinical information may be critical for better disease understanding.

The concept that the cardiac ECM can be a therapeutic target is emerging in several heart diseases [173] and is attractive in relation to CA, in which the interstitium is primarily affected. Approved therapies against AL and ATTR amyloidosis are focused on removing or stabilizing the amyloidogenic precursor [71,174–176]. This, however, is not always achievable, and even in such case, it does not invariably translate into profound organ response [71]. In AL amyloidosis, the depth of hematological response required for cardiac improvement varies across patients, and even minimal residual disease can result in damage progression [177,178]. Targeting deposited amyloid and interstitial dysfunction could be a novel, additive avenue with high potential impact. Existing fibrils continue to damage the heart through profound derangement of the extracellular space and can accelerate disease progression by seeding soluble precursors into aggregates [179,180]. So far, two approaches targeting extracellular events in amyloidosis have been designed, i.e. molecules interfering with the association between proteins and HSPG, and compounds aimed to promote fibril resorption [71]. The archetype of the former group is eprodisate, a sulfonated molecule structurally similar to heparan sulfate that competitively binds to the GAG-binding sites on SAA and inhibits fibril polymerization in tissues [181]. Eprodisate has been tested in two clinical trials on patients with renal AA amyloidosis, with conflicting results. While a first randomized trial suggested that this drug can slow renal function decline, a second phase III trial failed in confirming these results, and the study was terminated [181]. Regarding strategies to deplete deposited fibrils, several trials are currently ongoing in both AL and ATTR amyloidosis. Anti-amyloid approaches are substantially based on protein ligands directed against the fibrillar conformers and acting through the recruitment of the innate immune system [182–184]. At least three such compounds are being tested in AL [182,183,185,186] and two in ATTR amyloidosis [71,174,187]. The current trials will elucidate if fibril removal improves organ function, survival and quality of life, and may provide clinical evidence on whether amyloid depletion will be sufficient to recover the function of a biochemically deranged interstitium, in which other molecules, such as collagen and HSPGs, have accumulated. An open question concerns the extent to which current patient assessment methods can capture the qualitative, quantitative and functional changes of the extracellular compartment, and working to improve this task will be crucial in the future.

Future strategies to improve CA might target additional aspects connected with extracellular space derangement, such as aberrant accumulation of collagen or the metabolic consequences of ECV expansion. Designing novel strategies, however, will not be possible without deeper knowledge of the mechanisms through which ECM alterations translate into organ dysfunction in cardiac amyloidosis, and, in turn, without exploiting and developing adequate experimental models accounting for the extracellular space in this unique type of disease.

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Data availability

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

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