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Biomarkers of the extracellular matrix and of collagen fragments

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ABSTRACT

A great body of evidence has shown that extracellular matrix (ECM) alterations are present in the major types of cardiac diseases: ischemic heart disease, heart disease associated with pressure overload, heart disease associated with volume overload, and intrinsic myocardial disease or cardiomyopathy. Collagen, type I and III, is the principal structural protein found in the myocardium and its pro- or telopeptides are released into the circulation during the course of cardiovascular diseases. Therefore, these peptides may reflect collagen synthesis and break-down and also represent a much more useful tool to address ECM changes from a distance. Clinical trials have been performed during recent years to examine the usage of these peptides as diagnostic or prognostic biomarkers in heart failure (HF) patients. This review aims to summarize published data concerning cardiac ECM and its circulating biomarkers. Studies that focused on collagen metabolism related biomarkers in patients with HF are analyzed. Finally, limitations associated with the clinical use of the aforementioned biomarkers are also discussed.

1. Introduction

It has been over 25 years since Karl Weber focused our attention on cardiac extracellular matrix (ECM) regarding myocardial remodeling in various cardiovascular diseases based on pioneering work by his group and others [1]. A great body of evidence has shown that ECM alterations are present in 4 major types of cardiac diseases: ischemic heart disease, heart disease associated with pressure overload, heart disease associated with volume overload, and intrinsic myocardial disease or cardiomyopathy [2].

ECM consists of a macromolecular network of fibers. Collagen is the principal structural protein, whereas a basement membrane, proteoglycans, glycosylaminoglycans, and bioactive signaling molecules are also significant constituents [3]. The ECM network is a metabolically active structure in the sense that there is a continuous turnover of its elements, mainly a dynamic balance between synthesis and degradation of collagen, which is estimated to be from 80 to 120 days [4].

In the past, the myocardial collagen fraction was determined in cardiac biopsies. However, during the past 10 years, there has been a growing interest in noninvasive methods to detect cardiac collagen. Late gadolinium enhancement (LGE) and extracellular volume fraction are two cardiac magnetic resonance (CMR) imaging techniques to detect fibrotic areas in the heart [5]. Given the dynamic nature of ECM, the costs and time consumption of CMR , the ECM related changes cannot be assessed by classical imaging alone [6]. Therefore, circulating biomarkers that reflect collagen synthesis or degradation might be much more useful tool to address ECM changes from a distance, especially if these changes should be followed on multiple occasions over time by the bedside [7].

This review aims to summarize published data concerning cardiac ECM and its circulating biomarkers. Studies that focused on collagen metabolism related biomarkers in patients with heart failure (HF) are discussed.

1.1. ECM metabolism

The cardiac ECM is predominantly composed of fibrillar collagen type I (85%) and type III (11%) [8,9]. Type I has a poor specificity, forms thicker fibers and has a high degree of cross linking between the fiber, thus conferring tensile strength and resistance to stretch and deformation. Type III is more specific to the heart, has a relatively small diameter and provides resilience and elasticity [10–12]. Furthermore, small amounts of types IV and V are observed in the basement membrane of the myocytes, perivascular, and in the pericellular space [8,13]. As mentioned above proteoglycans, glycosylaminoglycans

Abbreviations: BNP, brain natriuretic peptides; CMR, cardiac magnetic resonance; ECM, extracellular matrix; EDTA, ethylenediaminetetraacetic acid; HF, heart failure; LGE, late gadolinium enhancement; MMPs, matrix metalloproteinases; PICP, carboxy terminal propeptide of procollagen type I; PIIICP, procollagen type III carboxy-terminal propeptide; PINP, amino-terminal propeptide of procollagen type I; PIIINP, procollagen type III amino-terminal propeptide; TIMP, tissue inhibitors of metalloproteinases.

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and bioactive signaling molecules represent less abundant elements of the ECM.

Collagen turnover is regulated by fibroblasts and by fibroblasts differentiated to myofibroblasts [2,14]. These cells respond to mechanical stretch, wall stress, autocrine and paracrine factors generated locally (such as angiotensin II) and growth factors (such as transforming growth factor –β or connective tissue growth factor), and hormones derived from the circulation (e.g., aldosterone) [2]. In addition, a number of pro-inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-1 and -6) secreted by monocytes and macrophages also influence the function of fibroblasts and myofibroblasts [2]. The responses of these cells to all the aforementioned factors include changes in their rates of proliferation and migration and modifications in their capacity to synthesize and secrete fibrillar collagen precursors (namely the 2 more abundant subtypes present in the heart: procollagen types I and III), as well as enzymes that process procollagen precursors to mature collagen able to form fibrils and fibers (e.g., procollagen proteinases and lysyl oxidase), enzymes that degrade collagen molecules within fibers (e.g., matrix metalloproteinases [MMPs]), and signaling molecules that regulate the interaction of the extracellular matrix with parenchymal cells (e.g., matricellular proteins) [2].

1.2. Collagen synthesis

The fibrillar collagen is synthesized as a pre-procollagen, a pro-a-collagen chain within fibroblasts or myofibroblasts. In the endoplasmic reticulum, 3 pro-a-chains form a triple helix structure, known as procollagen [8,15]. All fibrillar procollagen types initially contain 2 propeptides: the amino (N)-propeptide and the carboxy (C)-propeptide. Once the procollagen is localized to the ECM, these propeptides are cleaved by proteinases in a 1:1:1 stoichiometry [8,16]. Cleavage of the propeptides is a prerequisite for the formation of type I and III collagen fibers. This holds true for the carboxy-terminal propeptide of procollagen type I (PICP) and possibly for the amino-terminal propeptide of procollagen type I (PINP) [8,17,18]. On the other hand, the carboxy-terminal and amino-terminal propeptides of collagen type III (PIIICP and PIIINP, respectively) are not completely cleaved during the conversion of procollagen type III into collagen type III, remaining to some extent in the final fiber. Moreover, fibril formation will still occur, together with the incorporation of these propeptides and thus also being released during fiber degradation [8,17,18]. After cleavage of the propeptides, the triple helix chain will form large collagen fibrils together with other collagen chains cross-linked by pyridinium and deoxy-pyridinium containing bonds (Fig. 1.) [18].

The removal of procollagen type I carboxy-terminal propeptide (PICP) and procollagen type III carboxy-terminal propeptide (PIIICP) is accomplished by procollagen C-proteinases. The N-terminal propeptides (PINP and PIIINP) are cleaved by members of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin type I repeats) family [8,19]. After cleavage of the propeptides, the propeptides are released into the blood, either directly or via the lymphatics [8,16]. Finally, they are degraded by the liver. Elimination of PICP occurs via endocytosis mediated by the mannose receptor, whereas PINP and PIIINP are removed via scavenger receptors [8,16,17]. However, elimination of the propeptides might also occur via the kidneys and via urine [8,16]. The N-terminal propeptides of collagen type I or III (PINP and PIIINP) and the C-terminal propeptides (PICP and PIIICP) are used as markers of collagen type I or III synthesis.

1.3. Collagen degradation

The degradation of collagen fibers is mediated by the matrix metalloproteinase (MMP) family of enzymes that can be inhibited by direct interaction with naturally occurring, specific tissue inhibitors of metalloproteinases (TIMP-1 to TIMP-4) [2,20]. Interstitial collagenase

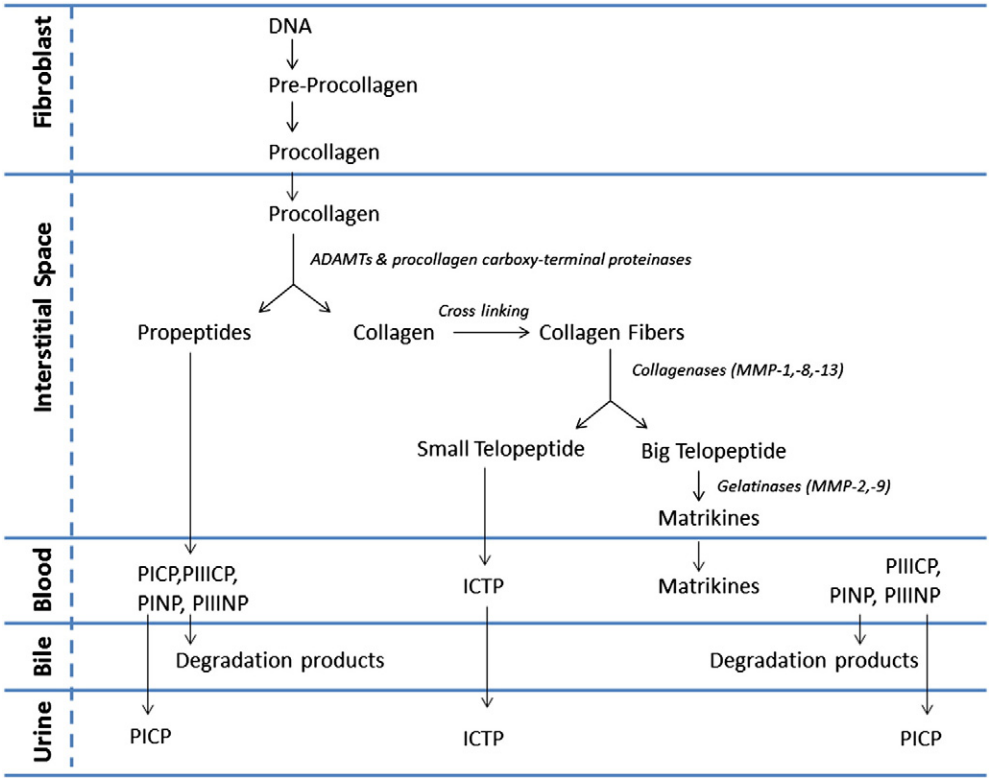

Fig. 1. Synthesis and degradation of collagen I and III. Adapted from [11] and [29]. PICP, procollagen type I carboxy-terminal propeptide; PINP, procollagen type I amino-terminal propeptide; ICTP, collagen type I cross-linked carboxy-terminal telopeptide; PIIICP, procollagen type III carboxy-terminal propeptide; PIIINP, procollagen type III amino-terminal propeptide; MMP, matrix metalloproteinase.