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Novel regulators of cardiac inflammation: Matricellular proteins expand their repertoire

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ABSTRACT

More than 20 years ago, Paul Bornstein coined the term matricellular protein to describe a group of secreted extracellular matrix proteins with de-adhesive properties. Though this is still true today, this family of proteins is vastly expanding with new emerging functions pushing the boundaries of this classic definition. In the heart, matricellular proteins have been extensively investigated in models of myocardial infarction, pressure overload, viral myocarditis and age-related cardiomyopathy with clear implications during cardiac fibrosis yet their involvement in regulating cardiac inflammation is less established. In this review, we describe our current understanding of the immune activation by damage- or pathogen-associated molecular pattern molecules during cardiac injury making a distinction between sterile versus non-sterile cardiac inflammation, and explain how matricellular proteins influence this crucial pathophysiological response in the heart.

Contents

1. Introduction

To secure sufficient supply of nutrients and oxygen to the entire body, the heart must be at its best performance at all times. Highly contractile cardiomyocytes are in close contact to the extracellular matrix, synergistically ensuring continuous cardiac output. However, damage to the myocardium either by injury, pathogens or drugs, can endangering cardiac output and therefore rapid repair mechanisms need to be in place. The recruitment (and subsequently the resolution) of inflammatory cells is vital in removing the threatening environmental factors, debris or dead cells in order to restore the damaged myocardium. In recent years, a role for the cardiac extracellular matrix in regulating inflammatory responses has started to emerge [1] yet our current knowledge on the interactions that take place is still in its infancy. This is further complicated by the need to delineate the various mechanisms by which endogenous 'self' ligands and exogenous 'non-self' ligands activate the immune system during cardiac diseases. In this review, we will first describe our current

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understanding of the various immune responses that take place during cardiac damage. We will then discuss the recent research that has established extracellular matrix proteins and matricellular proteins as crucial regulators of cardiac inflammation, highlighting their potential as a new therapeutic avenue for heart failure patients.

1.1. Danger recognition: DAMPs and PAMPs

Activation of any immune response begins with the detection of danger by resident immune cells (e.g. macrophages) as well as non-immune cells, which set off alarm bells triggering the release of inflammatory mediators. Whether it be debris, damage or an invading pathogen, they are all recognized by well-conserved receptors (pattern recognition receptors or PRRs). These detect either repeating patterns (pathogen-associated molecular patterns or PAMPs) or molecules that are produced during tissue injury (damage associated molecular pattern molecules, DAMPs) (Fig. 1). Though the system has to avoid activation by host molecules during healthy conditions, the detection of damaged 'self' is equally as important as the recognition and removal of pathogens or 'nonself'. The PRRs are a family of high affinity, low specificity innate immune receptors with protein domains that bind not only invading pathogens but also matrix elements. Most classes of human pathogens are recognized by the carbohydrate-recognition domains in the transmembrane or secreted C-Lectin Receptors, which can recognize highly complex structures composed of carbohydrate residues [2]. These receptors are capable of detecting intricate differences in the arrangement and branching of carbohydrate residues due to differential protein glycosylation by the protein source [3]. In addition, transmembrane Toll-Like Receptors and cytoplasmic Nodd-Like-Receptors recognize molecular patterns from very diverse collection of bacterial, fungal, viral and parasite-derived elements as well as degradation products of extracellular matrix proteins via their leucine rich repeat (LRR) domain [4–6]. Furthermore, DAMPs themselves can directly activate inflammatory transcription factors such as NFkB and IRF further promoting immune cells recruitment [7]. Adding to the complexity, another molecular pattern has been proposed to regulate immunity; the "self-associated molecular patterns" or SAMPs, such as complement regulatory protein CD200 [8] or glycans like heparan and dermatan sulfate [9], can inhibit innate immunity [10,11]. How a PRR distinguishes between the 'self' versus 'nonself' is unknown as the molecular composition appear to be similar yet somehow a distinction is made as to whether something is immunogenic or not [12]. As PAMPs, SAMPs and DAMPs are recognized by a limited set of receptors, it has been suggested that they can interact with each other thereby acting in synchrony. Possibly it is the combination of associated molecular pattern molecules in a given environment that will define the course of inflammation, creating an "immunogenic footprint" [13]. However, the detailed footprints of inflammatory responses during the different cardiac diseases needs to be further unraveled to completely understand the complexity of the signaling involved.

Though there may be an individual footprint during different cardiac diseases, the immune system struggles to provide a tailored immune response according to the type of injury as it relies on common PRRs for recognition and often the same clearance mechanisms to eliminate danger or clear debris. One exception that distinguishes PAMP- from DAMP-induced inflammation is the production of type I interferons, which modulate cell growth and establish an anti-viral state by recruiting cells such as cytotoxic T-cells that promote pathogen clearance [14–17]. Cardiotropic viruses invading the myocardium also induce cardiomyocyte death resulting in the production of DAMPs, further amplifying the immune response. Though it might seem compelling to think that attenuating inflammatory activity allows for increased viral replication, paradoxically more inflammation supports virus-driven cellular signaling for successful replication [18,19]. Therefore our increased understanding of the inflammation during viral myocarditis implies that effective therapies should aim for selective intervention instead of broad immunosuppression [20]. In sterile cardiac diseases like atherosclerosis or ischemia-induced cardiac injury, several endogenous TLR activators are involved in the initiation and even progression of disease. Endogeneous DAMPs, such as heat shock proteins [21], uric acid [22], DNA and RNA [23] but also extracellular matrix fragments such as hyaluronan fragments [24] and heparan sulfates [25], are released due to cell necrosis or matrix degradation, further amplify the inflammatory response [26].

1.2. Sterile and non-sterile inflammation: commonalities and distinctions

Recent reviews by prominent experts in the field demonstrate how far we have come in our understanding of the immunokinetics following

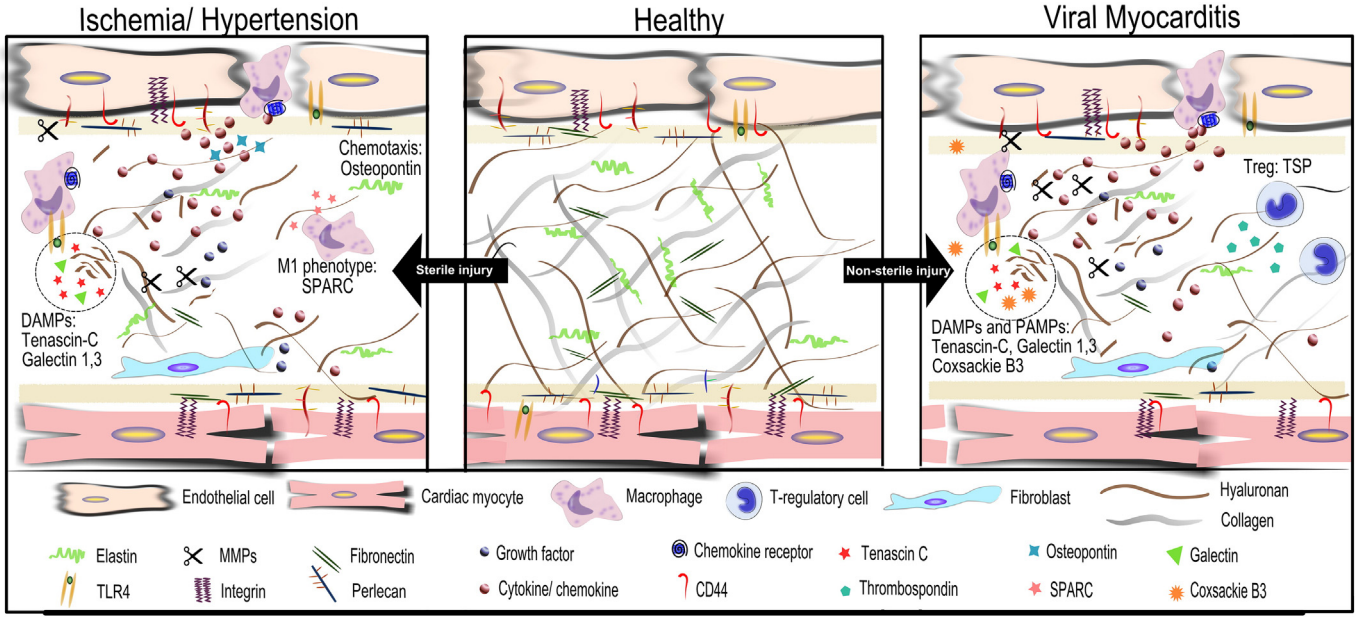

Fig. 1. Resident macrophages are activated when sensing DAMPs or PAMPs hence releasing matrix metalloproteinases as well as cytokines and chemokines. This leads to rapid recruitment of neutrophils and monocytes from the circulation. Both during sterile and pathogen induced cardiac damage matricellular proteins act as potent DAMPs, such as biglycan, tenascin C and galectins. TSPs strongly affect the activation of T-regulatory cells during viral myocarditis and regulated cardiac inflammation during sterile injury. Furthermore, matricellular proteins can also promote or inhibit immune cell recruitment or immune resolution as Osteopontin promotes the leukocyte recruitment while SPARC promotes the phenotypic shift of monocytes toward pro-inflammatory M1 macrophages during sterile injury.