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Review article

Matricryptic sites control tissue injury responses in the cardiovascular system: Relationships to pattern recognition receptor regulated events

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ABSTRACT

This review addresses new concepts related to the importance of how cells within the cardiovascular system respond to matricryptic sites generated from the extracellular matrix (ECM) following tissue injury. A model is presented whereby matricryptic sites exposed from the ECM result in activation of multiple cell surface receptors including integrins, scavenger receptors, and toll-like receptors which together are hypothesized to coactivate downstream signaling pathways which alter cell behaviors following tissue injury. Of great interest are the relationships between matricryptic fragments of ECM called matricryptins and other stimuli that activate cells during injury states such as released components from cells (DNA, RNA, cytoskeletal components such as actin) or products from infectious agents in innate immunity responses. These types of cell activating molecules, which are composed of repeating molecular elements, are known to interact with pattern recognition receptors that (i) are expressed from cell surfaces, (ii) are released from cells following tissue injury, or (iii) circulate as components of plasma. Thus, cell recognition of matricryptic sites from the ECM appears to be an important component of a broad cell and tissue sensory system to detect and respond to environmental cues generated following varied types of tissue injury.

Contents

1. Introduction

Recent years has witnessed an explosion of knowledge concerning how cells respond to cues from their surroundings including growth factors, cytokines, extracellular matrix, and components derived from microorganisms that infect cells and tissues. It appears clear that broad and overlapping mechanisms exist to sense changes in the extracellular environment to respond to the varied types of tissue injuries which occur. A key system that responds to tissue injury is the cardiovascular system in that it controls both the delivery of plasma components and inflammatory cells to sites of tissue injury. Thus, the cardiovascular system is particularly fundamental in controlling tissue injury by controlling oxygen tension, blood flow, vascular permeability, hemostasis, inflammation, and the response to local and systemic infections. This review will address new insights into how cryptic sites within extracellular matrix molecules (i.e., matricryptic sites) [1] play a role in such tissue injury responses and how they should be considered as a component of a broad sensory system including detection of cellular injury (via recognition of cell products such as

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DNA, RNA, actin, and lipids) and microbial, viral, or fungal products (via lipopolysaccharide, lipotechoic acid, formyl methionyl peptides, and single- or double-stranded RNA). We will also consider these issues in the context of the cardiovascular system, due to its central importance in controlling tissue injury but also its ability to regulate and propagate such signals from local to systemic responses.

2. Matricryptic sites within extracellular matrix molecules control tissue injury responses

A decade ago, we proposed the name matricryptic sites as newly exposed recognition sites that are revealed in ECM molecules when perturbations occur to such molecules [1]. Importantly, we were careful to include both proteins and carbohydrates such as glycoaminoglycans since they are critical regulators of ECM function as well. We also coined the term matricryptins which refers to fragments of ECM molecules that have biological functions. Others have utilized the term matrikines for these fragments [2]. A further point is that matricryptic sites are exposed in ECM molecules for a variety of reasons including: (i) enzymatic degradation, (ii) mechanical forces being exerted on the molecules, (iii) adsorption and heterotypic binding to other molecules, (iv) multimerization and self-assembly reactions, and (v) denaturation, for example, during thermal or oxidant-induced conformational changes [1]. The exposure of matricryptic sites within intact ECM molecules or following fragmentation as expressed by matricryptins leads to biological consequences such as (i) ECM assembly and multimerization; (ii) assembly of wound repair scaffolds consisting of ECM molecules with associated growth factors, cytokines, proteinases, and proteinase inhibitors and; finally, (iii) stimulation of receptor-mediated signal transduction to control cellular responses to tissue injury [1].

Many recent studies have identified new matricryptic sites and have further elucidated their functional relevance [2–8]. A critical ECM protein which dramatically illustrates the role of matricryptic sites is fibronectin [1,9–14]. Fibronectin has many known functions including self-assembly, multimerization through protein-protein binding, disulfide exchange and covalent binding, heterotypic interactions with native and denatured collagens, fibrinogen/fibrin, and glycosaminoglycans such as heparan sulfate [1] as well as important interactions with integrins and growth factors such as VEGF [15]. In each case, the interactions of fibronectin with itself, or its other binding partners, are markedly controlled by matricryptic sites within domains that are unfolded to expose new binding sites [11]. Recent and past work suggest that mechanical forces exerted on fibronectin by cells (through fibronectin–integrin–cytoskeletal interactions) lead to the exposure of matricryptic sites that further regulate fibronectin function and signal transduction events mediated through cell surface receptors [11,16]. Fibronectin also is highly susceptible to proteolytic degradation that leads to functional matricryptins being generated and which induce signal transduction.

A critically important matricryptic site is Arg-Gly-Asp (RGD) which is present in fibronectin and many other ECM proteins such as collagens, vitronectin, and osteopontin [1]. In most cases, it is not exposed within ECM proteins unless they adsorb to matrices, are proteolytically modified, or self-assemble [1]. Recent work shows that the RGD site in fibronectin is required for development through its interactions with $\alpha5\beta1$ and various αv integrins [17]. Interestingly, it is not absolutely required for fibronectin matrix assembly since there are other integrin binding sites within fibronectin such as an additional novel site recognized by $\alpha v\beta3$ [17]. Thus, combinations of integrins participate in stimulating the mechanical forces necessary to expose matricryptic sites controlling both self-assembly and disulfide cross-linking. A recent finding suggests that soluble fibronectin can bind $\alpha5\beta1$ (perhaps through the fibronectin synergy site) but not $\alpha v\beta3$ on fibroblasts showing that the RGD site is not exposed in soluble fibronectin [18]. Adsorption of fibronectin leads to exposure of its RGD site allowing either $\alpha v\beta3$ or $\alpha5\beta1$ to bind to this site. An additional finding which is of great interest is the ability of fibronectin to specifically bind VEGF [15], a fundamental regulator of tissue vascularization. Fibronectin, the fibronectin-binding integrin, $\alpha5\beta1$, and VEGF are all required for vascular development. VEGF binds to the C-terminal Hep2 domain of fibronectin [15] which is near its RGD sequence (also a matricryptic site). Heparin binding to fibronectin strongly induces binding to VEGF in a manner which does not require the retention of heparin suggesting that heparin induces a matricryptic site which then binds VEGF [15]. This interesting work suggests important cosignaling possibilities whereby the adjacent RGD site binding could bind $\alpha5\beta1$ and VEGF could signal through VEGFR2 to create unique signals to vascular cells (possibly through integrin/growth factor receptor interactions). Considerable new information suggests that ECM-associated growth factors may present unique signals compared to their soluble counterparts to control cell signaling [19].

3. Receptors for matricryptic sites include integrins, and two classes of pattern recognition receptors, scavenger receptors and toll-like receptors

A number of linear peptide sequences containing RGD (binds αv integrins), LDV ($\alpha4\beta1$ and $\alpha9\beta1$), and SVVYGLR ($\alpha4\beta1$ and $\alpha9\beta1$) bind integrins and are all likely to be matricryptic [1,20–22]. Interestingly, LDV was identified in the CS-1 alternative splice variant of fibronectin and SVVYGLR is directly adjacent to a thrombin proteolytic cut site in osteopontin which likely exposes this site, as well as an adjacent RGD sequence, and a separate $\alpha4\beta1$-binding peptide sequence (i.e., three distinct integrin binding sites) in this N-terminal matricryptin fragment of osteopontin [21]. Also, many years ago, my laboratory first reported that denatured proteins show affinity for the leukocyte $\beta2$ integrins, $\alpha M\beta2$ and $\alpha X\beta2$, but not $\alpha L\beta2$ [23]. Later work revealed that the von Willebrand factor A domain structure of αM directly binds to denatured proteins [24,25]. This latter finding that integrins bind denatured or modified proteins is similar to the affinity of a different class of leukocyte receptors, scavenger receptors (SRs) for such molecules.

SRs are composed of a diverse set of receptors of which the major classes are represented as class A and class B [26–28]. Class A SRs are homotrimeric receptors that are type II transmembrane proteins that are expressed by a variety of cells including leukocytes such as macrophages and dendritic cells as well as endothelial cells which express unique patterns or members of the family. They are characterized by a collagenous triple-helical domain with affinity for polyanionic sequences and which represents the binding sites for denatured or modified proteins such as modified LDLs (oxidized or acetylated) and other ligands. Class B receptors are type III transmembrane proteins and consist of CD36, a receptor for modified LDLs and the matricellular ECM protein, thrombospondin-1, and SR-B1, an important receptor controlling HDL uptake and cholesterol delivery to tissues [26,28]. In general terms, SRs are involved in taking up microorganisms and tissue debris through phagocytic uptake mechanisms. Of interest is that both $\alpha M\beta2$ and $\alpha X\beta2$ as well as $\beta3$ integrins, such as $\alpha v\beta3$, also participate in phagocytic uptake in macrophages by recognizing opsonic material (including denatured and modified proteins as well as fibronectin). This suggests the possibility that integrins and scavenger receptors work together and perhaps coassociate to mediate such phenomena. Uptake of oxidized lipids is thought to be an important pathogenic feature of atherosclerosis [29,30]. SRs such as SR-A, CD36, and LOX-1 are known to play critical roles in the development of atherosclerotic lesions [28,30]. Endothelial cells are also known to participate in uptake of oxidized LDL through SRs to be delivered to the intima to affect macrophage foam cell formation. In fact, the exposure of matricryptic sites within damaged ECM containing integrin recognition sites or SR-binding regions would be expected to cofacilitate uptake and removal of this debris. Interesting examples that are suggestive of overlapping