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Review

The role of thrombospondin-1 in cardiovascular health and pathology

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ABSTRACT

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality in the developed world and are becoming increasingly prevalent in the developing world. Although a range of therapies already exist for established CVDs, there is a significant interest in further understanding disease pathogenesis in order to improve treatment. Thrombospondin (TSP)-1 is an important extracellular matrix component that influences the function of vascular smooth muscle cells, endothelial cells, fibroblasts and inflammatory cells with important implications for CVDs. TSP-1 regulates matrix production and organisation thereby influencing tissue remodelling and promoting the generation of T regulatory cells that control the inflammatory response. Reported findings from *in vitro* and animal studies are conflicting and suggest differing effects of TSP-1 on various cellular mechanisms, depending on the experimental setting. Vascular cells express a number of TSP-1 receptors, such as CD36, proteoglycans and several integrins, which are regulated by specific contextual signals which may explain the varying effects that TSP-1 elicits in different environments. Different domains of TSP-1 activate distinct signalling pathways eventually resulting in quite different cellular phenotypes and tissue specific effects. The sum total of the various pathways activated likely determines the overall effect on angiogenesis or proliferation in a specific tissue. Hence defining a common mechanism of action of TSP-1 in CVD is complicated. Increasing the understanding of the role of TSP-1 in various CVDs will potentially provide new opportunities for therapeutic intervention using peptides derived from its various domains currently under evaluation in other diseases.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of death, disability and health cost in both the developed and developing worlds. Myocardial infarction (MI) and stroke account for approximately 12 million deaths worldwide each year. It is expected that by 2030, 7 of 10 deaths worldwide will be due to chronic diseases, and CVD is expected to remain the commonest cause of death [1]. Cigarette smoking, hypertension, dyslipidemia, diabetes and obesity remain important risk factors for CVD, accounting for more than 50% of the variation in disease prevalence [2]. Genetic factors also contribute to an individual's risk of developing CVD. A body of evidence has demonstrated that the biological changes related to CVDs are complicated and involve a myriad of cellular elements and subcellular signalling pathways. A range of therapies already exist for established CVDs, however there is a significant interest in further understanding disease pathogenesis in order to improve primary prevention, diagnosis and therapy.

The extracellular matrix (ECM) forms a complex meshwork composed of structural proteins (such as type I and III collagen), proteoglycans, glycosaminoglycans, and a basement membrane, which are responsible for maintaining tissue strength and structure. Matricellular proteins are non-structural proteins usually present at low concentrations within normal ECM but frequently expressed at increased levels following tissue injury or during pathological changes. Thrombospondin (TSP)-1 is a matricellular protein which was first identified within the ECM and subsequently shown to be a major component of α-granules of platelets which is released upon the activation of these cells [3]. TSP-1 is a calcium-binding protein that regulates cellular adhesion and migration; cytoskeletal organisation; and cell proliferation and apoptosis [4,5]. TSP-1 is constitutively present within blood vessels and interacts with a range of key proteins known to maintain vascular structure and homeostasis. TSP-1 also interacts with multiple cell-surface receptors, proteases, growth factors and various bioactive molecules. The classification of TSP-1 as a matricellular protein is due to the ability of TSP-1 to inhibit cell-substrate interactions, and hence it has been grouped along with genetically and structurally distinct multidomain protein groups as a counter-adhesive protein [6]. A number of studies have implicated TSP-1 in the pathogenesis of a range of CVDs [7–10]. The aim of the present review was to summarise previous research assessing the role of TSP-1 in CVDs using data from cell culture, animal models and human investigations.

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2. TSP-1 structure

TSPs are a family of five extracellular calcium binding matrix proteins and the family is separated into two groups since TSP-1 and TSP-2 are trimers (Group A) and TSP-3, TSP-4 and TSP-5/COMP (cartilage oligomeric matrix protein) are pentamers (Group B) [5,11,12]. Even though the TSP family members show structural similarity, they are differentially expressed in various tissue types suggesting that their roles are distinct and not redundant. TSP-1 is a 450 kDa homotrimeric glycosylated protein and each TSP-1 subunit consists of N-terminal and C-terminal globular (G) domains which are connected by a thin strand (Fig. 1). The N-domain is cleaved by several proteases (such as thrombin, plasmin, cathepsins, elastases, trypsin and chymotrypsin) and thus can either exist in a soluble state or in association with activated platelet membranes [11]. The free-thiols and the calcium modulated C-terminal region enable TSP-1 to form covalent bonds with other proteins such as thrombin. Individual chains of TSP-1 comprise a globular N-terminal domain, which is followed by an oligomerization domain containing the inter-chain disulphide bonds, followed by a type I procollagen (PC) homology region also known as von Willebrand C (vWC) repeat. The signature piece of TSP-1 is the central repeat region which follows the Type 1 PC region and includes 3 type I (TSP or properdin-like) repeats (TSR1), 3 epidermal growth factor (EGF) like repeats called TSP type 2 repeats (TSR2) and 7 calcium binding repeats called TSP type 3 repeats (TSR3), the last of which contains the RGD (Arg-Gly-Asp) sequence. In addition, there is a –COOH terminal domain that forms the lectin-like β-sandwich. For additional information, readers are requested to refer to previous reviews which have given extensive accounts of the structure of the TSP family members [12,13].

3. TSP-1 receptors

The conflicting and often opposing effects of TSP-1 reported in various cell types may be due to the presence of multiple domains in the TSP-1 sequence which can interact with an array of specific cellular receptors (Figs. 1 and 2). There are a number of cellular receptors for TSP-1, including CD36, proteoglycans, several integrins and CD47, which is the integrin associated protein (IAP) (reviewed in [4]). The heparin binding domain present in the N-terminal of TSP-1 binds to heparin sulphate proteoglycans [14], whereas the peptide sequence CSVTCG present in the TSR1 of TSP-1 interacts with CD36 [15]. The RGD sequence of the TSR3 interacts with a variety of integrin β subclass receptors [16] and the C-terminal cell-binding domain binds to CD47 [17]. Vascular cells have numerous integrins that recognises TSP-1 including α3β1, αIIbβ3, αvβ3, α4β1 and α5β1 [4]. TSP-1 also interacts with fibronectin and fibrinogen and binds to components of the fibrinolytic system such as plasminogen, urokinase and its inhibitor plasminogen activator inhibitor (PAI)-1 and to cathepsin G and elastase [18].

The scavenger receptor CD36 which is the primary TSP-1 receptor is expressed on a variety of cells and is responsible for most of the anti-angiogenic and inflammatory functions exhibited by TSP-1 [15,19]. The G-domain of TSP-1 which is specific to the TSP family is

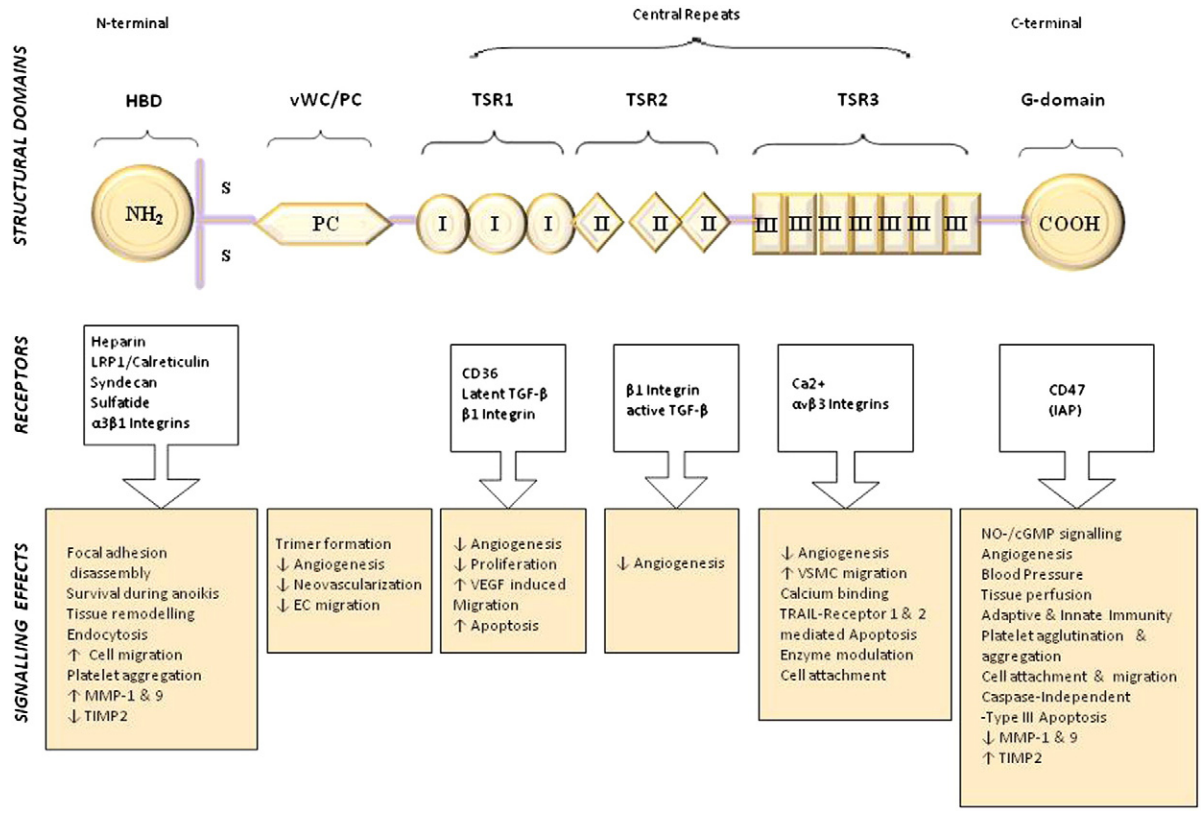

Fig. 1. Schematic diagram of the structure of TSP-1 monomeric subunit. The various domains of TSP-1 are depicted with the important receptors that have been identified for the different domains. Below the receptors are listed some of the functions or activities related to the specific domains. The important peptide sequences are also localised to the domains. TSP-1 consists of a globular NH2 (N)-terminal domain also known as the heparin binding domain (HBD), followed by an oligomerization domain containing the inter-chain disulphide bonds which help in trimer formation. This is followed by a type I procollagen homology region (PC) also known as von Willebrand type C (vWC) repeat and 3 type I (TSP or properdin-like) repeats (TSR1, 2 & 3). The signature piece of TSP-1 is the 3 type II (epidermal growth factor-like) repeats (TSR2), 7 type III (calcium binding) repeats (TSR3), the last of which contains the RGD sequence. The globular (G) C-terminal domain is the COOH-terminal domain that forms the lectin-like β-sandwich. The various components of the signature piece interact extensively to form 3 structural regions termed stalk, wire and globe and are further stabilised by disulphide bonds and bound calcium [13]. Abbreviations: MMP = matrix metalloprotenase; TIMP = tissue inhibitors of matrix metalloproteinase; ECs = endothelial cells; VEGF = Vascular endothelial growth factor; VSMCs = vascular smooth muscle cells; NO = nitric oxide; IAP = integrin-associated peptide; ↓ Anti or decrease; ↑ Pro or increase.