Immunology Letters 186 (2017) 15–19

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Review

β2-glycoprotein I and its antibodies involve in the pathogenesis of the antiphospholipid syndrome

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ARTICLE INFO

Article history:
Received 16 January 2017
Received in revised form 5 March 2017
Accepted 23 March 2017
Available online 24 March 2017

Keywords:
β2-glycoprotein I
Antibody
The antiphospholipid syndrome
Signaling

ABSTRACT

The antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis, and associated with dysfunctions of endothelial cells and monocytes. β2-glycoprotein I is a phospholipid-binding glycoprotein, and its antibodies have been reported to correlate strongly with thrombotic risk and play putative role in the pathogenesis of APS, whereas the biofunctions of anti-β2-glycoprotein I antibodies remain largely uncertain. It is noted that β2-glycoprotein I exhibits direct interaction with membrane Toll-like receptors, and through this interaction, the complex of β2-glycoprotein I and its antibodies induces intracellular signals via Toll-like receptors, resulting in activation of endothelial cells and monocytes, and expression of proinflammatory cytokines. In this review, we further discussed the recent findings of β2-glycoprotein I/antibody complex. Once activated by β2-glycoprotein I/antibody and their signals, endothelial cells release microparticle/extracellular vesicles which can further stimulate the surrounding rest cells with procoagulant and pro-inflammatory properties in a paracrine or/and autocrine manner. Novel evidence of β2-glycoprotein I/antibody complex bioactivities may provide insight into the molecular mechanisms that the complex regulates cell function and involves in APS pathogenesis.

Contents

Abbreviations: ADP, adenosine diphosphate; APS, antiphospholipid syndrome; ICAM, intercellular adhesion molecule; IL, interleukin; IRAK, IL-1 receptor-activated kinase; KLF, Krüppel-like factors; LPS, lipopolysaccharide; MAPK, MAP kinases; MD, myeloid differentiation factor; miRNA, micro-RNA; NFκB, nuclear factor κB; RLC, regulatory light chain; TLRs, toll-like receptors; TNF, tumor necrosis factor.

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http://dx.doi.org/10.1016/j.imlet.2017.03.013
0165-2478/

1. Background

The antiphospholipid syndrome (APS) is one of systemic autoimmune diseases with dysfunctions of endothelial cells, monocytes/macrophages, and possibly platelets, in combination of coagulant and fibrinolytic systems [1]. The etiology of APS is still unknown, but recently, several antiphospholipid antibodies have been detected in APS patients, possibly acting to regulate functions of endothelial cells and monocytes [2,3]. Among those antibodies, anti-β2-glycoprotein I antibodies are the mostly detectable antibody in humans, particularly with persistently elevated levels in APS patients [4,5], and has been considered to involve the development of APS [6].

APS is a clinic challenge with high incidence of thrombosis. Thrombosis in APS commonly affects deep veins of the lower extremities and the cerebral arterial circulation [7,8]. A portion of APS patients consequently suffer catastrophic illness conditions, resulting in high mortality and poor prognosis [1,7]. However, conventional therapies of APS include anticoagulation treatment with heparin followed by long-term anticoagulation against vitamin K, and the clinical effects are suboptimal [1,9]. It is necessary to expand current understanding on the pathogenesis of APS, and advance the current strategy of disease treatment.

Antiphospholipid antibodies are associated with arterial and venous thrombosis. In particular, anti-β2-glycoprotein I antibodies may correlate strongly with thrombotic risk and pregnancy morbidity [10], indicating the putative role of anti-β2-glycoprotein I antibodies in the pathogenesis of APS. Exploration of β2-glycoprotein I/anti-β2-glycoprotein I antibody bioactivities and their impacts on endothelial cells and monocytes (i.e. signals in particular) will facilitate our understanding on molecular mechanisms associated with the pathogenesis of APS, and shed light on novel strategies of the treatments against the disease.

2. Physical function of β2-glycoprotein I

β2-glycoprotein I, a 50 kDa phospholipid-binding glycoprotein, belongs to apolipoprotein superfamily. It consists of I–IV domains with conserved amino acid sequences and the fifth aberrant domain [11]. The former sequences exhibit two conformations, i.e., a circular or an open conformation, upon extracellular stimulations including antibody and lipopolysaccharide (LPS). The latter contains a phospholipid-binding site which provides binding of the protein to plasma membrane receptors and phospholipids including Toll-like receptors (TLRs) [6,11]. Via interactions with cellular membrane receptors or/and phospholipids, β2-glycoprotein I has potential to induce cell signals and regulate functions of endothelial cells and monocytes/macrophages, which involve in the pathogenesis of APS [6,11,12].

The physical functions of β2-glycoprotein I are still largely unknown. In vitro studies have shown that β2-glycoprotein I is capable of impacting hemostasis process, e.g., β2-glycoprotein I can inhibit adenosine diphosphate (ADP)-induced platelet contact activation and cell aggregation, and diminish thrombin generation, indicating the putative role of β2-glycoprotein I in regulation of the intrinsic coagulation pathway [13,14]. Further studies have noted that β2-glycoprotein I may serve as a scavenger protein of LPS. Once bound to LPS, β2-glycoprotein I performs conformational change, and enhances clearance of LPS from the circulation [15].

However, in vivo studies have shown that deficiency of β2-glycoprotein I in humans and mice fails to induce any significant abnormalities in hemostasis, e.g., bleeding or increase of thrombosis risks [16], indicating peripheral importance of β2-GPI for homeostasis of life. The exact roles of β2-glycoprotein I in health of humans need to be further elucidated.

3. Cellular signaling of β2-glycoprotein I and its antibodies

Despite the uncertain physical function of β2-glycoprotein I, it is well recognized that anti-β2-glycoprotein I antibodies exhibit multiple bioactivities through binding to β2-glycoprotein I [6]. Intriguingly, in the presence of anti-β2-glycoprotein I antibodies, I–IV domains of β2-glycoprotein I display open conformation, and escalate binding of domain V to cell surface receptors, triggering activation of intracellular downstream signals of those cell surface receptors [6,11].

Immunological studies have noted that β2-glycoprotein I exhibits physical association with a variety of plasmic membrane receptors inclusive of TLR4, TLR2, and possibly apoER2 [1,3]. Meanwhile, membrane phospholipids are perhaps requisite for intracellular TLRs signal transduction as well as cell activation upon β2-glycoprotein I/antibody complex stimulation. For instance, in the presence of β2-glycoprotein I/antibodies, annexin A2, calreticulin, and nucleolin form the assembly of a multiprotein complex with TLRs on the cell surface, and subsequently regulate cell functions [17,18]. Besides membrane phospholipids discussed above, phosphatidylserine is reported to involve in β2-glycoprotein I-induced macrophage interactions [19]. Intriguingly, the levels of phospholipid scramblase 1, a protein that regulates phosphatidylserine exposure, are increased in APS patients [20], indicating the putative roles of membrane phospholipids and related proteins in mediating β2-glycoprotein I-induced cell signals and inflammations [21].

TLR4 signals are likely the dominant signal pathway in endothelial cells and monocytes, which are associated with the complex of β2-glycoprotein I and its antibodies [2,22]. Sharing the similar patterns of LPS-induced TLR4 signals, both anti-β2-glycoprotein I IgM and IgG antibodies activate nuclear factor κB (NFκB) pathway in endothelial cells via their interactions with TLR4 and interleukin (IL)-1 receptor-activated kinase (IRAK) [23]. In addition, TLR2 is also implicated in β2-glycoprotein I-induced signals. β2-glycoprotein I has been shown to directly interact with TLR2 on plasmic membrane of endothelial cells, whereas deficiency of TLR2 abrogates binding of biotinylated β2-glycoprotein I to endothelial cells, and overrides intracellular NFκB activation [24].

In the past ten years, the intracellular signals of immunologic complex consisting of β2-glycoprotein I and its antibodies have been intensively studied. Through interactions with β2-glycoprotein I and TLR4, anti-β2-glycoprotein I antibodies from APS patients are capable to induce IRAK phosphorylation and subsequent NFκB activation in monocytes, regulate release of tumor necrosis factor (TNF) and tissue factors, and endow monocytes with proinflammatory and procoagulant phenotypes [25]. In concomitance with NFκB signaling, MAP kinases (MAPK) signals including MEK-1/ERK and p38 in monocytes induced by β2-glycoprotein I/anti-β2-glycoprotein I antibodies are also noted [26]. In general, β2-glycoprotein I and its antibody composed complexes induce activation of endothelial cells and monocytes through TLR4/myeloid differentiation factor (MD)-2/MyD88 and NF-kB signal pathways, and regulate expression of proinflammatory cytokines, including IL-6, IL-8, and TNF [27], suggestive of putative role of β2-glycoprotein I and its antibodies in association with dysfunction of endothelial cells and monocytes, as seen in APS.

Studies further showed the pivotal role of β2-glycoprotein I and its antibodies in regulation of interactions between monocytes and endothelial cells. Complex of β2-glycoprotein I and its antibodies from APS patients triggered MAPK signaling, and facilitated adhesion of monocytes to endothelial cells, whereas blockade of MAPK signaling by its inhibitors abrogated the complex-initiated monocytes and endothelial cell interactions [28].

The data above delineate the intracellular signal pathways including NFκB and MAPK in endothelial cells and monocytes