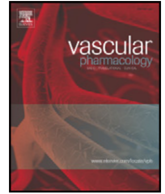
Vascular Pharmacology 54 (2011) 59–67

Contents lists available at ScienceDirect

Vascular Pharmacology

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



Review

The annexin A2 system and vascular homeostasis

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ARTICLE INFO

Article history:
Received 27 October 2010
Received in revised form 14 March 2011
Accepted 17 March 2011

Keywords:
Annexin A2
Fibrinolysis
Endothelial cells
Thrombosis
Angiogenesis

ABSTRACT

Optimal fibrin balance requires precisely controlled plasmin generation on the surface of endothelial cells, which line the blood vessel wall. As a co-receptor for plasminogen and tissue plasminogen activator (tPA), which are key factors in plasmin generation, the annexin A2 (A2) complex promotes vascular fibrinolysis. The intracellular A2 complex is a heterotetramer of two A2 monomers and two copies of the associated protein, p11. In response to endothelial cell activation, A2 is phosphorylated by src-kinase, and translocated to the cell surface in a highly regulated manner. Over-expression of A2 is seen in acute promyelocytic leukemia during the early hemorrhagic phase, while high titer antibodies to A2, as in antiphospholipid syndrome or cerebral venous thrombosis, are associated with thrombosis. In experimental hyperhomocysteinemia, moreover, derivatization of A2 by homocysteine leads to intravascular fibrin accumulation and dysangiogenesis, features that phenocopy the *Anxa2*$^{-/-}$ mouse. Exogenous A2 may also offer a novel therapeutic approach to ischemic thrombotic stroke, as administration of A2 in conjunction with conventional tPA-based thrombolytic therapy improved outcome in an animal model. Here, we discuss the role of the A2 system in vascular homeostasis, the molecular interactions that regulate its profibrinolytic activity, and its potential role in the pathogenesis and treatment of vascular disease.

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Contents

1. Introduction . . . 59
2. The annexin A2 system in fibrinolysis . . . 60
   2.1. The annexin A2 heterotetramer . . . 60
   2.2. Annexin A2-mediated profibrinolytic assembly . . . 60
   2.3. Cellular trafficking of annexin A2 . . . 61
   2.4. Regulation of cell surface annexin A2 expression . . . 62
3. Animal models of annexin A2 system-mediated fibrinolysis . . . 62
   3.1. A2-deficient mice . . . 62
   3.2. Hyperhomocysteinemia and blockade of A2 function . . . 63
   3.3. A2 in models of ischemic cerebral disease . . . 63
4. Annexin A2 in human hematovascular disease . . . 64
   4.1. Acute promyelocytic leukemia (APL) . . . 64
   4.2. Antiphospholipid syndrome (APS) . . . 64
   4.3. Cerebral venous thrombosis . . . 64
5. Concluding remarks . . . 65
Acknowledgements . . . 66
References . . . 66

1. Introduction

The efficient circulation of blood is dependent on a stable, patent network of blood vessels (Harvey, 1628). Through the process of hemostasis, vascular injury leads to formation of the primary hemostatic plug, which, as it matures, serves to stem the flow of blood. Formation of

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1537-1891/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.vph.2011.03.003

clot, or thrombus, reflects activation of the coagulation cascade, generation of thrombin, conversion of soluble circulating fibrinogen to insoluble fibrin, and entrapment of circulating blood cells. Once the injured vessel is repaired, fibrinolysis clears the fibrin containing thrombus, and restores vascular patency.

Although opposing processes, both blood coagulation (hemostasis) and clot dissolution (fibrinolysis) are vital to vascular homeostasis (Hajjar, 2009). In classical fibrinolysis, the sequential activation of specific proteases on the surface of the fibrin-containing thrombus culminates in production of plasmin, a protease that cleaves fibrin into defined soluble degradation products. Plasmin activation results from the cleavage of a single peptide bond at position R^{560}–V^{561}within its inactive zymogen, plasminogen (Plg). In highly regulated reactions, either of two physiologic activators, tissue plasminogen activator (tPA) or urokinase (uPA), can catalyze this reaction. It is interesting to note that, in tPA-dependent plasmin generation, fibrin serves as a potent cofactor for its own destruction.

Originally, fibrinolysis was viewed as a process restricted to plasma factors on the surface of a thrombus (Cesarman-Maus and Hajjar, 2005). However, prescient observations made in the late 1950s and early 1960s revealed the presence of small amounts of fibrinolytic activity in association with the vessel wall that were critically dependent upon an intact endothelium (Todd, 1958, 1964). This work foreshadowed the discovery of endothelial cell plasminogen and plasminogen activator receptors decades later.

Several groups have focused on understanding the molecular basis of vascular fibrinolysis, postulating that local generation of plasmin is enabled by receptors that promote fibrinolytic activity on the vessel surface (Hajjar, 2003). These receptors include the urokinase receptor (uPAR) (Blasi et al., 1994), which is expressed primarily on activated, migrating endothelial cells (EC) (Pepper et al., 1993), the annexin A2 complex, which binds both Plg and tPA on both resting and activated EC (Dassah et al., 2009; Kwon et al., 2005), and a series of plasminogen binding proteins expressed on many cell types (Andronicus et al., 2010; Miles et al., 2005).

2. The annexin A2 system in fibrinolysis

2.1. The annexin A2 heterotetramer

Annexin A2 (A2) is a 36-kDa protein member of the annexin superfamily of Ca^{2+}-dependent phospholipid-binding proteins, a dozen of which are expressed in humans (Moss and Morgan, 2004). A2 was originally identified in both avian and mammalian cells as a substrate of the transforming gene product, the $pp60^{src}$ tyrosine kinase, of the avian sarcoma virus (Erikson and Erikson, 1980). Later, it was found to be expressed in a spectrum of cell types. The ~30-kDa core domain of A2 contains four Ca^{2+}-binding "annexin" repeats, which are highly homologous to those of the other 60 annexin family members, while the smaller N-terminal "tail" domain is essentially unique (Gerke et al., 2005; Gerke and Moss, 2002).

In the cytoplasm, A2 exists in soluble, monomeric form. However, in the presence of protein p11, a member of the S100 family of proteins (S100A10), A2 forms a constitutively stable complex comprising two subunits each of A2 and p11 (Gerke and Weber, 1985; Waisman, 1995) (Fig. 1). The formation of the $(A2 \cdot p11)^2$ complex is largely mediated by hydrophobic contacts between the C-terminal region of p11 and the amino terminal tail of the A2 monomer (Becker et al., 1990; Johnsson et al., 1988; Kube et al., 1992; Rety et al., 1999). On A2, the p11-binding region, S^1–G^{14}, is closely related to three phosphorylation sites. Phosphorylation of S^{11}, within the p11 binding domain, has been observed to disrupt heterotetramer formation (Jost and Gerke, 1996), thereby constituting a molecular "switch" that might regulate the equilibrium between membrane-associated and cytosolic A2. Recent data suggest that serine phosphorylation of A2 may be regulated by plasmin (He et al., 2011). Whether phosphorylation of S^{25}, also a protein

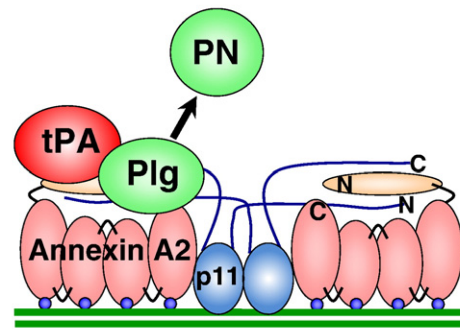

Fig. 1. A2 system assembly on the endothelial cell surface. The A2 heterotetramer is comprised to two p11 subunits and two A2 subunits. A2 consists of four "core" domains (pink) and an N-terminal "tail" domain (yellow). The heterotetramer binds both plasminogen (Plg) and tissue plasminogen activator (tPA), thereby accelerating plasmin (PN) generation. The orientation of carboxy (C)- and amino (N)-termini for A2 and p11 are shown.
Adapted from Gerke et al. (2005).

kinase C substrate, serves a similar function is unknown. Phosphorylation of Y^{23} by $pp60^{src}$ appears to regulate transit of A2 to the cell surface (Deora et al., 2004), and will be discussed in more detail below.

For most S100 proteins, calcium binding induces a conformational change that places helix III (H_{III}) in a more perpendicular orientation to helix IV (H_{IV}), forming a cleft that can more readily accept target proteins (Donato, 2001). Protein S100A10 (p11), however, is an exception to the calcium activation rule, as it permanently assumes a "calcium-on" state, due to replacement of the bidentate E65 with S70, and the monodentate D56 with C61 (Burger et al., 1996; Rety et al., 1999). The published crystal structure of p11 in complex with the N-terminal 13 amino acids of A2 (Rety et al., 1999) suggests that the basic unit of p11 structure is a non-covalently-linked homodimer, each component of which can bind the A2 tail peptide to form a heterotetramer. Upon binding, the A2 tail peptide assumes an α-helical conformation that presents key hydrophobic residues (V^3, I^6, L^7, and L^{10}) within a hydrophobic cleft formed by loop L_2 and helix H_{IV} of one monomer and helix H_I of the other. The C-terminal region of p11, particularly its hydrophobic residues within the C-terminal extension ($Y^{85}FVVHM^{90}$), such as Y^{85} and F^{86}, contributes critical contact points with A2.

2.2. Annexin A2-mediated profibrinolytic assembly

The link between A2 and fibrinolysis was discovered by members of our lab while seeking EC surface receptors for Plg and tPA (Hajjar et al., 1994) (Fig. 1). Our group discovered that Plg could bind directly to cultured ECs with high affinity (K_d 300 nM) and high specificity (Hajjar et al., 1986). We later found that the circulating form of Plg, N-terminal glutamic acid-plasminogen (Glu-Plg), was converted to a more readily activated form (N-terminal lysine-Plg) upon binding to ECs (Hajjar and Nachman, 1988), a concept that has been reinforced by others (Miles et al., 2003; Silverstein et al., 1988). These findings identified the EC surface as a profibrinolytic microenvironment. Plg binding to ECs can be blocked in the presence of lipoprotein(a) (Lp(a)), a highly atherogenic lipoprotein particle whose apoprotein, apoprotein (a), is structurally homologous to Plg (Hajjar et al., 1989; Miles et al., 1989). This finding suggested a mechanistic explanation for the observation that patients with elevated levels of Lp(a) are highly susceptible to atherosclerosis; inhibition of EC surface fibrinolysis was postulated to favor fibrin deposition and the accumulation of proatherogenic inflammatory cells.

In 1987, we reported that tPA could interact specifically with human ECs (Hajjar et al., 1987). While the higher affinity site possessed features of the physiologic plasminogen activator inhibitor type 1 (PAI-1) and could be blocked by uPA, the lower affinity site appeared to be novel. Ligand blotting of an EC plasma membrane

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