Platelets and galectins

Mirta Schattner

Laboratory of Experimental Thrombosis, Institute of Experimental Medicine-CONICET, National Academy of Medicine, Buenos Aires, Argentina
Correspondence to: Mirta Schattner. IMEX, Pacheco de Melo 3081, Buenos Aires (1425), Argentina. Email: mschattner@hematologia.anm.edu.ar.

Abstract: A major function of platelets is keeping the vascular system intact. Platelet activation at sites of vascular injury leads to the formation of a hemostatic plug. Activation of platelets is therefore crucial for normal hemostasis; however, uncontrolled platelet activation may also lead to the formation of occlusive thrombi that can cause ischemic events. Although they are essential for proper hemostasis, platelet function extends to physiologic processes such as tissue repair, wound remodeling and antimicrobial host defense, or pathologic conditions such as thrombosis, atherosclerosis, chronic inflammatory diseases and cancer. Platelets can be activated by soluble molecules including thrombin, thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), serotonin or by adhesive extracellular matrix (ECM) proteins such as von Willebrand factor (vWF) and collagen. Here we describe recent advances in the activation of platelets by non-canonical platelet agonists such as galectins. By acting either in soluble or immobilized form, these glycan-binding proteins trigger all platelet activation responses through modulation of discrete signaling pathways. We also offer new hypotheses and some speculations about the role of platelet-galectin interactions not only in hemostasis and thrombosis but also in inflammation and related diseases such as atherosclerosis and cancer.

Keywords: Galectins; thrombosis; platelets

Submitted Sep 10, 2014. Accepted for publication Sep 11, 2014.
doi: 10.3978/j.issn.2305-5839.2014.09.02
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2014.09.02

Introduction

Platelet activation and subsequent accumulation at sites of vascular injury are the first steps in hemostasis. Excessive platelet activation after atherosclerotic plaque rupture or endothelial cell erosion may also lead to the formation of occlusive thrombi, which are responsible for acute ischemic events. Platelets play important roles in several physiopathological processes beyond hemostasis and thrombosis, including promotion of innate immune and inflammatory responses, wound healing, atherosclerosis, sepsis, vascular restenosis, acute lung injury and tumor growth (1-3). When platelets perceive activating signals through their cell surface receptors, they undergo dramatic structural and chemical changes, involving a complex interplay of cell adhesion and signaling molecules (4).

Galectins are a family of animal lectins that bind beta-galactosides. Outside the cell, galectins bind to cell-surface and extracellular matrix (ECM) glycans and thereby affect a variety of cellular processes. However, galectins are also detectable in the cytosol and nucleus, and may influence cellular functions such as intracellular signaling pathways through protein-protein interactions with other cytoplasmic and nuclear proteins (5). Although experimental and clinical studies have extensively implicated galectins in the regulation of immune cell homeostasis and host-pathogens interactions, there is increasing evidence that galectins play important roles in diverse physiological and pathological processes, including immune and inflammatory responses, wound repair, tumor development and progression, neural degeneration and cardiovascular diseases, in particular development of atherosclerosis (6). We have recently described that three structurally divergent galectins (galectin-1, -3 and -8) either in a soluble or immobilized form, are capable of triggering a broad range of platelet responses including adhesion and spreading, aggregation, release of granule content and P-selectin expression through the interaction with the carbohydrate backbone of the major platelet receptors involved in hemostasis, e.g., GPIb/IX/V complex and integrin $\alpha_{IIb}\beta_3$ (7-11).

In this review we summarize recent knowledge on the role of galectins in platelet physiology and the critical potential implications of these emerging findings in thrombosis, inflammation, atherosclerosis and cancer.

Platelets

Platelets are small (2-4 mm) anucleated spherical cells released from bone marrow megakaryocytes during thrombopoiesis. They have a lifespan of 7 days in peripheral bloodstream circulation and exist for much of this time as quiescent sentinels of tissue injury. At sites of vascular injury, platelets come into contact with exposed subendothelial proteins and form a thrombus for preventing bleeding. However, platelet aggregation can also occlude atherosclerotic arteries causing cardiac and cerebrovascular diseases.

Upon vessel damage, platelets adhere to and become activated by the subendothelial collagen-von Willebrand factor (vWF) complex and thrombin. Platelet adhesion triggers a signaling cascade mediated by tyrosine kinases and G-protein coupled receptors, which guide full activation of the platelet and concomitant granule release, in turn resulting in recruitment and activation of additional platelets and the presentation of a procoagulant surface promoting formation of a fibrin-rich hemostatic plug at the injured site (12). Platelets contain three main type of granules: dense bodies contain molecules involved in platelet activation and aggregation such as nucleotides, cations, phosphates and bioactive amines such as serotonin. Lysosomal granules store enzymes such as proteases, phosphatases and glycosidases, which are responsible for matrix and protein degradation. With 40-80 per platelet, α-granules are the most abundant secretory vesicles and they contain over 300 soluble and membrane-bound molecules including microbicidal peptides, growth factors, soluble adhesion molecules and coagulation proteins. Additionally, proinflammatory molecules, such as cytokines, chemokines and interleukins, are stored in α-granules (4,13). As a consequence of platelet adhesion to subendothelium, platelets change shape from smooth disks to spiculated spheres with filopodia and pseudopodia. Thus, the cargo of the granules is released in the surrounding bloodstream and recruits and activates further platelets. In addition, membrane-bound molecules, for example, P-selectin, become translocated to the platelet surface, promoting platelet aggregation and interaction with immune and endothelial cells. The chemokines and interleukins stored in α-granules link platelets to antimicrobial host defense and inflammation. Platelets exert antimicrobial effector mechanisms, but also initiate an intense crosstalk with other arms of the innate and adaptive immunity, including neutrophils, monocytes/macrophages, dendritic cells, B cells and T cells (13). Furthermore, platelets generate microparticles (MPs) with P-selectin, glycoproteins (GPs) and CD154 on their surface (3). Platelet activation, in addition, also triggers endothelial cells to synthesize and secrete molecules which tightly control and limit thrombus formation.

Galectins

Galectins are structurally related carbohydrate-binding proteins, which are defined by their affinity for poly-N-acetyllactosamine-enriched glycoconjugates and sequence similarities in the carbohydrate recognition domain (CRD). These lectins are found in almost all organisms and to date 15 galectins have been found in mammals; although only 12 galectin genes are found in humans. According to their structure, galectins are classified into three groups: (I) 'proto-type' galectins, containing a single CRD including galectin-1, -2, -7, -10, -13 and -14; (II) chimeric galectins which contain a single CRD and a large amino-terminal non-lectin domain being galectin-3 its only representative; and (III) tandem-repeat type galectins that have two CRD linked by a peptide sequence of variable length and this subgroup includes galectin-4, -8, -9 and -12 (14). Although the CRD sequence is highly conserved among galectins, each member of this family recognizes subtly different glycan structures and show individual affinities for them (15). While galectins that contain one CRD can exist as dimers, galectin-3 can form pentamers and most galectins can form ordered arrays named lattices when they bind to multivalent glycoconjugates (6). Regarding their subcellular localization, galectins exhibit a unique pattern as they can be found in the nucleus, cytoplasm, outer plasma membrane and extracellular matrices shuttling between different compartments and displaying a combination of intra- and extracellular activities (15,16).

Galectins are pleiotropic regulators of cell physiology that participate in many essential processes such as cell adhesion, proliferation, differentiation and apoptosis (6,15,17,18). They also play unique roles in intracellular signaling pathways and cell cycle control (15,19). Moreover, galectins participate in wound healing and development as well (16).

Galectins are expressed in a wide variety of tissues. While some members, like galectin-1, -3, -8 and -9 show a wide tissue distribution, others such as galectin-12 or galectin-7 show a more restricted localization. Galectin-1, -3, -8 and -9 are found on cells of the hematopoietic lineage as well as in endothelial cells (6,11,14,20). Galectin-2, -4, -7 and -9 are expressed in different epithelia and galectin-12 is almost exclusively found in adipose tissue (6). Galectin expression is also modulated throughout cell activation, inflammation and in pathologic processes such as atherosclerosis and cancer.

Galectins induce platelet adhesion and aggregation

Platelet adhesion to the ECM at sites of vascular injury represents a key step for limiting bleeding. Under low shear rate, such as that found in veins and larger arteries, platelet adhesion to the vessel wall primarily involves binding to fibrilar collagen, fibronectin and laminin. However at conditions of elevated shear stress, the initial tethering and firm adhesion of platelets to the exposed subendothelium is mediated by the interaction of the platelet GP Ib/IX/V complex and the subendothelial bound vWF (12). However, as vWF-deficient mice have delayed but not absent arterial thrombus formation it was suggested that under these conditions GPIbα might bind other ligands that can mediate platelet adhesion. Interestingly, *in vitro* studies have shown that galectin-8 (9) and -1 (unpublished data) promote platelet adhesion and spreading and GPIbα was identified as a functional Galectin-8 counter-receptor (9). Thus, it could be conceivable that galectins may act directly as a substrate or may either behave as matricellular proteins that bind to platelet GPIb/IX/V complex thus contributing to the platelet adhesion to the ECM.

The capacity of platelets to form a thrombus depends on their ability to aggregate. After platelet adhesion to the injured endothelium, soluble agonists such as adenosine diphosphate (ADP), serotonin, thrombin and thromboxane A_2 (TXA_2), produced/released at the site of injury act in autocrine and paracrine manner to amplify platelet activation and to recruit circulating platelets to the developing thrombus. At a molecular level, platelet aggregation is mediated by a specific receptor on the platelet surface: the $\alpha_{IIb}\beta_3$ integrin (21). Like most traditional platelet agonists, both soluble galectin-1 and -8 promote the transition of this integrin from a low-affinity state (resting state) to a high-affinity state (active state), which results in the unmasking of neoepitopes in the $\alpha_{IIb}\beta_3$ complex, and allows fibrinogen binding which acts as a bridging molecule between platelets to form aggregates (7,9). This conformational change of $\alpha_{IIb}\beta_3$ integrin triggered by galectins is accompanied by a raise in intracellular calcium levels as well as morphological changes of platelets involving the rearrangement of the cytoskeleton including extension of filopodia and lamellipodia (spreading) and F-actin polymerization (7).

Both galectin-1 and -8 induce aggregation of platelets suspended either in plasma or buffer which indicates a relevant role of these lectins in physiological media (7,9). Although cell agglutination was one of the first biological activities described for these lectins, this effect on platelets was only observed at high galectin-1 and -8 concentrations. Platelet aggregation at lower concentrations is absent in fixed platelets, in the presence of calcium chelating agents, or eptifibatide (an $\alpha_{IIb}\beta_3$ antagonist), implying that platelet responses mediated by galectins could be related either to cell activation or to a clustering effect of platelet surface receptors depending on their concentration (7,9). Although both galectins were capable of promoting aggregation, galectin-8 was found to be 10 times more potent than galectin-1 in this stimulatory effect. Although the dimeric structure of galectin-8 would anticipate a more robust effect of this galectin compared to galectin-1, the observation that only the N-terminal domain was also able to trigger platelet activation indicates that lectin bivalency is not essential to promote activating effects on platelets (9). The differences in the concentration required to achieve a similar effect, could therefore reflect different downstream molecular signals triggered by each galectin.

The initial formation of platelet thrombus is rapidly reinforced by the generation and release of platelet TXA_2 and ADP (the main metabolite of arachidonic acid by the cyclo-oxigenase pathway, and a component of platelet dense granules respectively) which acting in a paracrine and autocrine manner promote further platelet activation (4). Both molecules are generated on platelet stimulation by galectin-1 and -8. Moreover, although the aggregation response triggered by low galectin-8 concentrations was inhibited in the presence of aspirin (cyclo-oxigenase inhibitor) and/or an ADP-scavenger, a full response was obtained at higher concentrations indicating that galectin-8 is a strong agonist that activate platelets independently from TXA_2 formation or ADP release (9).

What is the relevance of platelet activation mediated by galectins *in vivo*? Given the described effects of galectin-1 and -8 in platelet physiology, exposure of these endogenous

lectins in the subendothelium or in activated endothelial cells (20) is expected to trigger platelet adhesion, spreading and thrombus formation. Moreover, in the vascular system, platelets are another source of galectin-8 (9) that would be accessible upon platelet activation to eventually promote further thrombus growth. In support of these hypotheses, evaluation of hemostasis *in vivo* by tail bleeding revealed increased bleeding time in galectin-1 knockout animals, which was not associated to a lower platelet count. In addition, galectin-1-deficient platelets exhibited impaired kinetics of clot retraction and platelet spreading on fibrinogen in the presence of normal integrin $\alpha_{IIb}\beta_3$ expression. Galectin-1-deficient platelets showed normal α granule secretion and normal platelet aggregation. Therefore, galectin-1 appears to regulate integrin $\alpha_{IIb}\beta_3$ "outside-in" signaling events in platelets and is necessary for normal primary hemostasis *in vivo* (8). Whether this effect is specific for galectin-1 or is a general feature to all galectins, is an interesting question that remains to be investigated.

Thrombosis and disseminated intravascular coagulation are common complications in cancer patients. A hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate platelets and the coagulation system. Prothrombotic factors in cancer include the ability of tumor cells to produce and secrete procoagulant/fibrinolitic substances and inflammatory cytokines and the physical interaction between tumor cell and platelets (22). However, the mechanisms allowing the occurrence of prothrombotic states in cancer patients are not completely understood. The observed increased levels of galectin-1 and -8 in tumoral endothelial cells as well as in other malignant cells could represent a pathogenic mechanism involved in thrombosis and disseminated intravascular coagulation complications, commonly present in cancer patients. Given the pivotal role of galectin-1 and -8 in tumor progression, it could be conceivable that galectin-induced platelet activation might contribute to the pathogenesis of thrombosis in cancer patients.

Platelet-galectin interactions, potential regulators of the inflammatory, atherosclerosis and metastatic processes

The contribution of platelets to the inflammatory response is an outcome of the interaction of platelets with leukocytes and endothelial cells. Stimulated "sticky" platelets express on their cell surface, P-selectin and CD40L α-granule-stored proteins that enable recruitment and activation of leukocytes at sites of vascular injury as well as platelet adhesion to the endothelium. The interaction between the three types of cells creates a mutual feedback loop of reciprocal activation and inhibition leading to modulation of the inflammatory process (23,24).

Galectin-1, -3 and -8 are strong inducers of P-selectin expression (7,9,10). The major role of P-selectin on the platelet surface is the interaction with P-selectin glycoprotein ligand (PSGL-1), its counter-receptor on leukocytes, to form platelet-leukocyte aggregates (25). In fact, activation of platelets by galectin-1 in the presence of polymorphonuclear leukocytes results in a significant formation of heterotypic cell aggregates (7,9). The interaction of platelets with leukocytes promotes activation of both cell types, which is a crucial condition for triggering inflammation, vascular remodelling and thrombosis. Platelet-leukocyte aggregates represent an established link between inflammation and thrombosis in acute syndromes including coronary diseases and related disorders (26). The expression of P-selectin on the platelet surface, the formation of leukocyte-platelets aggregates and leukocyte activation are relevant events in deep vein thrombosis (DVT) (27). Given that galectins promote all these responses, binding of these lectins to platelets might represent potentially novel mechanism involved in DVT. Interestingly, galectin-3 binding protein has been found to be up-regulated in proteomics analysis of MP during DVT (28). While galectin-8 has been linked to proinflammatory processes (29,30), both, anti and proinflammatory activities have been ascribed to galectin-1 (6). Whether antiinflammatory effects occur at low concentrations of galectin-1, while proinflammatory effects prevail at high concentrations, still remains to be established. The fact that galectin-1 promotes platelet activation support the notion that under certain circumstances, galectin-1 could also act as a proinflammatory factor.

The interaction of P-selectin with PSGL-1 induces the up-regulation of tissue factor in the leukocyte membrane and the production of procoagulant MP. Besides, activation of platelets by galectin-1 (7) induces phosphatidylserine expressing MPs thus providing a catalytic surface for several enzyme complexes of the coagulation system. Together, these data indicate that either in a direct manner or through the activation of leukocytes, platelet-galectin interactions might contribute to activate the coagulation cascade thereby contributing to a prothrombotic state.

Similarly to P-selectin, vWF is stored in platelet α granules and in Weibel-Palade bodies of endothelial cells

from which is released during injury or inflammation. vWF is a large multimeric glycoprotein that allows platelet-endothelium, platelet-subendothelium and platelet-platelet interaction and is therefore important for platelet adhesion and thrombus formation, vWF is a biomarker for endothelial dysfunction and cardiovascular risk and high levels of vWF are found in both chronic and acute inflammation (31). The release of α granule stored vWF occurs after activation of platelets by galectin-1 (unpublished data) or -8 (9). Thus, P-selectin expression and vWF release mediated by galectins might play an important role in the pathogenesis of thrombus formation and the modulation of inflammatory responses.

Atherosclerosis is an inflammatory disorder and the interaction between activated endothelial cells and platelets has a major role in the initiation and progression of the atheroma plaque. We recently observed that platelets adhere to galectin-8-treated endothelial cells, strongly suggesting that galectin-8 might trigger an activation state on the endothelium in an inflammatory context (11). In this sense, we also found that galectin-8 induces a plethora of proinflammatory molecules in the endothelium that might not only trigger the local platelet adhesion/activation processes but also fuels a given pathological abnormality such as atherosclerosis. Although the expression of galectin-8 in human atherosclerotic lesions has not yet been explored, several groups demonstrated that galectins including galectin-1 participate in the initiation, progression and rupture of an atheroma plaque. Galectin-1, -3 and -8 are not only expressed by the different cellular components of the atheroma lesions (32-34) but they also promote smooth muscle cell proliferation and transformation of macrophages into foam cells through the uptake of modified lipoproteins or advanced glycation end products (AGEs) (35,36). The expression of galectins in the inner of atheroma plaque may not only represent strong amplifiers of platelet activation but may also be key components of the extremely thrombogenic core exposed after plaque rupture, the main trigger for acute thrombus formation and cause of unstable angina, myocardial infarction, transient ischemic attack, and stroke. Evidence for a role of galectins in atherosclerosis has also emerged from whole-genome association studies for myocardial infarction in Asian populations (32) although these findings were not reproduced in studies of populations with other ancestries (37).

It has been extensively shown that depletion or functional inactivation of platelets through a variety of genetic and pharmacological manipulations markedly reduces tumor progression and metastasis. Platelets may influence the metastatic potential of tumor cells via several mechanisms: (I) through the release of a variety of inflammatory mediators which may influence tumor growth and stroma formation; (II) through the expression of P-selectin, platelets may contribute to the stable adhesion to endothelium and/or transmigration of tumor cells outside of the vasculature; (III) through the formation of heterotypic aggregates between mucins in circulating cancer and P-selectin in activated platelets which may protect tumor cells against immune attack (38). The formation of mixed-cell aggregates between tumor cells expressing high levels of galectins and platelets might also represent a complementary molecular mechanism to mucins and P-selectin interaction by which platelets contribute to tumor progression and metastasis. Interestingly, and in contrast to mucin—P-selectin interactions, the interaction of tumor cells with platelets via galectins would not require the presence of activated platelets.

Control of angiogenesis by galectins involves the release of platelet-derived proangiogenic factors

Platelets are being recognized as major players in every step of vessel formation as they are a major storage of a broad array of growth factors, chemokines, cytokines, proteases and cell adhesion molecules (39). The pro-angiogenic substances contained within platelets include vascular endothelial growh factor (VEGF), basic fibroblast growth factor, platelet derived growth factor, epithelial growth factor, and stromal cell-derived factor-1α. Additionally, anti-angiogenic molecules are secreted by platelets and these include thrombospondin-1, endostatin, platelet factor-4, angiostatin, tissue inhibitor of metalloproteinases-1 and -4 and plasminogen activator inhibitor-1. It has been recently demonstrated that angiogenic factors are packed into morphologically distinct populations of α-granules in megakaryocytes and platelets (40,41) and can be differentially released based on selective engagement of platelet receptors, providing a mechanism by which platelets can locally and sequentially modulate angiogenesis (41). Although platelets contain both, pro and antiangiogenic molecules, there is a general consensus that platelets promote angiogenesis by stimulating chemotaxis, proliferation, and differentiation of endothelial cells and recruitment of progenitor cells to sites of vascular injury. The amplification of angiogenesis by platelets plays a positive and beneficial role in several processes, such as

pregnancy and tissue healing, where new vessel development is required. However, in clinical conditions associated with abnormal or excessive angiogenesis including cancer, atherosclerosis, and arthritis, platelets might contribute to the detrimental progression of these diseases.

Different members of the galectin family can selectively regulate the release of angiogenic molecules by platelets. Whereas galectin-1, -3, and -8 trigger VEGF release, only galectin-8 induce endostatin secretion (10). The ability of all three galectins to trigger VEGF release, but only galectin-8 being able to induce endostatin secretion is in agreement with the new paradigm of platelet granule secretion described above and point out that the differential release of VEGF or endostatin is not restricted to classical platelet agonists but can also be induced by non-canonical platelet activators such as galectins. Despite VEGF or endostatin secretion, platelet releasates generated by stimulation with each galectin stimulate angiogenic responses *in vitro* including endothelial cell proliferation and tubulogenesis. The platelet-angiogenic activity is independent of VEGF and is associated to the concerted action of other pro-angiogenic molecules distinctly released by each galectin (10). Altogether, these data highlights that secretion of platelet-derived angiogenic molecules may represent an alternative mechanism by which galectins promote angiogenic responses and its selective blockade may lead to the development of therapeutic strategies for angiogenesis-related diseases.

Perspectives

Over the last decade we have witnessed impressive advances regarding the biology of galectins and their role in cell homeostasis, in particular as regulators of the immune response. The information currently available indicates that galectins are expressed and secreted by several cell types in normal and pathological conditions. The emergence of galectins as soluble mediators capable of triggering platelet activation opens a new field of research that will provide further insights into the mechanisms linking inflammatory responses to thrombus formation and could expand our view of the role of platelets much beyond hemostasis to their pathophysiologic role during inflammation and cancer. As galectins are up-regulated in endothelial cells and tumors, and galectin stimulation results in platelet aggregation and secretion of soluble pro-angiogenic factors, selective targeting of these pathways may contribute to design novel therapeutic approaches to promote tissue regeneration and attenuate atherosclerosis, ischemic ulcers, diabetes or cancer.

Acknowledgements

The author apologizes to the many authors whose papers could not be cited and instead referred to other reviews owing to space limitations. Supported by grants from Agencia Nacional de Promoción Científica y Tecnológica. *Disclosure:* The author declares no conflict of interest.

References

1. Yeaman MR. Platelets: at the nexus of antimicrobial defence. Nat Rev Microbiol 2014;12:426-37.
2. Leslie M. Cell biology. Beyond clotting: the powers of platelets. Science 2010;328:562-4.
3. Ware J, Corken A, Khetpal R. Platelet function beyond hemostasis and thrombosis. Curr Opin Hematol 2013;20:451-6.
4. Rivera J, Lozano ML, Navarro-Núñez L, et al. Platelet receptors and signaling in the dynamics of thrombus formation. Haematologica 2009;94:700-11.
5. Di Lella S, Sundblad V, Cerliani JP, et al. When galectins recognize glycans: from biochemistry to physiology and back again. Biochemistry 2011;50:7842-57.
6. Yang RY, Rabinovich GA, Liu FT. Galectins: structure, function and therapeutic potential. Expert Rev Mol Med 2008;10:e17.
7. Pacienza N, Pozner RG, Bianco GA, et al. The immunoregulatory glycan-binding protein galectin-1 triggers human platelet activation. FASEB J 2008;22:1113-23.
8. Romaniuk MA, Croci DO, Lapponi MJ, et al. Binding of galectin-1 to $\alpha_{IIb}\beta_3$ integrin triggers "outside-in" signals, stimulates platelet activation, and controls primary hemostasis. FASEB J 2012;26:2788-98.
9. Romaniuk MA, Tribulatti MV, Cattaneo V, et al. Human platelets express and are activated by galectin-8. Biochem J 2010;432:535-47.
10. Etulain J, Negrotto S, Tribulatti MV, et al. Control of angiogenesis by galectins involves the release of platelet-derived proangiogenic factors. PLoS One 2014;9:e96402.
11. Cattaneo V, Tribulatti MV, Carabelli J, et al. Galectin-8 elicits pro-inflammatory activities in the endothelium. Glycobiology 2014;24:966-73.
12. Berndt MC, Metharom P, Andrews RK. Primary haemostasis: newer insights. Haemophilia 2014;20 Suppl 4:15-22.
13. Speth C, Löffler J, Krappmann S, et al. Platelets as immune cells in infectious diseases. Future Microbiol 2013;8:1431-51.
14. Rabinovich GA, Baum LG, Tinari N, et al. Galectins

and their ligands: amplifiers, silencers or tuners of the inflammatory response? Trends Immunol 2002;23:313-20.
15. Leffler H. Galectins structure and function--a synopsis. Results Probl Cell Differ 2001;33:57-83.
16. Laderach DJ, Compagno D, Toscano MA, et al. Dissecting the signal transduction pathways triggered by galectin-glycan interactions in physiological and pathological settings. IUBMB Life 2010;62:1-13.
17. Barondes SH, Castronovo V, Cooper DN, et al. Galectins: a family of animal beta-galactoside-binding lectins. Cell 1994;76:597-8.
18. Elola MT, Wolfenstein-Todel C, Troncoso MF, et al. Galectins: matricellular glycan-binding proteins linking cell adhesion, migration, and survival. Cell Mol Life Sci 2007;64:1679-700.
19. Liu FT, Patterson RJ, Wang JL. Intracellular functions of galectins. Biochim Biophys Acta 2002;1572:263-73.
20. Thijssen VL, Hulsmans S, Griffioen AW. The galectin profile of the endothelium: altered expression and localization in activated and tumor endothelial cells. Am J Pathol 2008;172:545-53.
21. Shattil SJ, Kim C, Ginsberg MH. The final steps of integrin activation: the end game. Nat Rev Mol Cell Biol 2010;11:288-300.
22. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer 2010;102 Suppl 1:S2-9.
23. Dole VS, Bergmeier W, Mitchell HA, et al. Activated platelets induce Weibel-Palade-body secretion and leukocyte rolling in vivo: role of P-selectin. Blood 2005;106:2334-9.
24. Etulain J, Schattner M. Current viewpoints on platelet contribution to inflammation. World J Hematol 2012;1:14-21.
25. Furie B, Furie BC. Role of platelet P-selectin and microparticle PSGL-1 in thrombus formation. Trends Mol Med 2004;10:171-8.
26. Totani L, Evangelista V. Platelet-leukocyte interactions in cardiovascular disease and beyond. Arterioscler Thromb Vasc Biol 2010;30:2357-61.
27. von Brühl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med 2012;209:819-35.
28. Diaz JA, Ramacciotti E, Wakefield TW. Do galectins play a role in venous thrombosis? a review. Thromb Res 2010;125:373-6.
29. Tribulatti MV, Cattaneo V, Hellman U, et al. Galectin-8 provides costimulatory and proliferative signals to T lymphocytes. J Leukoc Biol 2009;86:371-80.
30. Cattaneo V, Tribulatti MV, Campetella O. Galectin-8 tandem-repeat structure is essential for T-cell proliferation but not for co-stimulation. Biochem J 2011;434:153-60.
31. Vischer UM. von Willebrand factor, endothelial dysfunction, and cardiovascular disease. J Thromb Haemost 2006;4:1186-93.
32. Ozaki K, Inoue K, Sato H, et al. Functional variation in LGALS2 confers risk of myocardial infarction and regulates lymphotoxin-alpha secretion in vitro. Nature 2004;429:72-5.
33. Nachtigal M, Al-Assaad Z, Mayer EP, et al. Galectin-3 expression in human atherosclerotic lesions. Am J Pathol 1998;152:1199-208.
34. Chellan B, Narayani J, Appukuttan PS. Galectin-1, an endogenous lectin produced by arterial cells, binds lipoprotein(a) [Lp(a)] in situ: relevance to atherogenesis. Exp Mol Pathol 2007;83:399-404.
35. Papaspyridonos M, Smith A, Burnand KG, et al. Novel candidate genes in unstable areas of human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2006;26:1837-44.
36. Moiseeva EP, Javed Q, Spring EL, et al. Galectin 1 is involved in vascular smooth muscle cell proliferation. Cardiovasc Res 2000;45:493-502.
37. Kimura A, Takahashi M, Choi BY, et al. Lack of association between LTA and LGALS2 polymorphisms and myocardial infarction in Japanese and Korean populations. Tissue Antigens 2007;69:265-9.
38. Borsig L. The role of platelet activation in tumor metastasis. Expert Rev Anticancer Ther 2008;8:1247-55.
39. Patzelt J, Langer HF. Platelets in angiogenesis. Curr Vasc Pharmacol 2012;10:570-7.
40. van Nispen tot Pannerden H, de Haas F, Geerts W, et al. The platelet interior revisited: electron tomography reveals tubular alpha-granule subtypes. Blood 2010;116:1147-56.
41. Italiano JE Jr, Richardson JL, Patel-Hett S, et al. Angiogenesis is regulated by a novel mechanism: pro- and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood 2008;111:1227-33.

Cite this article as: Schattner M. Platelets and galectins. Ann Transl Med 2014;2(9):85. doi: 10.3978/j.issn.2305-5839.2014.09.02

