

Scientific Reports, 2017, vol.7, N1

Activated Monocytes Enhance Platelet-Driven Contraction of Blood Clots via Tissue Factor Expression

Peshkova A., Le Minh G., Tutwiler V., Andrianova I., Weisel J., Litvinov R.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 The Author(s). Platelet-driven reduction in blood clot volume (clot contraction or retraction) has been implicated to play a role in hemostasis and thrombosis. Although these processes are often linked with inflammation, the role of inflammatory cells in contraction of blood clots and thrombi has not been investigated. The aim of this work was to study the influence of activated monocytes on clot contraction. The effects of monocytes were evaluated using a quantitative optical tracking methodology to follow volume changes in a blood clot formed *in vitro*. When a physiologically relevant number of isolated human monocytes pre-activated with phorbol-12-myristate-13-acetate (PMA) were added back into whole blood, the extent and rate of clot contraction were increased compared to addition of non-activated cells. Inhibition of tissue factor expression or its inactivation on the surface of PMA-treated monocytes reduced the extent and rate of clot contraction back to control levels with non-activated monocytes. On the contrary, addition of tissue factor enhanced clot contraction, mimicking the effects of tissue factor expressed on the activated monocytes. These data suggest that the inflammatory cells through their expression of tissue factor can directly affect hemostasis and thrombosis by modulating the size and density of intra- and extravascular clots and thrombi.

<http://dx.doi.org/10.1038/s41598-017-05601-9>

References

- [1] Carr, M. E. Development of platelet contractile force as a research and clinical measure of platelet function. *Cell Biochem Biophys* 75, 674-678 (2003).
- [2] Stalker, T. J. et al. A systems approach to hemostasis: 3. Thrombus consolidation regulates intrathrombus solute transport and local thrombin activity. *Blood* 124, 1824-1831 (2014).
- [3] Lam, W. A. et al. Mechanics and contraction dynamics of single platelets and implications for clot stiffening. *Nat Mater* 10, 61-66 (2011).
- [4] Cines, D. B. et al. Clot contraction: compression of erythrocytes into tightly packed polyhedra and redistribution of platelets and fibrin. *Blood* 123, 1596-1603 (2014).
- [5] Muthard, R. W. & Diamond, S. L. Blood clots are rapidly assembled hemodynamic sensors: flow arrest triggers intraluminal thrombus contraction. *Arterioscler Thromb Vasc Biol* 32, 2938-2945 (2012).
- [6] Tutwiler, V. et al. Contraction of blood clots is impaired in ischemic stroke. *Arterioscler Thromb Vasc Biol* 37, 271-279 (2017).
- [7] Tutwiler, V. et al. Kinetics and mechanics of clot contraction are governed by the molecular and cellular composition of the blood. *Blood* 127, 149-159 (2016).
- [8] Auffray, C. et al. Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science* 317, 666-670 (2007).
- [9] Emson, C. T. Crosstalk between inflammation and thrombosis. *Maturitas* 47, 305-314 (2004).

- [10] Libby, P. & Simon, D. I. Inflammation and thrombosis: the clot thickens. *Circulation* 103 (2001).
- [11] Leatham, E. W., Bath, P. M., Tooze, J. A. & Camm, A. J. Increased monocyte tissue factor expression in coronary disease. *Br Heart J* 73, 10-13 (1995).
- [12] Eilertsen, K. E. & Osterud, B. Tissue factor: (patho)physiology and cellular biology. *Blood Coagul Fibrinolysis* 15, 521-538 (2004).
- [13] Schechter, A. D. et al. Tissue factor is induced by monocyte chemoattractant protein-1 in human aortic smooth muscle and THP-1 cells. *Biol Chem* 272, 28568-28573 (1997).
- [14] Osterud, B. The role of platelets in decrypting monocyte tissue factor. *Disease-a-month* 49, 7-13 (2003).
- [15] Mackman, N. Role of Tissue Factor in Hemostasis, Thrombosis, and Vascular Development. *Arterioscler Thromb Vasc Biol* 24, 1015-1022 (2004).
- [16] Weisel, J. W. & Litvinov, R. I. Mechanism of fibrin polymerization and clinical implications. *Blood* 121, 1712-1719 (2013).
- [17] Carr, M. E., Martin, E. J. & Carr, S. L. Delayed, reduced of inhibited thrombin production reduced platelet contractile force and results in weaker clot formation. *Blood Coagul Fibrinolysis* 13, 193-197 (2002).
- [18] Jennings, L. K., Fox, J. E., Edwards, H. H. & Phillips, D. R. Changes in the cytoskeletal structure of human platelets following thrombin activation. *J Biol Chem* 256, 6927-6932 (1981).
- [19] Osterud, B., Olsen, J. O. & Bjorklid, E. What is blood borne tissue factor? *Thromb Res* 124, 640-641 (2009).
- [20] Basavaraj, M. G. et al. The role of TFPI in regulation of TF-induced thrombogenicity on the surface of human monocytes. *Thromb Res* 126, 418-425 (2010).
- [21] Idell, S. et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. *J Clin Invest* 84, 695-705 (1989).
- [22] Osterud, B. & Flaegstad, T. Increased tissue thromboplastin activity in monocytes of patients with meningococcal infect: related to an unfavorable prognosis. *Thromb Haemost* 49, 5-7 (1983).
- [23] Lorenzet, R. et al. Generation of procoagulant activity by mononuclear phagocytes: a possible mechanism contributing to blood clotting within malignant tissues. *Blood* 62, 271-273 (1983).
- [24] Wilcox, J. N., Smith, K. M., Schwartz, S. M. & Gordon, D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci USA* 86, 2839-2843 (1989).
- [25] Annex, B. H. et al. Differential expression of tissue factor protein in directional atherectomy specimens from patients with stable and unstable coronary syndromes. *Circulation* 91, 619-622 (1995).
- [26] Marmur, J. D. et al. Identification of active tissue factor in human coronary atheroma. *Circulation* 94, 1226-1232 (1996).
- [27] Ardissino, D. et al. Tissue-factor antigen and activity in human coronary atherosclerotic plaques. *Lancet* 349, 769-771 (1997).
- [28] Moons, A. H., Levi, M. & Peters, R. J. Tissue factor and coronary artery disease. *Cardiovasc Res* 53, 313-325 (2002).
- [29] Jander, S. et al. Expression of tissue factor in high-grade carotid artery stenosis: association with plaque destabilization. *Stroke* 32, 850-854 (2001).
- [30] Asada, Y. et al. The role of tissue factor in the pathogenesis of thrombosis and atherosclerosis. *J Atheroscler Thromb* 4, 135-139 (1998).
- [31] Jude, B., Zawadski, C., Susen, S. & Corseaux, D. Relevance of tissue factor in cardiovascular disease. *Arch Mal Coeur Vaiss* 98, 667-671 (2005).
- [32] von Bruhl, M. et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med* 209, 819-835 (2012).
- [33] Tutwiler, V., Wang, H., Litvinov, R. I., Weisel, J. W. & Shenoy, V. B. Interplay of platelet contractility and viscoelasticity of fibrin/erythrocytes in blood clot contraction. *Biophys J* 112, 714-723 (2017).
- [34] Neve, B. P. et al. PPAR α agonists inhibit tissue factor expression in human monocytes and macrophages. *Circulation* 103, 207-212 (2001).
- [35] Marx, N. et al. PPAR α activators inhibit tissue factor expression and activity in human monocytes. *Circulation* 103, 212-219 (2001).
- [36] Wolberg, A. S. Primes to understand fibrinogen in cardiovascular disease. *Arterioscler Thromb Vasc Biol* 31, 4-6 (2016).
- [37] Butenas, S., Bouchard, B. A., Brummel-Ziedins, K. E., Parhami-Seren, B. & Mann, K. G. Tissue factor activity in whole blood. *Blood* 105, 2764-2770 (2005).
- [38] Nguyễn, P., Broussas, M., Cornillet-Lefèbvre, P. & Potron, G. Coexpression of tissue factor and tissue factor pathway inhibitor by human monocytes purified by leukapheresis and elutriation. Response of nonadherent cells to lipopolysaccharide. *Transfusion* 39, 975-982 (1999).
- [39] von Ahsen, N., Lewczuk, P., Schütz, E., Oellerich, M. & Ehrenreich, H. Prothrombin activity and concentration in healthy subjects with and without a prothrombin G20210A mutation. *Thromb Res* 99, 549-556 (2000).

- [40] Harker, L. A., Hanson, S. R. & Kelly, A. B. Antithrombotic strategies targeting thrombin activities, thrombin receptors and thrombin generation. *Thromb Haemost* 78, 736-741 (1997).
- [41] Zilberman-Rudenko, J. et al. Biorheology of platelet activation in the blood stream distal to thrombus formation. *Cell Mol Bioeng* 9, 496-508 (2016).
- [42] Puetz, V. et al. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. *Int J Stroke* 3, 230-236 (2008).
- [43] del Zoppo, G. J. et al. Tissue factor localization in non-human primate cerebral tissue. *Thromb Haemost* 68, 642-647 (1992).
- [44] Thomas, W. S. et al. Tissue factor contributes to microvascular defects after focal cerebral ischemia. *Stroke* 24, 847-853 (1993).
- [45] Jurk, K. et al. Platelets in patients with acute ischemic stroke are exhausted and refractory to thrombin, due to cleavage of the seven transmembrane thrombin receptor (PAR-1). *Thromb Haemost* 91, 334-344 (2004).
- [46] Liebeskind, D. S. et al. CT and MRI early vessel signs reflect clot composition in acute stroke. *Stroke* 42, 1237-1243 (2011).
- [47] Undas, A., Slowik, A., Wolkow, P., Szczudlik, A. & Tracz, W. Fibrin clot properties in acute ischemic stroke: relation to neurological deficit. *Thromb Res* 125, 357-361 (2010).
- [48] Diamond, S. L. Engineering design of optimal strategies for blood clot dissolution. *Annu Rev Biomed Eng* 1, 1427-1462 (1999).
- [49] Staels, B. & Fruchart, J. C. Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 54, 2460-2470 (2005).
- [50] Mackman, N. Regulation of the tissue factor gene 9, 883-889 (FASEB J) (1995).
- [51] Hoesel, B. & Schmid, J. A. The complexity of NF- κ B signaling in inflammation and cancer. *Mol Cancer* 12, 86 (2013).
- [52] Weyrich, A. S., McIntyre, T. M., McEver, R. P., Prescott, S. M. & Zimmerman, G. A. Monocyte tethering by P-selectin regulates monocyte chemotactic protein-1 and tumor necrosis factor- α secretion. Signal integration and NF- κ B translocation. *J Clin Invest* 95, 2297-2393 (1995).