Clinical Science 2018 vol.132 N2, pages 243-254

Impaired contraction of blood clots as a novel prothrombotic mechanism in systemic lupus erythematosus

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2018 The Author(s). The aim of this work was to examine a possible role of clot contraction/retraction in thrombotic complications of systemic lupus erythematosus (SLE). Using a novel automated method, we investigated kinetics of clot contraction in the blood of 51 SLE patients and 60 healthy donors. The functionality of platelets in the SLE patients was assessed using flow cytometry by expression of P-selectin and fibrinogen-binding capacity. The rate and degree of clot contraction were significantly reduced in SLE patients compared with healthy subjects, especially in the patients with higher blood levels of anti-dsDNA antibodies. The reduced platelet contractility correlated with partial refractoriness of platelets isolated from the blood of SLE patients to stimulation induced by the thrombin receptor activating peptide. To test if the anti-dsDNA autoantibodies cause continuous platelet activation, followed by exhaustion and dysfunction of the cells, we added purified exogenous anti-dsDNA autoantibodies from SLE patients to normal blood before clotting. In support of this hypothesis, the antibodies first enhanced clot contraction and then suppressed it in a time-dependent manner. Importantly, a direct correlation of clot contraction parameters with the disease severity suggests that the reduced compactness of intravascular clots and thrombi could be a pathogenic factor in SLE that may exaggerate the impaired blood flow at the site of thrombosis. In conclusion, autoantibodies in SLE can affect platelet contractility, resulting in reduced ability of clots and thrombi to shrink in volume, which increases vessel obstruction and may aggravate the course and outcomes of thrombotic complications in SLE.

http://dx.doi.org/10.1042/cs20171510

References

[1] Cervera, R., Khamashta, M.A., Font, J., Sebastiani, G.D., Gil, A., Lavilla, P. et al. (2003) Morbidity and mortality in systemic lupus erythematosus during a 10-year period. Medicine 82, 299-308, https://doi.org/10.1097/01.md.0000091181.93122.55

[2] Beyan, E., Beyan, C. and Turan, M. (2007) Hematological presentation in systemic lupus erythematosus and its relationship with disease activity. Hematology 12, 257-261, https://doi.org/10.1080/10245330701214145

[3] Palatinus, A. and Adams, M. (2009) Thrombosis in systemic lupus erythematosus. Semin. Thromb. Hemost. 35, 621-629, https://doi.org/10.1055/s-0029-1242716

[4] Giannouli, S., Voulgarelis, M., Ziakas, P.D. and Tzioufas, A.G. (2006) Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. Ann. Rheum. Dis. 65, 144-148, https://doi.org/10.1136/ard.2005.041673

[5] Kuwana, M., Kaburaki, J., Okazaki, Y., Miyazaki, H. and Ikeda, Y. (2006) Two types of autoantibody-mediated thrombocytopenia in patients with systemic lupus erythematosus. Rheumatology (Oxford) 45, 851-854, https://doi.org/10.1093/rheumatology/kel010

[6] Gasparyan, A.Y., Ayvazyan, L., Mikhailidis, D.P. and Kitas, G.D. (2011) Mean platelet volume: a link between thrombosis and inflammation? Curr. Pharm. Des. 17, 47-58, https://doi.org/10.2174/138161211795049804

[7] Pretorius, E., du Plooy, J., Soma, P. and Gasparyan, A.Y. (2014) An ultrastructural analysis of platelets, erythrocytes, white blood cells, and fibrin network in systemic lupus erythematosus. Rheumatol. Int. 34, 1005-1009

[8] Wahl, D.G., Bounameaux, H., de Moerloose, P. and Sarasin, F.P. (2000) Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. Arch. Intern. Med. 160, 2042-2048, https://doi.org/10.1001/archinte.160.13.2042

[9] Duffau, P., Seneschal, J., Nicco, C., Richez, C., Lazaro, E., Douchet, I. et al. (2010) Platelet CD154 potentiates interferon-a secretion by plasmacytoid dendritic cells in systemic lupus erythematosus. Sci. Trans. Med. 2, 47-63, https://doi.org/10.1126/scitranslmed.3001001

[10] Ekdahl, K.N., Bengtsson, A.A., Andersson, J., Elgue, G., Rönnblom, L., Sturfelt, G. et al. (2004) Thrombotic disease in systemic lupus erythematosus is associated with a maintained systemic platelet activation. Br. J. Haematol. 125, 74-78, https://doi.org/10.1111/j.1365-2141.2004.04858.x

[11] Afeltra, A., Vadacca, M., Conti, L., Galluzzo, S., Mitterhofer, A.P., Ferri, G.M. et al. (2005) Thrombosis in systemic lupus erythematosus: congenital and acquired risk factors. Arthritis Rheumatol. 53, 452-459, https://doi.org/10.1002/art.21172

[12] Haglund, A.C., Ronquist, G., Frithz, G. and Ek, P. (2000) Alteration of the fibrinogen molecule and its phosphorylation state in myocardial infarction patients undergoing thrombolytic treatment. Thromb. Res. 98, 147-156, https://doi.org/10.1016/S0049-3848(99)00225-X

[13] Ekdahl, K.N., Rönnblom, L., Nilsson, B. and Sturfelt, G. (1997) Increased phosphate content in complement component C3, fibrinogen, vitronectin, and other plasma proteins in systemic lupus erythematosus. Covariation with platelet activation and possible association with thrombosis. Arthritis Rheumatol. 40, 2178-2186, https://doi.org/10.1002/art.1780401212

[14] Lood, C., Amisten, S., Gullstrand, B., Jönsen, A., Allhorn, M. and Truedsson, L. (2010) Platelet transcriptional profile and protein expression in patients with systemic lupus erythematosus: up-regulation of the type I interferon system is strongly associated with vascular disease. Blood 116, 1951-1957, https://doi.org/10.1182/blood-2010-03-274605

[15] Martin, S.C., Forsberg, P.O. and Eriksson, S.D. (1991) The effects of in vitro phosphorylation and dephosphorylation on the thrombin-induced gelation and plasmin degradation of fibrinogen. Thrombosis Res. 61, 243-252, https://doi.org/10.1016/0049-3848(91)90100-B

[16] Boilard, E., Blanco, P. and Nigrovic, P.A. (2012) Platelets: active players in the pathogenesis of arthritis and SLE. Nat. Rev. Rheumatol. 8, 534-542, https://doi.org/10.1038/nrrheum.2012.118

[17] Peerschke, E.I., Yin, W. and Ghebrehiwet, B. (2010) Complement activation on platelets: implications for vascular inflammation and thrombosis. Mol. Immunol. 47, 2170-2175, https://doi.org/10.1016/j.molimm.2010.05.009

[18] Cines, D.B., Lebedeva, T., Nagaswami, C., Hayes, V., Massefski, W., Litvinov, R.I. et al. (2014) Clot contraction: compression of erythrocytes into tightly packed polyhedra and redistribution of platelets and fibrin. Blood 123, 1596-1603, https://doi.org/10.1182/blood-2013-08-523860

[19] Tutwiler, V., Litvinov, R.I., Lozhkin, A.P., Peshkova, A.D., Lebedeva, T., Ataullakhanov, F.I. et al. (2016) Kinetics and mechanics of clot contraction are governed by the molecular and cellular composition of the blood. Blood 127, 149-159, https://doi.org/10.1182/blood-2015-05-647560

[20] Tutwiler, V., Peshkova, A.D., Andrianova, I.A., Khasanova, D.R., Weisel, J.W. and Litvinov, R.I. (2017) Contraction of blood clots is impaired in acute ischemic stroke. Arterioscler. Thromb. Vasc. Biol. 37, 271-279, https://doi.org/10.1161/ATVBAHA.116.308622

[21] Carr, Jr, M.E., Martin, E.J. and Carr, S.L. (2002) Delayed, reduced or inhibited thrombin production reduces platelet contractile force and results in weaker clot formation. Blood Coagul. Fibrinolysis 13, 193-197, https://doi.org/10.1097/00001721-200204000-00004

[22] Kasahara, K., Kaneda, M., Miki, T., Iida, K., Sekino-Suzuki, N., Kawashima, I. et al. (2013) Clot retraction is mediated by factor XIII-dependent fibrin-aIIbb3-myosin axis in platelet sphingomyelin-rich membrane rafts. Blood 122, 3340-3348, https://doi.org/10.1182/blood-2013-04-491290

[23] Peshkova, A.D., Malyasev, D.V., Bredikhin, R.A., Le Minh, Giang and Litvinov, R.I. (2016) Contraction of blood clots is impaired in deep vein thrombosis. BioNanoScience 6, 457-459

[24] De Winter, J.C.F. (2013) Using the Student's t-test with extremely small sample sizes. PARE 18, 1-12

[25] Sullivan, G.M. and Feinn, R. (2012) Using effect size-or why the P value is not enough. J. Grad. Med. Educ. 4, 279-282, https://doi.org/10.4300/JGME-D-12-00156.1

[26] Litvinov, R.I. and Weisel, J.W. (2016) What is the biological and clinical relevance of fibrin? Semin. Thromb. Hemost. 42, 333-343, https://doi.org/10.1055/s-0036-1571342

[27] Von Brühl, M.L., Stark, K., Steinhart, A., Chandraratne, S., Konrad, I., Lorenz, M. et al. (2012) Monocytes, neutrophils and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J. Exp. Med. 209, 819-835, https://doi.org/10.1084/jem.20112322

[28] Ghasemzadeh, M. and Hosseini, E. (2013) Platelet-leukocyte crosstalk: linking proinflammatory responses to procoagulant state. Thromb. Res. 131, 191-197, https://doi.org/10.1016/j.thromres.2012.11.028

[29] Swystun, L.L. and Liaw, P.C. (2016) The role leukocytes in thrombosis. Blood 128, 753-762, https://doi.org/10.1182/blood-2016-05-718114

[30] Nabiullina, R.M., Shakurova, M.A., Maksudova, A.N., Zubaidova, L.D. and Litvinov, R.I. (2016) Fibrin clot structure and properties are altered in systemic lupus erythematosus. BioNanoScience 6, 345-347

[31] Spengler, M.I., Svetaz, M.J., Leroux, M.B., Bertoluzzo, S.M., Parente, F.M. and Bosch, P. (2014) Lipid peroxidation affects red blood cells membrane properties in patients with systemic lupus erythematosus. Clin. Hemorheol. Microcirc. 58, 489-495

[32] Muthard, R.W. and Diamond, S.L. (2012) Blood clots are rapidly assembled hemodynamic sensors. Arterioscler. Thromb. Vas. Biol. 32, 2938-2945, https://doi.org/10.1161/ATVBAHA.112.300312

[33] Wolberg, A.S. (2016) Primed to Understand Fibrinogen in Cardiovascular Disease. Arterioscler. Thromb. Vasc. Biol. 36, 4-6, https://doi.org/10.1161/ATVBAHA.115.306754

[34] Nesbitt, W.S., Westein, E., Tovar-Lopez, F.J., Tolouei, E., Mitchell, A., Fu, J. et al. (2009) A shear gradient-dependent platelet aggregation mechanism drives thrombus formation. Nat. Med. 15, 665-673, https://doi.org/10.1038/nm.1955

[35] Hathcock, J.J. (2006) Flow effects on coagulation and thrombosis. Arterioscler. Thromb. Vasc. Biol. 26, 1729-1737, https://doi.org/10.1161/01.ATV.0000229658.76797.30

[36] Ruggeri, Z.M. (2007) The role of von Willebrand factor in thrombus formation. Thromb. Res. 120, S5-S9, https://doi.org/10.1016/j.thromres.2007.03.011