Nanoscale 2017 vol.9 N36, pages 13707-13716

Morphometric characterization of fibrinogen's αc regions and their role in fibrin self-assembly and molecular organization

Protopopova A., Litvinov R., Galanakis D., Nagaswami C., Barinov N., Mukhitov A., Klinov D., Weisel J.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 The Royal Society of Chemistry. The flexible C-terminal parts of fibrinogen's Aα chains named the αC regions have been shown to play a role in fibrin self-assembly, although many aspects of their structure and functions remain unknown. To examine the involvement of the αC regions in the early stages of fibrin formation, we used high-resolution atomic force microscopy to image fibrinogen and oligomeric fibrin. Plasma-purified full-length human fibrinogen or des-αC fibrinogen lacking most of the αC regions, untreated or treated with thrombin, was imaged. Up to 80% of the potentially existing αC regions were visualized and quantified; they were highly heterogeneous in their length and configurations. Conversion of fibrinogen to fibrin was accompanied by an increase in the incidence and length of the αC regions as well as transitions from more compact conformations, such as a globule on a string, to extended and more flexible offshoots. Concurrent dynamic turbidimetry, confocal microscopy, and scanning electron microscopy revealed that trimming of the αC regions slowed down fibrin formation, which correlated with longer protofibrils, thinner fibers, and a denser network. No structural distinctions, except for the incidence of the αC regions, were revealed in the laterally aggregated protofibrils made of the full-length or des-αC fibrinogens, suggesting a pure kinetic effect of the αC regions on the fibrin architecture. This work provides a structural molecular basis for the promoting role of the αC regions in the early stages of fibrin self-assembly and reveals this stage of fibrin formation as a potential therapeutic target to modulate the structure and mechanical properties of blood clots.

http://dx.doi.org/10.1039/c7nr04413e

References

[1] J. M. Kollman L. Pandi M. R. Sawaya M. Riley R. F. Doolittle Biochemistry 2009 48 3877 3886
[2] G. Spraggon S. J. Everse R. F. Doolittle Nature 1997 389 455 462
[3] I. Pechik J. Madrazo M. W. Mosesson I. Hernandez G. L. Gilliland L. Medved Proc. Natl. Acad. Sci. U. S. A. 2004 101 2718 2723
[4] J. W. Weisel L. Medved Ann. N. Y. Acad. Sci. 2001 936 312 327
[5] Y. I. Veklich O. V. Gorkun L. V. Medved W. Nieuwenhuizen J. W. Weisel J. Biol. Chem. 1993 268 13577 13585
[6] G. Tsurupa I. Pechik R. I. Litvinov R. R. Hantgan N. Tjandra J. W. Weisel L. Medved Biochemistry 2012 51 2526 2538
[7] O. V. Gorkun Y. I. Veklich L. V. Medved' A. H. Henschen J. W. Weisel Biochemistry 1994 33 6986 6997

[8] R. I. Litvinov S. Yakovlev G. Tsurupa O. V. Gorkun L. V. Medved J. W. Weisel Biochemistry 2007 46 9133 9142
[9] N. E. Hudson F. Ding I. Bucay E. T. O'Brien O. V. Gorkun R. Superfine S. T. Lord N. V. Dokholyan M. R. Falvo Biophys. J. 2013 104 2671 2680
[10] L. Ping L. Huang B. Cardinali A. Profumo O. V. Gorkun S. T. Lord Biochemistry 2011 50 9066 9075
[11] E. A. Ryan L. F. Mockros J. W. Weisel L. Lorand Biophys. J. 1999 77 2813 2826
[12] J.-P. Collet J. L. Moen Y. I. Veklich O. V. Gorkun S. T. Lord G. Montalescot J. W. Weisel Blood 2005 106 3824 3830
[13] M. R. Falvo D. Millard E. T. O'Brien R. Superfine S. T. Lord J. Thromb. Haemostasis 2008 6 1991 1993
[14] C. C. Helms R. A. S. Ariens S. Uitte De Willige K. F. Standeven M. Guthold Biophys. J. 2012 102 168 175
[15] K. N. Mouapi J. D. Bell K. A. Smith R. A. S. Ariens H. Philippou M. C. Maurer Blood 2016 127 2241 2248
[16] J. R. Byrnes C. Duval Y. Wang C. E. Hansen B. Ahn M. J. Mooberry M. A. Clark J. M. Johnsen S. T. Lord W. A. Lam J. C. M. Meijers H. Ni R. A. S. Ariëns A. S. Wolberg Blood 2015 126 1940 1948
[17] Y. V. Matsuka L. V. Medved M. M. Migliorini K. C. Ingham Biochemistry 1996 35 5810 5816
[18] G. Tsurupa A. Mahid Y. Veklich J. W. Weisel L. Medved Biochemistry 2011 50 8028 8037
[19] G. Tsurupa L. Medved Biochemistry 2001 40 801 808
[20] D. F. Mosher J. Biol. Chem. 1975 250 6614 6621
[21] T. Tamaki N. Aoki Biochim. Biophys. Acta 1981 661 280 286
[22] Y. Sakata N. Aoki J. Clin. Invest. 1980 65 290 297
[23] J. W. Smith Z. M. Ruggeri T. J. Kunicki D. A. Cheresh J. Biol. Chem. 1990 265 12267 12271
[24] K. Suehiro J. Mizuguchi K. Nishiyama S. Iwanaga D. H. Farrell S. Ohtaki J. Biochem. 2000 128 705 710
[25] R. I. Litvinov D. H. Farrell J. W. Weisel J. S. Bennett J. Biol. Chem. 2016 291 7858 7867
[26] C. Duval P. Allan S. D. A. Connell V. C. Ridger H. Philippou R. A. S. Ariens Thromb. Haemostasis 2014 111 842 850
[27] S. V. Pizzo M. L. Schwartz R. L. Hill P. A. Mckee J. Biol. Chem. 1972 247 636 645
[28] B. Raynal B. Cardinali J. Grimbergen A. Profumo S. T. Lord P. England M. Rocco Thromb. Res. 2013 132 e48 e53
[29] B. Cardinali A. Profumo A. Aprile O. Byron G. Morris S. E. Harding W. F. Stafford M. Rocco Arch. Biochem. Biophys. 2010 493 157 168
[30] I. S. Yermolenko O. V. Gorkun A. Fuhrmann N. P. Podolnikova V. K. Lishko S. P. Oshkadyerov S. T. Lord R. Ros T. P. Ugarova J. Biol. Chem. 2012 287 41979 41990
[31] J. Koo M. H. Rafailovich L. Medved G. Tsurupa B. J. Kudryk Y. Liu D. K. Galanakis J. Bohdan Y. Liu D. K. Galanakis J. Thromb. Haemostasis 2010 8 2727 2735
[32] R. Burton G. Tsurupa L. Medved N. Tjandra Biochemistry 2006 45 2257 2266
[33] G. Tsurupa L. Tsonev L. Medved Biochemistry 2002 41 6449 6459
[34] R. F. Doolittle K. W. K. Watt B. A. Cottrell D. D. Strong M. Riley Nature 1979 280 464 468
[35] L. V. Medved' O. V. Gorkun P. L. Privalov FEBS Lett. 1983 160 291 295
[36] H. P. Erickson W. E. Fowler Ann. N. Y. Acad. Sci. 1983 408 146 163
[37] I. S. Yermolenko V. K. Lishko T. P. Ugarova S. N. Magonov Biomacromolecules 2011 12 370 379
[38] S. Sheng Y. Gao A. Khromov A. V. Somlyo A. P. Somlyo Z. Shao J. Biol. Chem. 2003 278 39892 39896
[39] N. Kodera D. Yamamoto R. Ishikawa T. Ando Nature 2010 468 72 76
[40] A. Miyagi T. Ando Y. L. Lyubchenko Biochemistry 2011 50 7901 7908
[41] L. Bintu M. Kopaczynska C. Hodges L. Lubkowska M. Kashlev C. Bustamante Nat. Struct. Mol. Biol. 2011 18 1394 1399
[42] A. D. Protopopova N. A. Barinov E. G. Zavyalova A. M. Kopylov V. I. Sergienko D. V. Klinov J. Thromb. Haemostasis 2015 13 570 579
[43] M. W. Mosesson S. Sherry Biochemistry 1966 5 2829 2835
[44] M. W. Mosesson J. S. Finlayson R. A. Umfleet D. Galanakis J. Biol. Chem. 1972 247 5210 5219
[45] D. Klinov B. Dwir E. Kapon N. Borovok T. Molotsky A. Kotlyar Nanotechnology 2007 18 225102
[46] D. V. Klinov I. V. Lagutina V. V. Prokhorov T. Neretina P. P. Khil Y. B. Lebedev D. I. Cherny V. V. Demin E. D. Sverdlov Nucleic Acids Res. 1998 26 4603 4610
[47] O. V. Gorkun A. H. Henschen-Edman L. F. Ping S. T. Lord Biochemistry 1998 37 15434 15441
[48] J. Schindelin I. Arganda-Carreras E. Frise V. Kaynig M. Longair T. Pietzsch S. Preibisch C. Rueden S. Saalfeld B. Schmid J.-Y. Tinevez D. J. White V. Hartenstein K. Eliceiri P. Tomancak A. Cardona Nat. Methods 2012 9 676 682
[49] J. W. Weisel C. Nagaswami Biophys. J. 1992 7 111 128
[50] V. J. Marder N. R. Shulman W. R. Carroll J. Biol. Chem. 1969 244 2111 2119

[51] L. A. Sherman M. W. Mosesson S. Sherry Biochemistry 1969 8 1515 1523
[52] B. Gron A. Bennick W. Nieuwenhuizen S. Bjornsen F. Brosstad Thromb. Res. 1988 52 413 424
[53] M. W. Mosesson D. K. Galanakis J. S. Finlayson J. Biol. Chem. 1974 249 4656 4664
[54] L. A. Sherman A. P. Fletcher S. Sherry J. Lab. Clin. Med. 1969 73 574 583
[55] B. Holm D. W. T. Nilsen H. C. Godal Thromb. Res. 1986 41 879 884
[56] B. Holm H. C. Godal Thromb. Res. 1984 35 279 290
[57] V. J. Marder N. R. Shulman J. Biol. Chem. 1969 244 2120 2125
[58] H. M. Princen H. J. Moshage J. J. Emeis H. J. Haard W. Nieuwenhuizen S. H. Yap Thromb. Haemostasis 1985 53 212 215
[59] A. Zhmurov A. E. X. Brown R. I. Litvinov R. I. Dima J. W. Weisel V. Barsegov Structure 2011 19 1615 1624