Dicle Tıp Dergisi /
Dicle Medical Journal

2012; 39 (3): 455-457
doi: 10.5798/diclemedj.0921.2012.03.0181

REVIEW ARTICLE / DERLEME

Role of platelets in inflammation

İnflamasyonda trombositlerin rolü

Kadir Serkan Yalçın[1], Gözde Tahtacı[2], Özlem Şahin Balçık[2]

ABSTRACT

Inflammation, which is extremely useful process for human body is the response of living vascular tissues to pathological phenomena that removes the pathogens and initiates the healing procedure. Microorganisms, physical trauma, chemical, mechanical, irradiation, or thermal injury, ischemia and immune reactions are most common causes of this exceptionally important event for human body. Platelets are non-nucleated cells in blood that produced in bone marrow as derived from megakaryocytes. Apart from stop bleeding and achieving hemostasis there are incredibly important roles of platelets in inflammation. Platelets contain important mediators for inflammation like neutrophils or macrophages and can alter the course of mechanism. In this article changing platelet function in inflammation and the effect of these functions to the process of inflammation will be discussed.

Key words: Platelet, inflammation, cytokines

ÖZET

İnflamasyon patolojik etkenlere karşı canlı dokular tarafından oluşturulan, patojeni uzaklaştırmaya yarayan ve iyileşme sürecini başlatan son derece önemli bir olaydır. Mikroorganizmalar, fiziksel ve kimyasal travmalar, termal yaralanma, iskemi ve immün reaksiyonlar inflamasyon nedeni olarak gösterilebilir. Plateletler, nükleusa sahip olmayan ve kemik iliğinde megakaryositlerden üretilen hücreler olup kanamanın durdurulması ve hemostazın devamında rol almasının yanısıra inflamasyonda da önemli rol almaktadır. Nötrofil ve makrofajlara benzer şekilde, inflamasyon mekanizmasına etki edecek çeşitli sitokin üretimi ve salınımı yaparlar. Bu derlemede inflamasyonda plateletlerin rolleri ve inflamasyonun plateletler üzerine etkileri tartışılacaktır.

Anahtar kelimeler: Trombosit, yangı, sitokinler

INTRODUCTION

Inflammation, which is extremely useful process for human body is the response of living vascular tissues to pathological phenomena that removes the pathogens and initiates the healing procedure. Microorganisms, physical trauma, chemical, mechanical, irradiation, or thermal injury, ischemia and immune reactions are most common causes of this exceptionally important event for human body. About 5000 years ago Celcus and Gallen define five cardinal signs of inflammation. These are robur (redness), calor (heat), tumor (swelling), dolor (pain) and finally functio laesa (loss of function).[1,2] This signs of inflammation still remain valid even today. If this process could not correctly limited it will predispose the occurrence of the pathological events. Particularly unpredictable results of inflammation may be occurs but this process is extremely important and necessary for the continuity of life.

Platelets are non-nucleated cells in blood that produced in bone marrow as derived from megakaryocytes. Apart from stop bleeding and achieving hemostasis there are incredibly important roles of platelets in inflammation. Like primary cells leading to cytokine release such as T-lymphocytes, macrophages etc.; platelets are affected too by this "cytokine storm" and give diverse responses. Three different types of granules (α-granules, dense granules, lysosomes) secreted from platelets when they activated by cytokines in inflammation. Except for being non-nuclei cells; platelets contains important mediators for inflammation like neutrophils or mac-

[1] *Fatih University Medical School Department of Internal Medicine, Ankara, Turkey*
[2] *Fatih University Medical School Department of Hematology, Ankara, Turkey*

Yazışma Adresi /Correspondence: *Dr. Kadir Serkan Yalçın,*
Fatih University Medical School Department of Internal Medicine, Ankara, Turkey Email: drkadirserkan@gmail.com

Geliş Tarihi/ Received: 09.10.2011, Kabul Tarihi / Accepted: 03.01.2012

Copyright © Dicle Tıp Dergisi 2012, Her hakkı saklıdır / All rights reserved

rophages and can alter the course of mechanism. In this article changing platelet function in inflammation and the effect of these functions to the process of inflammation will be discussed.

EFFECTS OF PLATELETS ON INFLAMMATION

The α-granules of platelets which are not homogenous particle contain 284 different proteins.[3] Especially these granules are responding differently to different stimulus.[4] Expressing adhesion molecules like P-selectin, growth factors or receptors on platelets that plays role in angiogenesis or coagulation regulated by these proteins. Dense granules contain divalent cations (Ca^{2+}, Mg^{2+}), lysosomal membrane proteins (LAMPs), adenine nucleotides (ATP, GTP, ADP and GDP) and serotonin. Released ADP is an important co-factor of platelet aggregation. ADP acts through the Gq-coupled P2Y1 and Gi-coupled P2Y12 receptors which are essential for primary haemostasis.[5] Platelet's lysosomes contain same proteins with other cells like hydrolases and cathepsins.[6] The presence of a local inflammatory activation changes coagulation system by triggering the procoagulant molecules. TNF-α is the first inflammatory cytokine that release from leukocyte and another cells of human body causes leukocyte recruitment.[7] Platelet activation in inflammation results that altering chemotactic, proteolytic, and adhesive properties of endothelial cells.[8] They release potent proinflammatory and mutagenic substances; thus formed alterations of endothelial cells cause acceleration and strengthen monocytes chemotaxis, adhesion, and transmigration to the location of inflammation. Similarly IL-1β is the major mediator in inflammation which has been secreted by platelets.[9] Thrombin activated platelets on endothelial cells induced IL-1β and this molecule causes the excretion of IL-1β depended cytokines such as IL-6, IL-8 which are major proinflammatory cytokines in inflammation.[10] Moreover by the agency of IL-1β endothelial cells surface expression of ICAM-1 and αvβ3 raises. Through the ICAM-1 and αvβ3 the migration and adhesion of inflammatory cells became straightforward and accelerated.[11-12]

Activated platelets are also source of cytokines which are called CXCL12, CCL5 (RANTES), CXCL4 (platelet factor 4), CXCL7 (CTAP-III) and CXCL12 (SDF-1). These cytokines are stored in alpha granules and secreted by platelets in inflammation for recruitment of monocytes, PMNL and even progenitor cells to atherosclerotic lesions.[13-15]

EFFECTS OF INFLAMMATION ON PLATELETS

Inflammation is a pathological process which occurs as a result of the division the physiological conditions and may cause such affects like release of cytokines, coagulation substances or growth factors on platelets. Thrombin occurrence one of the adverse affects of inflammation. Tissue factor (TF) has the major role of occurring thrombin in inflammatory process. In the models of experimental bacteremia, blocking tissue factor is completely prevents the formation of thrombin.[16,17] Also, intercalarily decline of normal endothelial function predispose the coagulation in vessels.[18] Sepsis is the closely related to mortality in especially intensive care unit patients that frequent and most important cause of inflammation. The severe sepsis is %11,9 cause of intensive care unit administration.[19] In this patients emerging platelet activating factor (PAF) is very important cytokine that is the linking the coagulation and inflammation process. In clotting PAF induce platelet aggregation in circulatory system on the other hand it mediate elevation of cytokine and eicosanoid secretion in inflammation.[20] Circulating mononuclear cells stimulated by IL-6, platelet-derived-growth factor (PDGF), and monocyte chemmoattractant protein (MCP-1) express TF which is the first step in coagulation.[21] IL-6 depended TF is most occurs in vivo experiments with low dose endotoxemia so the inhibition of IL-6 with specific antibodies eliminate the formation of TF and coagulation.[22] Thrombocytopenia may develop %15-58 of severe sepsis patient. The severity of thrombocytopenia seems to correlate with the severity of disease; but the mechanism is not fully understood.[23,24]

In inflammation C reactive proteins reaches very high levels and this molecule has a variable effect on platelets. In some studies increasing monomeric CRP levels causes inducing aggregatory response, but the native CRP has not any affect like this.[25] Insomuch as enzimatically digested CRP inhibited platelet aggregation and neutrophil adhesion.[26]

A direct relation between bacteria and platelet activation has been demonstrated wide variety in-vitro and in-vivo studies.[27] Especially some specific types of bacteria such as; Staphylococccus epider-

mis, Staphylococccus aureus, Helicobacter pylori, Porphyromonas gingivalis, Enterococcus spp. can cause more activation on platelets.[28-31]

As a result platelets are cells that play an active role in inflammation. They influenced by realizing cytokines and by this way releases some cytokines associated with active inflammation that affect the process. Recent studies suggest that this affect could be seen both pro-inflammatory and anti-inflammatory direction. Especially in intensive care patients, after the severe inflammation caused by sepsis disseminated intravascular coagulation (DIC) occurs. Studies on the cytokines that cause of this fatal situation continue. Finding new mechanisms in pathophysiology of this process and discovering of new molecules that changing course will be able to contribute to the solution of this important question.

REFERENCES

1. Janeway CA, Travers P, Walport M, and Shlomchik M. The immune system in health and disease. 6th ed. 2005, Garland Science Publishing. New York
2. Rather LJ. Disturbance of function (functio laesa): the legendary fifth alen to the four cardinal signs of . 303-22. cardinal sign of inflammation, added by G Celsus. Bull N Y Acad Med 1971; 47(3): 303-22.
3. Maynard DM, Heijnen HF, Horne MK, White JG, and Gahl WA. Proteomic analysis of platelet alphagranules using mass spectrometry. J Thromb Haemost 2007; 5(9): 1945-55.
4. Italiano JE, Richardson JL, Patel Hett S. Angiogenesis is regulated by a novel mechanism: proand antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood 2008;111(3): 1227-33.
5. Nurden AT. Platelets, inflammation and tissue regeneration. Thromb Haemost 2011; 105 (Suppl 1): p.13-33
6. Reed GL. Platelet Secretion, in Platelets, A.D. Michelson, Editor. Elsevier Science 2007; p. 309-18
7. Nathan C. Points of control in inflammation. Nature 2002;420(7):846-52.
8. Gawaz, M. Role of platelets in coronary thrombosis and reperfusion of ischemic myocardium. Cardiovasc Res 2004; 61(3): 498-511.
9. Hawrylowicz CM, Howells GL, Feldmann M. Platelet-derived interleukin 1 induces human endothelial adhesion molecule expression and cytokine production. J Exp Med 1991; 174(6) :785-90.
10. Kaplanski G. Interleukin-1 induces interleukin-8 secretion from endothelial cells by a juxtacrine mechanism. Blood 1994; 84: 4242-8.
11. Gawaz M. Platelets induce alterations of chemotactic and adhesive properties of endothelial cells mediated through an interleukin-1- dependent mechanism. Implications for atherogenesis. Atherosclerosis 2000; 148(12):75-85.
12. Lievens D, von Hundelshausen P. Platelets in atherosclerosis Thromb Haemost 2011;106(5): 827-38.
13. Shi G, Morrell CN. Platelets as initiators and mediators of inflammation at the vessel wall. Thromb Res. 2011;127(5):387-90.
14. Huo Y, Schober A, Forlow SB, et al. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. Nat Med. 2003; 9(3): 61-7.
15. von Hundelshausen P, Weber KS, Huo Y, et al. RANTES deposition by platelets triggers monocyte arrest on inflamed and atherosclerotic endothelium. Circulation. 2001;103(12): 1772-7.
16. Levi M, ten Cate H, Bauer KA, et al. Inhibition of endotoxin-induced activation of coagulation and fibrinolysis by pentoxifylline or by a monoclonal anti-tissue factor antibody in chimpanzees. J Clin Invest 1994;93(1): 114-20.
17. Pixley RA, De LC, Page JD, et al. The contact system contributes to hypotension but not disseminated intravascular coagulation in lethal bacteremia: in vivo use of a monoclonal anti-factor XII antibody to block contact activation in baboons. J Clin Invest 1993;91(1): 61-8.
18. Schouten M, Wiersinga WJ, Levi M. Poll T Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 2008; 83(6): 536-45.
19. Blanco J, Muriel-Bombı´n A, Sagredo V. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. Crit Care 2008; 12(6): 158-72.
20. Zimmerman GA, McIntyre TM, Prescott SM, Stafforini DM The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. Crit Care Med 2002; 30(2):294-301
21. Moons AH, Levi M, Peters RJ. Tissue factor and coronary artery disease. Cardiovasc Res 2002;53(3): 313-25.
22. Franco RF, de Jonge E, Dekkers PE, et al. The in vivo kinetics of tissue factor messenger RNA expression during human endotoxemia: relationship with activation of coagulation. Blood 2000; 96(9) : 554-9.
23. Li Z, Yang F, Dunn S, Kendall A, Gross K, Susan S. Smyth Platelets as immune mediators: Their role in host defense responses and sepsis Thrombosis Research 2011; 127: 184-88
24. Boldt J, Menges T, Wollbru¨ck M et al. Platelet function in critically ill patients. Chest 1994;106(6): 899-903.
25. Potempa LA, Zeller JM, Fiedel BA, Kinoshita CM, Gewurz H. Stimulation of human neutrophils, monocytes, and platelets by modified Creactive protein (CRP) expressing a neoantigenic specificity. Inflammation, 1988; 12(4): 391-405.
26. El Kebir D, Zhang Y, Potempa LA, C-reactive protein-derived peptide 201-206 inhibits neutrophil adhesion to endothelial cells and platelets through CD32. J Leukoc Biol. 2011; 90(6):1167-75.
27. Fitzgerald JR, Foster, TJ, and Cox D.The interaction of bacterial pathogens with platelets. Nat Rev Microbiol 2006. 4(6): 445-57.
28. Youssefian T, Drouin A, Masse JM, Guichard J, Cramer EM. Host defense role of platelets: engulfment of HIV and Staphylococcus aureus occurs in a specific subcellular compartment and is enhanced by platelet activation. Blood 2002;99(11):4021-9.
29. Usui Y, Ohshima Y, Ichiman Y, Ohtomo T, Suganuma M, and Yoshida K. Platelet aggregation induced by strains of various species of coagulasenegative staphylococci. Microbiol Immunol 1991;35(1): 915-26.
30. Usui Y, Ichiman Y, Suganuma M, and Yoshida K. Platelet aggregation by strains of enterococci. Microbiol Immunol 1991; 35(11): 933-42.
31. Byrne MF, Kerrigan SW, Corcoran PA. Helicobacter pylori binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenterology 2003; 124(7): 1846-54.