World Journal of Cardiology

Submit a Manuscript: http://www.f6publishing.com

World J Cardiol 2018 October 26; 10(10): 123-126

DOI: 10.4330/wjc.v10.i10.123

ISSN 1949-8462 (online)

EDITORIAL

T-cells in myocardial infarction: Culprit instigators or mere effectors?

Luca Liberale, Aldo Bonaventura, Fabrizio Montecucco

Luca Liberale, Center for Molecular Cardiology, University of Zürich, Schlieren 8952, Switzerland

Luca Liberale, Aldo Bonaventura, Fabrizio Montecucco, First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, Genoa 16132, Italy

Fabrizio Montecucco, IRCCS Ospedale Policlinico San Martino Genoa - Italian Cardiovascular, Network, 16132 Genoa, Italy

ORCID number: Luca Liberale (0000-0003-1472-7975); Aldo Bonaventura (0000-0002-4747-5535); Fabrizio Montecucco (0000-0003-0823-8729).

Author contributions: Liberale L wrote the manuscript; Bonaventura A and Montecucco F revised the draft and gave suggestions for its improvement.

Conflict-of-interest statement: Liberale L, Bonaventura A and Montecucco F declare no conflict of interest related to this publication.

Manuscript source: Invited manuscript

Correspondence to: Luca Liberale, MD, Postdoctoral Fellow, Doctor, First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, 6 viale Benedetto XV, Genoa 16132, Italy. luca.liberale@uzh.ch
Telephone: +39-10-3537940
Fax: +39-10-3538686

Received: May 29, 2018
Peer-review started: May 29, 2018
First decision: June 14, 2018
Revised: June 20, 2018

Accepted: June 28, 2018
Article in press: June 28, 2018
Published online: October 26, 2018

Abstract

Immune system activation and dysfunction characterize the early phase of reperfusion after a myocardial infarction (MI). Despite initially neglected, adaptive immunity has been recently showed to play an important role in this setting. In fact, the immune system can recognize sequestered antigens released by the necrotic tissue, initiating a deleterious autoimmune vicious circle leading to worse outcome. In their recent work, Angelini *et al* shed the light on a new feature of post-MI which involves two "old players" of post-ischemic myocardial injury: CD31 and matrix metalloproteinase (MMP)-9. Specifically, the authors showed that an enhancement of MMP-9 release could determine the cleavage of inhibitory CD31 from CD4+ T-cells surface in patients with Acute Coronary Syndromes (ACS). These findings open the room for new studies investigating the role of MMP9 in other pathological processes associated with a reduction of CD31 functionality, such as plaque instability and rupture. Of interest, in the case of a causative role for CD31 shedding in ACS would be confirmed, there might be a potential role for the administration of CD31 protein or analogue compounds to blunt post-ischemic cardiac inflammation and improve ACS outcome.

Key words: Matrix metalloproteinase; Lymphocytes; Autoimmunity; Inflammation; Myocardial infarction; Adaptive immunity

Core tip: CD31 and matrix metalloproteinases (MMP)-9 are known mediators that are upregulated during reperfusion after cardiac ischemia. By inhibiting T-cell

receptor-dependent lymphocyte activation, the functional CD31 could reduce post-ischemic inflammatory response; while MMP-9 is deeply involved in inflammatory cell recruitment and myocardial remodeling. A recent paper published in European Heart Journal linked these mediators by showing CD31 cleavage to be MMP-9 dependent in patients with acute coronary syndromes (ACS). Whether this process is causative of ACS or rather its effect still needs to be clarified.

Liberale L, Bonaventura A, Montecucco F. T-cells in myocardial infarction: Culprit instigators or mere effectors? *World J Cardiol* 2018; 10(10): 123-126 Available from: URL: http://www.wjgnet.com/1949-8462/full/v10/i10/123.htm DOI: http://dx.doi.org/10.4330/wjc.v10.i10.123

INTRODUCTION

Acute Coronary Syndromes (ACS)-including unstable angina and myocardial infarction (MI) are the most detrimental atherosclerosis-related complications being the leading causes of mortality worldwide and a considerable source of morbidity[1]. Although outstanding leap forwards of primary and secondary prevention measures, the issue of the residual risk for ischemic complication is still unsolved[2]. Also, it is now well-recognized that after a prompt reperfusion, as it is the case of vast majority of patients suffering from MI, the ischemic hearts need to face an additional damage directly induced by the re-establishment of blood flow itself[3]. The role of innate immunity in the determination of both residual risk and ischemia/reperfusion injury has been studied from decades and is now better established[4-6]. The adaptive immune system (*i.e.*, T-cells and B-cells) have only recently come into focus. Indeed, lymphocytes' ability to react only against specific non-self-antigens, as opposed to the reactivity against non-specific danger signal showed by innate immunity, excluded these mediators from the list of "guilty" parties for a long time. Only recently, the recognition of a role for the release of sequestered antigens from the necrotic tissue in the progressive diversification of autoreactive lymphocytes (*i.e.*, epitope spreading) shed the light on the potential involvement of adaptive auto-reactivity in the determination of post-MI outcome[7]. After an ACS, the necrotic heart tissue releases several danger-associated molecular patterns (DAMPs) together with cardiac intracellular proteins[8,9]. In this highly inflamed micro-environment, cardiac antigens can be recognized by autoreactive lymphocyte clones and trigger autoimmunity processes. Afterward, the same immune-mediated tissue injury supplies the amount of autoantigens necessary to maintain the auto-reactivity thus sustaining the dysfunctional immune cardiac process[9]. This editorial refers to the outstanding research article entitled "matrix metalloproteinases-9 might affect adaptive immunity in non-ST segment elevation ACS by increasing CD31 cleavage on CD4+ cells", recently published by Angelini *et al*[10] in European Heart Journal.

T-CELLS AND ACS

Although several studies have implicated T-cells in the pathophysiology of ACS, the knowledge about their specific role is still elusive. Considering the heterogeneity of T-cell subsets and the quickly evolving local and systemic environment after ACS, a tight regulation of rapidly changing T-cell phenotypes with regulator or effector functions is likely[11]. Experimental evidence highlights infiltrating T-cells as effector lymphocytes which have been antigen-restricted and primed in the heart-draining lymph nodes. Of interest, after ACS, particular subsets of pro-inflammatory CD28- CD4+ and Th17 lymphocytes are released in the blood stream and produce large amounts of interferon-γ and IL-17: Detrimental cytokines with known ability to increase cardiomyocyte death, fibroblast proliferation and pro-fibrotic gene expression[12-14]. Not only detrimental T-cells with effector functions are increased after ACS but they also display dysfunctional features. Indeed, they overexpress CD40 ligand in this way being more easily activated by antigen presenting cells[15]. Furthermore, a direct cytotoxic effect of infiltrating autoreactive CD8+ T-lymphocytes with specificity towards cardiac myosin has been described[16]. To further potentiate the detrimental role of T lymphocytes in the setting of MI, the raise of pro-inflammatory lymphocyte subsets is accompanied by a reciprocal reduction in CD4+CD25+Foxp3+ regulatory T-lymphocytes with a beneficial cardiac protective role[17].

MMP-9 AND CD31: A DANGEROUS ASSOCIATION

Post-transcriptional CD31 modifications showed capacity to affect normal T-lymphocyte function. Indeed, CD31 (also known as platelet endothelial cell adhesion molecule-1) was shown to regulate T lymphocyte activity through the inhibition of T cell receptor (TCR) signalling[18]. Of interest, CD31 extracellular domain is shed from the lymphocyte surface during ACS and this contributes to the over activation of adaptive immunity[19]. In their recent article, Angelini *et al*[10] added one more piece to this puzzle by showing matrix metalloproteinase (MMP)-9 to be involved in CD31 cleavage in lymphocytes from ACS patients. Firstly, they confirm CD31 shedding to be a specific feature of lymphocytes in ACS, as compared to samples from healthy subjects but also patients with stable angina (SA). Then, the authors demonstrated *in vitro* that down-regulation of the functional CD31 domain in ACS is associated with TCR activation and is led by post-transcriptional mechanisms since post-stimulation levels of CD31 mRNA were similar in ACS and SA cells. Finally, after observing CD31 to be a possible substrate for MMP-9 by using an dedicated software predicting novel substrates and their cleavage sites, the auth-

ors show lymphocytes from ACS patients to produce higher enzyme levels after stimulation and CD31 active domain to be preserved by MMP-9 inhibition. Based on these results, the authors propose a new sequence of events that might characterize ACS onset in which the increased release of MMP-9 causes CD31 cleavage, thus affecting TCR-dependent T-cell activation and causing T-cell hyperactivity[10].

PERSPECTIVES

Angelini *et al*[10] added knowledge to the field of dysfunctional adaptive immunity in ACS. At the same time, they raise new appealing questions. In particular, CD31 is known to mediate also endothelial-endothelial interactions, thus allowing the constitution of the continuous and protective intimal cell monolayer[20]. Now, further investigations are advisable to assess whether the inflammation-induced overproduction of MMP-9[21] could reduce these interactions and potentially contribute to endothelial erosion and plaque instability. Under this point of view, CD31 was previously described to target macrophage activation, as well as cytokine and chemokine release within atherosclerotic plaques and aneurysmal peri-aorta[22]. Also, it would be of interest to show CD31 modifications in lymphocytes to take act before ACS onset. In general, this is a very common weakness of studies focused on cellular phenotype during ACS due to the requirement of intact cells for fluorescent-activated sorting which does not allow sample storage before the dosage. Animal studies could help in assessing this causal connection.

Given the fact that CD31 protein or analog molecules are already available[23], answering these questions could point out CD31 replacement as a potential therapeutic approach to blunt inflammation and modulate tissue damage in acute cardiovascular diseases (such as MI and stroke) that are characterized by an impaired adaptive immunity.

REFERENCES

1 **Benjamin EJ**, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD, Ferguson JF, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Lutsey PL, Mackey JS, Matchar DB, Matsushita K, Mussolino ME, Nasir K, O'Flaherty M, Palaniappan LP, Pandey A, Pandey DK, Reeves MJ, Ritchey MD, Rodriguez CJ, Roth GA, Rosamond WD, Sampson UKA, Satou GM, Shah SH, Spartano NL, Tirschwell DL, Tsao CW, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation* 2018; **137**: e67-e492 [PMID: 29386200 DOI: 10.1161/CIR.0000000000000558]

2 **Piepoli MF**, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37**: 2315-2381 [PMID: 27222591 DOI: 10.1093/eurheartj/ehw106]

3 **Yellon DM**, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med* 2007; **357**: 1121-1135 [PMID: 17855673 DOI: 10.1056/NEJMra071667]

4 **Carbone F**, Liberale L, Bonaventura A, Cea M, Montecucco F. Targeting Inflammation in Primary Cardiovascular Prevention. *Curr Pharm Des* 2016; **22**: 5662-5675 [PMID: 27549380 DOI: 10.2174/1381612822666160822124546]

5 **Montecucco F**, Liberale L, Bonaventura A, Vecchiè A, Dallegri F, Carbone F. The Role of Inflammation in Cardiovascular Outcome. *Curr Atheroscler Rep* 2017; **19**: 11 [PMID: 28194569 DOI: 10.1007/s11883-017-0646-1]

6 **Bonaventura A**, Liberale L, Vecchié A, Casula M, Carbone F, Dallegri F, Montecucco F. Update on Inflammatory Biomarkers and Treatments in Ischemic Stroke. *Int J Mol Sci* 2016; **17**: pii: E1967 [PMID: 27898011 DOI: 10.3390/ijms17121967]

7 **Vanderlugt CL**, Miller SD. Epitope spreading in immune-mediated diseases: implications for immunotherapy. *Nat Rev Immunol* 2002; **2**: 85-95 [PMID: 11910899 DOI: 10.1038/nri724]

8 **Lv H**, Lipes MA. Role of impaired central tolerance to α-myosin in inflammatory heart disease. *Trends Cardiovasc Med* 2012; **22**: 113-117 [PMID: 22902177 DOI: 10.1016/j.tcm.2012.07.005]

9 **Liao YH**, Cheng X. Autoimmunity in myocardial infarction. *Int J Cardiol* 2006; **112**: 21-26 [PMID: 16837084 DOI: 10.1016/j.ijcard.2006.05.009]

10 **Angelini G**, Flego D, Vinci R, Pedicino D, Trotta F, Ruggio A, Piemontese GP, Galante D, Ponzo M, Biasucci LM, Liuzzo G, Crea F. Matrix metalloproteinase-9 might affect adaptive immunity in non-ST segment elevation acute coronary syndromes by increasing CD31 cleavage on CD4+ T-cells. *Eur Heart J* 2018; **39**: 1089-1097 [PMID: 29211854 DOI: 10.1093/eurheartj/ehx684]

11 **Bluestone JA**, Mackay CR, O'Shea JJ, Stockinger B. The functional plasticity of T cell subsets. *Nat Rev Immunol* 2009; **9**: 811-816 [PMID: 19809471 DOI: 10.1038/nri2654]

12 **Yan X**, Shichita T, Katsumata Y, Matsuhashi T, Ito H, Ito K, Anzai A, Endo J, Tamura Y, Kimura K, Fujita J, Shinmura K, Shen W, Yoshimura A, Fukuda K, Sano M. Deleterious effect of the IL-23/IL-17A axis and γδT cells on left ventricular remodeling after myocardial infarction. *J Am Heart Assoc* 2012; **1**: e004408 [PMID: 23316306 DOI: 10.1161/JAHA.112.004408]

13 **Liuzzo G**, Biasucci LM, Trotta G, Brugaletta S, Pinnelli M, Digianuario G, Rizzello V, Rebuzzi AG, Rumi C, Maseri A, Crea F. Unusual CD4+CD28null T lymphocytes and recurrence of acute coronary events. *J Am Coll Cardiol* 2007; **50**: 1450-1458 [PMID: 17919564 DOI: 10.1016/j.jacc.2007.06.040]

14 **Liuzzo G**, Kopecky SL, Frye RL, O'Fallon WM, Maseri A, Goronzy JJ, Weyand CM. Perturbation of the T-cell repertoire in patients with unstable angina. *Circulation* 1999; **100**: 2135-2139 [PMID: 10571971 DOI: 10.1161/01.CIR.100.21.2135]

15 **Aukrust P**, Müller F, Ueland T, Berget T, Aaser E, Brunsvig A, Solum NO, Forfang K, Frøland SS, Gullestad L. Enhanced levels of soluble and membrane-bound CD40 ligand in patients with unstable angina. Possible reflection of T lymphocyte and platelet involvement in the pathogenesis of acute coronary syndromes. *Circulation* 1999; **100**: 614-620 [PMID: 10441098 DOI: 10.1161/01.CIR.100.6.614]

16 **Huber SA**, Graveline D, Born WK, O'Brien RL. Cytokine production by Vgamma(+)-T-cell subsets is an important factor determining CD4(+)-Th-cell phenotype and susceptibility of BALB/c mice to coxsackievirus B3-induced myocarditis. *J Virol* 2001; **75**: 5860-5869 [PMID: 11390587 DOI: 10.1128/JVI.75.13.5860-5869.2001]

17 **Han SF**, Liu P, Zhang W, Bu L, Shen M, Li H, Fan YH, Cheng

K, Cheng HX, Li CX, Jia GL. The opposite-direction modulation of CD4+CD25+ Tregs and T helper 1 cells in acute coronary syndromes. *Clin Immunol* 2007; **124**: 90-97 [PMID: 17512253 DOI: 10.1016/j.clim.2007.03.546]

18 **Clement M**, Fornasa G, Guedj K, Ben Mkaddem S, Gaston AT, Khallou-Laschet J, Morvan M, Nicoletti A, Caligiuri G. CD31 is a key coinhibitory receptor in the development of immunogenic dendritic cells. *Proc Natl Acad Sci USA* 2014; **111**: E1101-E1110 [PMID: 24616502 DOI: 10.1073/pnas.1314505111]

19 **Flego D**, Severino A, Trotta F, Previtero M, Ucci S, Zara C, Pedicino D, Massaro G, Biasucci LM, Liuzzo G, Crea F. Altered CD31 expression and activity in helper T cells of acute coronary syndrome patients. *Basic Res Cardiol* 2014; **109**: 448 [PMID: 25344833 DOI: 10.1007/s00395-014-0448-3]

20 **Lertkiatmongkol P**, Liao D, Mei H, Hu Y, Newman PJ. Endothelial functions of platelet/endothelial cell adhesion molecule-1 (CD31). *Curr Opin Hematol* 2016; **23**: 253-259 [PMID: 27055047 DOI: 10.1097/MOH.0000000000000239]

21 **Papazafiropoulou A**, Tentolouris N. Matrix metalloproteinases and cardiovascular diseases. *Hippokratia* 2009; **13**: 76-82 [PMID: 19561775]

22 **Fornasa G**, Clement M, Groyer E, Gaston AT, Khallou-Laschet J, Morvan M, Guedj K, Kaveri SV, Tedgui A, Michel JB, Nicoletti A, Caligiuri G. A CD31-derived peptide prevents angiotensin II-induced atherosclerosis progression and aneurysm formation. *Cardiovasc Res* 2012; **94**: 30-37 [PMID: 22293851 DOI: 10.1093/cvr/cvs076]

23 **Groyer E**, Nicoletti A, Ait-Oufella H, Khallou-Laschet J, Varthaman A, Gaston AT, Thaunat O, Kaveri SV, Blatny R, Stockinger H, Mallat Z, Caligiuri G. Atheroprotective effect of CD31 receptor globulin through enrichment of circulating regulatory T-cells. *J Am Coll Cardiol* 2007; **50**: 344-350 [PMID: 17659202 DOI: 10.1016/j.jacc.2007.04.040]

P- Reviewer: Aksu T, Altarabsheh SE, Dai X, Iacoviello M
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu YXJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com