International Journal of Cardiology 276 (2019) 293–294

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Who is the principal offender?

Koichiro Sugimura

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

ARTICLE INFO

Article history:
Received 19 October 2018
Received in revised form 28 October 2018
Accepted 30 October 2018
Available online 2 November 2018

Keywords:
Atherosclerosis
Acute coronary syndrome
Immune system
Helper T cells

Recently, therapeutic strategy targeted to systemic inflammation has been proved to be effective for atherosclerotic diseases. In CANTOS study, anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering [1]. Immunotherapy, including anti-inflammatory therapy, opens new possibilities in the treatment of atherosclerotic disease.

Progression of atheromatous plaques and focal inflammation has been well established. In atheromatous plaques, both innate and adaptive immune responses play important roles for the progression.

Additionally, systemic immunity has been reported to have close associations with destabilization of atherosclerotic plaque and the onset of acute coronary syndrome.

Helper T cells (CD4+ lymphocytes) are the key regulators of adaptive immunity. The main helper T-cell subsets are the TH1, TH2, TH17, and follicular helper (TFH) CD4+ T cells. In this subset of patients with ACS, helper T-cell imbalance might contribute to plaque destabilization through multiple pathways.

Regulatory T cell (Tregs) induces immunosuppression through multiple mechanisms, including inhibition of dendritic cell maturation and function [2]. In patients with ACS, several reports showed low levels of circulating Tregs [3,4].

TH17 cells are characterized by the master regulator transcription factor responsible for IL-17 production. The TH17 subset is expanded in patients with ACS [5], and the TH17/Treg balance might play a role in the development of inflammatory disorders, including atherosclerosis, and autoimmune diseases. However, in a cohort of patients with ACS, lower serum levels of IL-17 were associated with a higher risk of major cardiovascular events [6].

CD4þ+CD28null T cells are distinct from classic helper T cells in several respects. The pro-inflammatory functions of CD4+CD28null T cells include the production of high levels of IFN-g, tumor necrosis factor alpha (TNF-a). They also express cytotoxic molecules such as granzyme B and perforin, which enable them to kill endothelial cells and smooth muscle cells [7], and expand in several diseases associated with chronic inflammation. The frequency of CD4+CD28null T cells significantly increases the risk of ACS [8].

Liuzzo G et al. firstly showed that a higher CD4+CD28null frequency and a higher CD4+CD28null/Treg ratio in non-ST elevation myocardial infarction patients with ruptured fibrous cap, and inverse correlation between CD4+CD28null/Treg ratio and cap-thickness, by OCT imaging analysis and flow-cytometry. Cytotoxic function of CD4+CD28null T cells could enhance the inflammatory response and contribute to atherosclerotic plaque destabilization. However, one study failed to replicate the differences in frequency of CD4+CD28null T cells from ACS and controls patients [9]. Then, previous report showed that Th17/Treg functional imbalance exists in patients with ACS, suggesting a potential role for Th17/Treg imbalance in plaque destabilization and the onset of ACS [10]. Although the direct comparison in the role of CD4+CD28null T cells and Th17 cells for instability of atheromatous plaque was not examined in this study, it could be said that the imbalance of immune system may play important roles for development and destabilization of atherosclerotic plaque.

Therefore, a prospective study could be needed to confirm whether is the principal offender for risk of developing, having, or experiencing ACS. Immune therapy may open the new way in the management for arteriosclerotic diseases.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[2] S. Sakaguchi, M. Ono, R. Setoguchi, et al., Foxp3$^+$ CD25$^+$ CD4$^+$ natural regulatory T cells in dominant self-tolerance and autoimmune disease, Immunol. Rev. 212 (2006) 8–27.
[3] A. Mor, G. Luboshits, D. Planer, et al., Altered status of CD4$^+$CD25$^+$ regulatory T cells in patients with acute coronary syndromes, Eur. Heart J. 27 (2006) 2530–2537.

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.08.101.
E-mail address: ksugimura@cardio.med.tohoku.ac.jp.

https://doi.org/10.1016/j.ijcard.2018.10.109
0167-5273/

[4] S.F. Han, P. Liu, W. Zhang, et al., The oppositedirection modulation of $CD4^+CD25^+$ Tregs and T helper 1 cells in acute coronary syndromes, Clin. Immunol. 124 (2007) 90–97.
[5] Y. Zheng, Z. Wang, L. Deng, et al., Modulation of STAT3 and STAT5 activity rectifies the imbalance of Th17 and Treg cells in patients with acute coronary syndrome, Clin. Immunol. 157 (2015) 65–77.
[6] T. Simon, S. Taleb, N. Danchin, et al., Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction, Eur. Heart J. 34 (2013) 570–577.
[7] T. Namekawa, M.R. Snyder, J. Yen, et al., Killer cell activating receptors function as costimulatory molecules on $CD4^+CD28^{null}$ T cells clonally expanded in rheumatoid arthritis, J. Immunol. 165 (2000) 1138–1145.
[8] G. Liuzzo, R.A. Montone, M. Gabriele, et al., Identification of unique adaptive immune system signature in acute coronary syndromes, Int. J. Cardiol. 168 (2013) 564–567.
[9] F.H. Téo, R.T. de Oliveira, R.L. Mamoni, et al., Characterization of $CD4^bCD28^{null}$ T cells in patients with coronary artery disease and individuals with risk factors for atherosclerosis, Cell. Immunol. (1) (2013) 11–19.
[10] X. Cheng, X. Yu, Y.J. Ding, et al., The Th17/Treg imbalance in patients with acute coronary syndrome, Clin. Immunol. 127 (2008) 89–97.