International Journal of Cardiology 297 (2019) 118

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Letter to the Editor

The therapeutic potential of targeting CD40-TRAF6 pathway in cardiovascular diseases

Peng Zhong, Minxiao Chen, Bin Kong, Hui Fu, Jingjing Zhang, He Huang *

Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan 430060, China
Cardiovascular Research Institute of Wuhan University, Wuhan 430060, China
Hubei Key Laboratory of Cardiology, Wuhan 430060, China

ARTICLE INFO

Article history:
Received 20 July 2019
Accepted 2 August 2019

Keywords:
CD40
TRAF6
Inflammation
Cardiovascular diseases

Dear Editor:

The costimulatory CD40-CD40L receptor/ligand dyad is a well-known driver of atherosclerosis and other chronic inflammatory diseases [1]. However, long-term inhibition of CD40 or CD40L results in immune suppression and/or thromboembolic events, and is therefore not feasible as a therapy [2].

Upon activation, CD40 can recruit tumor necrosis factor receptor-associated factors (TRAFs) to elicit intracellular signaling [3]. The C-terminal tail of CD40 has a distal binding site that can bind TRAF2, TRAF3, and TRAF5, and a proximal binding site for TRAF6. Genetic site mutation study showed that the beneficial effects of targeting CD40 in inflammatory disease such as atherosclerosis can be attribute to the blockage of CD40-TRAF6 interaction, and the immune suppression effects is attributed to the blockage of the CD40-TRAF2/3/5 interaction [3,4]. Therefore, targeting specifically to the CD40-TRAF6 pathway could be a better strategy in inflammatory diseases without disturbing the CD40-associated immunity [3].

Very recently, targeting CD40-TRAF6 pathway by small molecule inhibitors was further demonstrated to reduce adverse cardiac remodeling in pressure overload-induced heart failure (HF) which is published in *international journal of cardiology* [5]. In this study, inhibition of CD40-TRAF6 interaction improved cardiac function and structural remodeling in TAC-induced HF mice model, which is associated with a reduction in macrophage and T-cells influx in the myocardium [5]. These results indicated a pathogenic role of CD40-TRAF6 signaling in pathological cardiac conditions by recruiting immune cells and inflammatory cells into myocardium.

Taken together, these studies demonstrated that targeting CD40-TRAF6 interaction will be a potential strategy in the prevention and treatment of cardiovascular diseases.

Declaration of Competing Interest

The authors declare that there is no duality of interest associated with this manuscript.

Acknowledgements

This work was supported by the financial support from Wuhan University (Grant number: 2042019kf0074) and National Natural Science Foundation of China (Grant number: 81500657).

References

[1] T.T.P. Seijkens, C.M. van Tiel, P.J.H. Kusters, D. Atzler, O. Soehnlein, B. Zarzycka, et al., Targeting CD40-induced TRAF6 signaling in macrophages reduces atherosclerosis, J. Am. Coll. Cardiol. 71 (2018) 527–542.
[2] C. Ahonen, E. Manning, L.D. Erickson, B. O'Connor, E.F. Lind, S.S. Pullen, et al., The CD40-TRAF6 axis controls affinity maturation and the generation of long-lived plasma cells, Nat. Immunol. 3 (2002) 451–456.
[3] E. Lutgens, D. Lievens, L. Beckers, E. Wijnands, O. Soehnlein, A. Zernecke, et al., Deficient CD40-TRAF6 signaling in leukocytes prevents atherosclerosis by skewing the immune response toward an antiinflammatory profile, J. Exp. Med. 207 (2010) 391–404.
[4] M.M. Donners, L. Beckers, D. Lievens, I. Munnix, J. Heemskerk, B.J. Janssen, et al., The CD40-TRAF6 axis is the key regulator of the CD40/CD40L system in neointima formation and arterial remodeling, Blood 111 (2008) 4596–4604.
[5] L. Bosch, J. de Haan, T. Seijkens, C. van Tiel, M. Brans, G. Pasterkamp, et al., Small molecule-mediated inhibition of CD40-TRAF6 reduces adverse cardiac remodelling in pressure overload induced heart failure, Int. J. Cardiol. 279 (2019) 141–144.

* Corresponding author at: Department of Cardiology Research Institute, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan, 430060, Hubei, China.
E-mail address: Huanghe1977@whu.edu.cn (H. Huang).

https://doi.org/10.1016/j.ijcard.2019.08.008
0167-5273/© 2019 Elsevier B.V. All rights reserved.