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Commentary

Cardiac Troponin I autoantibodies and their potential role in cardiac remodelling

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In this article of *EBioMedicine*, Wu et al. were able to identify Enolase 1 (ENO 1) located on the membrane of cardiomyocytes as potential target of cardiac Troponin I autoantibody (cTnIAAb) derived from acute myocardial infarction (AMI) patients [1]. In mice and in *in vitro* models, the authors were able to identify apoptosis signalling pathways mediated by cTnIAAb. These novel insights in the contribution of cTnIAAbs to the pathogenesis of AMI related ventricular remodelling were ascribed to ENO 1 mediated Phosphatase and Tensin homolog (PTEN) and Akt signalling pathway. Taken together, these insights in cTnIAAb mediated myocardial dysfunction could contribute to a better understanding of the pathophysiological relevance triggered by cTnIAAb in at least some AMI patients, indicating a new role and potential clinical implications of cTnIAAbs. The results of Wu et al. offer the possibility to investigate new potential therapeutic targets such as ENO 1 in cTnIAAb positive AMI patients. To understand the importance of their findings, we need to examine current knowledge of cTnIAAbs in basic research as well as in clinical practice.

In basic research, the important role of cTnIAAb was first described in 2003 by Okazaki et al.. They were able to identify cTnIAAb causing dilated cardiomyopathy (DCM) phenotype in mice. However, they could not observe signs of inflammation [2]. The study of Wu et al. showed similar results [1]. The authors did not observe any infiltration of immune cells after administration of cTnIAAb *in vivo* as well. In contrast to studies investigating the effect of cTnIAAb, Göser et al. showed that immunization of susceptible mice with whole cTnI autoantigen led to formation of cTnIAAb inducing subsequent inflammatory response and fibrosis in a DCM dependent manner [3]. Moreover, preimmunization of mice with cTnI prior to left anterior descending coronary artery ligation led to greater infarct size, more fibrosis and inflammation, indicating the negative role of cTnIAAbs in development of post AMI remodelling effects in mice models [3,4].

Prior to the results presented by Wu *et al.*, exact pathomechanisms of cTnIAAb leading to fibrosis and myocardial dysfunction were unknown. Okazaki *et al.* attributed their observed effects to Ca^{2+} overload of cardiomyocytes, caused by augmented Ca^{2+} influx via L-Type Ca^{2+} channels [2]. In contrast to that, Wu *et al.* provide a new mechanism of cTnIAAb by affecting PTEN and Akt signalling via ENO 1 binding [1]. Thus, the authors pointed out the relevance of apoptosis, a highly regulated kind of cell death, mediated via cTnIAAb. So far, less was known about contribution of cTnIAAbs to the process of apoptosis. Though, the involvement of other cardiac autoantibodies in apoptosis was already described. It has been shown that anti-myosin autoantibodies cross react with beta adrenoceptor causing myocardial dysfunction and apoptosis of cardiomyocytes [5].

In addition to studies in mouse models, the importance of apoptosis for the development of cardiovascular diseases in human was already described. Hence, in patients developing post AMI heart failure, apoptosis contributes to ventricular remodelling [6]. Wu et al. showed that activation of apoptotic signalling pathways in AMI patients could be attributed to the binding of cTnIAAb to ENO 1 [1]. However, so far clinical implications of cTnIAAb positive tested post AMI patients remained widely unclear, due to conflicting results from clinical studies [5]. Clinical observations, which emphasize the pathomechanism identified by Wu et al., were published by Leuschner et al.. They reported an impairment of LVEF in AMI cTnIAAb positive patients compared to patients tested negative against cTnIAAbs. Hence, Leuschner et al. suggest a negative role of cTnIAAbs in ventricular remodelling after AMI [7]. In 2017, Fan et al. also reported that cTnIAAbs are independent predictors of left ventricular remodelling in patients with ST-elevation myocardial infarction [8]. Due to the unknown mechanisms underlying these effects, the clinical relevance for cTnIAAb positive AMI patients remained unclear [9]. However, findings reported by Wu et al., who identified cTnIAAb to be involved in apoptosis, could explain the negative effects observed for cTnIAAb positive patients. Thus, the study of Wu et al. strengthens the clinical impact of cTnIAAbs.

In conclusion, the mechanistical insights provided by Wu et al. could help getting a better understanding of post AMI remodelling effects mediated *via* cTnIAAb. Thus, ENO 1 or direct interceptions of cTnIAAbs in post AMI patients represent a potential therapeutic target, which could also have a clinical relevance. However, further investigations such as clinical studies are needed to elucidate the role of cTnIAAbs in cardiac remodelling.

Authors' contribution

All authors contributed equally to this work.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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References

[1] Wu Y, Qin Y-h, Liu Y, Zhu L, X-X Zhao, Y-Y Liu, et al. Cardiac troponin I autoantibody induces myocardial dysfunction by PTEN signaling activation. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.08.045.
[2] Okazaki T, Tanaka Y, Nishio R, Mitsuiye T, Mizoguchi A, Wang J, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. Nat Med 2003;9(12):1477–83.
[3] Goser S, Andrassy M, Buss SJ, Leuschner F, Volz CH, Ottl R, et al. Cardiac troponin I but not cardiac troponin T induces severe autoimmune inflammation in the myocardium. Circulation 2006;114(16):1693–702.
[4] Volz HC, Buss SJ, Li J, Goser S, Andrassy M, Ottl R, et al. Autoimmunity against cardiac troponin I in ischaemia reperfusion injury. Eur J Heart Fail 2011;13(10):1052–9.
[5] Kaya Z, Leib C, Katus HA. Autoantibodies in heart failure and cardiac dysfunction. Circ Res 2011;110(1):145–58.
[6] Abbate A, Biondi-Zoccai GG, Bussani R, Dobrina A, Camilot D, Feroce F, et al. Increased myocardial apoptosis in patients with unfavorable left ventricular remodeling and early symptomatic post-infarction heart failure. J Am Coll Cardiol 2003;41(5):753–60.
[7] Leuschner F, Li J, Goser S, Reinhardt L, Ottl R, Bride P, et al. Absence of auto-antibodies against cardiac troponin I predicts improvement of left ventricular function after acute myocardial infarction. Eur Heart J 2008;29(16):1949–55.
[8] Fan Y, Chen Y, Wan Z, Zhou D, Ma A. The prognostic value of autoantibodies against beta1-adrenoceptor and cardiac troponin-I for clinical outcomes in STEMI. J Cardiovasc Med (Hagerstown) 2017;18(1):34–41.
[9] O'Donohoe TJ, Ketheesan N, Schrale RG. Anti-troponin antibodies following myocardial infarction. J Cardiol 2017;69(1):38–45.