Prognostic evaluation of soluble CD40L in acute myocardial infarction: is not fancy, is science!

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Provenance: This is a Guest Correspondence by Section Editor Zhijun Han, MD (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

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Acute myocardial infarction (AMI) is a critical clinical presentation of coronary artery disease (CAD). As pointed out previously by us (1), major clinical research efforts have been dedicated to the identification of patients at higher risk and to the diagnosis of CAD and AMI. Although a great pool of information concerning systemic inflammation markers have been so far collected in different cardiovascular conditions, the evolution of AMI is not well depicted (1).

CD40 ligand (CD40L) is a signalling molecule (2), implicated in thrombosis and inflammatory response to vascular injury (3). CD40L binds to CD40 a member of tumour necrosis factor family of cell surface interaction molecules. Both proteins are expressed on many immune cells, such as lymphocytes, monocytes, dendritic cells, neutrophils, and mast cells, and on non-immune cells, such as platelets and vascular cells (2). CD40L, its soluble form sCD40L, and membrane-bound CD40 determine the inflammatory or immune response through secondary messengers, such as cytokines, chemokines and transcription factors (2,4), orchestrating the activation and recruitment of different leukocyte subsets to the vessel wall and inflammation sites (5).

Previous studies have demonstrated that both soluble and bound forms of CD40L exert several roles in atherothrombosis other than simply supporting cell adhesion. Henn *et al*. (6) proposed that *in vivo*, once platelets were strongly activated in the vascular system, CD40L would be rapidly expressed on aggregating cells and available to interact with CD40 on the neighbouring endothelial cells and on monocytes trapped in the thrombus. Furthermore, CD40L could also have a direct participation in the thrombotic process either in thrombus stabilization (7) or in its formation at the infarct-related artery (8). Several studies showed high affinity of soluble CD40L (sCD40L) and CD40L for CD40 when TNF-α receptors and integrins are expressed (7). sCD40L is also a ligand of glycoprotein (GP) IIb/IIIa, and its release from activated platelets can be blocked by GP IIb/IIIa antagonists (9,10), suggesting a control of sCD40L release by interrupting platelet CD40L/GP IIb/IIIa axis. sCD40L can induce the formation of platelet aggregates, and therefore a role in the coordination of different cell types interactions could be proposed to CD40L (11).

In the context of CAD several *in vitro* studies evidenced the relevance of CD40L/sCD40L in endothelial dysfunction (4,6,10), activation of different types of vascular cells (12), leukocyte trafficking and homing (5), among other distinctive processes of the atherosclerotic pathology.

Although a great pool of information concerning CD40L

(membrane-bound and soluble forms) have been so far collected in different cardiovascular conditions, the onset of AMI and its evolution was not well depicted until our articles had been published (13,14).

In the Editorial "*Measuring soluble CD40 ligand: it is a fancy prognostic biomarker in STEMI-patients?*" A. Dominguez-Rodriguez does not question the validity of our results or our methods.

The editorial comment gives indications on what a biomarker should be, and recommends that scientific research should be limited, suggesting that the existence of previous indicators can not justify the search for new and better ones.

The author also declares that indicators to evaluate myocardial infarction already exist, such as cardiac troponin and brain natriuretic peptide. We agree that these two indicators are indeed clinically valuable. However, a large body of literature has shown that they have a limited prediction capacity, whether in terms of risk, infarction severity or myocardial recovery.

Extensive research efforts have been put forward to discover new biomarkers with prognostic potential to assess myocardial infarction patients, including sCD40L. However, before our recent study (13,14) results were not conclusive.

Without being "ultra-enthusiastic", as claimed in Dominguez-Rodriguez comment, we believe that our work provides a novel approach to this problem, paving the way to a previously unforeseen line of research, which seems to be very promising.

Indeed, the results of our previous research (13,14) have shown that sCD40L has the characteristics of a true bioindicator, in the sense that:

(I) the magnitude of sCD40L concentrations correlates with different clinical conditions, clearly differentiating patient evolution after myocardial infarction;

(II) sCD40L enables us to predict the disease evolution, which is not accomplished by the previous bioindicators.

We therefore think that we have given a valuable and honest contribution to this field, and we do not understand the statements or the purpose of these Comments.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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