Mannose-binding lectin: an ancient molecule with new implications in myocardial infarction

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This editorial refers to ‘Influence of functional deficiency of complement mannose-binding lectin on outcome of patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention’†, by M. Trendelenburg et al., on page 1181

The earliest possible revascularization of the occluded vessel and reperfusion of the ischaemic tissue is currently the most effective therapy for ST-segment elevation myocardial infarction (STEMI). Prompt reperfusion is a key determinant of infarct size, which again is a major predictor of morbidity and mortality in STEMI patients. Advances in percutaneous coronary intervention (PCI) technology and especially in peri-interventional anticoagulation strategies have significantly improved the outcome of these patients in the past years. However, still ~6% of patients do not survive to hospital discharge, and the identification of such patients at increased risk remains difficult and the necessary therapeutic consequences unclear.1 However, it becomes increasingly evident that early reperfusion alone is insufficient to prevent myocardial damage and prevent STEMI-related mortality. Furthermore, interventional revascularization after temporary ischaemia itself causes additional tissue damage and cell death, an important phenomenon referred to as myocardial ischaemia/reperfusion (I/R) injury. Despite restoration of epicardial flow, reperfusion triggers endothelial and cardiomyocyte damage that impairs myocardial perfusion and cardiac function, and may eventually contribute more to myocardial damage than the ischaemic event itself.2 The principles of I/R injury were first described by Jennings et al. in the 1960s,3 4 and since then a great amount of research has been conducted to elucidate the underlying mechanisms of this phenomenon, that might lead to the development of adjuvant cardioprotective therapies. Several contributing pathophysiological pathways have been described in small animal models. Yet, none of the biochemical markers or the deduced therapeutic strategies has progressed from an experimental setting into clinical practice, emphasizing the complexity of I/R injury.

Trendelenburg and co-workers from the University Hospital in Basel, Switzerland, have presented data from 890 acute STEMI patients that show a significantly lower mortality in patients with low serum levels of the pattern recognition molecule mannos-binding lectin (MBL).3 Their study used stored serum samples from the placebo-treated control population from the multicentre APEX-AMI trial6 thereby enabling a simple study set-up and a large patient number. The APEX-AMI trial investigated the use of the monoclonal antibody fragment pexelizumab vs. placebo in addition to angioplasty in 5745 STEMI patients. While treatment with this complement inhibitor disappointingly failed to improve the clinical endpoints, the trial enabled several interesting spin-off studies on different prognostic factors in the well-characterized study population.2

The clinical findings presented by Trendelenburg et al.3 support previous experimental studies in mice6 and gain clinical relevance by the possibility of performing a risk stratification based on a relatively simple enzyme-linked immunosorbent assay (ELISA) and the strong suggestion that MBL might serve as a therapeutic target in patients with genetically determined high MBL levels.

MBL, also referred to as mannos-binding protein, is a soluble factor encoded by the MBL2 gene and secreted by the liver. It is a member of the collectin family of proteins that share a collagen-like region and a lectin region, and consists of three 248 amino acid subunits that assemble into the biologically active oligomer.

As a pattern recognition molecule and part of the innate immune system, it recognizes terminal mannose groups in a variety of bacteria, resulting in opsonization. It plays an important role in this evolutionarily conserved defence strategy that prevents host infection by other organisms in an unselective manner.5

In 1976 a group of young children was described that suffered from recurrent infections due to genetically determined low MBL levels,10 suggesting that this molecule has importance in the transition of maternal antibody protection and acquired immunity. Functional MBL levels are determined by three point mutations that interfere with the oligomerization of the protein11 and a further polymorphism in the promoter region of the gene. Interestingly, between 5% and 25% of adults have genetically determined low MBL levels and are generally not immunocompromised.

The study presented by Trendelenburg et al. now strongly suggests a protective effect of such an innate immunodeficiency...
in the setting of acute myocardial infarction. This is in good concordance with several basic research studies in the field that demonstrate a harmful role of the innate immune system in myocardial I/R injury. Recently, Toll-like receptors were shown to be essential mediators of ischaemic cardiomyopathy and I/R injury, which could be attenuated in mice by treatment with specific anti-TLR2 antibodies.12,13

The study of Trendelenburg et al.5 now adds MBL to the promising potential therapeutic targets from the group of pattern recognition molecules, to improve patient outcome in addition to revascularization.

Although the difference in mortality between patients with MBL deficiency (here defined as <100 ng/mL) and patients with MBL levels above this cut-off is impressive (0.79% vs. 5.5% mortality), many questions remain that this observational study cannot answer.

First of all, the effect of MBL deficiency does not fit into the classical concept of I/R injury, as no direct evidence of decreased myocardial damage could be detected: creatine kinase (CK) and CK-MB levels did not differ between the two populations and the clinical benefit was limited to the endpoint of mortality alone, but was not detectable in the combined endpoint of death, shock, and congestive heart failure. The authors hypothesize that low MBL levels reduce the rate of fatal arrhythmias, whereas the degree of heart failure remains unchanged (Figure 1). Presuming that the underpowered isolated mortality endpoint is sustained in other studies, this hypothesis lacks experimentally proven mechanistic support at the moment. In addition, although Trendelenburg et al. provide some data on altered complement activation in their study population, the basic mechanisms of the protective effect of low MBL levels remain unclear and leave much room for basic research in this field. Based on their results, a true causality between MBL levels and mortality cannot be deduced and one has to remember that the MBL level was just one of many factors that the APEX-AMI investigators correlated with mortality in their study population. Therefore, a chance result is still possible despite the statistical significance achieved.

Trendelenburg and his co-workers are to be congratulated on their exciting results and it is very likely that we, as cardiologists, will soon have to familiarize ourselves more with the basic concepts of innate immunity, as the importance of this ancient defence mechanism in our myocardial infarction patients becomes increasingly evident.

Conflict of interest: none declared.

References