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EDITORIAL COMMENT

Cardiac Myosin Protein C

New Roles, New Questions, Potential Opportunities*

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Over the past decade, remarkable advances in our understanding of innate and adaptive immunity have revealed that the immune system centrally regulates the pathogenesis of many cardiovascular diseases conventionally not viewed as primarily inflammatory in nature. Adaptive immunity is a specialized immune response that involves the generation of antigen-specific T-cell subsets and antibodies produced by B cells. The contribution of T cells has been recognized as critical to cardiovascular conditions such as cardiac remodeling and heart failure (HF), and B cell-mediated production of autoantibodies (AAbs) has emerged as another potential mechanism contributing to HF development and progression (1).

The heart stays protected from immune responses to self-antigens through immune tolerance mechanisms to cardiac-specific antigens. These mechanisms involve intricate crosstalk between antigen-presenting cells and $CD4^+$ T cells, resulting in deletion of autoreactive T cells. We are beginning to understand how disruption of such processes allows exposure of cardiac proteins that are no longer being recognized as "self" and thus activate the adaptive immune response to trigger inflammation. This appears to occur when the supply of cardiac self-antigens increases after a myocardial insult, resulting in persistent induction of antigen-specific T cells that induce B cell production of AAbs to such antigens (2) and likely contribute the intensity of inflammation in myocardial structures found in patients with HF.

Myocardial injury post-ischemia has been thought to be the predominant initiating event triggering cardiac protein release and subsequent induction of AAbs. However, several studies have reported the presence of circulating AAbs critically linked to HF in patients with dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), 2 conditions not usually associated with ischemic injury. As suggested in a prospective human study, circulating AAbs to cardiac antigens can precede disease manifestation and may independently predict DCM development (3). Antibodies targeted to several cardiac proteins, including troponin I and beta adrenergic receptors, among others, have been identified in patients with DCM, HCM, and ischemic HF (1). Additionally, removal of AAbs by immunoadsorption may be of therapeutic benefit as demonstrated in trials focused on nonspecific removal of AAbs. However, the presence of anti-cardiac protein-specific AAbs may not always be harmful because some antibodies seem to be protective in chronic HF (4). Thus, there is a clear need to identify new AAbs in specific HF populations to predict patient outcomes or treat specific patient populations.

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In this issue of *JACC: Basic to Translational Science*, Lynch et al. (5) explore whether cardiac myosin binding protein C (cMyBP-C), a sarcomeric regulatory protein that controls cardiac contractile and relaxation functions, can serve as an early indicator of

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cardiac dysfunction and patient outcome in acute coronary syndrome (ACS). The original investigations of cMyBP-C in human disease identified truncation mutations of cMyBP-C as causative in HCM and in cases of familial DCM. Post-translational modification of cMyBP-C tightly regulates systolic and diastolic functions, and dysregulation of cMyBP-C can reduce cardiac function. More recently, the authors and others have demonstrated that cMyBP-C can be degraded and released into the circulation post myocardial infarction in rodent models, as well as in a small cohort of patients with ST-segment elevation myocardial infarction (STEMI) (6). These observations set the stage for the current observational study by Lynch et al. (5). In an elegant set of studies using serum samples from patients with ACS, DCM, and HCM and from donors with no cardiovascular disease, the authors used enzyme-linked immunosorbent analysis (ELISA) to measure circulating levels of AAbs to full length cMyBP-C as well as to multiple different purified cMyBP-C fragments. Preadsorbtion studies with cMyBP-C fragments demonstrated that incubation of antigenic fragments with patients' sera reduced ELISA reactivity, confirming specificity of the assay. The presence of specific AAbs titers to such proteins was then associated with different clinical variables. The authors found that AAbs to full-length cMyBP-C can be detected in all groups, although with higher prevalence (72.3%) in patients hospitalized with ACS. Additionally, all groups presented AAbs to the C3-C10 domains of cMyBP-C but not for the N-terminal domains. Remarkably, whereas AAb titers were strongly associated with decreased left ventricular ejection fraction (LVEF), increased levels of biomarkers of tissue damage (myoglobin) and increased filling pressures (N-terminal pro-B-type natriuretic peptide 1 [NT-proBNP1]) in ACS patients, no significant associations could be established between clinical variables such as LVEF and AAb titers, to either full length cMyBP-C or its fragments in patients with HCM or DCM. Within the ACS group, the authors additionally demonstrated a strong association between high cMyBP-C AAb titers, specifically those to C3-C10 fragments, with decreased LVEF in STEMI patients but not in non-STEMI. Notably, AAbs to 2 or more fragments correlated with increased levels of troponin I at day 1 post MI in ACS patients. The authors suggest that cMyBP-C AAbs are associated with cardiac damage and worsened cardiac function in patients with ACS upon arrival to the emergency department immediately post MI.

The significance and novelty of this study stem from, first, the identification of the most common antigenic regions of human cMyBP-C; second, from the establishment of normal ranges of cMyBP-C AAbs in humans; and third, from their association with several clinical variables specific for ACS patients, and even more so in patients that could be classified as STEMI, compared to patients negative for AAbs in such regions. This study identified equally intriguing basic science and clinical questions for future investigation. On the basic and mechanistic front, what causative role might AAbs to cMyBP-C play in the pathophysiology of cardiac dysfunction and HF after MI? Also, if they do contribute to this, could they serve as potential targets of novel therapies? The authors take care in their interpretation not to equate their observed correlations of cMyBP-C AAb levels with necessarily causing reduced LVEF. Perhaps AAbs to the C terminus of cMyBP-C serve simply as markers of more cMyBP-C cellular release and, thus, of larger areas of ischemic myocardium, which could potentially explain some of the correlation of cMyBP-C AAbs with reductions in LVEF. On the other hand, these findings could suggest an alternate possibility that AAbs to cMyBP-C might actually play a role in cardiac dysfunction. If so, targeted immunoadsorption to cMyBP-C-reactive AAbs to specific fragments could be of potential therapeutic interest.

From the clinical research perspective, the correlation between select cMyBP-C AAbs and markers of reduced LV systolic function and decompensation after MI also raises important future diagnostic questions. For example, risk assessment for post-STEMI complications such as HF and sudden death remains imperfect, and improved prediction of these outcomes could potentially guide decision making for management of these patients. Moreover, in an era when HF after MI predicts poor outcomes and readmission with HF affects important quality metrics, any refinements in our ability to identify and stratify HF risk after MI could prove valuable. It remains unknown whether cMyBP-C AAbs may provide this information, but testing this should be relatively straightforward.

Although these results represent an important first step to using ELISA detection of AAbs to cMyBP-C fragments as early biomarkers for patient outcome, there are some limitations inherent in the nature of this study with patient samples. Current efforts are being made to evaluate the prevalence, model of action, and potential therapeutic modulation of AAbs. The complexity of cardiac damage involves several antigenic proteins being released that induce self-reactive T cells and AAbs, with complex mechanisms of action within the heart. Thus, we can expect information in the near future regarding the antigenic

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capabilities and mechanistic actions of cMyBP-C and its fragments in the B cell immune response in early and in later stages post MI once healing has taken place and patients may develop HF. Despite these, Lynch et al. (5) clearly demonstrate the exciting translational potential of cMyBP-C AAbs to improve the basic understanding of adaptive immune mechanisms in heart disease and to serve as an early biomarker for the prediction of cardiac function and patient outcome in patients with ACS.

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