Inflammatory Biomarkers in Acute Coronary Syndromes
Part IV: Matrix Metalloproteinases and Biomarkers of Platelet Activation
Ehrin J. Armstrong, MD, MSc; David A. Morrow, MD, MPH; Marc S. Sabatine, MD, MPH

This final part of our review series addresses matrix metalloproteinases (MMPs) and biomarkers of platelet activation and concludes with a general discussion of biomarkers in acute coronary syndromes (ACS).

Metalloproteinases
MMPs are zinc-dependent endopeptidases with collagenase and/or gelatinase activity (Table). Degradation of collagen fibrils compromises plaque stability and the integrity of the endothelial basement membrane, predisposing advanced atheromas to rupture.1

MMP-1, -2, and -9
MMP-1, a collagenase expressed in the interstitium, is quickly upregulated in animal models of coronary ischemia/reperfusion. MMP-2 is a gelatinase capable of degrading type IV collagen, the major collagen of the subendothelial basement membrane. MMP-9 is a gelatinase widely implicated in ventricular remodeling and the development of heart failure.2

MMPs are highly expressed in atherosclerotic plaques, with selective enrichment at the shoulder regions.3 Patients with ACS have increased plasma levels of MMP-1, -2, and -9.4 The time course of elevation is highly variable: some groups have found that MMP-1, -2, and -9 levels are not elevated at presentation but that they increase during the subsequent 7 to 14 days.5 Other groups have reported no significant elevation in MMP-2 but a rapid rise and fall of MMP-9 within the first week after ACS.

Few data exist on the association, if any, between MMP levels during ACS and cardiovascular outcomes. In a study of 24 patients with ACS, elevations in MMP-1 at 7 and 14 days after ACS were negatively correlated with left ventricular ejection fraction.6 The slow elevation of MMP levels after ACS and the lack of clinical outcome data do not currently make MMPs useful biomarkers for therapeutic decision making or risk stratification in ACS. They do, however, remain an active area of investigation as a therapeutic target.

Pregnancy-Associated Plasma Protein A
Pregnancy-associated plasma protein A (PAPP-A) was originally described as a peptide specifically elevated in pregnancy, and it is often used as a first-trimester screening tool for chromosomal abnormalities. Biochemically, PAPP-A is a zinc-binding metalloproteinase that indirectly activates insulin-like growth factor (IGF), a potent mitogen and chemotactic agent for vascular smooth muscle cells.7 Because inhibition of IGF signaling has been shown to delay atherosclerosis,8 it is possible that PAPP-A indirectly promotes atherosclerosis and/or restenosis by increasing the activity of IGF. Consistent with this hypothesis, increased PAPP-A levels after angioplasty have been implicated as a possible mechanism for restenosis.9

Ruptured and eroded plaques obtained at autopsy have demonstrated PAPP-A expression in their shoulder regions and in the extracellular matrix of eroded plaques.10 In that study, PAPP-A was not associated with troponin I (TnI) or creatine kinase-MB elevations, suggesting that PAPP-A may have diagnostic utility in identifying patients with ACS but no detectable myocardial necrosis.10 In a prospective study of consecutive patients with TnI-negative ACS, elevated PAPP-A levels were associated with a relative risk of 2.3 for the combined end points of cardiovascular mortality, nonfatal myocardial infarction (MI), or...
Inflammatory Biomarkers in ACS

<table>
<thead>
<tr>
<th>Marker</th>
<th>Pathophysiological Contribution</th>
<th>Strength of Clinical Data</th>
<th>Future Clinical Applications/Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metalloproteinases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-1, -2, -9</td>
<td>Plaque stability, myocardial toxicity</td>
<td>Single cohort</td>
<td>• Uncertain application as biomarker</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Activation of IGF</td>
<td>Multiple cohorts</td>
<td>• Possible validation as therapeutic target</td>
</tr>
<tr>
<td>Platelet activation</td>
<td></td>
<td></td>
<td>• Possible use in ACS without troponin elevation</td>
</tr>
<tr>
<td>sCD40L</td>
<td>Platelet-monocyte aggregates</td>
<td>Multiple cohorts</td>
<td>• Requires standardized, commercial assay</td>
</tr>
<tr>
<td></td>
<td>Platelet aggregation and activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sP-selectin</td>
<td>Soluble form may limit inflammation</td>
<td>Multiple cohorts</td>
<td>• Possible validation as therapeutic target</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited by lack of specificity for ACS</td>
</tr>
</tbody>
</table>

See text for explanation of abbreviations.

revascularization within 6 months. In a c7E3 Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) substudy, PAPP-A values $\simeq 12.6$ mIU/L were an independent predictor of cardiovascular events in both the entire cohort and in patients with TnT-negative ACS. Validation of this marker in a series of patients presenting with chest pain confirmed that PAPP-A identified a group of patients who were at increased risk of adverse cardiovascular events, regardless of troponin status. These studies suggest that PAPP-A may define subsequent cardiovascular risk in the large subset of patients with unstable angina and no troponin elevation.

**Biomarkers of Platelet Activation and Platelet-Monocyte Aggregates**

Biomarkers of platelet activation may provide clues regarding the extent of basal platelet activation in patients at risk for ACS and may also predict the severity of the inflammatory response in patients with ACS.

**Soluble CD40 Ligand**

CD40 ligand (CD154) is a transmembrane glycoprotein of the tumor necrosis factor-α family. Initially implicated in immune cell activation and isotype switching, CD40L signaling, through its cognate ligand CD40, has since been shown to promote atherosclerosis and plaque instability. Platelets constitutively express CD40 and, on activation, express CD40L that is cleaved to a soluble form (sCD40L) over the course of minutes to hours. sCD40L may retain inflammatory effects through promotion of platelet-monocyte aggregates and production of reactive oxygen species.

In addition to inflammatory properties, platelet CD40L stabilizes platelet-platelet aggregates by interaction of its KGD sequence with integrin $\alpha_{IIb}\beta_3$, the major platelet integrin and target of numerous anti-platelet agents used during treatment of ACS. sCD40L binding to $\alpha_{IIb}\beta_3$ and/or CD40 initiates further platelet activation, suggesting that sCD40L may function in an autocrine loop to promote local platelet activation within developing aggregates.

In patients with ACS, sCD40L identified a subgroup who were at increased 6-month risk of death or non-fatal MI. In patients with elevated sCD40L values treated with abciximab, their 72-hour risk was reduced to that of patients with low sCD40L levels. This benefit was observed in patients with and without troponin elevations, and no benefit of abciximab was observed in patients with elevated troponin levels but low sCD40L levels.

A nested case-control study of patients from Orbofiban in Patients with Unstable coronary Syndromes (OPUS)-TIMI 16 showed that patients who experienced death, MI, or congestive heart failure had significantly higher levels of sCD40L than did matched controls and that sCD40L provided prognostic ability independent of TnI or C-reactive protein (CRP). A large prospective study also confirmed that patients presenting with chest pain subsequently determined to have ACS and elevated sCD40L values were at increased risk of adverse coronary events relative to patients with ACS but no elevations in sCD40L.

**P-Selectin**

P-selectin is a transmembrane cell adhesion molecule stored in endothelial Weibel-Palade bodies and platelet $\alpha$-granules. Endothelial cell P-selectin mediates tethering and rolling of leukocytes along the activated endothelium, whereas platelet P-selectin mediates formation of platelet aggregates in pulsatile high-shear-stress conditions. The majority of soluble P-selectin appears to be derived from platelets, because soluble P-selectin levels are correlated with other established platelet markers but not with endothelial markers.

Attempts to use plasma P-selectin for risk stratification in ACS have yielded conflicting results. Some studies have suggested that P-selectin may be useful in risk stratification for patients presenting with chest pain; other uses of plasma P-selectin in ACS risk stratification have not been confirmed. Given its possible pathophysiological role in platelet microaggregate formation and thrombosis,
P-selectin remains a possible therapeutic target.

Conclusions and Future Directions
This review series has delineated pathophysiological subdivisions to the inflammatory arm of an etiologic approach to the management of ACS. Biomarkers for each of the pathophysiological steps may indicate independent risk and may provide insights into the relative pathophysiological contributions that inflammatory processes play in the development of ACS.

Biomarkers can provide 3 types of information in patients with ACS. First, a biomarker may be useful for the immediate diagnosis of disease; e.g., troponin elevations in the proper clinical context may be diagnostic of a non–ST-segment elevation MI (NSTEMI). Currently, inflammatory biomarkers do not define a disease entity but rather predict risk. However, it is plausible that we may one day categorize patients with elevated myeloperoxidase or PAPP-A values but no troponin elevations as a separate subcategory of ACS. Such patients may have a different underlying pathophysiology triggering their ACS, e.g., very unstable plaque or denuded endothelium.

Second, a biomarker can assist in risk stratification. Such stratification can include the risk of adverse events acutely (in hospital) or chronically (during extended follow-up). Inflammatory biomarkers to date have shown differing utility in each of these categories. Myeloperoxidase and sCD40L are each robust markers for early risk and may also provide independent risk stratification in patients with NSTEMI. In contrast, CRP levels are correlated most closely with long-term mortality risk.

Third, a biomarker can ideally direct therapeutic decision making. Among established inflammatory biomarkers, only interleukin-6, CRP, and sCD40L may meet this last criterion. In patients with NSTEMI ACS, elevated interleukin-6 values may predict greater benefit from an early invasive strategy. Achieved CRP levels in patients treated with statins after NSTE ACS independently predict risk of long-term mortality. Patients with NSTE ACS and elevated sCD40L values may derive greater benefit from glycoprotein IIb/IIIa inhibitors than the overall population with ACS.

Ultimately, we envision a panel of inflammatory biomarkers, together with biomarkers of myocyte necrosis, hemodynamic stress, vascular damage, and accelerated atherosclerosis, as part of a multimarker cassette that will unravel the pathophysiological underpinnings of the ACS in a given patient, direct risk stratification, and determine the most effective therapeutic interventions.

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References


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