Clinical and Population Studies

Variations in Platelet Proteins Associated With ST-Elevation Myocardial Infarction

Novel Clues on Pathways Underlying Platelet Activation in Acute Coronary Syndromes

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Objective—Our aim in this study was to provide novel information on the molecular mechanisms playing a major role in the unwanted platelet activation associated with ST-elevation myocardial infarction (STEMI).

Methods and Results—We compared the platelet proteome of 11 STEMI patients to a matched control group of 15 stable chronic ischemic cardiopathy patients. In addition, we did a prospective study to follow the STEMI patients over time. Proteins were separated by high-resolution 2D gel electrophoresis, identified by mass spectrometry, and validated by Western blotting. Platelets from STEMI patients on admission displayed 56 protein spot differences (corresponding to 42 unique genes) compared with the control group. The number of differences decreased with time during the patients’ follow-up. Interestingly, the adapter protein CrkL and the active form of Src (phosphorylated in Tyr418) were found to be upregulated in platelets from STEMI patients. Major signaling pathways related to the proteins identified include integrin, integrin-linked kinase, and glycoprotein VI (GPVI) signaling. Interestingly, a study on an independent cohort of patients showed a higher degree of activation of GPVI signaling in STEMI patients.

Conclusion—CrkL, the active form of Src, and GPVI signaling are upregulated in platelets from STEMI patients. (Arterioscler Thromb Vasc Biol. 2011;31:2957-2964.)

Key Words: acute coronary syndromes ■ platelets ■ GPVI signaling ■ proteomics

A
cute coronary syndromes (ACSs) encompass unstable angina, non-ST segment elevation (NSTE) myocardial infarction, and ST-segment elevation myocardial infarction (STEMI). The latter usually occurs when thrombus forms on a ruptured atheromatous plaque and causes a prolonged occlusion of an epicardial coronary artery.1 There is no doubt platelets play a fundamental role in the pathogenesis of an ACS, being implicated in the thrombus formation that follows the atheroma plaque rupture.2 Activated platelets release proteins in the coronary circulation of ACS patients, such as matrix metalloproteinases, that contribute to sustained intracoronary platelet activation.3 Following an ACS, antiplatelet therapy is recommended to reduce the growth of a thrombus. Primary targets of such therapy are molecules involved in platelet activation and aggregation. Nevertheless, there is a need for the development of a new generation of safer and more effective antithrombotic drugs with larger therapeutic windows and for a better understanding of the pathogenic processes that lead to thrombotic occlusion of blood vessels linked to an acute event.2

Proteomics has emerged as a promising tool in cardiovascular research, and more precisely in the study of ACSs.4 Studies have included plasma, monocytes, and, very recently, platelets.5–8 The objective of these studies was the identification of novel screening and diagnostic biomarkers that might help to predict the disease and provide novel information on the molecular events associated with it, hopefully leading to the identification of novel drug targets. We have been involved in the platelet studies and thus have recently published a high-resolution 2D gel electrophoresis–based study of the platelet proteome of patients with NSTE-ACS.7 We now present the first analysis of the platelet proteome from patients with STEMI compared with matched stable coronary artery disease (SCAD) controls. We also did a prospective study to follow the STEMI patients over time and a specific analysis of the collagen receptor glycoprotein VI (GPVI) signaling cascade in an independent cohort of patients. Our primary objective was to provide, through a global proteomic approach, novel information on the molecular mechanisms playing a major role in the unwanted platelet activation associated with STEMI.
Methods

Patients

Eleven patients admitted into a tertiary hospital in the north-west of Spain presenting with STEMI (defined as angina pain of at least 20 minutes’ duration with elevated cardiac enzymes and ST-segment elevation of at least 0.1 mV in 2 or more contiguous leads or presumably new left bundle branch block) entered the study. Exclusion criteria were inflammatory or neoplastic diseases; coagulation disorders; platelet-associated disorders; other significant heart disease except left ventricular hypertrophy secondary to hypertension; chronic drug therapy (except for drugs required to treat preexisting clinical atherosclerosis or its risk factors); and having experienced surgical procedures, major traumas, thromboembolic events, or revascularization procedures in the previous 3 months.

The study was approved by the local Ethics Committee (Galician Clinical Investigation Ethics Committee) and developed according to the principles outlined in the Declaration of Helsinki. At the moment of diagnosis, the patients were asked to participate in the study. In case of acceptance, they signed the informed consent, and 27 mL of blood were collected in sodium citrate BD Vacutainer tubes for analysis. All samples were obtained within the first 12 hours following the initiation of the symptoms, after arrival at the emergency department. In most cases, patients were administered aspirin before arrival to hospital, so aspirin-pretreated patients were admitted in the study. Some patients had also clopidogrel treatment and were also admitted. However, patients previously treated with anti-\( \alpha_\mathrm{IIb}\beta_\mathrm{3} \) drugs were excluded because in this case discrimination was easier (these drugs are administered at the hospital). When anti-\( \alpha_\mathrm{IIb}\beta_\mathrm{3} \) drugs had been already administered before blood extraction, we decided to exclude those patients to minimize the use of antiplatelet drugs in the study and also because it would have been difficult to find good SCAD matched controls. A second blood sample was taken on day 5 to investigate whether there was a fast reversal of the changes observed in the platelet proteome on admission. Another blood sample was taken after 6 months. Blood was also collected from 15 matched SCAD patients experiencing stable chronic ischemic cardiopathy. Such a group was decided to be the most adequate control group because of the clinical characteristics of the STEMI patients. SCAD patients were required not to have a history of acute cardiovascular event within the year before the inclusion in the study. An age- and sex-matched healthy control group consisting of 10 volunteers was also included for validation studies.

Platelet Isolation

Platelets were isolated by an established method that limits contamination from other blood cells as described previously. Washed platelets were resuspended in Tyrodes-HEPES (134 mmol/L NaCl, 0.34 mmol/L Na\(_2\)HPO\(_4\), 2.9 mmol/L KCl, 12 mmol/L NaHCO\(_3\), 20 mmol/L HEPES, 5 mmol/L glucose, 1 mmol/L MgCl\(_2\), pH 7.3) at 6\( \times 10^8 \) platelets/mL and allowed to rest for 30 minutes at room temperature. Platelets were then spun down at 10,000 \( g \) in the presence of 1 mmol/L EGTA and, after addition of 5 \( \mu \)L of a protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO), immediately frozen in liquid nitrogen for a few seconds followed by the addition of 2D gel electrophoresis sample buffer (see below). Protein samples were stored at \(-80^\circ C\).

For GPVI signaling studies, 500-\( \mu \)L aliquots of platelets (6\( \times 10^9 \)/mL) were warmed at 37°C for 10 minutes in the presence of 1 mmol/L EGTA, 10 \( \mu \)mol/L indomethacin, and 2 U/mL apyrase before stimulation for 90 seconds with collagen-related peptide (CRP) (final concentration of 10 \( \mu \)g/mL). Stimulations were with constant stirring at 1200 rpm in a Chrono-log aggregometer. Unstimulated (basal) samples were processed in parallel but treated with CRP diluent (0.01 mol/L acetic acid containing 0.1% fatty acid–free BSA) alone. Basal and stimulated platelets were lysed for Western blot analysis as described previously.

Proteomic Analysis

Protein quantitation was done with the Coomassie Plus protein reagent (Thermo Scientific, Asheville, NC). Six hundred micrograms of protein were loaded onto each gel to allow detection of low abundant proteins. An individual gel was run for each blood sample, from each STEMI patient, at 3 different times: on admission, after 5 days, and after 6 months. One sample was obtained from each SCAD patient. The remaining protein was used for Western blotting.

For each sample, protein was dissolved in 500 \( \mu \)L of 2D sample buffer (5 mol/L urea, 2 mol/L thiourea, 2 mol/L tributylphosphine, 65 mmol/L dithiothreitol, 65 mol/L CHAPS, 0.15 mol/L NDSB-256, 1 mmol/L sodium vanadate, 0.1 mmol/L sodium fluoride, and 1 mmol/L benzamidine). Ampholytes (Servalyte 4-7) were added to the sample to a final concentration of 1.6% (v/v). The first dimension was on immobilized pH gradient strips 4 to 7, 24 cm (GE Healthcare). The second dimension was by SDS-polyacrylamide gel electrophoresis (PAGE) on 10% gels. Protein staining was with Sypro Ruby fluorescent dye. Differential image analysis was with Ludesi REDFIN 3 software (Lund, Sweden). Further information on the 2D gel electrophoresis protocol and image analysis can be found in the Supplemental Methods, available online at http://atvb.ahajournals.org.

Western Blotting

Western blot analyses were carried out on polyvinylidene difluoride membranes using the following primary antibodies and dilutions: rabbit anti-Crkl (1:500) from Santa Cruz Biotechnology, Inc (Santa Cruz, CA), rabbit anti-Src (pTyr418) (1:1000) from Invitrogen (Camarillo, CA), mouse anti-phosphotyrosine monoclonal antibody (clone 4G10) (1:1000) from Millipore (Billerica, MA), and a Bruker Amazon electron transfer dissociation ion trap. A database search was performed with the Mascot v2.1 search tool (Matrix Science, London, United Kingdom) screening SwissProt (release 56.0). Further details on the analysis can be found in the Supplemental Methods.

Ingenuity Pathways Analysis

Ingenuity Pathways Analysis software (Ingenuity Systems) was used to investigate possible interactions between all the identified proteins. Interactive pathways were generated to observe potential direct and indirect relations among the differentially expressed proteins.

Statistical Analysis

Data for categorical or dichotomous variables are expressed as percentages and were compared using the \( \chi^2 \) test or the Fisher exact test. Unless stated otherwise, data for continuous variables are expressed as the median and interquartile range and were compared by Mann-Whitney test. The differential proteomic analysis was done analyzing all the spots between patients with STEMI and SCAD: for a given spot, the probability value was calculated using the quantified and normalized volumes for the matched spot in each of the images and applying the Mann-Whitney test.

All probability values were 2-tailed, and values of \(<0.05\) were considered to indicate statistical significance. All analyses were performed using SPSS 17.0 software for Windows (SPSS Inc, Tokyo, Japan).

Results

Patients’ Characteristics

Eleven patients admitted to hospital with the diagnosis of STEMI and 15 age and gender-matched patients with SCAD...
were included in the proteomic study. The matching was also based on antiplatelet treatment performed before blood extraction. There were only a few clinical differences between both groups, as shown in Table 1 and Supplemental Table I. Patients included in the SCAD control group had a higher prevalence of 1-vessel coronary disease, whereas in STEMI patients, complex, multivessel lesions were more frequent. Prehospital admission use of angiotensin-converting enzyme inhibitors and statins was more prevalent in the SCAD group. Finally, regarding laboratory results, patients with acute events presented higher leukocyte and glucose levels and lower protein and mean platelet volume compared with stable patients.

### Platelet Proteome Analysis of STEMI Patients

A mean (±SD) of 2426±53 protein features were found on pI 4 to 7 gels corresponding to platelets from SCAD patients, whereas 2466±56 protein features were found in the STEMI samples. We focused on the identification of disappearing and appearing spots, as well as up- and downregulation of spot intensities where the fold change was at least 1.5 (with

\[ P < 0.05 \]

By applying these criteria, 56 protein features were detected as differentially regulated when comparing the platelet proteome of STEMI patients on admission versus SCAD controls (Figure 1). All protein features were successfully identified by mass spectrometry. They corresponded to 42 different open reading frames (Supplemental Tables II and III). Forty of the protein features identified were upregulated in STEMI samples gels, whereas 16 were downregulated. Eight proteins were represented in the gels by more than 1 spot, and 8 spots had more than 1 protein, normally from the same family.

The number of proteins differentially regulated in platelets from STEMI patients, as compared with stable controls, was decreasing with time. As mentioned above, on admission there were 56 differentially regulated protein features. Of those 56, only 32 remained significantly different at day 5. After 6 months, only 4 protein spots remained significantly different (Supplemental Table IV).

The 42 differentially regulated proteins identified in the STEMI study can be divided in the following functional groups: cytoskeletal (38%), signaling (24%), extracellular/vesicles/secretory trafficking pathway (21%), and other (17%). A close-up view of a selection of differentially regulated proteins is shown in Figure 2. A selection of proteins was validated by Western blotting. Below, we present data on signaling proteins.

### Table 1. Clinical Characteristics of ST-Elevation Myocardial Infarction and Stable Coronary Artery Disease Patients (Proteomic Study)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Myocardial Infarction (n=11 Patients)</th>
<th>Stable Coronary Artery Disease (n=15 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69 (50–79)</td>
<td>67 (47–73)</td>
</tr>
<tr>
<td>Females, %</td>
<td>27.3</td>
<td>20.0</td>
</tr>
<tr>
<td>Hx arterial hypertension, %</td>
<td>45.5</td>
<td>60.0</td>
</tr>
<tr>
<td>Hx diabetes mellitus, %</td>
<td>18.2</td>
<td>26.7</td>
</tr>
<tr>
<td>Hx dyslipidemia, %</td>
<td>36.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Hx coronary artery disease, %</td>
<td>18.2</td>
<td>100.0</td>
</tr>
<tr>
<td>Platelets/μL</td>
<td>268 000 (178 000–303 000)</td>
<td>223 000 (199 000–239 500)</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>90.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>36.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Other antiplatelets, %</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anticoagulants, %</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as the median and interquartile range or percentage of patients. Further information can be found in Supplemental Table I. Hx indicates medical history. *P < 0.05.*

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**Figure 1.** High-resolution 2D gel electrophoresis–based proteome analysis of platelets from ST-segment elevation myocardial infarction (STEMI) patients. Shown are representative 2D gel electrophoresis gel images of STEMI and stable coronary artery disease (SCAD) circulating platelets (isoelectric focusing; pH range 4–7; second dimension: 10% SDS-PAGE). The figure shows the location on the 2D gels of those spots differentially regulated when comparing STEMI patients and SCAD controls. Protein identifications are shown by the identification numbers in Supplemental Table II. Further information can be found in Supplemental Table III.
Active Src (pTyr418) Is Upregulated in Platelets From STEMI Patients

Our proteomic analysis revealed 1 spot corresponding to Src downregulated in platelets from STEMI patients (Figure 2A). Src is a 60-kDa nonreceptor tyrosine kinase involved in initiating signaling from various tyrosine kinase-linked platelet receptors. Src and other members of the Src kinase family are tightly regulated by tyrosine phosphorylation, so we hypothesized that the difference we were observing could be due to Src phosphorylation/dephosphorylation. Full catalytic activity of Src requires phosphorylation of tyrosine 418, which is located in the catalytic domain. By using a specific anti-Src (pTyr418) antibody, we demonstrated that the active form of Src was upregulated in platelets from STEMI patients (Figure 3). This apparent contradiction with the proteomic results is not actually a contradiction: when there is an increase in phosphorylation of a given protein, spots corresponding to hypophosphorylated forms may diminish in intensity, whereas the intensity of spots corresponding to hyperphosphorylated forms, in a more acidic region, goes up. In our case, we did not detect the latter. Some possible reasons for that are that spots of interest were hidden by other surrounding spots in the stained gel (corresponding to more abundant proteins) or they were detected but the difference was below the 1.5-fold change cutoff level. We should also bear in mind that Western blotting is much more sensitive than gel staining.

The Adapter Protein CrkL Is Upregulated in Platelets From STEMI Patients

CrkL is a GPVI signaling protein that serves as an adapter for Syk tyrosine kinase. We found this protein in 1 spot upregulated in platelets from STEMI patients (see Figure 2C). Validation studies confirmed this result (Figure 3).

Ingenuity Pathways Analysis

Ingenuity Pathways Analysis software (Ingenuity Systems) was used to investigate possible interactions between all the identified proteins to highlight predominant networks and pathways. Interestingly, 35 of the 42 differentially regulated proteins identified are interconnected as a part of a common network related to tissue and cell morphology (Supplemental Figure I). The top molecular and cellular functions are cell-to-cell signaling and interaction, cellular assembly and organization, and cell morphology (Supplemental Figure IIA). The top 3 canonical pathways related to the proteins identified are actin cytoskeleton signaling, integrin signaling, and integrin-linked kinase signaling (Supplemental Figure IIB). In addition, 7 differentially regulated proteins are also known to be involved in platelet activation by the collagen receptor GPVI: α-actinin-1, Src, SKAP-55 homologue, Gads, SH2 domain-containing tyrosine phosphatase-1.
Table 2. Selection of Proteins Involved in Platelet Signaling Differentially Regulated in ST-Elevation Myocardial Infarction vs Stable Coronary Artery Disease Patients

<table>
<thead>
<tr>
<th>Protein</th>
<th>Uniprot Code</th>
<th>Spot</th>
<th>Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-3-3 protein εδ</td>
<td>1433Z_HUMAN</td>
<td>242</td>
<td>-1.80*</td>
</tr>
<tr>
<td>α-Actinin-1</td>
<td>ACTN1_HUMAN</td>
<td>2222</td>
<td>+2.93*</td>
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<tr>
<td></td>
<td>ACTN1_HUMAN</td>
<td>2224</td>
<td>+2.58*</td>
</tr>
<tr>
<td></td>
<td>ACTN1_HUMAN</td>
<td>2311</td>
<td>+2.32*</td>
</tr>
<tr>
<td>Cdc42</td>
<td>CDC42_HUMAN</td>
<td>2006</td>
<td>+1.82*</td>
</tr>
<tr>
<td>CrkL</td>
<td>CRKL_HUMAN</td>
<td>1642</td>
<td>+1.63</td>
</tr>
<tr>
<td>GADS</td>
<td>GRAP2_HUMAN</td>
<td>2005</td>
<td>-1.79</td>
</tr>
<tr>
<td>Inositol monophosphatase 1</td>
<td>IMPA1_HUMAN</td>
<td>717</td>
<td>-1.61</td>
</tr>
<tr>
<td>Myosin-9</td>
<td>MYH9_HUMAN</td>
<td>1623</td>
<td>+1.69*</td>
</tr>
<tr>
<td></td>
<td>MYH9_HUMAN</td>
<td>1918</td>
<td>+1.98*</td>
</tr>
<tr>
<td></td>
<td>MYH9_HUMAN</td>
<td>2313</td>
<td>+2.69*</td>
</tr>
<tr>
<td>Src</td>
<td>SRC_HUMAN</td>
<td>1835</td>
<td>-1.83</td>
</tr>
<tr>
<td>SKAP-HOM</td>
<td>SKAP2_HUMAN</td>
<td>279</td>
<td>-1.51*</td>
</tr>
<tr>
<td>Talin-1</td>
<td>TLN1_HUMAN</td>
<td>793</td>
<td>+2.08*</td>
</tr>
<tr>
<td></td>
<td>821</td>
<td>+2.45*</td>
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<tr>
<td></td>
<td>830</td>
<td>+2.92*</td>
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<td></td>
<td>891</td>
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<td>1149</td>
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<td>+3.61*</td>
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<td></td>
<td>1240</td>
<td>-1.71</td>
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<td></td>
<td>1544</td>
<td>+2.28*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1573</td>
<td>+1.87*</td>
<td></td>
</tr>
<tr>
<td>SHP-1</td>
<td>PTN6_HUMAN</td>
<td>1723</td>
<td>-1.61</td>
</tr>
</tbody>
</table>

A negative fold change indicates that the protein feature is downregulated in ST-elevation myocardial infarction, whereas a positive fold change indicates that the spot is upregulated in the acute group. SKAP-HOM indicates SKAP-55 homologue.

*Differentially regulated features have a P value of <0.05 except those marked with an asterisk (*), which have a P value of <0.01.

Results

Cdc42,13 and CrkL.12 A selection of differentially regulated proteins related to platelet signaling is shown in Table 2.

GPVI Signaling Is Upregulated in STEMI Patients

As mentioned above, our data suggest the involvement of GPVI signaling in the acute event. To further explore this issue mechanistically, we recruited an independent cohort of patients to investigate the activation state of the GPVI signaling cascade. The clinical characteristics of the patients (Supplemental Table V) were similar to those of the original study. Platelets from 6 STEMI patients, 6 matched SCAD controls, and 6 sex- and age-matched healthy controls were in vitro activated with the GPVI specific agonist CRP in the presence of EGTA (which prevents platelet aggregation during GPVI activation) and inhibitors of secondary mediators (ADP, thromboxanes). Those inhibitors were used to make sure changes in the proteome were specifically due to GPVI signaling.13 A comparison between basal (unactivated) and CRP-activated platelets was carried out for the 3 groups of patients (STEMI, SCAD, healthy). To do so, equal amounts of protein from each patient belonging to the same group were pooled for each study point (basal, CRP) and loaded in a 4% to 12% gradient Bis-Tris gel. Because GPVI signaling goes primarily through tyrosine phosphorylation, a Western blot was carried out with the 4G10 antiphosphotyrosine antibody. As expected, there was an increase in tyrosine phosphorylation when platelets were activated with CRP, but interestingly, such increase was higher in STEMI patients (Figure 4). Moreover, because Src family kinases play a fundamental role in GPVI signaling, we reprobed the membranes with the anti-Src (pTyr418) antibody, which recognizes the active form of the kinase. As can be seen in Figure 4, CRP stimulation induced an ∼2-fold augment in Src-pTyr418 levels. Interestingly, there was also an increase in Src-pTyr418 levels in platelets from STEMI patients compared with controls, both in basal and CRP-activated platelets. This confirms the data from our proteomic study and shows a higher activation of GPVI signaling in platelets from STEMI patients. Further research is under way to study in detail by proteomics the GPVI signaling cascade in a bigger group of patients to identify those proteins that contribute more importantly to the differences observed.

Discussion

The present study constitutes the first proteomic analysis of platelets from STEMI patients, and it complements our recent study on NSTE-ACS patients.7 The 2 analyses were done separately because of the clinical characteristics of each group of patients, so the SCAD control groups were different. The results presented here provide novel information on the molecular events related to the unwanted platelet activation that takes place in STEMI, identifying the main pathways involved, and confirming a higher activation of the GPVI signaling cascade in platelets from STEMI patients.

The study design is in agreement with recent platelet proteomic and transcriptomic studies on ACS.7,16,17 We selected patients with SCAD as a control group to focus on differences linked to atherothrombotic events, bypassing the influence of antiplatelet drugs. Nevertheless, a healthy control group was included during the validation stage, as done in the transcriptomic studies mentioned above. No significant differences were observed between SCAD and healthy groups in the validation studies. Study limitations are mentioned in the discussion section shown in the supplemental material.

Regarding the clinical characteristics of the patients, there was an obvious dissimilarity in treatment of the two study groups, with SCAD patients having more frequent preadmission prescription of angiotensin-converting enzyme inhibitors and statins because this group presented an already established diagnosis of ischemic heart disease, compared with patients with acute events, in whom this diagnosis was mostly performed for the first time. Additional discussion of laboratory differences between patient groups can be found in the supplemental material.

Focusing on the proteomic analysis, we found 56 protein features to be differentially regulated between platelets from STEMI and SCAD patients. The fact that those spots were related to 42 unique genes suggests some cases of extensive posttranslational modifications, quite common in platelets
following activation, such as phosphorylations or natural proteolysis. The latter also explains some cases where proteins had an experimental molecular weight significantly lower than the theoretical one. The number of differences was higher than in the NSTE-ACS study we recently carried out—40 protein spots related to 22 unique genes—which is not surprising because the acute event was more severe in the case of STEMI, and blood samples were collected closer to the initiation of the event. That would be also one of the explanations for why there was not a bigger overlap between both studies. Nevertheless, there are similarities, and thus, signaling and cytoskeletal proteins were the main functional groups of proteins identified in both studies, with an important number of differentially regulated proteins involved in integrin and GPVI signaling. Moreover, Ingenuity Pathways Analysis software revealed that most proteins identified in both NSTE-ACS and STEMI studies are involved in a network related to cell morphology.

Signaling Pathways as Possible Future Targets for Antiplatelet Therapy: Upregulation of GPVI Signaling in STEMI

In the past few years, studies identifying platelet receptors and signaling mechanisms have yielded a trove of new targets for antiplatelet therapy. For example, recent studies have shown that several cell-surface receptor-ligand interactions occur on close contact between platelets, such as the binding of the ligand semaphorin 4D to its receptors, CD72 and plexin B1. These receptors mediate platelet-platelet interactions and thrombus retraction and hence are attractive therapeutic targets. Proteomics has contributed to depicting the main signaling pathways in platelets, leading to the identification of novel receptors and signaling proteins, some of them potential antithrombotic targets. We have been among the pioneers in the field. In this way, the complexity of outside-in and inside-out signaling has begun to be unraveled. However, redundancy in signaling pathways makes it difficult to identify clear therapeutic targets. Nevertheless, there are some exceptions. For instance, the binding of the cytoskeletal protein talin-1 to the cytoplasmic domain of integrin was shown to be required for activation of the integrin. Moreover, changing a single amino acid in the cytoplasmic domain of integrin selectively disrupted talin-1 binding and reduced arterial thrombosis in an animal model showing that blockade of this interaction could be a new antithrombotic strategy. Interestingly, most of the proteins identified in the present study are interconnected in a common network that primarily involves cytoskeletal and signaling proteins, processes closely related to platelet activation. Indeed, integrin and GPVI signaling are among those pathways highlighted by our study. Src family kinases play a major role in these signaling cascades, especially in the case of the collagen receptors GPVI and αIIbβ3 integrin. Moreover, changing a single amino acid in the cytoplasmic domain of β3-integrin selectively disrupted talin-1 binding and reduced arterial thrombosis in an animal model showing that blockade of this interaction could be a new antithrombotic strategy. Interestingly, most of the proteins identified in the present study are interconnected in a common network that primarily involves cytoskeletal and signaling proteins, processes closely related to platelet aggregation. Indeed, integrin and GPVI signaling are among those pathways highlighted by our study. Src family kinases play a major role in these signaling cascades, especially in the case of the collagen receptors GPVI and αIIbβ3 integrin. Interestingly, we demonstrate the active form of Src is upregulated in STEMI patients, which suggests an important role for those pathways—where Src family kinases are essential—in the acute event.

The integrin αIIbβ3, mainly responsible for platelet aggregation, is a well-known antiplatelet target. Integrin αIIbβ3...
was the first platelet collagen receptor to be identified and serves as an adhesion receptor,\textsuperscript{11} so its involvement in the acute activation of platelets makes sense in a collagen-rich environment. The novelty of our study is to highlight other 3 platelet signaling pathways related to platelet activation in ACS: actin cytoskeleton signaling, integrin-linked kinase signaling, and GPVI signaling. The latter is an interesting target. It has been recently shown that platelet GPVI binds to collagenous structures in the core region of human atheromatous plaque and is critical for atheroproggression in vivo.\textsuperscript{24} Indeed, inhibition of GPVI both via GPVI-Fc and anti-GPVI antibodies resulted in protection against atherosclerosis in rabbit and mice models.\textsuperscript{25} However, at present there are no drugs in clinical use that block the binding of platelets to collagen and von Willebrand factor and hence their adhesion to the blood vessel wall. Our results reinforce the idea that GPVI signaling, together with integrin and integrin-linked kinase signaling, may be a good antiplatelet target for ACSs. For example, in addition to the Src results, we found CrkL to be upregulated in patients with STEMI. This adapter protein has been shown to be involved in GPVI signaling.\textsuperscript{12} CrkL consists of Src homology 2 and Src homology 3 protein-binding domains and mediates assembly of protein complexes in signaling.\textsuperscript{26} More precisely, it is an adapter for Syk, a tyrosine kinase critical for collagen induced-platelet activation through GPVI.\textsuperscript{27} This association, demonstrated in vivo and in vitro, could provide an explanation for the translocation of Syk to the cytoskeleton during platelet aggregation.\textsuperscript{27} As was the case with the active form of Src, the upregulation of CrkL in patients with STEMI could be indicative of an upregulation of pathways where this protein has been reported to play a role, such as the GPVI signaling cascade. We confirmed the latter by a specific GPVI signaling study on an independent cohort of patients. As shown in Figure 4, there was an upregulation of GPVI signaling in STEMI patients. These results confirm our initial data and are also consistent with recent reports that demonstrate that GPVI surface expression is elevated in platelets from ACS patients.\textsuperscript{28,29}

Conclusions

This study provides novel information on platelet proteome changes related to STEMI and, in combination with our recent study of platelets from NSTE-ACS patients, allows highlighting of those signaling pathways more implicated in the unwanted platelet activation associated with the acute event: actin cytoskeleton signaling, integrin signaling, integrin-linked kinase signaling, and GPVI signaling. In line with the above, the adapter protein CrkL—known to participate in GPVI signaling—and the active form of the tyrosine kinase Src were found to be upregulated in platelets from STEMI patients. Moreover, we show for the first time an upregulation of GPVI signaling in STEMI patients. We hope that our study will pave the way for future research on novel therapeutic targets and platelet-related biomarkers in ACS.

Acknowledgments

We thank María Moure and Ana Seoane from the Cardiology Department at the Santiago University Hospital for assistance in collecting samples; Esteban Gutiérn and Mónica Paz from the Mass Spectrometry and Proteomics Unit, Universidade de Santiago de Compostela, for analyzing samples by liquid chromatography–tandem mass spectrometry; and Prof Mabel Loza from the Department of Pharmacology, Universidade de Santiago de Compostela, for her continuous support.

Sources of Funding

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Disclosures

None.

References


Variations in Platelet Proteins Associated With ST-Elevation Myocardial Infarction: Novel Clues on Pathways Underlying Platelet Activation in Acute Coronary Syndromes
Andrés F. Parguíña, Lilian Grigorian-Shamagian, Rosa M. Agra, Diego López-Otero, Isaac Rosa, Jana Alonso, Elvis Teijeira-Fernández, José Ramón González-Juanatey and Ángel García

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http://atvb.ahajournals.org/content/suppl/2011/09/15/ATVBAHA.111.235713.DC1

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SUPPLEMENT MATERIAL

Supplementary Methods

CRP reagent

Collagen-related peptide (CRP), with the sequence Gly-Cys-Hyp-(Gly-Pro-Hyp)₁₀-Gly-Cys-Hyp-Gly-NH₂, was provided by Dr. Richard W. Farndale, from the University of Cambridge (UK), and crosslinked with SPDP (3-(2-pyridyldithio)propionic acid N-hydroxysuccinimide ester) by Dr. Yotis A. Senis, at the University of Birmingham (UK).

Two-dimensional gel electrophoresis

Immobilized pH gradient (IPG) strips (4-7, 24 cm, GE Healthcare (Uppsala, Sweden)) were rehydrated in the sample, and isoelectric focusing (IEF) was in a Multiphor (GE Healthcare) for 85 Kvh at 17°C. Following focusing, the IPG strips were immediately equilibrated for 15 min in 4 M urea, 2 M thiourea, 130 mM DTT, 50 mM Tris pH 6.8, 2% w/v SDS, 30% v/v glycerol. The IPG strips were placed on top of the second dimension gels and embedded with 0.5% melted agarose. Proteins were separated in the second dimension by SDS-polyacrylamide gel electrophoresis (PAGE) on 10% gels strengthened with Rhinohide™ (Invitrogen), as described in the manufacturer’s manual, at run conditions of 10°C, 20 mA per gel for 1 h, followed by 40 mA per gel for 4 h by using an Ettan Dalt 6 system (GE Healthcare). Following electrophoresis, gels were fixed in 10% methanol/7% acetic acid for 1 hour, and stained overnight with Sypro Ruby fluorescent dye. After staining, gels were washed for 1 hour in 10% methanol/7% acetic acid, and scanned in a Typhoon 9410 (GE Healthcare).
**Western blotting**

For 1D western blotting, 6 µg of protein were loaded in each lane of 4-12% NuPAGE Bis-Tris gels (Invitrogen) and, following electrophoresis, electrotransferred onto polyvinylidene fluoride (PVDF) membranes (GE Healthcare). The membranes were blocked in 5% BSA in TBS-T (20 mM Tris-HCl (pH 7.6), 150 mM NaCl and 0.1% Tween 20) overnight at 4°C and incubated for 90 min at room temperature with the following primary antibodies: rabbit anti-CrkL (1:500) from Santa Cruz Biotechnology, Inc. (Delaware, CA, USA), rabbit anti-Src [pY418] (1:1000) from Invitrogen (Camarillo, CA, USA), mouse antiphosphotyrosine mAb (1:1000) from Millipore (Billerica, MA, USA), and mouse anti-GAPDH (0.5 µg/ml) from Ambion (Austin, TX, USA). Following washes in TBS-T, the blots were exposed to horseradish peroxidase-labelled goat anti-rabbit or goat anti-mouse antibodies (dilution 1:5000) (Pierce, Rockford, USA) for 1 hour. Membranes were washed again and processed using an enhanced-chemiluminiscence system (ECL, Pierce, Rockford, USA) and quantified by densitometry.

**Differential image analysis**

Due to the high amount of images to be processed for the proteomic analysis, images were sent to the Ludesi Analysis Center (Lund, Sweden, [http://www.ludesi.com](http://www.ludesi.com)) for professional image analysis using Ludesi REDFIN 3 software. That allowed an optimal control over potential technical variations. Spot detection, segmentation and matching followed a strict protocol to ensure a high level of correctness. Gels were matched by using all-to-all spot matching, avoiding the bias caused by the use of a reference gel. The integrated intensity of each of the spots was measured, and the background
corrected and normalized. Normalization removes systematic gel intensity differences originating, for example, from variations in staining, scanning time and protein loading by mathematically minimizing the median expression difference between matched spots. This allows a satisfactory quantification and comparison of different gels. Differential expression of proteins was defined on the basis of >1.5-fold change between group averages and p < 0.05.

**Mass Spectrometric Analysis**

Proteins were manually in-gel digested with trypsin following the protocol defined by Shevchenko *et al.*[^1] Proteins were reduced with DTT and alkylated with iodoacetamide prior to trypsin digestion. Proteins were identified using a 4800 MALDI-TOF/TOF analyzer (Applied Biosystems). For that analysis, dried peptides were dissolved in 4 µL of 0.5% formic acid. Equal volumes (0.5 µL) of peptide and matrix solution, consisting of 3 mg alpha-cyano-4-hydroxycinnamic acid (α-CHCA) dissolved in 1 mL of 50% acetonitrile in 0.1% trifluoroacetic acid, were deposited using the thin layer method, onto a 384 Opti-TOF MALDI plate (Applied Biosystems). Mass spectrometric data were obtained in an automated analysis loop using 4800 MALDI-TOF/TOF analyzer (Applied Biosystems). MS spectra were acquired in reflectron positive-ion mode with a Nd:YAG, 355 nm wavelength laser, averaging 1000 laser shots and using at least three trypsin autolysis peaks as internal calibration. All MS/MS spectra were performed by selecting the precursors with a relative resolution of 300 (FWHM) and metastable suppression. Automated analysis of mass data was achieved by using the 4000 Series Explorer Software V3.5. MS and MS/MS spectra data were combined through the GPS Explorer Software v3.6. Database search was performed with the Mascot v2.1 search tool (Matrix Science, London, UK) screening SwissProt (release 56.0). Searches were
restricted to human taxonomy allowing carbamidomethyl cysteine as a fixed modification and oxidized methionine as potential variable modification. Both the precursor mass tolerance and the MS/MS tolerance were set at 30 ppm and 0.35 Da, respectively, allowing 1 missed tryptic cleavage site. All spectra and database results were manually inspected in detail using the above software.

Some of the identifications were confirmed by LC-MS/MS. In those cases, digested peptide mixtures dissolved in 0.1% formic acid were separated in an EASY-nLC (Proxeon, Bruker Daltonik GmbH) with a reverse phase nanocolumn (Easy column SC200 C18 3um 120A 360um OD/75um ID, L=10cm) from Proxeon. Ionized peptides were analyzed in a Bruker Amazon ETD ion trap. Automated analysis of mass data was achieved by Data Analysis 4.0 and BioTools 3.2 from Bruker Daltonik GmbH. Database search was performed with the Mascot v2.3 search tool (Matrix Science, London, UK) screening SwissProt (release 57.15). Searches were restricted to human taxonomy allowing carbamidomethyl cysteine as a fixed modification and oxidized methionine as potential variable modification. Both the precursor mass tolerance and the MS/MS tolerance were set at 0.3 and 0.4 Da, respectively, allowing 1 missed tryptic cleavage site. All spectra and database results were manually inspected in detail using the above software, especially in the case of identifications based on one peptide hit. For the latter, positive identification by MS was only accepted when more than 50% y-ions were obtained for a peptide comprising at least eight amino acids long and no missed tryptic cleavage site. Positive hits corresponded to Mascot scores > 40 plus the fulfillment of the above criteria.
Supplementary Discussion

Study limitations

The study presents some limitations that should be taken in consideration. Ideally, STEMI patients entering the study should have been with no drug therapy that could interfere with the analysis so the control group would have been healthy subjects; however that was not feasible for obvious reasons. In order to compensate for this factor, we chose a control group consisting in SCAD patients matched in the best possible way to the acute group. Nevertheless, a healthy control group was included during the validation studies. Secondly, the small volume of blood available per patient did not allow running a higher number of gels. In addition, there are limitations inherent to 2-DE, such as the potential under-representation of very hydrophobic proteins. Sample limitation was also an impediment to do further functional analyses related to the proteins identified; more samples will be needed to do so.

Clinical differences between patients – Lab measurements

Lab differences between the SCAD group and patients with STEMI such as higher leucocytes or glucose levels in the later were mostly related to patophysiology of acute versus stable conditions, underlying both clinical situations. Although disconcerting, the slightly higher MPV in SCAD patients may be due to a chronic inflammatory state with ongoing process of platelet consumption that leads to an increase in platelet size to compensate for a persistent decrease in platelet count, tendency that in fact we also observed in this group. A similar finding was observed in another study, where it was suggested that acute myocardial infarction is an acute process of platelet activation that is unrelated to changes in MPV. Finally, higher, although non-statistically significant, prevalence of diabetes, hypertension, cerebrovascular disease and, even, more frequent
statin prescription in the control group may all be responsible for increased platelet size in SCAD patients as it was described in several previous publications.\textsuperscript{3,4} Interestingly, MPV is not related to platelet aggregation and the extent of CAD.\textsuperscript{4}

**References:**


**Supplementary Table I.** Clinical characteristics of STEMI and SCAD patients (expanded version).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Myocardial Infarction (N = 11 patients)</th>
<th>Stable Coronary Artery Disease (N = 15 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (50 – 79)</td>
<td>67 (47 – 73)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>27.3</td>
<td>20.0</td>
</tr>
<tr>
<td>Hx Arterial Hypertension (%)</td>
<td>45.5</td>
<td>60.0</td>
</tr>
<tr>
<td>Hx Diabetes Mellitus (%)</td>
<td>18.2</td>
<td>26.7</td>
</tr>
<tr>
<td>Hx Smoking (%)</td>
<td>18.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Hx Dyslipidemia (%)</td>
<td>36.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Hx Coronary Artery Disease (%)*</td>
<td>18.2</td>
<td>100</td>
</tr>
<tr>
<td>Hx Cerebro-vascular Disease (%)</td>
<td>0</td>
<td>6.7</td>
</tr>
<tr>
<td>Hx Congestive Heart Failure (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hx Peripheral Artery Disease (%)</td>
<td>0</td>
<td>13.3</td>
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</table>

**Laboratory Measurements**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Myocardial Infarction (N = 11 patients)</th>
<th>Stable Coronary Artery Disease (N = 15 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.9 (12.8 – 15.6)</td>
<td>15.0 (13.7 – 15.6)</td>
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<tr>
<td>Leucocytes/µL*</td>
<td>13000 (7820 – 17210)</td>
<td>7600 (6100 – 9800)</td>
</tr>
<tr>
<td>Platelets/µL</td>
<td>268000 (178000 – 303000)</td>
<td>223000 (199000 – 239500)</td>
</tr>
<tr>
<td>Mean Platelet Volume (fL)*</td>
<td>8.2 (7.7 – 8.7)</td>
<td>9.2 (8.6 – 10.0)</td>
</tr>
<tr>
<td>Glucose (mg/dl)*</td>
<td>140 (122 – 177)</td>
<td>113 (90 – 134.5)</td>
</tr>
<tr>
<td>Creatinin (mg/dl)</td>
<td>1.1 (1.0 – 1.3)</td>
<td>1.1 (0.9 – 1.3)</td>
</tr>
<tr>
<td>Proteins (mg/dl)*</td>
<td>6.0 (5.8 – 6.5)</td>
<td>7.0 (6.7 – 7.3)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>185 (150.5 – 210)</td>
<td>161 (135 – 192)</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>113 (87 – 139.5)</td>
<td>90 (86 – 118)</td>
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<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>27 (24 – 49)</td>
<td>37 (31.5 – 40.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>125 (96.5 – 165)</td>
<td>115 (60.5 – 153.5)</td>
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</table>

**Chronic Treatments**

<table>
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<tr>
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<th>Stable Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>90.9</td>
<td>100.0</td>
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<tr>
<td>Clopidogrel (%)</td>
<td>36.4</td>
<td>40.0</td>
</tr>
<tr>
<td>Other antiplatelets (%)</td>
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<td>0</td>
</tr>
<tr>
<td>Anticoagulants (%)</td>
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<td>0</td>
</tr>
<tr>
<td>ACE Inhibitors (%)*</td>
<td>9.1</td>
<td>66.7</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers (%)</td>
<td>27.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Statins (%)*</td>
<td>9.1</td>
<td>100</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
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<th>Variable</th>
<th>Acute Myocardial Infarction</th>
<th>Stable Coronary Artery Disease</th>
</tr>
</thead>
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<tr>
<td>Echocardiography (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Coronariography (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1-Vessel disease (%)*</td>
<td>36.4</td>
<td>78.6</td>
</tr>
<tr>
<td>Left Descending Artery disease (%)</td>
<td>45.5</td>
<td>42.9</td>
</tr>
<tr>
<td>PTCA (%)</td>
<td>100</td>
<td>85.7</td>
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</tbody>
</table>

Data are presented as the median and interquartile range or percentage of patients. Abbreviations used: ACE: angiotensin converting enzyme; PTCA: percutaneous transluminal coronary angioplasty; * p<0.05
**Supplementary Table II.** Platelet proteins differentially regulated in STEMI versus SCAD patients.

<table>
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<tr>
<th>Function</th>
<th>Protein</th>
<th>Uniprot Code</th>
<th>Spot</th>
<th>Fold Change</th>
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</thead>
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<tr>
<td>Cytoskeletal</td>
<td>Actin, cytoplasmic 1 OR 2</td>
<td>ACTB_HUMAN OR ACTG_HUMAN</td>
<td>320</td>
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<td></td>
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<td></td>
<td>587</td>
<td>+1.98*</td>
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<td></td>
<td></td>
<td>682</td>
<td>+2.36*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>714</td>
<td>+7.79*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>751</td>
<td>+2.49*</td>
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<td></td>
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<td></td>
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<td>+2.34*</td>
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<td>+3.60*</td>
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<td>+1.94*</td>
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<td></td>
<td>994</td>
<td>+3.26*</td>
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<td></td>
<td></td>
<td></td>
<td>999</td>
<td>+2.37*</td>
</tr>
<tr>
<td></td>
<td>Alpha-actinin-1 / Alpha-actinin-4</td>
<td>ACTN1_HUMAN AND ACTN4_HUMAN</td>
<td>2222</td>
<td>+2.93*</td>
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<td></td>
<td>2224</td>
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<td>Gelsolin</td>
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<td>1918</td>
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<td>671</td>
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<td>Twinfilin-2</td>
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<td>Crk-like protein (CrkL)</td>
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<tr>
<td>Inositol monophosphatase 1</td>
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<td>Proto-oncogene tyrosine-protein kinase Src</td>
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<td>-1.83</td>
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<tr>
<td>Serine/threonine-protein phosphatase PP1-alpha, and beta, catalytic subunits</td>
<td>PP1A_HUMAN AND PP1B_HUMAN</td>
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<td>Src kinase-associated phosphoprotein 2 (SKAP-HOM)</td>
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<td>-3.79*</td>
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Differentially regulated features have a p<0.05 except those marked with an asterisk, which have a p<0.01. A negative fold change indicates the protein feature is down-regulated in STEMI whereas a positive fold change indicates the spot is up-regulated in the acute group.
**Supplementary Table III. Additional data on MS protein identification**

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Talin-1  TLN1_HUMAN  34.70 ± 30.41 / 60.80 ± 36.66  154511 / 269767  5.24 / 5.77  +2.45"
830 29 / 15 288 716.39 ALHYGR
719.40 VDEKTK
736.42 LITSMR
740.44 ALAVNPR
743.43 IFQAHK
744.42 ELVAGQK
746.42 ASDNLVK
861.49 FLPSELFR
872.52 AVTQALNR
1065.53 TSTPEDFIR
1222.58 ALDGAFTEENR
1242.62 FLPSELRDEH
1335.75 VSHVLAALQAGNR
1416.78 LAAQAAQSVATITR
1453.71 EAAYHPVEAPDVR
1463.75 TMLESGGGLIQTAR
1492.89 AVAEQIPLVLQGVR
1521.84 TLAESALQLLYTAK
1563.82 AAFEEQEQENETVVK
1726.88 TLSPQOQMAIIDQGTK
1782.94 *DLIQASLAASVQQLAPR
1861.95 MVGGIAQIAQAEEMLR
1935.92 EADESLNFEEQILEAAK
2198.12 VSQMAQYFEPLTLAAVGAAASK
2249.07 *SNTSPEELGPLANQLTSODYGR
2310.17 VGAIPANALDGDQWSQQLISAAR
2317.13 DKAPGGQLECETAAILNSCLR
<p>| 891 | 18 / 7 | 181 | 716.40 | SLAQAAR | Talin-1 | TLN1_HUMAN | 109.37 ± 49.71 / 33.58 ± 20.98 | 100272 / 269767 | 5.24 / 5.77 | -1.75 |
| 719.40 | VDEKTK | | | | | | | | |
| 731.40 | DLGVEK | | | | | | | | |
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| 763.46 | AGFLDLK | | | | | | | | |
| 872.51 | AVTQALNR | | | | | | | | |
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| 1335.75 | VSHVLAALQAGNR | | | | | | | | |
| 1453.71 | EAAAYHPEVAPDVR | | | | | | | | |
| 1782.94 | °DLQASLAQGQAPR | | | | | | | | |
| 2195.18 | LGAASLGAEDPETQVGLINAVK | | | | | | | | |
| 2249.07 | °SNTSPEELQLANQLTSDYGR | | | | | | | | |
| 2317.12 | DKAGPSAECEIAlALNSCLR | | | | | | | | |
| 993 | 7 / 19 | 88 | 730.41 | NNDLVR | Tropomodulin-3 | TMOD3_HUMAN | 88.39 ± 34.56 / 37.31 ± 29.16 | 37604 / 39594 | 5.27 / 5.08 | -2.01 |
| 734.42 | MALPFR | | | | | | | | |
| 1328.64 | °GYQFTGQGPR | | | | | | | | |
| 1471.68 | DREDVYPYGEK | | | | | | | | |
| 1493.74 | SNDPVATAFAQMLK | | | | | | | | |
| 1509.73 | SNDPVATAFAQMLK | | | | | | | | |
| 2294.20 | °ILPVFDEPPNPTNVIESLKR | | | | | | | | |
| 994 | 8 / 24 | 122 | 795.46 | IJAPPERR | Actin, cytoplasmic 1 OR Actin, cytoplasmic 2 | ACTB_HUMAN OR ACTG_HUMAN | 697.57 ± 177.95 / 298.38 ± 85.67 | 39491 / 41737 OR 41793 | 5.32 / 5.29 OR 5.31 | +3.28 |
| 1132.54 | GYSFTTAER | | | | | | | | |
| 1515.76 | IWHTFYNELR | | | | | | | | |
| 1516.73 | QEYDESQPSVR | | | | | | | | |
| 1629.83 | GYSFTTAERIEVR | | | | | | | | |
| 1639.88 | LLDAGRDLTYLMK | | | | | | | | |
| 1790.89 | °SYELPDDQVITIGNER | | | | | | | | |
| 1954.05 | VAEEHPVLLTEAPLNPK | | | | | | | | |
| 999 | 3 / 11 | 84 | 1132.55 | GYSFTTAER | Actin, cytoplasmic 1 OR Actin, cytoplasmic 2 | ACTB_HUMAN OR ACTG_HUMAN | 176.14 ± 55.53 / 48.96 ± 22.99 | 39072 / 41737 OR 41793 | 5.31 / 5.29 OR 5.31 | +2.37 |
| 1790.90 | °SYELPDDQVITIGNER | | | | | | | | |
| 1954.05 | VAEEHPVLLTEAPLNPK | | | | | | | | |
| 1063 | 10 / 36 | 359 | 795.47 | °IAPPERR | Actin, cytoplasmic 1 OR Actin, cytoplasmic 2 | ACTB_HUMAN OR ACTG_HUMAN | 1626.55 ± 635.46 / 1023.85 ± 216.8 | 26098 / 41737 OR 41793 | 5.28 / 5.29 OR 5.31 | +2.34 |
| 872.52 | EVRDIK | | | | | | | | |
| 1014.50 | DLTYLMK | | | | | | | | |
| 1132.53 | °GYSFTTAER | | | | | | | | |
| 1516.71 | QEYDESQPSVR | | | | | | | | |
| 1790.90 | °SYELPDDQVITIGNER | | | | | | | | |
| 2231.08 | DLYANTVLSGTTMPGADIWR | | | | | | | | |
| 2359.15 | KDLYANTVLSGTTMPGADIWR | | | | | | | | |
| 1077 | 5 / 16 | 133 | 976.45 | AGFAGDDAPR | Actin, cytoplasmic 1 OR Actin, cytoplasmic 2 | ACTB_HUMAN OR ACTG_HUMAN | 232.05 ± 67.54 / 119.88 ± 34.29 | 27039 / 41737 OR 41793 | 5.23 / 5.29 OR 5.31 | +3.60² |
| 1088 | 11 / 53 | 593 | 789.41 | *SVEALR | Peroxiredoxin-2 | PRDX2_HUMAN | 101.36 ± 90.83 / 184.11 ± 119.43 | 20986 / 21891 | 5.33 / 5.66 | +1.59³ |
| 1095 | 5 / 14 | 207 | 795.47 | IAPPERS | Actin, cytoplasmic 1 OR Actin, cytoplasmic 2 | ACTB_HUMAN OR ACTG_HUMAN | 269.76 ± 76.65 / 134.27 ± 71.96 | 20300 / 41737 OR 41793 | 5.25 / 5.29 OR 5.31 | +1.94³ |
| 1098 | 7 / 28 | 130 | 803.41 | WIDDDR | Ras-related protein Rab-6B | RAB6B_HUMAN | 305.64 ± 116.83 / 84.59 ± 30.46 | 20247 / 23462 | 5.22 / 5.41 |
| 5 / 42 | 103 | 1158.66 | IRTVEINEK | Ras-related protein Rab-35 | RAB35_HUMAN | 305.64 ± 116.83 / 84.59 ± 30.46 | 20247 / 23025 | 5.22 / 8.53 | -1.82 |</p>
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Talin-1  TLN1_HUMAN  258.27 ± 73.90 / 149.67 ± 51.47  103949 / 269767  5.36 / 5.77  -1.71

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NAD-dependent malic enzyme, mitochondrial  MAOM_HUMAN  48.32 ± 29.92 / 121.11 ± 78.28  58292 / 65444  5.62 / 7.52  +2.27
<p>| 1264 | 18 / 17 | 270 | 708.43 | IFVTKK | Vinculin | VINC_HUMAN | 114.25 ± 70.63 / 172.96 ± 69.22 | 69629 / 123799 | 5.55 / 5.50 | +1.73(^3) |
|      |        |     | 743.45 | LADLRR |          |           |                         |             |            |          |
|      |        |     | 756.43 | PVFHTR |          |           |                         |             |            |          |
|      |        |     | 771.45 | GVQQAIR|          |           |                         |             |            |          |
|      |        |     | 930.44 | GEGESPOAR|        |           |                         |             |            |          |
|      |        |     | 934.45 | DMPPAIFK|        |           |                         |             |            |          |
|      |        |     | 1183.56| LANVMMGPYR|      |           |                         |             |            |          |
|      |        |     | 1191.61| MSAEINEIIR|       |           |                         |             |            |          |
|      |        |     | 1457.79| AQQVSGQLVDLTAK| |           |                         |             |            |          |
|      |        |     | 1470.69| DPSASPAGDAGEQAIR| |           |                         |             |            |          |
|      |        |     | 1484.81| *VDQLTAQLADLAAR| |           |                         |             |            |          |
|      |        |     | 1509.71| MLOQMTDMQVADLR|        |           |                         |             |            |          |
|      |        |     | 1915.97| CDVQDQMTDMQVADLR| |           |                         |             |            |          |
|      |        |     | 1990.01| LVQAAQMLQDPYSVPAR| |           |                         |             |            |          |
|      |        |     | 2036.06| *GILSGTDLLLTFDEAEVR| |           |                         |             |            |          |
|      |        |     | 2076.18| *AIPDLTAQVAAVQAAVSNLVR| |           |                         |             |            |          |
|      |        |     | 2164.15| GILSGTDLLLTFDEAEVRK| |           |                         |             |            |          |
|      |        |     | 2230.21| VAMANIQPQMVLGATSIARR| |           |                         |             |            |          |
|      |        |     |        |        |          |           |                         |             |            |          |
| 1280 | 11 / 26 | 106 | 768.43 | SAHQVAR | Pyruvate kinase isozymes M1/M2 | KPYM_HUMAN | 340.30 ± 99.64 / 149.21 ± 41.95 | 65952 / 57937 | 5.62 / 7.96 | -2.51(^3) |
|      |        |     | 787.43 | QAHLVR |          |           |                         |             |            |          |
|      |        |     | 840.51 | APIAVTR |          |           |                         |             |            |          |
|      |        |     | 1019.52| GDYPLEAVR|        |           |                         |             |            |          |
|      |        |     | 1197.65| LDIDSPPITAR|         |           |                         |             |            |          |
|      |        |     | 1359.71| NTGIICTIGPASR|         |           |                         |             |            |          |
|      |        |     | 1779.88| GADFVTVENEGGSLGSK| |           |                         |             |            |          |
|      |        |     | 1837.91| *RFDEILEASDGIMVAR|        |           |                         |             |            |          |
|      |        |     | 1875.90| *FGVEQDVMVFASIFIR| |           |                         |             |            |          |
|      |        |     | 1931.98| EAEAAHYQLQFEELR|        |           |                         |             |            |          |
|      |        |     | 2465.28| TATESFASDLRPVVAALDTK| |           |                         |             |            |          |
|      |        |     |        |        |          |           |                         |             |            |          |
| 1397 | 14 / 35 | 163 | 1041.52| HDLDLCR | Serine/threonine-protein phosphatase PP1-beta catalytic subunit | PP1B_HUMAN | 346.17 ± 185.50 / 211.55 ± 94.21 | 36276 / 37187 | 5.45 / 5.84 | -1.51 |
|      |        |     | 1157.51| GNHECASINR|       |           |                         |             |            |          |
|      |        |     | 1191.59| IVQMTAEAVR|        |           |                         |             |            |          |
|      |        |     | 1194.53| IYQFYDECK|       |           |                         |             |            |          |
|      |        |     | 1198.62| YPENFLLR |          |           |                         |             |            |          |
|      |        |     | 1313.67| GVSFTFGADVVSK|      |           |                         |             |            |          |
|      |        |     | 1350.60| IYQFYDECKR|       |           |                         |             |            |          |
|      |        |     | 1439.79| IKYQENFFLLR|       |           |                         |             |            |          |
|      |        |     | 1571.80| FLNRHDL DLCR|      |           |                         |             |            |          |
|      |        |     | 1639.82| *AHQVVEDGEYEFFAK| |           |                         |             |            |          |
|      |        |     | 1660.80| ICGQDIQTYTILLR|     |           |                         |             |            |          |
|      |        |     | 1761.88| YQQQILNSG PRVTPPR| |           |                         |             |            |          |
|      |        |     | 1762.88| IVQMTAEVRL GCIK| |           |                         |             |            |          |
|      |        |     | 1795.83| AHQVVEDGEYEFFAKR| |           |                         |             |            |          |</p>
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| Serine/threonine-protein phosphatase PP1-alpha catalytic subunit | PP1A_HUMAN | 346.17 ± 185.50 / 211.55 ± 94.21 | 36276 / 37512 | 5.45 / 5.94 |

| Talin-1 | TLN1_HUMAN | 270.97 ± 80.80 / 145.26 ± 76.79 | 91692 / 269767 | 5.63 / 5.77 | +2.28 |

<p>| Pyruvate kinase isozymes M1/M2 | KPYM_HUMAN | 83.52 ± 23.42 / 37.19 ± 34.75 | 46271 / 57937 | 5.62 / 7.96 | +1.64 |
| 1573 | 22 / 10 | 194 | 716.38 | AHHYGR | 746.40 | ASDNLVK | 805.42 | AIADMLR | 861.49 | FLPSELK | 918.50 | EEITGTLR | 1011.63 | KLEQLKPR | 1031.54 | ERELEER | 1032.56 | IRMLDGTVK | 1140.60 | ALETTEHIR | 1162.52 | EGTETFADHR | 1242.62 | FLPSELREH | 1316.68 | GEDVIATANL | 1416.76 | LAQAQQSSVATITR | 1453.71 | *EAYHPEVAPDVR | 1572.77 | GELVFCSPFPAP | 1633.83 | VAGSVTTELQIAEAMK | 1663.82 | AAFEEQENETVVK | 1861.95 | MVGGIAGIA0AEEMLR | 1935.92 | *EAEELNFVFEQIEAAK | 2195.17 | LGNASLGAEDPETQVILNVA | 2235.14 | LASEKPAVAAENEEIGSHIK | 2292.17 | IGITNHiDEYSYRL|MEEK |
| 1561 | 13 / 13 | 148 | 744.41 | IEEAQQR | 756.43 | PVFHTD | 771.45 | GVGQAI | 787.44 | VENAARK | 834.45 | DMPPAFIK | 1183.57 | LANVNFYPR | 1191.61 | MSAEINEIIR | 1157.70 | AQVPSOQLLDVTAK | 1470.69 | DPSASPGDAGEGQAIR | 1484.80 | *VDQLTAQLADLAAAR | 1990.00 | LQVAAMQMGSDPVYPAK | 2036.05 | GILGTSDDLTTFDEAEV | 2076.08 | *AIPDLQAPVAAVGAASNLVR |
| 1623 | 9 / 6 | 100 | 1205.64 | TDLLEPYNK | 1310.68 | VLLGKGDSEHK | 1647.81 | IMGPEEDEGMOLLR | 1662.68 | LMATLRNTPNV | 1726.95 | *Q0DQANPALEAFGNAK | 1743.86 | NLPIYSEEEVEMYK |</p>
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   - SRC_HUMAN: 50937 / 59835
   - SRC_HUMAN: 5.99 / 7.10
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2. **Pyruvate kinase isozymes M1/M2**
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3. **Myosin-9**
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<td>Myosin-9</td>
<td>448.45 ± 171.71 / 740.29 ± 175.79</td>
<td>MYH9_HUMAN</td>
<td>2313</td>
<td>+2.69 ± 2.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2311</td>
<td>13 / 20</td>
<td>302</td>
<td>KTAPYK</td>
<td>Alpha-actinin-1</td>
<td>ACTN1_HUMAN</td>
<td>13 / 20</td>
<td>+2.32 ± 2.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2313</td>
<td>12 / 7</td>
<td>78</td>
<td>SMAVAAR</td>
<td>Myosin-9</td>
<td>MYH9_HUMAN</td>
<td>12 / 7</td>
<td>+2.69 ± 2.25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Identifications were by MALDI-MS unless stated otherwise. Peptides submitted to MS/MS, as an additional analysis that led to the same protein identification, are marked with an asterisk. All differential proteins have a $p$ value lower than 0.05 except those marked with $^\dagger$ which have a $p<0.01$. $^\ddagger$Number of matched peptides. $^\ddagger$Coverage of full length protein by tryptic peptides. $^a$Peptides identified with ESI-TRAP, they were doubly charged ions.
### Supplementary Table IV. List of proteins differentially regulated in STEMI patients’ platelets at different times in comparison with stable patients (SCAD).

<table>
<thead>
<tr>
<th>Protein</th>
<th>Uniprot Code</th>
<th>Spot</th>
<th>Fold Change on admission</th>
<th>Fold Change 5 days</th>
<th>Fold Change 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-3-3 protein zeta/delta</td>
<td>1433Z_HUMAN</td>
<td>242</td>
<td>-1.80*</td>
<td>-1.81*</td>
<td></td>
</tr>
<tr>
<td>Actin, cytoplasmic 1 OR 2</td>
<td>ACTG_HUMAN OR ACTB_HUMAN</td>
<td>320</td>
<td>+3.70*</td>
<td>+3.91*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>317</td>
<td>+1.98*</td>
<td>+1.97*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>587</td>
<td>+2.36*</td>
<td>+3.04*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>682</td>
<td>+7.79*</td>
<td>+5.97*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>714</td>
<td>+2.49*</td>
<td>+2.79*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>751</td>
<td>+2.34*</td>
<td>+1.69*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1063</td>
<td>+3.60*</td>
<td>+2.11*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1077</td>
<td>+1.94*</td>
<td>+1.87*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1095</td>
<td>+3.26*</td>
<td>+1.90*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>994</td>
<td>+2.37*</td>
<td>+1.57*</td>
<td></td>
</tr>
<tr>
<td>Alpha-actinin-1 and 4</td>
<td>ACTN1_HUMAN AND ACTN4_HUMAN</td>
<td>2222</td>
<td>+2.93*</td>
<td>+3.02*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2311</td>
<td>+2.32*</td>
<td>+1.64*</td>
<td></td>
</tr>
<tr>
<td>Cdc42</td>
<td>CDC42_HUMAN</td>
<td>2006</td>
<td>+1.82*</td>
<td>+2.67</td>
<td></td>
</tr>
<tr>
<td>Drebrin</td>
<td>DREB_HUMAN</td>
<td>201</td>
<td>+2.99*</td>
<td>+1.89</td>
<td></td>
</tr>
<tr>
<td>Gelsolin</td>
<td>GELS_HUMAN</td>
<td>654</td>
<td>+2.22*</td>
<td>+3.43</td>
<td></td>
</tr>
<tr>
<td>Glycogen phosphorylase, brain form</td>
<td>PYGB_HUMAN</td>
<td>1712</td>
<td>+1.70*</td>
<td>+1.61</td>
<td></td>
</tr>
<tr>
<td>Glycogenin-1</td>
<td>GLYG_HUMAN</td>
<td>671</td>
<td>+1.87*</td>
<td>+2.68</td>
<td>+2.01</td>
</tr>
<tr>
<td>Myosin regulatory light polypeptide 9</td>
<td>MYL9_HUMAN</td>
<td>78</td>
<td>-1.65*</td>
<td>-2.43*</td>
<td></td>
</tr>
<tr>
<td>Myosin-9</td>
<td>MYH9_HUMAN</td>
<td>2313</td>
<td>+2.69*</td>
<td>+1.80</td>
<td></td>
</tr>
<tr>
<td>Proto-oncogene tyrosine-protein kinase Src</td>
<td>SRC_HUMAN</td>
<td>1835</td>
<td>-1.83</td>
<td>-1.91</td>
<td></td>
</tr>
<tr>
<td>Pyruvate kinase isozymes M1/M2</td>
<td>KPYM_HUMAN</td>
<td>1280</td>
<td>-2.51*</td>
<td>-2.45</td>
<td></td>
</tr>
<tr>
<td>Ras-related protein Rab-1B</td>
<td>RAB1A_HUMAN AND RAB1B_HUMAN</td>
<td>737</td>
<td>-3.79*</td>
<td>-2.20*</td>
<td></td>
</tr>
<tr>
<td>Ras-related protein Rap-1A</td>
<td>RAP1A_HUMAN</td>
<td>2006</td>
<td>+1.82*</td>
<td>+2.67*</td>
<td></td>
</tr>
<tr>
<td>Serine/threonine-protein phosphatase PP1-alpha, and beta, catalytic subunits</td>
<td>PP1A_HUMAN AND PP1B_HUMAN</td>
<td>1397</td>
<td>-1.51</td>
<td>-1.56</td>
<td>-1.63</td>
</tr>
<tr>
<td>Talin-1</td>
<td>TLN1_HUMAN</td>
<td>821</td>
<td>+2.45*</td>
<td>+1.75*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>830</td>
<td>+2.92*</td>
<td>+2.03*</td>
<td>+1.68*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1206</td>
<td>+3.61*</td>
<td>+3.08*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1240</td>
<td>-1.71</td>
<td>-2.02*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1544</td>
<td>+2.28*</td>
<td>+2.08*</td>
<td></td>
</tr>
<tr>
<td>Thrombospondin-1</td>
<td>TSP1_HUMAN</td>
<td>119</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3258</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Tubulin beta-1 chain</td>
<td>TBB1_HUMAN</td>
<td>671</td>
<td>+1.87*</td>
<td>+2.68*</td>
<td>+2.01</td>
</tr>
<tr>
<td>Vinculin</td>
<td>VINC_HUMAN</td>
<td>1584</td>
<td>+2.25*</td>
<td>+1.59*</td>
<td>-1.50</td>
</tr>
</tbody>
</table>

Differentially regulated protein features not present in this table were only significant on admission. All differentially regulated protein spots have a p<0.05 except those highlighted with an asterisk, which have a p<0.01.
Supplementary Table V. Clinical characteristics of STEMI and SCAD patients for the GPVI signaling study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Myocardial Infarction (N = 6 patients)</th>
<th>Stable Coronary Artery Disease (N = 6 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 (55 - 75)</td>
<td>69 (56 - 81)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Hx Arterial Hypertension (%)</td>
<td>66.7</td>
<td>50.0</td>
</tr>
<tr>
<td>Hx Diabetes Mellitus (%)</td>
<td>16.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Hx Smoking (%)</td>
<td>16.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Hx Dyslipidemia (%)</td>
<td>33.3</td>
<td>50.0</td>
</tr>
<tr>
<td>Hx Coronary Artery Disease (%)*</td>
<td>33.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Hx Cerebro-vascular Disease (%)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hx Congestive Heart Failure (%)</td>
<td>16.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Hx Peripheral Artery Disease (%)</td>
<td>16.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Laboratory Measurements**

<table>
<thead>
<tr>
<th></th>
<th>Acute Myocardial Infarction</th>
<th>Stable Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)*</td>
<td>13.8 (13.1-15.5)</td>
<td>12.2 (11.4-13.3)</td>
</tr>
<tr>
<td>Leucocytes/µL</td>
<td>10765 (5000-15000)</td>
<td>6950 (5500-10000)</td>
</tr>
<tr>
<td>Platelets/µL</td>
<td>269333 (204000-363000)</td>
<td>221200 (179000-271000)</td>
</tr>
<tr>
<td>Mean Platelet Volume (fL)*</td>
<td>8.5 (7.8-9)</td>
<td>9.9 (7.9-11.8)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>147 (100-230)</td>
<td>125 (80-213)</td>
</tr>
<tr>
<td>Creatinin (mg/dl)</td>
<td>1.1 (0.7-1.7)</td>
<td>0.9 (0.7-1.5)</td>
</tr>
<tr>
<td>Proteins (mg/dl)</td>
<td>6.1 (5.7-7.1)</td>
<td>6.5 (5.9-6.9)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>164 (109-225)</td>
<td>165 (135-188)</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>105 (51-142)</td>
<td>96 (84-112)</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>37 (28-47)</td>
<td>39 (24-63)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>132 (79-181)</td>
<td>102 (46-136)</td>
</tr>
</tbody>
</table>

**Chronic Treatments**

<table>
<thead>
<tr>
<th></th>
<th>Acute Myocardial Infarction</th>
<th>Stable Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>83.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Clopidogrel (%)</td>
<td>16.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Other antiplatelets (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anticoagulants (%)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ACE Inhibitors (%)</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers (%)</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>Statins (%)*</td>
<td>16.7</td>
<td>83.3</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th></th>
<th>Acute Myocardial Infarction</th>
<th>Stable Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography (%)</td>
<td>83.3</td>
<td>50.0</td>
</tr>
<tr>
<td>Coronarigraphy (%)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>1-Vessel disease (%)</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Left Descending Artery disease (%)</td>
<td>66.7</td>
<td>66.7</td>
</tr>
<tr>
<td>PTCA (%)</td>
<td>100.0</td>
<td>83.3</td>
</tr>
</tbody>
</table>

Data are presented as the median and interquartile range or percentage of patients. Abbreviations used:
ACE: angiotensin converting enzyme; PTCA: percutaneous transluminal coronary angioplasty; * p<0.05
Supplementary Figure II
Supplementary Figure Legends

**Supplementary Figure I. STEMI study: Network Analysis of differentially regulated proteins by Ingenuity Pathways Analysis software (Ingenuity Systems, CA).** The identified protein interaction network is related to tissue and cell morphology and includes 35 of the 42 differentially regulated proteins identified. Proteins identified by differential analysis are shown as shaded nodes with their gene names. Solid lines represent direct interactions, dotted represent indirect interactions. Arrows from one node to another indicate that this node acts upon the other. Lines without arrows represent binding.

**Supplementary Figure II. STEMI study: Molecular functions and canonical pathways identified by Ingenuity Pathways Analysis software (Ingenuity Systems, CA).** A) Top molecular functions. B) Top canonical pathways.