Plasma proteomics identify plaque-related proteins that predict long-term recurrent coronary events in patients with acute coronary syndrome

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Background: Coronary plaque burden and composition drive recurrent ischaemic events in coronary artery disease.

Purpose: We first investigated the association between plasma proteins and coronary plaque characteristics in a cohort of asymptomatic individuals with low-intermediate Framingham Risk Score. Plaque-related proteins were further evaluated in a second cohort of patients with acute coronary syndrome (ACS) to determine their prognostic value for predicting future myocardial infarction (MI).

Methods: We profiled 1305 plasma proteins using an aptamer-based array (SOMAscan) in asymptomatic individuals who had undergone 384-slice coronary computed tomography angiography. Plaques were categorized by composition as calcified or non-calcified. First, we identified proteins that were different (based on multiple testing adjusted p-values: q-value <0.05) between 250 ACS patients who suffered a recurrent MI event on follow-up compared with another 250 ACS patients who remained event-free using Mann-Whitney U test. Next, protein candidates that also correlated (Pearson’s p<0.05) with specific categories of plaque composition were evaluated using a cox proportional hazards model to determine the risk of recurrent MI, adjusting for potential confounders in the second cohort.

Results: A total of 65 and 120 plasma proteins were significantly associated with calcified and non-calcified plaques respectively in the asymptomatic cohort (N=79). Of these 185 proteins, 23 proteins were differentially expressed (DE) between ACS patients with and without recurrent MI events (median follow-up 1811 days).

The top three up-and down-regulated proteins in the recurrent MI group were macrophage-capping protein, trefoil factor 3 and cystatin-SN (median FC 1.22, 1.17 and 1.17; q-value 4.34X10-6, 2.18X10-4, 3.17X10-3 respectively) and fibroblast growth factor 20, lymphotixin a2/b1 and vascular endothelial growth factor receptor 2 (median FC 0.92, 0.94 and -0.090; q-value 1.31X10-3, 9.45X10-3 and 3.90X10-3) respectively. The quartiles of these protein concentrations were also associated with risk of recurrent MI (log-rank test p-value range from 2.71X10-7 to 0.04). Of the DE proteins, the adjusted hazards ratio (HR) of cystatin-SN in the highest quartile(Q4) was 1.44 times that of the first quartile(Q1) (adjusted HR: 1.44, 95% CI: 0.93-2.2) and higher plasma concentration of cystatin-SN was associated with increasing risk of recurrent MI events (Trend test p=0.004). On the other hand, the highest quartile of fibroblast growth factor 20 was associated with 44% reduction in risks of recurrent MI adjusted HR: 0.56, 95% CI of HR: 0.35-0.87), with significant trend test (p= 0.0096).

Conclusions: Large-scale plasma proteomics identified novel plaque-related proteins predictive of recurrent coronary events in patients with ACS. Further studies may help unravel the biological underpinnings of these circulating proteins and their potential as novel prognostic biomarkers.
Abstract: Plasma proteomics identify plaque-related proteins that predict long-term recurrent coronary events in patients with acute coronary syndrome.

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Figure 1. Kaplan-Meier (KM) curves illustrating the association between circulating biomarker concentrations (quartiles) and recurrence of MI after hospitalization with ACS. (A) Higher concentration of cystatin-SN was associated with higher risk of recurrent MI (log-rank test p < 0.001), (B) Lower concentration of fibroblast growth factor 20 were associated with higher risk of recurrent MI (log-rank test <0.001).