Prospective Study on Circulating MicroRNAs and Risk of Myocardial Infarction

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kcl.ac.uk/schools/medicine/research/cardio/bhfcentre/
Strategies to deliver new vascular biomarkers?

Endothelial dysfunction

Fatty streak formation

Advanced lesion

MiRNAs
Dr. A. Zampetaki

Lipidomics

Proteomics
MicroRNAs
Small Non-Coding RNAs

Transcription | Processing | Translation
---|---|---
DNA | RNA | mRNA | Protein

Another layer of complexity for regulating gene expression
Circulating MicroRNAs
New Biomarkers for Cardiovascular Disease?
Response to Cardiovascular Risk Factors
Bruneck Study

- Population-based \( (n=1000) \)
- Prospective \( (1990-2010) \)
- Assessment every 5 years
- Follow-up >90%
- Person-based progression model
- Age 40-79 years at baseline
Concepts of Network Topology

- Human Taqman miRNA arrays for 754 small non-coding RNAs
- 12 pooled samples (n=60)
- Common cardiovascular risk factors (RR, smoking, DM, LDL)
- 120 miRNAs and 1020 co-expression links
• Control network (green)
• Control & DM network (blue)
• DM network (red)
Function of MiR-126
Facilitator of VEGF Signalling
Fish et al Developmental Cell, 2008
Function of MiR-126
Integration of Hemodynamics and VEGF Signaling

Nobili et al, Nature, 2010
Function of MiR-126 Null Mice Prone to Vascular Leakage

Wang et al, Developmental Cell, 2008

- 40% die during embryogenesis from vascular leakage.
- The mice that survive to adulthood are prone to vascular rupture and lethality following myocardial infarction.
Risk of Myocardial Infarction
20 miRNAs, n=822, 10-year follow-up (1995-2005)
### Risk of Myocardial Infarction

20 miRNAs, n=822, 10-year follow-up (1995-2005)

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MiR-126</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.93 (0.71, 1.22)</td>
<td>0.606</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>0.90 (0.68, 1.20)</td>
<td>0.483</td>
</tr>
<tr>
<td>+ miR-197</td>
<td>1.63 (0.95, 2.80)</td>
<td>0.076</td>
</tr>
<tr>
<td>+ miR-223</td>
<td>1.69 (1.06, 2.71)</td>
<td>0.029</td>
</tr>
<tr>
<td>Multivariable model 2 (+ miR-197, -223)</td>
<td>2.53 (1.40, 4.59)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable model 3 (+ miR-197, -223)</td>
<td>2.69 (1.45, 5.01)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>MiR-197</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.77 (0.58, 1.03)</td>
<td>0.076</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>0.75 (0.56, 1.01)</td>
<td>0.061</td>
</tr>
<tr>
<td>+ miR-223</td>
<td>0.96 (0.63, 1.46)</td>
<td>0.856</td>
</tr>
<tr>
<td>+ miR-126</td>
<td>0.49 (0.28, 0.85)</td>
<td>0.012</td>
</tr>
<tr>
<td>Multivariable model 2 (+ miR-126, -223)</td>
<td>0.57 (0.33, 0.97)</td>
<td>0.037</td>
</tr>
<tr>
<td>Multivariable model 3 (+ miR-126, -223)</td>
<td>0.56 (0.32, 0.96)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>MiR-223</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.70 (0.53, 0.93)</td>
<td>0.015</td>
</tr>
<tr>
<td>Multivariable model 1</td>
<td>0.69 (0.52, 0.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>+ miR-197</td>
<td>0.71 (0.47, 1.07)</td>
<td>0.101</td>
</tr>
<tr>
<td>+ miR-126</td>
<td>0.45 (0.29, 0.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariable model 2 (+ miR-126, -197)</td>
<td>0.48 (0.30, 0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable model 3 (+ miR-126, -197)</td>
<td>0.47 (0.29, 0.75)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
### Integrated Discrimination Improvement
Upon addition of miRNAs to Framingham Risk Score

#### Table 2
Summary Statistics of MI Risk Reclassification by Addition of miR-126, miR-197, and miR-223 to a Model With the FRS for Hard Coronary Heart Disease

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated discrimination improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.003331</td>
<td>0.000364–0.006297</td>
<td>0.028</td>
</tr>
<tr>
<td>Cases</td>
<td>0.043967</td>
<td>0.001742–0.086191</td>
<td>0.041</td>
</tr>
<tr>
<td>Overall</td>
<td>0.047297</td>
<td>0.004969–0.089626</td>
<td>0.029</td>
</tr>
</tbody>
</table>
Cellular Origin?
Ischemia/Reperfusion by Thigh Cuff Inflation (n=11)
Cellular Origin?
Presence in Platelets and Platelet Microparticles

A

Platelets

B

Microparticles

Expression level (log10)

miRNAs

miR-223
miR-197
miR-24
miR-126
miR-21

miR-223
miR-197
miR-24
miR-126
miR-21
Platelet Contribution
Correlation of MiRNAs to Platelet Microparticles

Baseline versus Day 2 post ischemia/reperfusion
MicroRNAs in Vascular and Metabolic Disease

Anna Zampetaki, Manuel Mayr

Circulation Research 2012, 110:508-522

Platelet Contribution?

Global Knock-out

Systemic Inhibitors

miR-223
miR-126
miR-103
Let-7
miR-21
miR-107
miR-24
miR-222
Conclusions
Validation in Independent Cohorts

- This is the first population-based study on circulating miRNAs.
- We identified a miRNA signature for DM and risk of MI.
- Currently, we monitor cardiovascular risk factors, but there is no good soluble biomarker to directly assess the health of blood vessels and identify “vulnerable” patients.

**FOCUS ISSUE: BIOMARKERS**

Small RNA Biomarkers Come of Age*

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