Prospective Study on Circulating MicroRNAs and Risk of Myocardial Infarction

Manuel MAYR, MD, PhD
Professor of Cardiovascular Proteomics
British Heart Foundation Centre
Disclosures

- Drs. Zampetaki, Drozdov, Kiechl, P. Willeit, J. Willeit, and M. Mayr filed a patent application.
- Dr. Chowienczyk is a shareholder in Cennon Diagnostics (blood pressure measurement technology unrelated to the present study).
- All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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
DNA → RNA

Processing
RNA → mRNA

Translation
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
Diabetes Mellitus Reveals Its Micro-Signature

- Control network (green)
- Control & DM network (blue)
- DM network (red)
Function of MiR-126

Facilitator of VEGF Signalling

Fish et al Developmental Cell, 2008

Diagram showing the interaction between VEGF, VEGFR-2, miR-126, PIK3R2, PI3K, RAF1, SPRED1, AKT, and ERK, and their role in angiogenesis and vascular integrity.
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)
Integrated Discrimination Improvement
Upon addition of miRNAs to Framingham Risk Score

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<th>Statistic</th>
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Cellular Origin?

Ischemia/Reperfusion by Thigh Cuff Inflation (n=11)
Cellular Origin?
Presence in Platelets and Platelet Microparticles

A
Platelets

B
Microparticles

miRNAs

Expression level (log10)

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

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