miR-24 and YKL-40 in Abdominal Aortic Aneurysm

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Abdominal Aortic Aneurysm (AAA)

- Dilation of the infrarenal aorta (> 3.0cm)
- AAAs are common, lethal
  - 5-16% men; 1-2% women ≥ 65y/o
- Associated with atherosclerosis
  - Family History
  - Age
  - Male Sex
  - Hypertension
  - History of Smoking
  - Diabetes (-)
- No effective therapy for early disease
Murine AAA Model: PPE Infusion

AAA Diameters Measured by US

Expansion in mm

Pre 3 7 10 14 21 28

Post-Operative Days

MALE
SALINE
FEMALE
DIABETIC
AGED
NICOTINE
MALE
FEMALE
DIABETIC
SALINE
microRNA Microarray - Mouse (Agilent™)

Diabetes
- 87
- 65
- miR-21
- miR-29b
- miR-23b-24-27b

Nicotine
- 97

Female
- 93

Aged
- 72
- miR-21
- miR-29b
- miR-23b-24-27b
Gene Expression Microarray – Mouse (Agilent™)

988 targets of the miR-23b-24-27b family
miR-23b-24-27b and Targets in PPE-AAA
Regulation of AAA by miR-24/YKL-40

Cytokines

YKL-40

(miR-24)

(phospho)-AKT

Apoptotic effects on macrophages, T-cells, eosinophils

Chi31 Fold Change vs. sham

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Legend:
- scr-miR
- anti-24
- pre-24
Modulation of miR-24 in Mouse AAA

sham

PPE + scr-miR

PPE + anti-24

PPE + pre-24

AAD vs. baseline (%)
miR-24 Modulation in AngII-Induced AAA

1000 ng/min/kg of AngII for 28 days
miR-24 Regulation \textit{in vitro}

![Graph showing the regulation of miR-24 under various conditions.](chart.png)
miR and Gene Expression in Human AAA
miR-24 and YKL-40 in Plasma
Pathology of AAA - Therapeutic Opportunities

- Transmural inflammation
- SMC phenotypic changes and apoptosis
- Impaired ECM remodeling
- Loss of elastin layer integrity

→ Progressive luminal expansion

miR-21
miR-29b
miR-24

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J Clin Invest 2012
unpublished
Conclusions

• microRNAs regulate gene expression in the aortic wall
  • miR-24 regulates inflammatory activity (and remodeling) during AAA development via YKL-40
  • miR-24 and YKL-40 are differentially regulated in human AAA tissue samples
  • YKL-40 is a novel biomarker of AAA disease severity

• Modulating miR-24 represents a new therapeutic option to control inflammatory processes during AAA development
  • Effect of systemic miR-24 modulation is yet unknown

→ local delivery mechanisms desirable