A novel human arterial transcriptomic signature associated with major adverse cardiovascular events and oxidative stress

Abstract category: Functional Genomics, Transcriptomics, Proteomics and Metabolomics of Cardiovascular Disease

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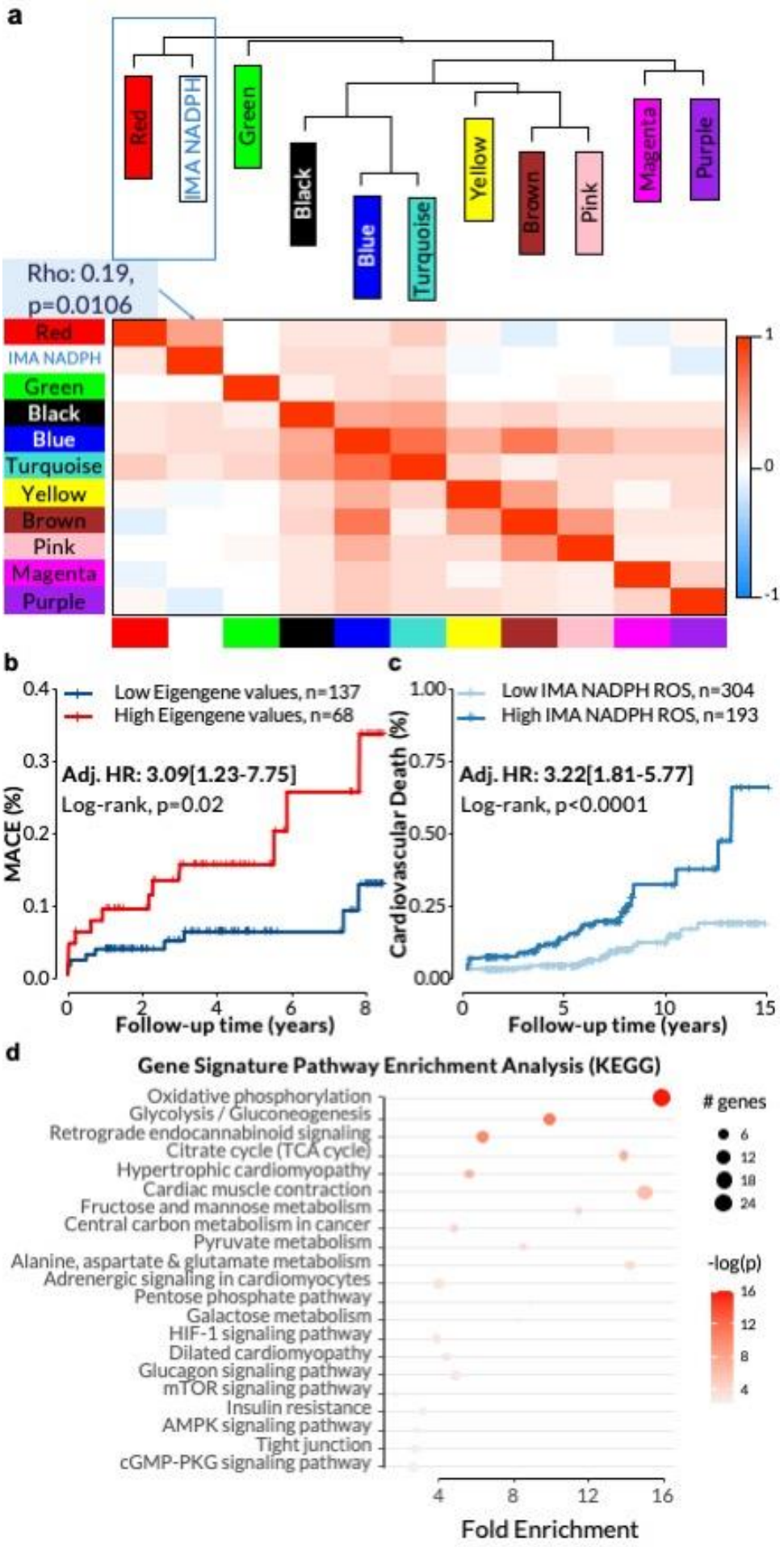
Introduction: The biology of the human vascular wall is implicated in cardiovascular pathology. Human transcriptomics can be linked with clinical outcomes to guide future research and drug development. We sought to apply discovery network transcriptomics to internal mammary arteries (IMAs) obtained from patients undergoing cardiac surgery, in order to identify redox-related molecular pathways within the vascular wall that can be treated therapeutically.

Methods: Weighted correlation network analysis was conducted in sequencing data from the Arm 1 population of 205 patients, in whom sequencing was performed in RNA isolated from the internal mammary artery (IMA). The association with future incidence of major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and new-onset heart failure) was assessed using Cox regression models (adjusted for age, sex, hypertension, dyslipidaemia, diabetes mellitus, and plasma TNFa). Arm 2 included 497 patients in whom segments of IMA were used for ex-vivo quantification of NADPH-stimulated superoxide production by lucigenin-enhanced chemiluminescence, as a measure of NADPH-oxidases activity.

Results: We identified 10 coexpressed gene 'modules' in the human arterial wall, through unsupervised transcriptomic analysis in Arm 1. The "red" module was found to cluster with arterial NADPH oxidase activity while its eigengene values summarising modular coexpression had the most significant correlation (a). For an optimal cut-off, patients with high eigengene values for the "red" module showed a 4-fold higher risk of MACE (b). The Study Arm 2 population was followed up for a median of 6.35 years [IQR: 3.97-8.38]. During this period, 50 cardiovascular deaths (10%) and 101 (20.3%) MACE occurred. High NADPH oxidases activity was indeed independently predictive of cardiovascular mortality (c) and MACE with an adjusted hazard ratio of 1.58 [95% CI: 1.07-2.36], p=0.02. Enrichment analysis within the red module highlighted 'Oxidative phosphorylation', 'Glycolysis and Gluconeogenesis', and 'Hypoxia-Induced Factor-1 (HIF-1) signaling pathway' amongst the top enriched pathways (d).

Conclusion: We demonstrate for the first time that arterial oxidative stress leads to high risk of MACE in patients with atherosclerosis. We also identify a novel, redox-related arterial transcriptomic signature that predicts long-term cardiovascular risk. Pathways related with oxidative stress, or mitochondrial electron transport chain, or glucose metabolism or HIF-1 in the human arterial wall, may be rational therapeutic targets to reduce cardiovascular risk in secondary prevention.


a
Red
IMA NADPH
Green
Black
Blue
Turquoise
Yellow
Brown
Pink
Magenta
Purple
Rho: 0.19,
p=0.0106
1
0
-1
b
Low Eigengene values, n=137
High Eigengene values, n=68
Adj. HR: 3.09[1.23-7.75]
Log-rank, p=0.02
MACE (%)
Follow-up time (years)
c
Low IMA NADPH ROS, n=304
High IMA NADPH ROS, n=193
Adj. HR: 3.22[1.81-5.77]
Log-rank, p<0.0001
Cardiovascular Death (%)
Follow-up time (years)
d
Gene Signature Pathway Enrichment Analysis (KEGG)
Oxidative phosphorylation
Glycolysis / Gluconeogenesis
Retrograde endocannabinoid signaling
Citrate cycle (TCA cycle)
Hypertrophic cardiomyopathy
Cardiac muscle contraction
Fructose and mannose metabolism
Central carbon metabolism in cancer
Pyruvate metabolism
Alanine, aspartate & glutamate metabolism
Adrenergic signaling in cardiomyocytes
Pentose phosphate pathway
Galactose metabolism
HIF-1 signaling pathway
Dilated cardiomyopathy
Glucagon signaling pathway
mTOR signaling pathway
Insulin resistance
AMPK signaling pathway
Tight junction
cGMP-PKG signaling pathway
genes
-log(p)
Fold Enrichment