ATHEROSCLEROSIS – AHEROTHROMBOSIS – CLINICAL EVENTS

STROKE
TIAs

ACS

PAD
CARDIOVASCULAR DISEASE - ATHEROTHROMBOSIS

atherosclerosis

Acute Ischemic Syndromes

- Contenders:
  - Platelets
  - White cells & RBCs
  - EPCs
  - Inflammation
  - Microparticles
Risk Factors for Plaque Progression and Clinical Complication

Local Factors
- Atheromatous Core (size/consistency)
- Cap Thickness/Consistency
- Cap Inflammation

Systemic Factors
- Smoking
- Inflammation
- Cholesterol
- Diabetes Mellitus
- Homocysteine
- HTA
- Fibrinogen
- Impaired Fibrinolysis

**Risk Factors**
- Impaired Fibrinolysis
- Fibrinogen
- Smoking
- Diabetes Mellitus
- Homocysteine
- HTA
- Cholesterol
- Impaired Fibrinolysis
**Figure 2.** Event Rates for Lesions That Were and Those That Were Not Thin-Cap Fibroatheromas, at a Median Follow-up of 3.4 Years.

Event rates associated with 595 nonculprit lesions that were characterized as thin-cap fibroatheromas (TCFA) and 2114 that were not by means of radiofrequency intravascular ultrasonographic imaging are shown according to minimal luminal area (MLA) and plaque burden (PB) as detected on gray-scale intravascular ultrasonography. The inset shows an example of a thin-cap fibroatheroma imaged by radiofrequency ultrasonography. Data on prevalence are for one or more such lesions per patient. Lesions in patients with indeterminate events were excluded. (For additional details, see Table 6 in the Supplementary Appendix.) CI denotes confidence interval.
HIGH RISK PLAQUES AND STRUCTURAL CHALLENGES

- Unstable plaque
  - Low in collagen
  - Necrotic Core
    (rich in lipids, inflammatory cells, lymphocytes, microcalcifications)
  - Thin fibrous cap (<65um)

Falk E et al

Badimon L, Juan O.

HIGH RISK PLAQUES

rupture

↑ lipid core
↓ smooth muscle cells
↓ collagen fibers
↑ inflammatory cells
↑ necrotic core/thin fibrous plaque

structural failure

plaque EROSION / DISRUPTION

Badimon L 2011
Infiltrated lipids impair human coronary VSMC repair mechanisms

VSMC +/− agLDL (16 hours)

double sided scrape-wound

% regenerated area

Time (hours)

control

agLDL

8 hours after wounding

- rosvastatin
+ rosvastatin

C
nLDL
agLDL

C
nLDL+R
C+R

nLDL
agLDL

Infiltrated lipids impair human coronary VSMC repair mechanisms.

MRLC, MLC, caldesmon, actinin, tropomyosin, transgelin

signal transduction
energy pathway
proliferation
redox
calcium ion binding
protein synthesis/folding
cytoskeleton organization/cytokinesis

Proteome of human coronary SMC

Cytosol

Tris Fraction

Cytosk./membrane

Urea-Chaps Fraction

Total spots 880 ± 176

% Distribution

Distribution by pl

Fraccion Tris (16%)
Fracción Urea-Chaps (48%)
Both Fractions (36%)
agLDL induce changes in the proteomic profile of myosin regulatory light-chain (MRLC) in SMC

Western blot analysis

control

agLDL

µg/mL 0 50 100 150

p-MRLC

Total-MRLC

Localization of MRLC in VSMC at the migrating front

Confocal microscopy

Total MRLC

P-MRLC

control

agLDL

F-Actin (red): Allexa -594 Phalloidin
MRLC ; P-MRLC (green): FITC

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<th>noHTA&gt;HTA</th>
<th>noIAM&gt;IAM</th>
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PO functions
Angiogenesis in Human Coronary Atherosclerotic Plaques
Juan O. & Badimon L. ICCC Database.
THE VASCULAR WALL AND THE ENDOTHELium

- Endothelium (vWF)
- VSMCs (alfa actin)

Modified from Badimon L, 2005
2D-gel electroforesis

Paracrine Factors

Autocrine Factors
2D-gel electroforesis

Sequential protein extraction

MALDI-ToF

1. Trypsin digestion
2. Peptide extraction

Adquisition and spectral analysis

HUVEC

/-+LDL

180 mg/dl

PROTEOMICS

PROTEOMICS
INDUCED ENDOTHELIAL CELL CYTOSOLIC PROTEOME

RED, upregulated proteins; GREEN, downregulated proteins; WHITE, IPA-generated protein

Color intensity, level of regulation

BADIMON L, ALARCON JL, CARDUS A, PADRO T. UNPUBLISHED OBSERVATIONS
INDUCED ENDOTHELIAL CELL CYTOSOLIC PROTEOME

Badimon L, Alarcon JL, Cardus A, Padro T. Unpublished observations
## TOP 16 PROTEINS: IPA-GRAPH-CONNECTIVITY

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<th>Symbol</th>
<th>Protein name</th>
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<td>EIF2AK2</td>
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14-3-3 Proteins

Mean Values in 2D

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<th>gamma</th>
<th>epsilon</th>
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CTRL

+ LDL 180 mg/dl

Proteins
14-3-3γ Proteins

Western blot

control  LDL

33 KDa→

Dose-response effects of LDL on 14-3-3 γ levels

LDL: 180 mg/dl

LDL (mg/dl)

14-3-3 gamma (u.a.)
ATHEROSCLEROSIS

- VESSEL REMODELING
- NEOVESSEL FORMATION
- INFLAMMATION
- REGULATORY EFFECTS

ENDOTHELIAL CELLS
CARDIOVASCULAR RESEARCH CENTER
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M. BALDELLOU
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L. CASANI
A. CARDUS
J. CUBEDO
R. ESCATE
R. FERRER
M. G.-ARGUINZONIS
R. HERNANDEZ-VERA
O. JUAN
V. LLORENTE-CORTES
R. LUGANO
B. MOLINS
B. OÑATE
T. PADRO
E. PEÑA
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  And Cardiac Transplant Team

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