Cardiovascular disease, studies at the cellular and molecular level

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Bioscience in the 21st Century
October 4, 2010
Content

• Introduction – The number 1 killer in America
  – Some statistics
  – Recommendations

• The disease process
  – Damage
  – Current treatments

• Control of vascular tone

• Investigating the system
  – Metabolomics
  – Protein investigations
Risk Factors

• High blood pressure (above 120/80 mm Hg)
• High cholesterol [aim for below 100 mg/dL LDL cholesterol and above 50 mg/dL HDL, or aim for total cholesterol below 200 mg/dL]
• High Body Mass Index (BMI) [above 30]
• Smoking
• Drinking
• Diabetes
Metabolic Syndrome

• **Central obesity** (excessive fat tissue in and around the abdomen)
• **Atherogenic dyslipidemia** (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
• **Insulin resistance or glucose intolerance** (the body can’t properly use insulin or blood sugar)
• **Pro-thrombotic state** (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
• **Raised blood pressure** (130/85 mmHg or higher)
• **Pro-inflammatory state**
Obesity

• Diet
• Portion size
• Physical Activity
• Genes

• Fat as an endocrine tissue
  – Makes leptin – lowered desire to eat, more use of stored fat
  – Makes inflammatory signaling molecules
  – Decreases synthesis of signals that in turn cause a decrease in blood pressure
  – with the result being increased blood pressure

Ob/ob mouse from “Nutritional Science”
Chart 2-1 Trends in the age-adjusted prevalence of health conditions
US adults ages 20 to 74


http://circ.ahajournals.org/cgi/content/full/19/3/e21/FIG2191262


http://circ.ahajournals.org/cgi/content/full/119/3/e21/FIG2191262
Age-adjusted death rates for CHD, stroke, lung and breast cancer for white and black females (United States: 2005).

Source: NCHS and NHLBI.
Chart 3-6. Ten year risk for CHD by risk factors

Statins

Rosamond, W. et al.
Circulation 2007;115:e69-e171

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<td>No</td>
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Direct Costs (Billions of dollars) of the 10 Leading Diagnostic Groups (United States: 2009). Source: NHLBI.
Recommendations

- Limit your saturated fat intake (trans fat too)
- Consume less than 200 (300) mg/day cholesterol
- Eat fish regularly
- Limit your salt intake (less than 2300 mg/day)
- Consume vegetables and whole grains
- Diet options for lowering cholesterol
  - Plant sterols and/or soluble fiber
- Eat only enough calories to maintain weight (or reach a healthy weight)
- At least 30 min of moderate physical activity/day
Progression of Vascular Disease

MedlinePlus Medical Encyclopedia
Atherosclerosis

- Leads to narrowing/blocking of arteries
  - Blocked flow to the heart
    - Myocardial Infarction (heart attack)
  - Blocked flow to the brain
    - Ischemic Stroke

Bypass
Atherosclerosis is Geometrically Focal

Flow, along with other factors, contributes to risk.

Meron Mengistu
Contraction of blood vessels

• Angiotensin is a major contraction signal that increases blood pressure transiently

Diuretics, Ace inhibitors, β-blockers, Calcium channel blockers
Relaxation of blood vessels

- NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP
• But cGMP is typically rapidly degraded by proteins called PDEs

\[
\text{cGMP} \rightarrow \text{GMP}
\]

• PDE3 is primarily in cardiac muscle
• PDE6 is primarily in the retinas
• PDE5 is primarily in vascular smooth muscle
Sildenafil citrate

- Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
- Therefore in vascular smooth muscle cells cGMP remains elevated longer.
- Viagra is a trade name for sildenafil citrate
Statins and complications?

• Some individuals do not tolerate statins well, and they sometimes develop myopathy.
• How can we detect this early?
• Searching for a marker.
• “omics”
  – Genomics (transcriptomics)
  – Proteomics
  – Metabolomics
    • Examining metabolic products and/or intermediates
Identifying possible markers

Sample injector

T regulated oven

Column: packed or open tubular (capillary)

GC-MS

Mass spectrometer detector

Gas: He, N₂, H₂

Picture from Wikipedia
Cell proliferation and wound repair

- Lack of contact, damaging chemicals, etc.
- Growth factors, Angiotensin
- Immune system
Finding a player (protein)

The human genome has only about 23,000 protein-encoding genes; it seems like the search should be possible, if not easy.

http://www.bordalierinstitute.com/target1.html

http://www.estradalab.org/research/index.html
Matrix-assisted laser desorption/ionization Mass Spectrometry, a technique sometimes used to characterize and/or identify proteins.

http://www.psrc.usm.edu/mauritz/maldi.html

http://www.pharmaceutical-technology.com/contractors/imaging-analysis/anagnostec/anagnostec2.html
What can you know about the protein you identify?

- Sequence of the protein – gene source
- Location
- Structure
- Function
- Amounts present

AGACYSSTRKGQN.....