

Biomarkers in health care

By
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Introduction

- In this section we will discuss...
- Biomarkers in inflammation & immune disorders
- Biomarkers of diabetes
- Biomarkers of liver diseases
- Biomarkers of pulmonary diseases
- Biomarkers of aging
- Biomarkers applications beyond health care

Biomarkers in health care

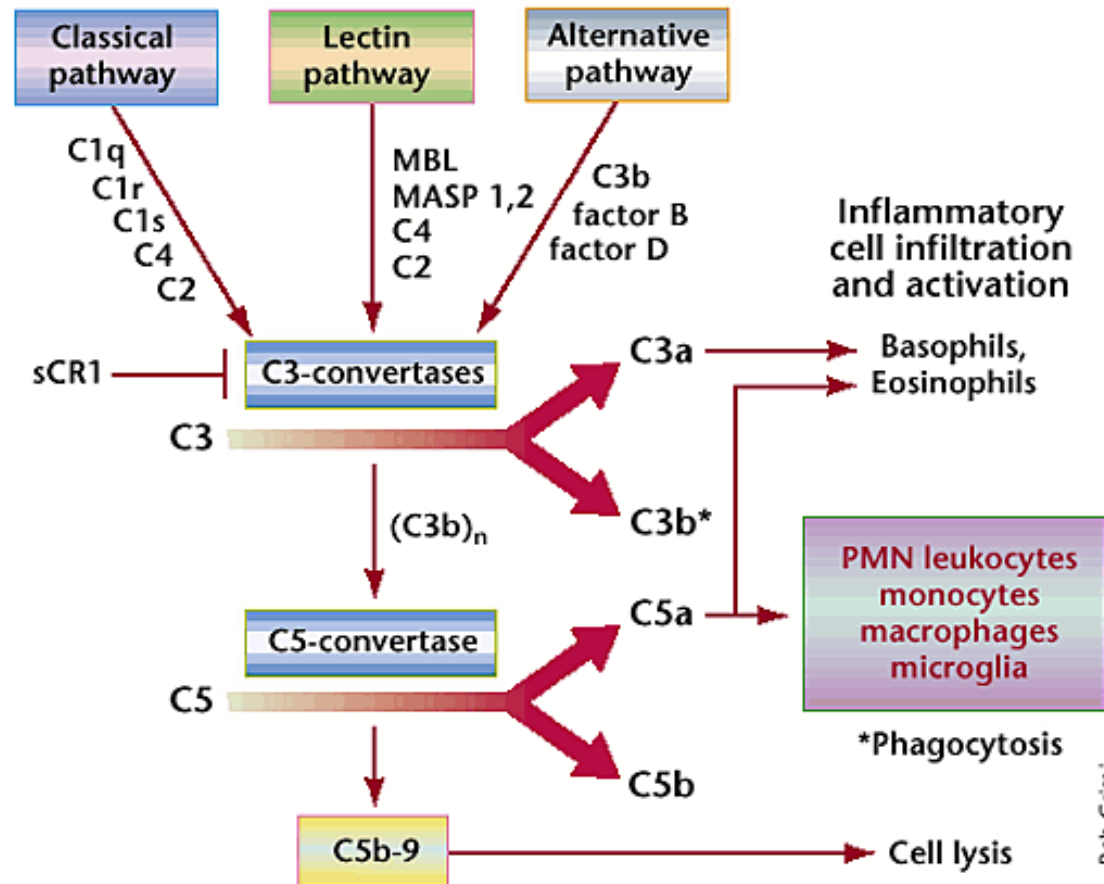
- Studying biomarkers of different pathological states will help to improve the management by
- Proving a better understanding of pathomechanism
- Improving diagnosis and determining prognosis
- Providing a base for development of drugs and following its efficacy

Biomarkers in health care

- Biomarkers of inflammation & immune disorders
- Inflammation is characterized by many disorders and is tissue dependent
- Rheumatoid arthritis, diabetes can be characterized by inflammation
- Complement system is activated in all inflammatory conditions
- Generally measured by serum C3 and C4 proteins with some limitations
- C-reactive protein (CRP) is also important

Introduction

- Complement system



Biomarkers in health care

- **Biomarkers of inflammation & immune disorders**
- Large number of immune disorders in association with inflammation are characterized by expression of cell surface biomarkers of cytokines produced by T and B cells
- **Cytokines** – generally produced by immune cells and used for intercellular communication and intracellular signal transduction

Biomarkers in health care

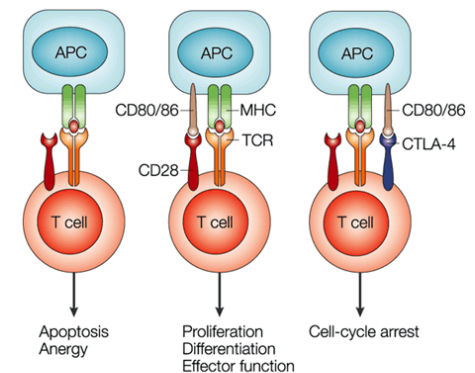
- **Biomarkers of failed organ transplants**
- Major histocompatibility complex proteins play big role
- HLA in case of humans
- HLA typing and matching necessary for organ transplants
- DynaChip HLA antibody analysis system can be used

Locus	Number of alleles (allotypes)
HLA - A	218
HLA - B	439
HLA - C	96
There are also HLA - E, HLA - F and HLA - G	Relatively few alleles

Locus	Number of alleles (allotypes)
HLA - DP _A	12
HLA - DP _B	88
HLA - DQ _A	17
HLA - DQ _B	42
HLA - DR _A	2
HLA - DR _{B1}	269
HLA - DR _{B3}	30
HLA - DR _{B4}	7
HLA - DR _{B5}	12
There are also HLA - DM and HLA - DO	Relatively few alleles

Biomarkers in health care

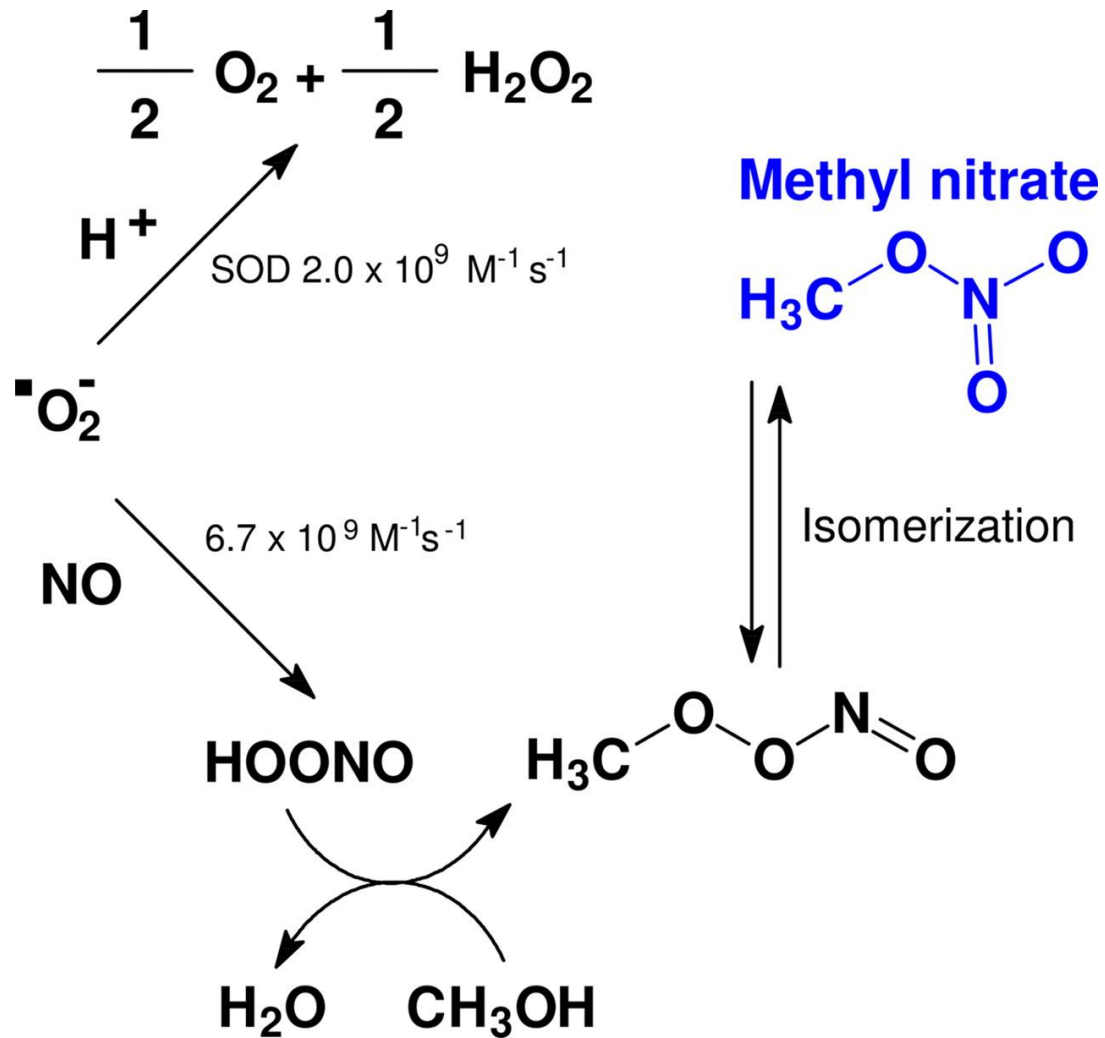
- Biomarkers of failed organ transplants
 - Graft vs host disease (GVHD)
- There is a need to monitor graft rejection after transplantation to adjust immunosuppressive drug regime
- Reactive T cell receptor (TCR) against graft is of importance
- CD28 a co-stimulant expressed on T cell is also important
- Microarray analysis.....



Biomarkers in health care

- Biomarkers of Diabetes Mellitus
- Type I and type II
- Well known about low insulin, increased free fatty acids and ketones in serum
- Methyl nitrate in exhale is strongly correlated with acute hyperglycemia of type I
- Exhale test can be non-invasive biomarker of hyperglycemia
- Oxidative process plays major role in production of methyl nitrate

Schematic representation of methyl nitrate formation in vivo.



B. J. Novak et al. PNAS 2007;104:15613-15618

Biomarkers in health care

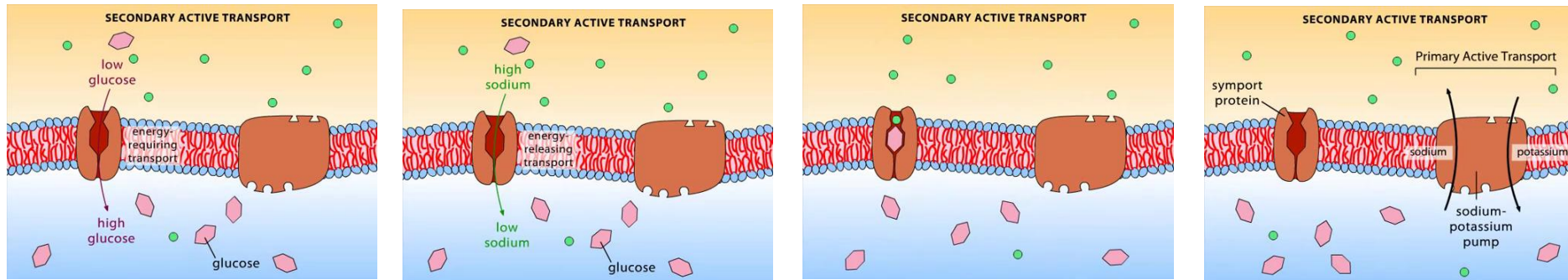
- **Biomarkers of Diabetes associated oxidative stress**
- Peroxidase activity, glutathione and plasma beta-carotene are very low in diabetic patients
- Enzyme superoxide dismutase (SOD) is very high in diabetic patients
- Lipid hydroxy peroxidases and lipoperoxidases are significantly high in diabetes which is indication of oxidative damage to proteins

Biomarkers in health care

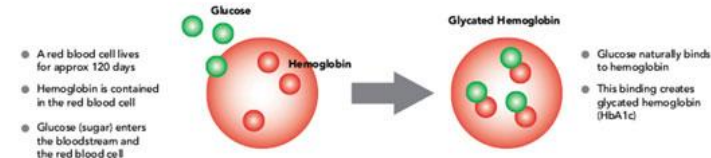
- **Biomarkers of nephropathy in Diabetes**
- Glomerular filtration rate (GFR) below 60 ml/min/L of type 2 diabetes patients showed elevated triglycerides, low density lipoproteins (LDL)....
- **Biomarkers of inflammation associated diabetes**
- Elevated CRP, cell adhesion molecules, interleukin 6 (IL-6)
- Especially in type 1 diabetes

Biomarkers in health care

- Other biomarkers of diabetes
- Lack of C-Peptide – Na, K ATPase activation



- Less endothelial nitric oxide synthase (eNOS)
- Glycosylated hemoglobin (HbA1c)



Biomarkers in health care

- Other biomarkers of diabetes

Biomarkers of hyperglycemia

- Increased serum-free fatty acids and ketones
- Exhaled methyl nitrate

Biomarkers of diabetes-associated oxidative stress

- Elevated serum malondialdehyde, lipid hydroperoxides
- Elevated levels of plasma thioredoxin
- Elevated superoxide dismutase in RBCs
- Elevated plasma protein carbonyl levels
- Increased urinary 8-hydroxy-2'-deoxyguanosine

Biomarkers of inflammation

- C-reactive protein
- Plasma-soluble cell adhesion molecules
- Monocyte IL-6
- Nitrotyrosine

Biomarkers of renal complications in type 2 diabetes mellitus

- Elevated triglycerides
- Elevated low-density lipoprotein
- Elevated apolipoprotein B
- Elevated soluble tumor necrosis factor receptor

Biomarkers of endothelial dysfunction in type 2 diabetes mellitus

- E-selectin
- Intercellular adhesion molecule 1
- Vascular cell adhesion molecule 1

Biomarkers of insulin resistance

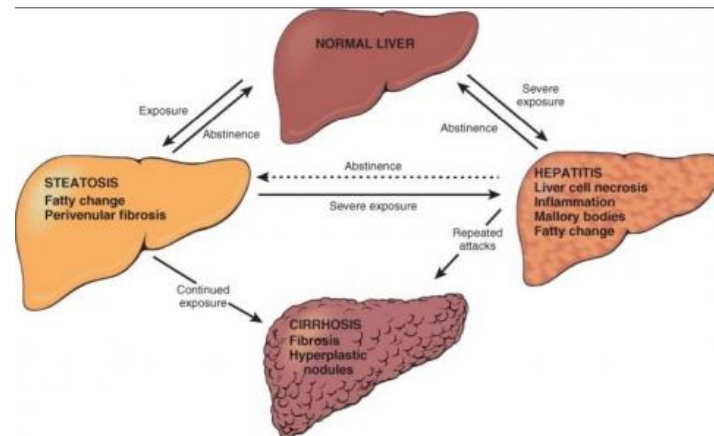
- Serum retinol binding protein-4

Biomarkers of diabetes with cardiovascular complications

- Adiponectin
- Glycosylated hemoglobin

Biomarkers in health care

- **Biomarkers of Liver diseases**
- Breath ethanol, ethane and acetone can be useful
- Tests for cirrhosis of liver (hepatitis B,C infections), tests for tropomyosin
- Alpha glutathione S-transferase (alpha-GST) is a very sensitive biomarker for liver injury



Biomarkers in health care

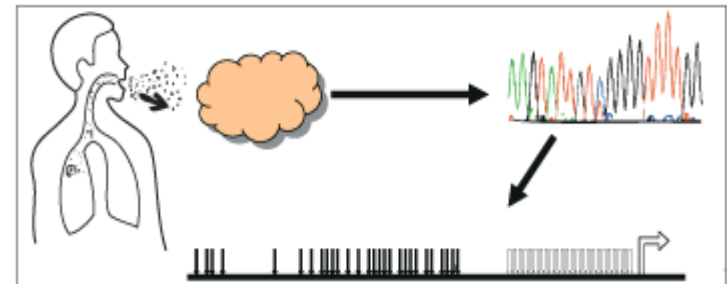
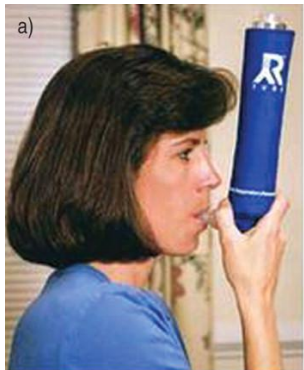
- Biomarkers of Liver diseases
- Fibromax™
- Uses 5 algorithm tests
 1. Fibrotest – liver fibrosis
 2. Actitest – liver active
 3. Steatotest – fatty liver
 4. Nashtest – non-alcoholic steatohepatitis
 5. Ashtest – liver damage

Biomarkers in health care

- Biomarkers of pulmonary diseases
- Breath condensation test for oxidative damage induced biomarkers
 - H_2O_2
 - Glutathione
 - F2-isoprostanes...

Biomarkers in health care

- **Biomarkers of pulmonary diseases**
- Breath condensation test for oxidative damage induced biomarkers
 - H₂O₂
 - Glutathione
 - F₂-isoprostanes...



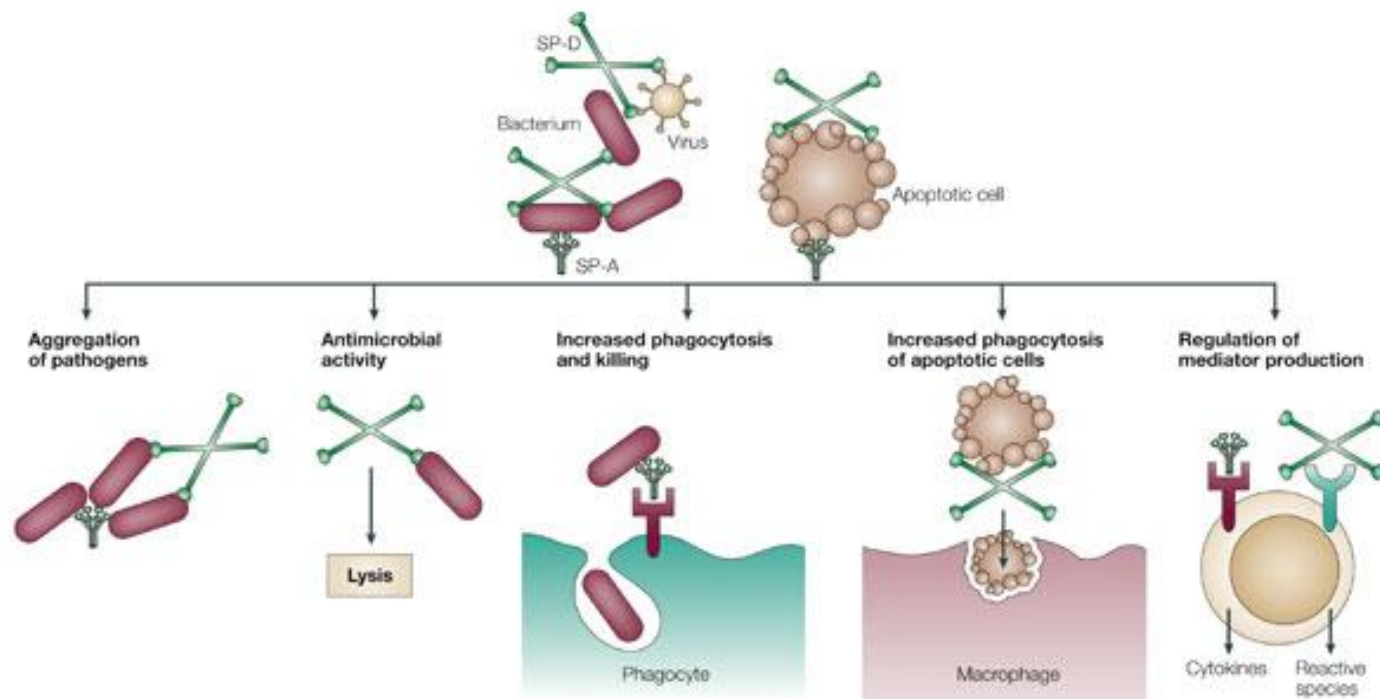
To collect exhaled breath condensate (EBC), patients breathe normally into a mouthpiece connected to a cold condenser. Tagged bisulfite genomic sequencing is performed on DNA recovered from the EBC to produce a detailed DNA methylation map of 6 tumor suppressor genes.

Biomarkers in health care

- **Biomarkers of pulmonary diseases**
- High levels of IL-8 and Intracellular cell adhesion molecule -1 (ICAM-1) in serum
- Pulmonary collectins
 - Surfactant protein A (SP-A)
 - Surfactant protein D (SP-D)
 - Acts as enhancers of phagocytosis (**opsonins**)
 - Useful marker in pulmonary fibrosis, lung maturity acute respiratory distress syndrome

Biomarkers in health care

- Biomarkers of pulmonary diseases



Biomarkers in health care

- Biomarkers of pulmonary diseases
- COPD – decreased VEGF and increased PIGF
- Airway obstruction in smokers – increased chromagranin A
- Asthma – increased exhale of NO, Tcell type 2 activation cytokine profiles (IL-8 and TNF- α)
 - IgE level of an allergen

Biomarkers in health care

- **Biomarkers of aging**

Physiological measurements

Core body temperature

Blood pressure

24-h energy expenditure

Endocrinological biomarkers

Dehydroepiandrosterone sulfate

Insulin levels

Genes as biomarkers

DNA damage

DNA methylation

Mitochondrial mutations

Advanced glycation end products (AGEs): e.g., carboxymethyl-lysine

Biomarkers in health care

- Biomarkers beyond health care
- Bioterrorism
 - Specific microbial biomarker screening
- Exposure to environmental toxins
 - DNA damage, mutations as biomarkers for environmental exposure
 - Epidemiological applications

Introduction

- Next class.....
 - Biomarkers of Cancer