What is the exposome?

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About 2/3 of people die of chronic diseases … mostly from heart disease and cancer

Worldwide deaths, 2010 (50M) (Data from Lozano et al., *Lancet*, 2012)

- Chronic diseases: 63%
- Cardiovascular: 44%
- Cancer: 22%
- Infectious, maternal and childhood diseases: 24%
- Other: 1.8%
- Injuries, etc.: 12%
- Respiratory: 11%
- Digestive: 8.2%
- Neurological: 6.0%
- Urogenital, blood & endocrine: 4.0%
- Diabetes: 3.6%
- Other: 1.8%

Mostly from heart disease and cancer.
Genes or environment?

The population attributable fraction (PAF) represents the proportion of disease cases that would be prevented if the causal factor were eliminated.
E-risks of cancer

Finding unknown causes of cancer

- Elaborating genetic factors employs high-tech omics (GWAS and genome sequencing)
  - But has explained relatively little cancer risk
- Elaborating exposures relies on low-tech questionnaires, etc.
  - But has explained more than a third of cancer risk
- To find unknown causes of cancer, we must level the playing field
Complementing the Genome with an “Exposome”: The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

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Scientific citations to ‘exposome’ (Google Scholar)

- Wild, CEBP Commentary
- 1st NAS workshop
- Rappaport & Smith, Science Perspective
- 2nd NAS workshop
- Exposomics & HELIX (EU Programs)
- HERCULES (NIEHS Center)
- CHEAR (NIEHS RFA)
- Phenome Center (ICL)

Number of citations:
- 0
- 200
- 400
- 600
- 800
- 1000
- 1200
- 1400
- 1600

Year:
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
Disease pathways

Causal pathway (c)

Reactive pathway (r)

G = genome
E = exposome
R = transcriptome
P = proteome
M = metabolome (all small molecules and metals)

S. Rappaport, Biomarkers, 2012, 17(6), 48: 3-9
Chemical communication

G-factors

- DNA
- RNA
- Enzymes
- Receptors
- Cytokines
- Transcription factors
- Lipids
- Hormones
- Neurotransmitters

Signaling molecules and metabolites

Disease traits

Secondary traits

Mr

Pr
Chemical communication

- **G**
- **Rc**
- **Pc**
- **Disease traits**
- **Rr**
- **Pr**
- **Secondary traits**
- **Mr**

**E-factors**

- Foreign DNA and RNA
- Antigens
- Pollutants
- Microbial metabolites
- Drugs
- Food nutrients & toxins

**E-plots**
Altering communication

S. Rappaport, Biomarkers, 2012, 17(6), 48: 3-9
Capturing all exposures

Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, 70% to 90% of disease risks are probably due to differences in environments (1–3). Yet, epidemiologists increasingly use genome-wide association studies (GWAS) to investigate diseases, while relying on questionnaires to characterize “environmental exposures.” This is because GWAS represent the only approach for exploring the totality of any risk factors (genes, in this case) associated with disease prevalence. Moreover, the value of costly genetic information is diminished when inaccurate and imprecise environmental data lead to biased inference regarding gene-environment interactions (4). A more comprehensive and quantitative view of environmental exposure is needed if epidemiologists are to discover the major causes of chronic diseases.

An obstacle to identifying the most important environmental exposures is the fragmentation of epidemiological research along lines defined by different factors. When epidemiologists investigate environmental risks, they tend to concentrate on a particular category of exposures involving air and water pollution, occupation, diet and obesity, stress and behavior, or types of infection. This slicing of the disease pie along parochial lines leads to scientific separation and confuses the definition of “environmental exposures.” In fact, all of these exposure categories can contribute to chronic diseases and should be investigated collectively rather than separately.

To develop a more cohesive view of environmental exposure, it is important to recognize that toxic effects are mediated through chemicals that alter critical molecules, cells, and physiological processes inside the body. Thus, it would be reasonable to consider the “environment” as the body’s internal chemical environment and “exposures” as the amounts of biologically active chemicals in this internal environment. Under this view, exposures are not restricted to chemicals (toxics) entering the body from air, water, or food, for example, but also include chemicals produced by inflammation, oxidative stress, lipid peroxidation, infections, gut flora, and other natural processes (5, 6) (see the figure). This internal chemical environment continually fluctuates during life due to changes in external and internal sources, aging, infections, life-style, stress, psychosocial factors, and preexisting diseases.

The term “exposome” refers to the totality of environmental exposures from conception onwards, and has been proposed to be a new paradigm to assess how a lifetime of exposure to environmental factors affects the risk of developing chronic diseases.
A glimpse of the blood exposome

Normal blood concentrations (1,561 chemicals)
**Chemical space of the blood exposome**

*All chemicals*  
\[ n = 1,561 \]  
(weighted by blood conc.)

*Extraordinary diversity (>100 chemical classes from many sources)*

*Small circulating molecules*  
(‘metabolome’) provide one important avenue for characterizing biologically relevant exposures

*Chemicals with disease-risk citations*  
\[ n = 336 \]  
(weighted by # citations)

*Epidemiologists look for chemicals that cause diseases, regardless of their sources (endogenous, food, pollution, drugs).*

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Rappaport et al. Environ Health Perspect, 2014

SM Rappaport
Exposome-wide association studies (EWAS)

By applying EWAS with biospecimens from healthy and diseased subjects, we can discover useful biomarkers.

Then we can target these biomarkers in large populations.

http://www.flickr.com/photos/paulieparker/246707763/
Biospecimens for EWAS?

Reactive biomarkers obscure causal pathways (reverse causality). Validation of exposure biomarkers requires biospecimens obtained prior to disease (prospective cohorts).
Untargeted EWAS

Blood exposome

Causal biomarkers

Pollutant biomarkers

Endogenous biomarkers

Biomarkers of exposure

Diseased vs. healthy subjects

Reactive biomarkers

Biomarkers of disease

Drug biomarkers

Food biomarkers

Based on: S. Rappaport, Biomarkers, 2012, 17(6), 48: 3-9
Future of the exposome and disease etiology

- Transformative research happens once in a generation
- Between 1988 and 2010 genomic research dominated investigations of disease etiology despite disappointing results
- Exposomic research via EWAS will find causes of disease and could dominate the next generation of etiologic research
  - This will require integrated omics technologies - that measure chemicals comprehensively and efficiently in appropriate biospecimens - combined with advanced bioinformatics,
  - and government-academia-industry partnerships
Best wishes from Berkeley

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