Epigenetics, A Link between Environmental Pollutants and Cancer?
- Can we do better to prevent cancer?

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Cancer, A Worldwide Public Health Problem

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012.

The most common causes of cancer death are cancers of:

• lung (1.59 million deaths)
• liver (745 000 deaths)
• stomach (723 000 deaths)
• colorectal (694 000 deaths)
• breast (521 000 deaths)
• oesophageal cancer (400 000 deaths)

The International Agency for Research on Cancer (IARC) 2014
What Causes Cancer?

Cancer is a result of the interaction between the genetic factors and environmental/lifestyle factors:

• **Lifestyle factors**: Diet, physical inactivity, alcohol, smoking

• **Chemical carcinogens, such as** asbestos, components of tobacco smoke, aflatoxin (a food contaminant); **toxic heavy metals, air pollutants, plastic- and fast-food related chemicals, and pesticides**...

• **Biological carcinogens**, such as infections from certain viruses, bacteria or parasites
Is Cancer Preventable?

More than 30% of cancer deaths could be prevented by

Modifying or avoiding key risk factors, including:
  Lifestyle improvement
  Improve our environment/reduce environmental exposure
  Treatment of infection

Early detection
  Early diagnosis
  Screening: HPV testing for cervical cancer; PAP cytology test for cervical cancer; mammography screening for breast cancer

Intervention: Chemical agents, behavioral intervention
Modifying or avoiding key risk factors
Epigenetics?

- Study of mechanisms that regulate gene expression states without changes in DNA sequence
  - Genetically determined
  - Environmentally Inducible
  - Reversible
Epigenetics? 

- Epigenetics is the interface between the fixed genetics and ever-changing environment
Three Epigenetic Components

- **Histone modifications:**
  - Globular proteins that undergo posttranslational modifications
  - Histone acetylation increases gene expression activity
  - Histone methylation inhibit or increase gene expression depending on the modified amino acid position

- **MicroRNAs (miRNAs):**
  - A set of small and non-protein-coding RNAs.
  - microRNAs regulate expression of target genes at the posttranscriptional level by binding to 3’-untranslated regions of target mRNAs

- **DNA methylation:**
  - Occurs at CpG sites
  - Addition of a methyl group to the 5’ position of the cytosine ring
  - Gene-specific methylation changes and global hypomethylation
DNA Methylation Modifiers

• Aging
• Diet/Nutrition
• Lifestyle factors
• Inflammation
• Environmental pollutants
Epigenetic Markers - Genetically Determined and Environmentally Regulated

Twin Epigenetics
Epigenetic Markers - Genetically Determined and Environmentally Regulated

Twin epigenetics - Analysis of 80 MZ Twin Pairs between 3-73 years of age

(Braga et al. PNAS 2005)
A Life Course Perspective of Epigenetics
Environmental Pollutants may Cause Cancer via Epigenetic Mechanism
Burden of Cancer in China

• In China, 3.1 million patients were diagnosed with cancer and 2.2 million deaths caused by cancer in 2012. (WHO, 2014)

• In 2012, more than half of global new cases of liver cancer and esophageal cancer were in China, as well as 51% and 49% mortality cases, respectively. 40% of global incidence and mortality of stomach cancer cases were in China as well as one third of global lung cancer cases. (WHO, 2014)
Environmental Pollution - A Major Public Health Concern

Air Pollution

• Seven cities in China are ranked among the ten most polluted cities in the world. (Asian Development Bank, 2012)

• Less than 1% of the 500 largest cities in China meet the air quality standards recommended by WHO (PM$_{10} < 20$ μg/m$^3$). (Asian Development Bank, 2012)

• According to 2010 Global Burden of Disease (GBD) report, each year 1.2 million deaths and 25 million health life year lost are due to air pollution in China. (WHO, 2012)
Air pollutants

Air pollution: causing approximately 800,000 deaths worldwide on an annual basis

Particulate Matter (PM) - Complex mixture of solid and liquid particles - combustion products, sulphates, nitrates, metals, biological materials
Daily PM$_{2.5}$ Level in Beijing between 2008-2014
Air Pollution in Beijing

• Traffic derived air pollution is particularly critical in Beijing
  - Very high population density
  - Rapid increase in vehicles
  - Limited control of emissions
  - Factories in and around Beijing

• Providing a unique research opportunity for identifying potential PM-induced molecular changes that may not easily be detectable in low exposed populations
Our Beijing Air Pollution Study, 2008

- **Particle Mass**: PM$_{2.5}$ measured using active portable samplers
- **Traffic Particles**: Elemental Carbon (EC) measured by reflectance on PM$_{2.5}$ filters

<table>
<thead>
<tr>
<th>Group</th>
<th>PM$_{2.5}$ (µg/m$^3$)</th>
<th>EC (µg/m$^3$)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>P value</td>
</tr>
<tr>
<td>Office workers (n=120)</td>
<td>94.6 (64.9)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Truck Drivers (n=120)</td>
<td>126.8 (68.8) &lt;0.001</td>
<td>17.3 (6.7) &lt;0.001</td>
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</tbody>
</table>
Beijing Air Pollution Study

Results

• Mitochondrial MT-TF and MT-RNR1 DNA methylation was positively associated with metal-rich PM exposure.

• Decreased blood and mtDNA copy number with increased exposure to black carbon and ambient PM$_{10}$ exposure.
Beijing Air Pollution Study

Results

• Exposure to PM and its heavy metals is associated with hypo-methylation tandem repeats that were found to associated with cancers.

• Measuring tandem-repeat hypo-methylation in easy-to-obtain blood specimens might identify individuals with biological effects and potential cancer risk from PM exposure.
DNA Methylation and Cancer Incidence and Mortality in a US Population
Normative Aging Study (NAS) Cohort

- **NAS cohort (1963 ~ Now):**
  - N=2280
  - Age at enrollment: 20–70 years old
  - Longitudinal investigation of aging in Boston Area

- **Follow-Up:**
  - Questionnaire and medical examinations every 3 to 5 years;
  - Blood donation and genetic/epigenetic biomarkers were available since 1999.
Cancer Incidence and Mortality Follow-up

• Baseline Cancer
  – Study subjects with cancer: 219 (28% of 794)
  – Cancer free: 575 (72% of 794)
• Incidence Follow-up (n=575)
  – Median incidence follow-up time: 114 months (6,222 person-year)
  – Cancer diagnoses were confirmed on clinical records
  – Results: 130 new cases
• Mortality Follow-up (n=793, 1 participant had unknown date of death)
  – Median mortality follow-up time: 172 months (9,449 person-year)
  – Questionnaires and death certificate
  – Results: 67 deaths from cancer
Methylation Markers Studied

- Alu
- LINE-1
- Intercellular adhesion molecule-1 (ICAM)
- Interferon gamma (IFNγ)
- Interleukin-6 (IL6)
- Toll-like receptor-2 (TLR2)
- Inducible nitric oxide synthase (iNOS)
- 8-oxoguanine DNA glycosylase (OGG)
- Carnitine acetyltransferase (CRAT)
- Genome wide DNA methylation
Application of Optical Biomarkers to Early Detection of Gastrointestinal (GI) Cancers
Field Carcinogenesis and Cancer Early Detection

- **Ideal markers for early cancer detection:**
  Simple, minimally intrusive, sufficiently sensitive, and cost-effective

- **Field Carcinogenesis**
  - Increased susceptibility of an entire area to carcinogenesis
  - It represents the impact of the field-of-injury concept that the genetic and environmental risk factors confer a fertile mutational field throughout the area
Field Carcinogenesis Detection Using PWS

- Partial-Wave Spectroscopy (PWS) enables the sensitive detection of nanoscale cellular structural changes in field carcinogenesis

- Cellular Nano-architectural changes precede the microscopic morphological changes

- Visible-light microscopy allows morphological analysis only at micron scales due to the diffraction limit

- **Number of cells: 30**

- PWS analysis is performed off-site
PWS Image of Rectal Colonocytes from Control and Colon Cancer Patients

Representative PWS generated pseudocolor heatmap of Ld for the colonocytes from the circled region of control patient (C–E) and similarly are for patients with cancer (F–H).
Clinical Implications - Approach to Population Screening

- High risk population
- Nanocytology (PWS) prescreen
- Conventional cancer screening
- Neoplasia-harboring patient
Validation of optical biomarkers in large population -
Shanghai PWS and Gastrointestinal Track Cancer Study

Why China?

• Fast patient recruitment
• Low cost
• Large patients’ pool
• Cancers different from US
  - Different risk factors (Liver cancer)
  - Different incident/mortality rate
    (prostate, gastric)
Take Home Message:

• Environmental pollutants may cause cancers via epigenetic mechanism
• Educate the general population to live a healthy lifestyle
• Early detection is the key for cancer prevention
• Invention may be a solution to prevent highly-exposed individuals from cancer development – long way to go!
• Large population-based researches are urgently needed in different populations
Thank You!

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