Nutrition, epigenetics and health

Nigel Belshaw

nigel.belshaw@ifr.ac.uk
Content

• Introduction to epigenetics
• Epigenetics in chronic diseases and ageing
• The impact of diet and lifestyle on the epigenome
• Summary and future
**Genetics vs epigenetics**

**Genetics** - sequence

**Epigenetics** – “outside” sequence

Modifications to DNA or chromatin that affect the higher order structure (“packaging”).
Epigenetic modifications

• Histone modifications - the histone code
  - Acetylation, methylation, ubiquitylation, phosphorylation, etc

• DNA methylation
DNA methylation

- Enzyme-mediated methylation of cytosines only in CpG dinucleotides
DNA methylation affects chromatin structure
Roles for DNA methylation

• Silencing parasitic DNA elements such as transposons, retroviruses, etc

• Genomic imprinting – controlling maternal or paternal-specific gene expression

• X inactivation

• Tissue or cell-specific gene expression
Aberrant epigenetic events implicated in chronic diseases

• CVD – Ordovás and Smith (2010)

• Type 2 diabetes mellitus – Pirola et al (2010), Wren and Garner (2005)

• Alzheimer’s and cognitive disorders – Chouliaras et al. (2010), Gräff and Mansuy (2009)

• Cancer....
Colon (Bowel) Cancer

- 3rd most common cancer in UK (>37,500 new cases / year)
- Men > women (~2:1)
- ~16,000 deaths / year (16% down in last decade)
- ~50% of newly diagnosed will survive >5 years (doubled in last 30 years)
The role of lifestyle in the risk of colon cancer.

Age-standardised incidence of CRC in 21 regions in 2002

The increasing Incidence of colorectal cancer in Japan during the 20th century coincided with westernisation of the diet/lifestyle.


Cancer and Ageing

• Age is the number one risk factor for colon cancer

• Age has even been called a potent carcinogen (DePinho (2000) Nature)

• Age-associated changes in the colon include more cell proliferation and less cell death
The adenoma-carcinoma sequence is the general model for colorectal carcinogenesis...

**Precancerous Field Changes**

The vulnerable mucosa is characterised by an age-associated loss of tissue homeostasis, including increased cell growth, decreased cell death, genetic changes (somatic mutations e.g. APC, K-ras), and epigenetic changes (aberrant DNA methylation).

**Disease Process**

Genetic changes (somatic mutations e.g. APC, K-ras) lead to the development of small adenomas, which eventually progress to carcinomas.
Abnormal DNA methylation in colon cancer

Ehrich M et al. PNAS 2008;105:4844-4849

7 colon cancer cell lines
48 colon cancer samples
48 normal tissue samples
6 normal control DNAs

~3 different groups of tumours.
Different prognoses?
Different treatments?
An early role for aberrant DNA methylation in colon carcinogenesis

Dnmt3b promotes tumorigenesis in vivo by gene-specific de novo methylation and transcriptional silencing

Heinz G. Linhart,1 Haijiang Lin,1,6 Yasuhiro Yamada,2 Eva Moran,1 Eveline J. Steine,1 Sumita Gokhale,1 Grace Lo,3 Erika Cantu,3 Mathias Ehrich,4 Timothy He,5 Alex Meissner,1 and Rudolf Jaenisch1,3,7
Genes and Development (2007) 21, 3110-22

Genes methylated by DNA methyltransferase 3b are similar in mouse intestine and human colon cancer

Eveline J. Steine,1 Mathias Ehrich,2 George W. Bell,1 Arjun Raj,3 Seshamma Reddy,1 Alexander van Oudenaarden,3 Rudolf Jaenisch,1 and Heinz G. Linhart1,4,5
Aberrant DNA methylation is associated with the field effect...

CGI methylation profiling in the morphologically normal mucosa

- Patients free of polyps or cancer: Sensitivity = 62%, Specificity = 79% ($p = 0.0167$)
  - SFRP5, WIF1 and SFRP4

- Polyp patients: Sensitivity = 84%, Specificity = 70% ($p = 1.25 \times 10^{-5}$)
  - APC, HPP1, p16, SFRP4, ESR1 and WIF1

- Cancer patients

(Belshaw et al. 2008)
Many genes are aberrantly methylated in normal tissue in an age-dependent manner.

(Belshaw et al. 2008)
• Young MZ twins are epigenetically very similar but diverge with age.
• Divergence is greatest in twins who have spent the longest time apart suggesting epigenetic drift (age-related methylation) is due to lifestyle.
• Cell types studied – lymphocytes, buccal, muscle and adipose
The impact of age, nutrition and metabolic factors on DNA methylation in the colonic mucosa

- Cross-sectional study of >200 healthy volunteers with significant meta-data
- Quantified the methylation status of several genes in normal colon tissue

<table>
<thead>
<tr>
<th>Cofactor</th>
<th>( r )</th>
<th>( p^{1}(r) )</th>
<th>( B )</th>
<th>( p(B) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.447</td>
<td>1.004E-10</td>
<td>2.411</td>
<td>2.580E-09</td>
</tr>
<tr>
<td>BMI</td>
<td>0.150</td>
<td>0.039</td>
<td>0.760</td>
<td>0.046</td>
</tr>
<tr>
<td>SerumFolate</td>
<td>0.173</td>
<td>0.017</td>
<td>0.872</td>
<td>0.030</td>
</tr>
<tr>
<td>WhiteCells</td>
<td>-0.095</td>
<td>0.194</td>
<td>-0.902</td>
<td>0.044</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.155</td>
<td>0.032</td>
<td>1.218</td>
<td>0.006</td>
</tr>
<tr>
<td>Selenium</td>
<td>-0.103</td>
<td>0.155</td>
<td>-0.963</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Variables contributing significantly to the variation in DNA methylation selected by genetic algorithm

<table>
<thead>
<tr>
<th>Gene</th>
<th>Age</th>
<th>Variables</th>
<th>White Cells</th>
<th>Monocytes</th>
<th>Selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIF1</td>
<td>Age</td>
<td>BMI, Serum Folate, White Cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFRP1</td>
<td>Age</td>
<td>Red Cell Folate, Monocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFRP2</td>
<td>Age</td>
<td>Fatness Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>Age</td>
<td>Vitamin D, Fatness Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOX17</td>
<td>Age</td>
<td>White Cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPP1</td>
<td>Age</td>
<td>Monocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR1</td>
<td>Age</td>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYOD</td>
<td>Age</td>
<td>Serum Folate, Vitamin D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N33</td>
<td>Age</td>
<td>Waist, Serum Folate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA1</td>
<td>Age</td>
<td>Serum Folate, Vitamin D, Selenium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Positive correlation  
Negative correlation  
Sex-specific effect
The maintenance of gut health – preventing mucosal vulnerability

Normal mucosa

TIME

Epigenetic changes

‘Vulnerable’ mucosa

DIET
ADIPOSITY
PHYSICAL ACTIVITY

Disrupted homeostasis
Compromised renewal
Increased risk of disease

Do these epigenetic changes compromise tissue homeostasis?
How is the “environmental signal” transduced to the epigenome?
Are these epigenetic changes reversible?
Nutrition in Epigenetics
Mihai D. Niculescu (Editor),
Paul Haggarty (Editor)
ISBN: 978-0-8138-1605-0
May 2011, Wiley-Blackwell
The importance of DNA methylation

• It is a flexible genomic parameter that can change in response to exogenous influences.

• It constitutes a missing link between genetics, disease and the environment (perhaps especially diet).

• It is widely thought to play a significant (perhaps decisive) role in the aetiology of many human pathologies and ageing.
Epigenetic changes: how the genome learns from experience

TIME

DIET, LIFESTYLE + ENVIRONMENT
Future prospects

• Epigenetic epidemiology and Epigenome-wide association studies (EWAS)

• Novel (predictive) biomarkers of health/(risk of) disease

• Reversibility
Strategic Relevance

BBSRC’s strategic research priority 3 – Basic bioscience underpinning health

• “Basic bioscience is vital to reveal the biological mechanisms underlying normal physiology and homeostatic control during early development and through life.”

• “A key research goal is to develop a better understanding of the role of diet and physical activity and the mechanisms by which they affect development and health.”

Some key priorities 2010-2015

• Generate new knowledge of the biological mechanisms of ageing, and the maintenance of health

• Establish greater understanding of how diet affects health throughout life, including EPIGENETIC effects, complex dietary exposures and gut function
Acknowlegements

IFR
Ian Johnson
Henri Tapp
Giles Elliott
Wing Leung
Carol Connor
Lawrence Barrera
Guus Kortman
Jack Dainty
Kasia Przybylska
Stefan Mann

UEA
Mark Williams and team

NNUH
Mike Lewis
Nandita Pal
Jamie Sington

Newcastle University
John Mathers and team

Washington University
Annette Fitzpatrick