Investigating epigenetic mechanisms for cancer prevention

International Agency for Research on Cancer
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Outline

I. Introduction to epigenetics
II. Results from epigenomic studies on environmentally-related cancers
III. Summary and perspectives

Introduction to epigenetics.

Original Article
Open
Scrutinizing the epigenetics revolution

Meloni and Testa, 2014

Epigenetics defines all (mitotically) heritable changes in gene expression that are not coded in the DNA sequence itself

Epigenome defines the totality of epigenetic marks in a cell type
Introduction to epigenetics.

Four types of epigenetic mechanisms

Long non-coding RNAs

Introduction to epigenetics.

Crosstalk among environmental exposures and epigenetic events in cancer

Results from epigenomic studies

I. Long non-coding RNAs in the development of hepatocellular carcinoma

II. DNA methylation signature of Human Papilloma Virus (HPV) in head and neck squamous cell carcinomas
**What long non-coding RNAs are and why to study them**

Long non-coding RNAs are a further layer of the epigenetic mechanisms controlling cellular fate.

**Hypotheses and Aims**

**Hypothesis**

Changes in the expression of lncRNAs may be an early event during human hepatocarcinogenesis playing a role in translating environmental exposures into epigenetic modifications.

**General Aims**

I. To obtain the most complete profile of lncRNAs in normal, cirrhotic tissues surrounding tumours and HCC by RNA-Sequencing. 20 cases + 10 control livers.

II. To identify differentially expressed lncRNA in HCC or earlier steps of HCC development.

III. To identify the signaling pathways in which lncRNAs may play a functional role in human liver carcinogenesis.

**Results: Differential and co-expression analyses**

- 7% of DEGs in HCC compared with the adjacent cirrhotic tissues are lncRNAs.
- DE lncRNAs mostly divided into 2 classes: cell cycle-related and liver metabolism-related.
- Disruption of the co-expression patterns is often observed in cirrhotic tissues.
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Meta-analysis of DNA methylome in HNSCCs

3 studies: TCGA, UCL, IARC-UniNice. 450k CpG sites analyzed (Illumina)

338 cases, 66 HPV+ (mostly HPV16) ⇒ 327 cases, 62 HPV+

Global DNA methylation levels separate HPV positive vs HPV negative HNSCCs

HPV+ HNSCC show a distinct DNA methylation signature

Top 100 DMPs

5-probes methylation signature

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
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</thead>
<tbody>
<tr>
<td>HPV+</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td>HPV-</td>
<td>3</td>
<td>261</td>
</tr>
</tbody>
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Sensitivity: 95.2%
Specificity: 98.5%
Positive Pred Value: 93.6%
Negative Pred Value: 98.9%
Overall error rate: 2.2%

A small set of differentially methylated CpGs may be capable to identify with high confidence different etiological factors in tumour tissues
Conclusions and perspectives

- Epigenome is an interface between genome and environment and is profoundly altered in cancer.
- Epigenomic studies may allow the identification of more sensitive or specific biomarkers of exposure or disease.
- Epigenome-wide association studies have been recently implemented and first results seem promising in the identification of association between exposure and markers of cancer risk in some specific exposure context. Some challenges remain in study design, statistical modeling and interpretation of these studies.
- Experimental studies using adequate animal models and in vitro systems should be encouraged. They have the potential to improve the understanding of mechanistic aspects of the complex interactions between multiple exposures, epigenetics response and cancer development relevant to humans.

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Back-up slides