Epigenetics of Cancer
A New Way to Manage Oncology Patients
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I. Introduction

In the 1940s, Conrad Waddington introduced the term epigenetics, literally “over genetics.” The field occupies the object of ambiguity and contention, however is broadly accepted as the mitologically and/or meiotically heritable changes in gene expression that occur without changes in DNA sequence.

Epigenetics

The punctuation marks in the genome

- D差异化起始和end of genes.
- Provide structure to the chromosome.
- Leads to genes being expressed (Active) or not expressed (Silent, inactive).
- Chemically Stable.
- Heritable and Reversible.
- Modulated by environmental factors.

Figure 1. Epigenetic modifications control gene expression leading to gene activation or gene silencing. DNA domains that promote from the core histones are subject to covalent modification that include lysine (K) acetylation by HAT and methylation by HMT. DNMT, DNA methylation by converted SAM to 5′-methylcytosine DNA; HMDD, histone deacetylases.

Epigenetics in cancer

A partnership of genetic abnormalities in malignant cellular transformation

Normal Tissue

Hyperplasia

Neoplasia

Invasion

CpG island

CpG hypermethylated

CpG unmethylated

CpG hypomethylated

Figure 2. Epigenetic alteration can lead to tumor progression. There is a progressive loss of DNA methylation content, an increased frequency of hypermethylated CpG islands, and an increased histone modification instability in cancer development.

II. Objectives

- Highlight the role that the changes of epigenetic landscape could have on the genesis of cancer.
- Detect potential epigenetic targets in cancer cells which can contribute to the management of cancer patients in different areas.
- Analyze the real applicability of those potential epigenetic targets and its benefit to oncology patients.

III. Methodology

Data presented in this poster comes from:

30 out of 50 recent papers and reviews selected according to their quality and publication date.

Keywords: (alone or in combination): epigenetics, cancer, DNA methylation, biomarker, detection, prognosis, treatment response, epigenetic therapy.

Figure 3. Three main sources of information governed the performance of this project. Literature research on PubMed and ScienceDirect for paper published prior the end of May 2010, six weeks course offered by the education platform Coursera and congress assistance. Ontology thesis consulting from TEO database and Google Books service were also used in this bibliographic work.

IV. Results

In order to understand the role and advantages that epigenetics could have on the clinic as a biomarker it is necessary to consider the early onset of epigenetic modifications in tumor development and the gradual manner of acquisition. The reversal property of epimutations will be necessary to comprehend the mechanism that most of epigenetic therapies are using or trying to use.

Epigenetic Biomarkers in Cancer Detection

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Sample</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>Urine / Blood plasma / Ejaculate</td>
<td>GSTP1</td>
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</table>

GSTP1 has been found hypomethylated in at least 80% of prostate cancer tissues. The noninvasive analysis of this epigenetic mark in circulating DNA could be considerate as an alternative to the widely used prostate specific antigen (PSA) associated to prostate cancer, but also to prostate or benign prostatic hyperplasia providing false positive results in prostate cancer screening.

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<thead>
<tr>
<th>Cancer</th>
<th>Sample</th>
<th>Target</th>
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<tbody>
<tr>
<td>Lung Cancer</td>
<td>Bronchial aspirate / Blood plasma</td>
<td>SHOX2</td>
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SHOX2 is hypomethylated in 90% of lung cancer tumors. A Blood-based test for SHOX2 methylation resulted in an overall sensitivity of 62% and in a specificity of 90%. Current tests such as computed tomography show early stage cancers but X-rays used may cause lung damage. SHOX2 methylation analysis could be simple, quick, and not harmful tool in patients suspected of having lung cancer.

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<thead>
<tr>
<th>Cancer</th>
<th>Sample</th>
<th>Target</th>
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<tbody>
<tr>
<td>Colorectal Cancer</td>
<td>Blood plasma / Feces</td>
<td>SEPT9</td>
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SEPT9 blood-based methylation detection test with a specificity of 90% could be a good choice for the screening of individuals at risk of developing colorectal cancer. This test could also be an effective to the routinely invasive and discomfort test used in the include occult blood test, colonoscopy and sigmoidoscopy.

Epigenetic Biomarkers in Cancer Prognosis

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<tr>
<th>Cancer</th>
<th>Sample</th>
<th>Target</th>
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<tbody>
<tr>
<td>Breast Cancer</td>
<td>Blood plasma</td>
<td>BRCA1</td>
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BRCA1 is critical for double-stranded DNA breaks repair. Defects in the DNA repair machinery due to methylation in BRCA1 accelerate the development of breast cancer and therefore is associated with poor outcome. BRCA1 methylation could be a predictive marker in the clinical management of patients.

Epigenetic Biomarkers in Treatment Response

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<th>Cancer</th>
<th>Sample</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma Cancer</td>
<td>Blood plasma</td>
<td>MGMT</td>
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</table>

MGMT promoter hypermethylation has been used to predict cancer patients’ treatment response to Temozolomide. Those human primary tumors undergoing hypermethylation of this gene encodes a DNA repair protein that removes alkyl groups, will be more sensitive to chemotherapeutic drug such as Temozolomide used as an alkylating agent in glioblastomas.

V. Conclusions

- What clearly comes out from this work is that disruption of epigenetic landscape is a central contributor to human cancer, traditionally seen as a “genetic disease”.
- For its heritability, stability, detection at early stages and quantification in human cells by genome-wide and gene-specific methods, DNA methylation is perfectly as a biomarker.
- The possibility to analyze the reliable biomarker in surrogate tissues such as blood or other body fluids obtained through minimally invasive procedures justify its implementation as routine analytic procedure in oncology.
- The reversal property of epimutations has enabled the development of small-molecule inhibitors against chromatin regulators with the aim to repair the epigenetic landscape in cancer cells.
- It is essential a good quality basic research to detect what goes wrong in cancer epigenetics, but is becoming increasingly necessary one step further and contribute directly in patients’ benefit.

Footnotes: L.M.E. performed this work under the “Bachelor’s Degree Final Project” program from Universitat Autònoma de Barcelona, as undergraduate student of Biomedical Sciences.