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 remains the object of ambiguity and contention, however is broadly accepted as the mitotically and/or meiotically heritable changes in gene expression that occur without changes in DNA sequence.

Epigenetics

The punctuation marks in the genome

- Demarcate the start and end of genes.
- Provide structure to the chromosome.
- Leads to gens being expressed (**Active**) or not expressed (**Silent**, inactive).
- Chemically Stable.
- Heritable and Reversible.
- Modulated by environmental factors.

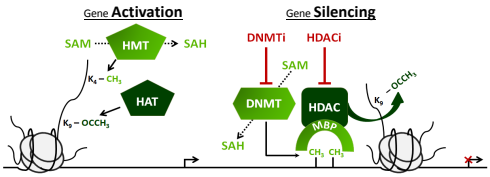


Figure 1. Epigenetic modifications control gene expression leading to gene activation or gene silencing. Tail domains that protrude from the core histones are subject to covalent modification that include lysine (K) acetylation by HAT and methylation by HMT. DNMTs methylate DNA by convertint SAM to SAH, a mechanism that can be inhibited by DNMTi. MBPs recognise methylated DNA and recruit HDACs, which deacetylate lysines in the histone tails, leading to a repressive state.

***HMT**, histone methyltransferase; **HAT**, histone acetyltransferase; **DNMT**, DNA methyltransferase; **DNMTi**, DNMT inhibitor; **SAM**, S-adenosylmethionine; **SAH**, S-adenosylhomocysteine; **MBP**, methyl-binding domain; **HDAC**, histone deacetylase; **HDACi**, HDAC inhibitors.*

Epigenetics in cancer

A partnership of genetic abnormalities in malignant cellular transformation

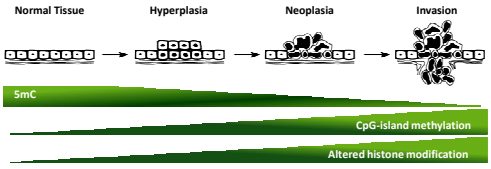


Figure 2. Epigenetic alteration can lead to tumor progression. There is a progressive loss of total DNA methylation content, an increased frequency of hypermethylated CpG islands, and an increased histone-modification imbalance in cancer development.

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 data of publication.

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

"Epigenetic Control of Gene Expression" course

Course of **6 weeks** Offered by **The University of Melbourne**

"Barcelona Conference on Epigenetics and Cancer"

"Challenges, Opportunities and perspectives"

November, 21 and 22, 2013

6 Sessions **23 Speakers** **50 Posters**

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 2014; six weeks course offered by the education platform Coursera; and congress assistance. Doctoral thesis consulting from TESEO 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.

Biomarkers

Epigenetic Biomarkers in Cancer Detection

Cancer: Prostate Cancer
Sample: Urine / Blood plasma / Ejaculate
Target: *GSTP1*

GSTP1 has been found hypermethylated 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 prostatitis or benign prostatic hyperplasia providing false positive results in prostate cancer screening.

Cancer: Lung Cancer
Sample: Bronchial aspirate / Blood plasma
Target: *SHOX2*

SHOX2 is hypermethylated in 96% 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 useful simple, quick, and not harmful tool in patients suspected of having lung cancer.

Cancer: Colorectal Cancer
Sample: Blood plasma / Feces
Target: *SEPT9*

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 alternative to the routinely intrusive and discomfort test used in the include occult blood test, colonoscopy and sigmoidoscopy.

Epigenetic Biomarkers in Cancer Prognosis

Cancer: Breast Cancer
Sample: Blood plasma
Target: *BRCA1*

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.

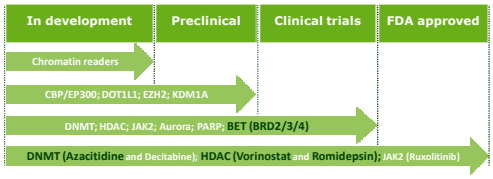
Epigenetic Biomarkers in Treatment Response

Cancer: Glioblastoma Cancer
Sample: Blood plasma
Target: *MGMT*

MGMT promoter hypermethylation has been used to predict cancer patients's treatment response to Temozolomide. Those human primary tumors undergoing hypermetilation of this gene which 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.

Therapies

Targets and Stages of Epigenetic Drug Development



DNMT inhibitors

Azacitidine has been licensed by the FDA for use in all subtypes of in the treatment of **myelodysplastic syndrome (MDS).**

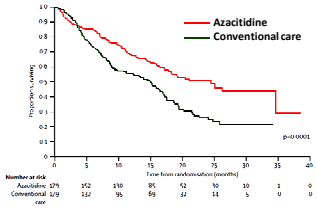


Figure 4. Kaplan-Meier survival curves for azacitidine and conventional care groups in a randomised, open-label, phase III study. Azacitidine treatment was associated with a significant improvement in overall survival comparing it with best supportive care. Fenaux, P. *et al. Lancet Oncol.* **10,** 223–32 (2009).

HDAC inhibitors

HDACs reverse lysine acetylation and its expression levels appear to be altered in numerous malignancies. HDAC inhibitors such as **Vorinostat** and **Romidepsin** have recently been granted FDA approval for clinical use in patients with **cutaneous T cell lymphoma**.

BET inhibitors

BET inhibition is an effective treatment for **MLL-fusion leukaemia.**

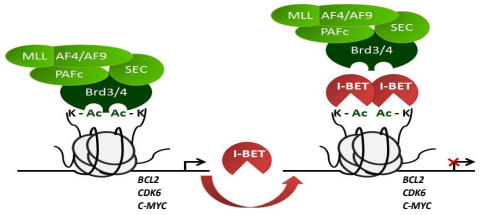


Figure 5. Schematic model proposing the mode of action for I-BET in MLL-fusion leukaemia. MLL target genes *(BCL2, CDK6, MYC)* are down regulated by I-BET due to the displacement of BRD3/4, PAFc and SEC components from chromatin.

***MLL**, mixed lineage leukaemia; **BET**, bromodomain and extra terminal family of proteins; **I-BET**, BET inhibitors; **SEC**, super elongation complex; **PAFc**, polymerase-associated factor complex.*

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 perfect 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 going one step further and contribute directly in patients' benefit.

Footnote: 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.