The Modifying Role of Epigenetics in Breast Cancer

Rachel Yung, MD
University of Washington, Seattle Cancer Care Alliance
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November 10, 2018
No Disclosures
How might Epigenetics effect Breast Cancer Treatment?
Objectives

• Define epigenetics and the mechanisms by which it occurs

• Recall examples of epigenetics in development and inherited disease

• Explore the role of epigenetics in cancer development

• Understand the burgeoning field of epigenetics in breast cancer pathology and treatment
What is Epigenetics?

Changes in gene expression without a change in DNA sequence.
Change in phenotype without a change in genotype.
Can be passed on through cell divisions or even generations.

Mechanisms:
1. DNA accessibility
2. DNA methylation
3. Histone modifications
4. Noncoding RNAs
Why is epigenetics important?
Significance of the non-coding genome

Montalbano, Canver and Sanjana, 2017
What is the Epigenome?

- the entirety of epigenetic code across all of the cells in the body
- the epigenome can be reprogrammed, whereas the genome cannot
- reprogramming of the epigenome can occur during
  - stages of normal development
  - response to environmental exposures
  - acquired disease states
  - in response to medications that target epigenetic regulators
Epigenetics: A Familiar Example

Early Embryo → X-Inactivation → Adult with unique coat pattern
## Epigenetics and Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptom</th>
<th>Aetiology</th>
</tr>
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<tbody>
<tr>
<td>ATR-X syndrome</td>
<td>Intellectual disabilities, (\alpha)-thalassaemia</td>
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<td>Fragile X syndrome</td>
<td>Chromosome instability, intellectual disabilities</td>
<td>Expansion and methylation of CGG repeat in FMR1 5’ UTR, promoter methylation</td>
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<td>Organ overgrowth</td>
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<td>(\alpha)-Thalassaemia (one case)</td>
<td>Anaemia</td>
<td>Methylation of (\alpha)2-globin CpG island, deletion of HBA1 and HBQ1</td>
</tr>
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<td>Various cancers</td>
<td>Microsatellite instability</td>
<td>De novo methylation of MLH1</td>
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**Important Note!** Epigenetics influences the phenotype of many diseases that are caused by genetic mutations.

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### Important Note!

Epigenetics influences the phenotype of many diseases that are caused by genetic mutations.

How does Epigenetics work?
Chromatin Structure and Modifications
<table>
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<tr>
<th>Chromatin Organization</th>
<th>Transcriptional State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naked DNA</td>
<td>Visible nucleosomes</td>
</tr>
<tr>
<td>Less active</td>
<td>Actively transcribed chromatin (interphase)</td>
</tr>
<tr>
<td>condensed chromatin</td>
<td>Condensed chromatin (metaphase)</td>
</tr>
</tbody>
</table>
Histone Modification
Enzymes that Modify Histones and DNA

HATs, HMTs, DNMTs: writers
HDACs, demethylases: erasers
Bromodomains, Chromodomains: readers

In general:
- Active genes have heavily acetylated histones
- “Primed” genes (inactive genes in an activatable state) have less heavily acetylated histones
- Heterochromatin: Silenced genes are not very heavily acetylated, but are heavily methylated on DNA and on histones
Methylation is self-reinforcing

Histone deacetylases (HDAC) deacetylate lysine residues as a prerequisite for their subsequent methylation.

DNA methyltransferases (DNMT) participate in multiprotein complexes that contain HDACs and HMTs.

The HP1 protein recognizes MeK9 and, as this protein also binds the histone methyltransferase (HMT), heterochromatin can spread.

Histone (H3) modifications include lysine (K) acetylation (Ac) and lysine methylation (Me). Lysines at other positions are also modified.

Methyl-C binding proteins (MBD) can be loaded onto methylated DNA through their interactions with both HDACs and HMTs.

Feinberg & Tycko, Nature Reviews Cancer
Covalent DNA Modifications - Methylation

Cytosine  methylated Cytosine

Typical mammalian DNA methylation landscape
Covalent DNA Modifications - Methylation

Cytosine  methylated Cytosine

Typical mammalian DNA methylation landscape
Non-coding RNAs regulate gene expression

**IncRNAs: diverse mechanisms**

- HOTAIR
- XIST
- ANRIL
- TSIX
- XITE
- INK4B/ARF/INK4A
- DHFR ncRNA
- TFIIIB

**Small RNAs**

- siRNA pathway
- miRNA pathway
- miRNA-encoding genes
- Nucleus
- Cytoplasm
- Dicer
X-inactivation
Epigenetics in Cancer
Classic Epigenetics in Cancer

Pfeifer, Molecular Sciences, 2018
Epigenetic Changes with Hypermethylation

Pfeifer, Molecular Sciences, 2018
Mammary Cell Development & Epigenetics
Normal Breast Tissue Development
Epigenetics Breast Cancer and the Environment
### Major Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>100</td>
</tr>
<tr>
<td>Age (30 vs. 70)</td>
<td>10</td>
</tr>
<tr>
<td>Intraepithelial neoplasia (DCIS, LCIS, ADH, etc.)</td>
<td>2 to 10</td>
</tr>
<tr>
<td>Prior breast/ovarian cancer</td>
<td>2 to 10</td>
</tr>
<tr>
<td>1° relative younger than age 60 at diagnosis</td>
<td>2</td>
</tr>
<tr>
<td>Germ-line mutations responsible for hereditary breast cancer</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Breast Density (slightly increased vs. extremely dense)</td>
<td>1.79 to 4.64</td>
</tr>
</tbody>
</table>
Modifiable Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk (RR) or Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Hormone Therapy</td>
<td>~26% ↑</td>
</tr>
<tr>
<td>Obesity (&gt;82 kg vs. &lt;59 kg)</td>
<td>2.85 ↑</td>
</tr>
<tr>
<td>Alcohol intake (4 drinks/day vs. non-drinkers)</td>
<td>1.32 ↑</td>
</tr>
<tr>
<td>Parity (Nulliparous vs. parous by 20yo)</td>
<td>2 ↑</td>
</tr>
<tr>
<td>Breast Feeding</td>
<td>4.3% ↓ Qyr</td>
</tr>
<tr>
<td>Exercise (strenuous exercise ≥ 4 hrs/week)</td>
<td>30% to 40% ↓</td>
</tr>
</tbody>
</table>

37% of attributable risk is due to modifiable risk factors
Epigenetic changes with life events

Choline/Folic Acid
- Alters DNA methylation pattern
- In Utero
  - DNA - globally demethylated then subsequently remethylated

Puberty
  - The gland further develops its rudimentary structures

Pregnancy
  - DNA is hypomethylated

Lactation
  - DNA is hypomethylated
  - H3 & H4 are hyperacetylated
  - Mammary Carcinoma
    - DNA is hypermethylated
    - H3 & H4 are hypoacetylated
Epigenetic changes with pregnancy

Early Parity, <20 and <25, reduces risk of breast cancer 50% and 38%

Mouse study of parous vs nulliparous
• Epigenetics is involved in differentiation of tissue
• Evaluated epigenome for early and late changes
• Differential Methylation of Igfr
• Corresponded with mRNA (protein product)
• IGF/GH pathway is implicated in BC risk
• Persistently epigenetic changes with parity may explain the difference in risk of Breast Cancer

Katz, CRB 2014
Increased Epigenetics Age in Normal Breast Tissue of Luminal A Breast Cancer Patients

• 35 case, 53 controls
• “Epigenetic Clock”
  • Biomarker of aging
  • Measure methyl of 353 CpGs
• Age and epigenetic age correlated
• Cases and Controls differed
  • (p<0.001)
• Smoking correlated w/DNAmAge
Breast Cancer Epigenetics
Epigenetics and Breast cancer development

Normal

- DNA methylation
  - RARβ
  - SFRP1
  - CCND2

- Histone Modification/Enhancer
  - HDAC1
  - HDAC2
  - HDAC6

- Noncoding RNA
  - miR-21
  - miR-98
  - miR-93
  - miR-200c

ADH/DCIS

- DNA methylation
  - APC
  - HOXA1
  - RASSF1A

- Histone Modification/Enhancer
  - H4K16ac
  - H4K12ac

- Noncoding RNA
  - HOTAIr
  - miR-10b
  - let-7d

Invasive

- DNA methylation
  - HOTAIR
  - EZH2

- Histone Modification/Enhancer
  - HDAC9
  - EZH2

- Noncoding RNA
  - miR-210
  - miR-221

DeVaux, J MamGlad, 2018
Epigenetic Changes in Breast Cancer

Holliday, Breast Cancer Research 2018
Epigenetics in BC Subtypes

• DNA Methylation patterns can reflect breast cancer subtypes
• Can lead to cancer heterogeneity
• Demethylation in the binding sites at the enhancers of three well-studied transcriptional factors, ERα, FOCA1, and GATA has been detected in ER+ breast cancers in comparison to normal breast tissue

Branham, Oncogenesis 2012
DNA Methylation – Explaining “BRCAness”

- 30% of TNBC cases have a BRCA mutation
- However, a large number of tumors share the molecular features of BRCA-mutant cancer, a state defined as “BRCAness”
- May be due to the hypermethylation of the promoter region of the BRCA1 gene
- Mutually exclusive relationship between a BRCA1 mutation and promoter methylation
- TNBC with BRCAness may respond to PARPi, platinum agents, and anthracycline
miRNAs in Breast Cancer

Mandujano-Tinoco, BCRT, 2018, Review
Promising Clinical applications of miRNA

• 1) Diagnosis, Prognosis, classification and biomarkers
  • miRNAs can be stable for 10 years in ffpe sections
  • Liquid biopsies/Predict tumor subtypes
  • Potentially Predict chemo-resistance

• 2) Drugable
  • Antagonize upregulated miRNA with antisense oligonucleotides (anti-MiRs)
  • Enhance downregulated miRNAs with Mi RNA replacement with miRNA mimics
  • Delivery of miRNA with vectors, liposomes, nanoparticles and nanocells

Mandujano-Tinoco, BCRT, 2018, Review
Epigenetic strategies in Treatment of Breast Cancer
Pearls from early clinical work

• Poor results with epigenetic drugs at cytotoxic doses
  • Significant toxicity
  • Not durable response

• Improved results used at low dose
  • Ex: AZA and Decitabine in MDS and heme malignancies

• Promising results as adjunct = "Epigenetic priming"
  • Restore sensitivity (to hormone or chemotherapy)
  • sensitize cancer cells to the host immune system
  • boost the effects of immunotherapies such as check-point inhibitors

Ronnekleiv-Kelly, Cancer Treatment Reviews 2017
Clinical trials of epigenetic therapy as adjunct

Table 2
Select trials of combination epigenetic therapy and chemotherapy in advanced cancer. Primary cancer highlighted in bold.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient pathology</th>
<th>AIM</th>
<th>Epigenetic therapy</th>
<th>Chemotherapy</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronel et al. [36]</td>
<td>Stage IVB Cervical Cancer (n = 36)</td>
<td>Evaluate efficacy of CTx + Epigenetic Tx versus CTx alone</td>
<td>Hydralazine (DNMTi), Valproic Acid (HDACi)</td>
<td>Topotecan, Cisplatin</td>
<td>10 months versus 6 months PFS, (p = 0.03)</td>
</tr>
<tr>
<td>Juergens et al. [20]</td>
<td>Progressive, metastatic NSCLC (n = 45)</td>
<td>Evaluate efficacy of DNMTi plus HDACi in chemotherapy refractory disease</td>
<td>Azacitidine (DNMTi), Entinostat (HDACi)</td>
<td>Variable following epigenetic tx</td>
<td>DS or PR in 12/45, durable response (&gt;2 years) in 5/45</td>
</tr>
<tr>
<td>Witta et al. [38]</td>
<td>Advanced stage (IIIB/IV NSCLC progressed on prior therapy (n = 132)</td>
<td>Evaluate HDACi in reversing EGFR-TKI resistance in NSCLC</td>
<td>Entinostat (HDACi)</td>
<td>Erlotinib (EGFR-TKI)</td>
<td>E-cadherin high expression benefit (9.4 months versus 5.4 months OS)</td>
</tr>
<tr>
<td>Ramalingam et al. [39]</td>
<td>Advanced stage (IIIB/IV NSCLC previously untreated (n = 94)</td>
<td>Evaluate HDACi in reversing EGFR-TKI resistance in NSCLC</td>
<td>Vorinostat (HDACi)</td>
<td>Carboplatin and Paclitaxel</td>
<td>RR 34% versus 12.5% (p = 0.02); OS 13 months versus 9.7 months (p = 0.17)</td>
</tr>
<tr>
<td>Yardley et al. [40]</td>
<td>Locally advanced or stage IV Breast Ca progressed on AI (n = 130)</td>
<td>Evaluate HDACi effect of sensitization to AI therapy</td>
<td>Entinostat (HDACi)</td>
<td>Exemestane (AI)</td>
<td>Median OS 28.1 versus 19.8 months (p = 0.036)</td>
</tr>
<tr>
<td>Fu et al. [41]</td>
<td>Advanced stage (IIIB/IV) platinum refractory Ovarian Ca (n = 30)</td>
<td>Evaluate ability of DNMTi in reversing platinum resistant or platinum refractory ovarian ca</td>
<td>Azacitidine (DNMTi)</td>
<td>Carboplatin</td>
<td>1 cCR, 3 cPR and 10 patients with SD</td>
</tr>
<tr>
<td>Matei et al. [42]</td>
<td>Advanced stage, heavily treated, platinum-res Ovarian Ca (n = 17)</td>
<td>Evaluate efficacy of DNMTi in reversing platinum resistant or platinum refractory ovarian ca</td>
<td>Decitabine (DNMTi)</td>
<td>Carboplatin</td>
<td>RR 35% (1 cCR, 3cPR); Median PFS 10.2 months</td>
</tr>
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NSCLC = non small cell lung cancer, CTx = chemotherapy, DNMTi = DNMT inhibitor, HDACi = HDAC inhibitor, PFS = progression free survival, OS = overall survival, SD = stable disease, cPR = clinical partial response, cCR = clinical complete response, EGFR = epidermal growth factor receptor, TKI = tyrosine kinase inhibitor.
## Epigenetic Drugs in Clinical Trials

**Table 3**

Trials in Epigenetic Therapy.

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<th>Type</th>
<th>Group</th>
<th>Drug</th>
<th>Disease</th>
<th>Trial</th>
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<tr>
<td>Monotherapy</td>
<td>DNMTi</td>
<td>Asacitidine</td>
<td>ABC</td>
<td>NCT01349959</td>
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<td></td>
<td></td>
<td>DAC</td>
<td>NSCLC</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>SGI-110</td>
<td>MDS, Ovarian, AML, Colon, HCC</td>
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<tr>
<td>HDACi</td>
<td>Vorinostat</td>
<td>Advanced CTCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Romidepsin</td>
<td>CTCL</td>
<td>NCT000091559</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproic acid</td>
<td>Breast Cancer</td>
<td>NCT01900730</td>
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<tr>
<td></td>
<td></td>
<td>Entinostat</td>
<td>Hodgkin’s lymphoma, kidney cancer, ABC</td>
<td>NCT01349959</td>
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<tr>
<td></td>
<td>Givinostat</td>
<td></td>
<td>Chronic myeloprolif neoplasms</td>
<td>NCT01761968</td>
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<td>Panobinostat</td>
<td></td>
<td>Hodgkins lymphoma</td>
<td>NCT01034163</td>
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<td></td>
<td></td>
<td>Multiple myeloma</td>
<td>NCT01023308</td>
</tr>
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<td>Combination therapy</td>
<td>Epi + Chemo</td>
<td>Vorinostat/5-FU/Leucovorin</td>
<td>CRC</td>
<td>NCT00942266</td>
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<tr>
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<td></td>
<td>SGI-110/Irinotecan</td>
<td>CRC</td>
<td>NCT01896856</td>
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<td></td>
<td>Valproic acid/Hydralazine/cisplatin</td>
<td>Cervical Cancer</td>
<td>NCT01896856</td>
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<td></td>
<td>Carboplatin/DAC</td>
<td>Ovarian Cancer</td>
<td>NCT01045538</td>
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<td>AZA/Abraxane/Gemcitabine</td>
<td>Pancreatic Cancer</td>
<td>NCT01845805</td>
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<tr>
<td>Epigenetic Priming</td>
<td>Epi + Radiation</td>
<td>Vorinostat + Radiotherapy</td>
<td>GI Cancer</td>
<td>NCT02349867</td>
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<td></td>
<td></td>
<td>Vorinostat/Gemcitabine/Paclitaxel/Sorafenib tosylate</td>
<td>Pancreatic Cancer</td>
<td>NCT00983268</td>
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<tr>
<td></td>
<td>Epi + Immune</td>
<td>AZA/Romidepsin/PD-1 Ab</td>
<td>CRC</td>
<td>NCT02512172</td>
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<td></td>
<td>SGI-110/GVAX/Cyclophosphamide</td>
<td>CRC</td>
<td>NCT01966289</td>
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<tr>
<td></td>
<td></td>
<td>AZA + Entinostat/Nivolumab</td>
<td>NSCLC</td>
<td>NCT01928576</td>
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<td></td>
<td></td>
<td>Entinostat/Aldesleukin (Interleukin-2)</td>
<td>Met Kidney Cancer</td>
<td>NCT01038778</td>
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<td></td>
<td>Decitabine/Autologus dendritic cell vaccine and poly-ICLC</td>
<td>Pediatric high-grade glioma/MB/CNS pNT</td>
<td>NCT02332889</td>
</tr>
</tbody>
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HDACi in Breast Cancer: Exemestane + Entinostat

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS). (A) Vertical tick marks represent the PFS time of patients without progressive disease. (B) Vertical tick marks represent the survival time of patients alive or lost to follow-up as of the last contact.

PFS 8.5 vs 2.7mo in high vs low acetylation after treatment

Yardley JCO 2013
Vorinistat + AI Trial with FES-PET

Scan 1 (baseline)  | FES | SUV  | 2.5 |
Scan 2 (response) | FES | SUV  | 3.2 |
Scan 3 (progression) | FES | SUV  | 2.8 |
Scan 1 (baseline)  | FDG | SUV  | 8.0 |
Scan 2 (response) | FDG | SUV  | 6.0 |
Scan 3 (progression) | FDG | SUV  | 13.2 |

Linden, ASCO poster 2018
Can we improve on IMpassion?
Summary and future directions

• Epigenetics plays an important role in cell differentiation
• Similar epigenetic mechanisms are seen in tumorigenesis
• Epigenetics plays a role in cancer subtype type
• Epigenetics modifies cancer progression and response to treatment
• Epigenetics may be a mechanism to evaluate for minimal residual disease and prognosis
• Epigenetic therapy may be used as an adjunct to overcome resistance to endocrine therapy, chemotherapy or immunotherapy
Thanks!