ROLE OF THE EPIGENETIC REGULATION OF CHROMATIN IN BREAST CANCER

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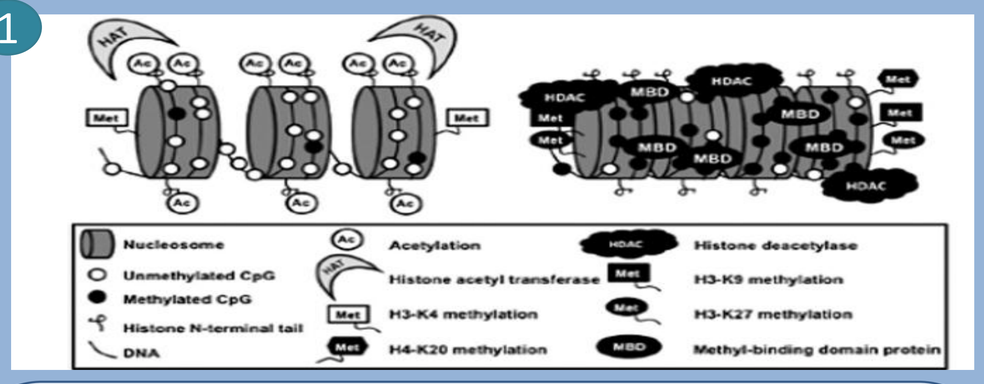
HISTONE MODIFICATIONS

1



Histone acetylation enhances transcription and it is catalyzed by histone acetyltransferases. This modification is also involved in DNA repair. Histone deacetylation represses transcription and it is catalyzed by HDACs.

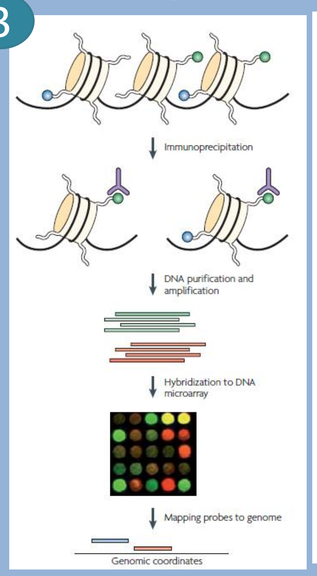
Histone methylation silences tumour suppressor genes and the transcription of genes involved in DNA repair, chromatin remodelling, cell cycle regulation, metastasis, apoptosis, etc. This is the cause of the chromatin structure change; it's catalyzed by DNA methyltransferases which maintain DNA methylation patterns.

Histone phosphorilation is critical in DNA damage response, it's catalyzed by kinases and it can activate/deactivate proteins.

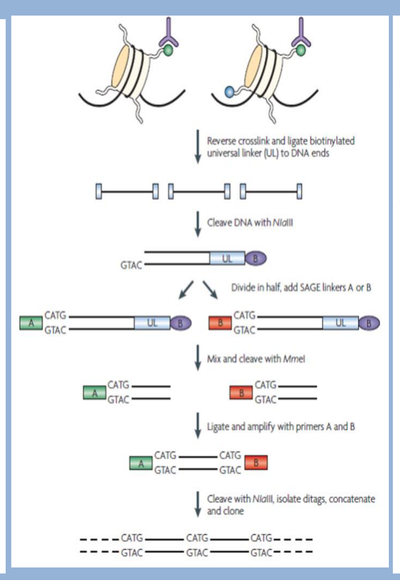
HOW TO DETECT HISTONE MODIFICATIONS?

3

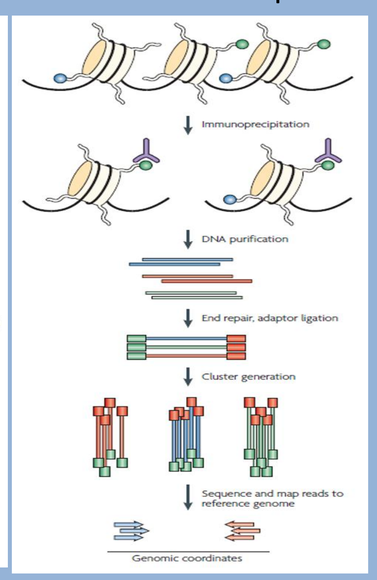
ChIP-chip



ChIP-SAGE



ChIP-Seq



MAIN HISTONE MODIFICATIONS IN BREAST CANCER

Histone modification	Gene expression	Level	Effect
H3K9Ac	Activates	High	Low lymph node state
		Low	Large tumour size
H4K16Ac	Repress	Low	Large tumour size Positive vascular invasion
H4R3Me2	Activates	High	Low lymph node state
		Low	Large tumour size
H3K27Me	Repress	High	Poor prognosis

THERAPIES

Therapies based on reverse histone modifications use inhibitors of histone deacethylases (HDACi). They promote apoptosis in cancer cells and the reactivation of tumour suppressor genes and genes needed in cellular cycle. The developed HDACi are non selective. The main clinical results and biomarker evaluation are ongoing or unpublished yet.

Vorinostat, a HDACi, inhibits proliferation and it is in Phase 2 to be approved for breast cancer (Vorinostat is tolerable and safe). It is used with chemotherapeutic agents like Tamoxifen (phase 2), aromatase inhibitor (phase 2), Trastuzumab (phase1/2) and Iapatinib (phase 1/2).

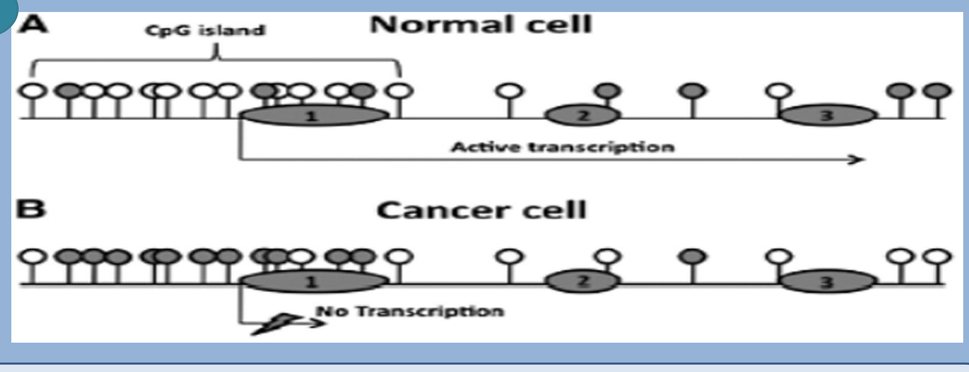
Entinostat (MS-275) is another HDACi in phase 2 for breast cancer. It is used with Tamoxifen (phase 2) or Iapatinib (phase 1/2).

REFERENCES

1. Rando OJ., 2012: 2. Kristensen L.S., et al, 2009; 3 and 4. Schones D. E., Zhao K., 2008; 5. Bannister AJ., Kouzarides T., 2011; Elsheik SE., et al, 2009; Lustberg M., et al, 2011

DNA METHYLATION

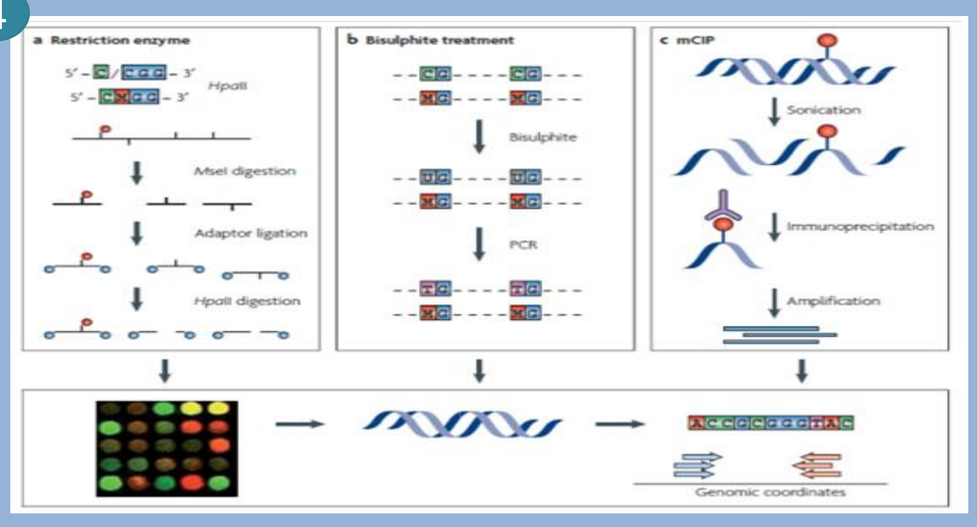
2



The DNA methyltransferases transfer the methyl group from S-adenosyl methionine (SAM) to a cytosine of the dinucleotide CpG present in the human promoters. This modification is associated with silencing of genes due to a closer conformation of the chromatin. It has an important role in the regulation of transcription and it's usually altered in malignant transformation. There are three active methyltransferases, one maintenance methyltransferase (DNMT1) and two methyltransferases de novo (DNMT3A and DNMT3B).

HOW TO DETECT DNA METHYLATION?

4



ALTERED GENES IN BREAST CANCER

DNA methylation	Function	Genes
Hypermethylation	DNA repair	BRCA1, MGMT, MuLL homolog 1 (MLH1), RAD9
	Metastasis	Cadherin 13 (CDH13), Cystatin E/M (CST6), Spleen tyrosine kinase (SYK)
	Cell Cycle regulation	Adenylate kinase 5 (AK5), Cyclin D2 (CCND2), Cyclin-dependent kinase inhibitors (CDKN1C and CDKN2A), ER, FOX2A, P16 INK4, Progesterone receptor (PR), Retinoic acid receptor (RAR), Ras association domain family protein 1 (RASSF1A), Runt-related transcription factor 3 (RUNX3), Stratifin (SFN), Secreted frizzled-related protein 1 (SFRP1), WNT inhibitory factor 1 (WIF1), Wener Syndrome, RecQ helicase-like (WRN), Wilms tumour 1 (WT1)
	Apoptosis	Adenomatous polyposis of the colon (APC), B-cell CLL/lymphoma 2 (BCL2), Death-associated protein kinase (DAPK), Deleted in colorectal carcinoma (DCC), Hypermethylated in cancer 1 (HIC1), Homeobox A5 (HOXA5), TMS1, TWIST
Hypomethylation	Metastasis	Breast cancer-specific gene 1 protein (BCSG1), Caveolin 1 (CAV1), Cadherin (CDH1, CDH3), N-acetyltransferase 1 (NAT1), Plasminogen activator, urokinase (UPA)

THERAPIES

Therapies based on reverse the DNA methylation effects are those that use inhibitors of DNA methyltransferases (DNMTs). In breast cancer the two principals are 5-azacitidine and 5-aza-2'-deoxixitidine (decitabine) approved by the FDA. They incorporate themselves during the replication where in the DNA is a cytosine, generating a covalent union. Clinical results and biomarker evaluation of these therapies are ongoing.

AZA single agent is in phase 2 in breast cancer primary operable. These therapies can be administered with chemotherapeutic agents like entinostat (phase 2) or tamoxifen (phase ½) in order to increase the effects.

CONCLUSIONS

Epigenetics are very important for developing Breast cancer due to their high frequency. This is related with the creation of new detection technologies helping to diagnose the illness. The reversibility of their effects is the clue to generate new effective therapies for the treatment.