ROLE OF HISTONE PTMs IN BREAST CANCER

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The **AIMS** approached were
1. Histone PTMs as biomarkers for breast cancer?
2. Gene specific pattern of histone PTMs?
3. Use of histone PTMs in anti-cancer therapy ?

INTRODUCTION

HISTONE PTMs

Functional groups added covalently onto residues at histone terminal tails.
They regulate chromatin state, altering gene expression.

Enzymatic activity:

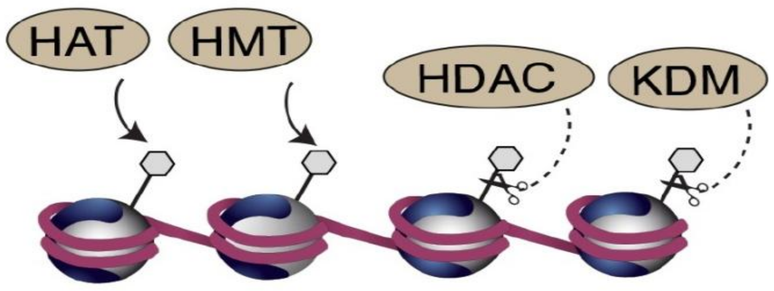


Figure 1. Enzymes having opposing activities maintain steady-state levels of histone marks.

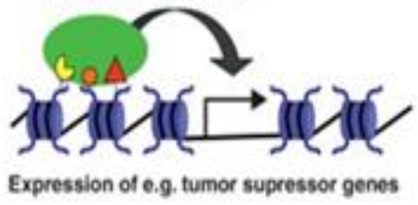
HATs and HMTs use acetyl CoA and SAM , respectively, as donors in their reactions.

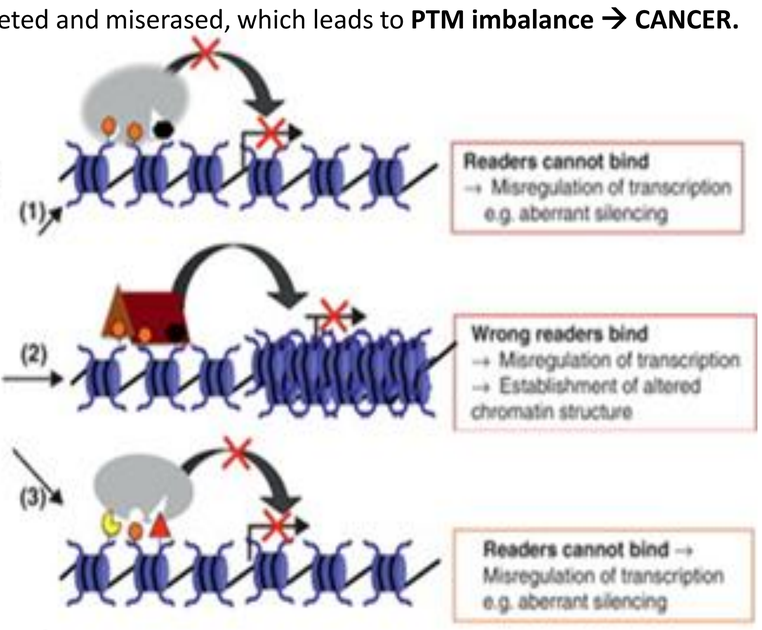
Cancerous cells have a generally low level of PTMs.
There are two histone PTMs modifications considered as hallmarks for cancer: loss of **H4K16ac** and **H4K20me3**.
Some modifications are associated with transcriptional states (H3K9ac or H3K4me3 → active; H3K9me2 or H4K20me3 → repression) or with specific tumours.

HISTONE PTMs & CANCER

PTMs can be miswritten, misinterpreted and miserased, which leads to **PTM imbalance → CANCER.**

Disturbed histone PTMs
- Mutations of writers and erasers
- Overexpression of writers and erasers
- Chemical activation / inhibition of writers and erasers
- Mutation of histones





BREAST CANCER & PTMs

18% of all female tumours → MOST COMMON & 2nd MOST LETHAL CANCER

Tumour	ER exp.	PR exp.	HER2 exp.	Prognosis
luminal a	+/-	+/-	-	Favourable
luminal b	+/-	+/-	+	Favourable
triple negative	-	-	-	Poor
HER2+	-	-	+	Poor

Table 1. Breast cancer classifications and prognosis according to gene expression.

ENZYMATIC ACTIVITY
A one to one relation was seen between methylations and HMTs. However, it was different regarding acetylations, although some HATs were seen with a higher prevalence than others, such as p300 and the CREB binding protein (CBP) or NCOAs.

Histone PTM	Enzyme	Expression in cancer cells
H3K4me1/me2	LSD1	Increased
H3K4me	PLU-1	Increased
H3K4me2	MLL2	Decreased
H3K9me3	SUV39H1	Increased
H4K20me3	SUV420H1 and SUV420H2	Decreased
H3K27me	EZH2	Increased

Table 2. Histone PTMs co-regulated by particular enzymes. shows the expression in breast cancer cells of some enzymes responsible for the modifications of PTMs.

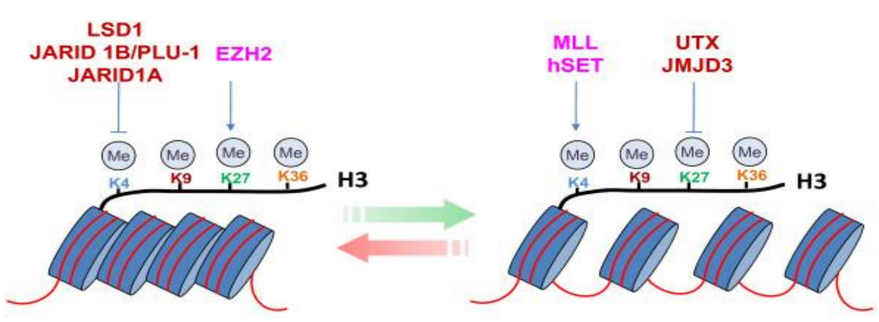
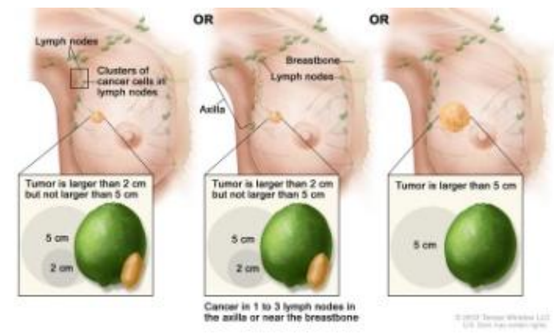


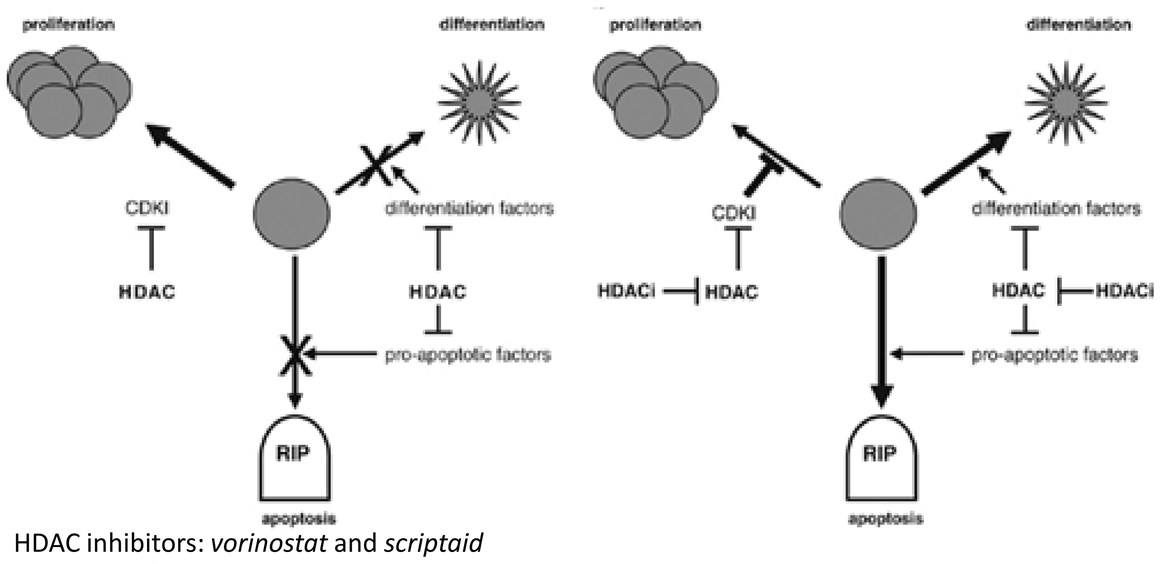
Figure 4. Model of dynamic interplay of enzymes mediating methylation of histone lysines. Methylases are shown in pink and demethylases are shown in brown.

Correlation between histone PTMs, tumour phenotype and clinical outcome:
- **High level** of ac and me → favourable prognosis ; **low level** → poor prognosis.
- Common specific PTMs: H3K9ac, **H3K18ac**, **H4K12ac**, H4K16ac, **H3K4me2**, H3K9me3*, H3K27me*, **H4K20me3***and **H4R3me2**.
- H4K20me3: reduced. More invasive fashion, thus worse prognosis.
- H3K9me3: increased. Transcriptional repression → migration and invasion.
- H3K27me: increased. More aggressive cells.

Clinico-pathological factors are associated with specific histone modification patterns:
Low levels of: H4R3me2, H3K9ac and H4K16ac → LARGER TUMOUR SIZES.
High levels of H3K9ac and H4R3me2 → LOW LYMPH NODE STAGE.
Low level of H4K16ac → VASCULAR INVASION



ANTI-CANCER THERAPIES:
PTMs are reversible → **epigenetic drugs.**
Out of all the enzymes involved in histone PTMs, therapies have focused on HDAC rather than HATs, PKMTs or PKDMs (little is known about their possible effects due to their range of action).



HDAC inhibitors: *vorinostat* and *scriptaid*
Vorinostat → targets HDAC class I and II. Inhibits proliferation of both ER+ and ER- breast cancer cells.
Scriptaid → relieves transcriptional repression and induces ER expression in ER- breast tumours.

COMBINATORIAL THERAPIES:
HDACi before chemotherapy → opening of the DNA, ease the way of chemotherapy agents in.
HDACi + DNMTi → increased ER expression compared to HDACi alone.
Examples of therapies in clinical trials: vorinostat+tamoxifen; entinostat+5-azacitidine (basal tumours)

CONCLUSIONS

Histone PTMs have a correlation with cancer and with breast tumours phenotypes and prognosis but further data need to be collected in order for them to be considered biomarkers. Ex: global loss of H4K16ac or H4K20me, more aggressive tumours when cells had a low level of H4K20me3, etc.

No locus-specific alterations in histone PTMs have been found to date. Further research should be warranted in order to delve into the topic.

Histone PTMs were very important when developing new therapies to fight breast cancer. Due to their reversible nature, enzymes in charge of PTMs were targeted. HDAC inhibitors have provided very promising results in mono-therapies (i.e. scriptaid) and in combinatorial therapies (vorinostat + tamoxifen).

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