The role of epigenetic mechanisms in cancer development

MED 213

The Genetic Bases of Cancer

Oncogenes
Tumor suppressor genes
Repair genes

Biological,chemical and physical agents leading to genetic and epigenetic modification, and mechanisms of action

Genetic mechanisms in Familial vs Sporadic Cancers

Pathways in Carcinogenesis

The role of epigenetic mechanisms in cancer development

Molecular targets for Cancer Therapy

Epigenetic and genetic interactions in cancer

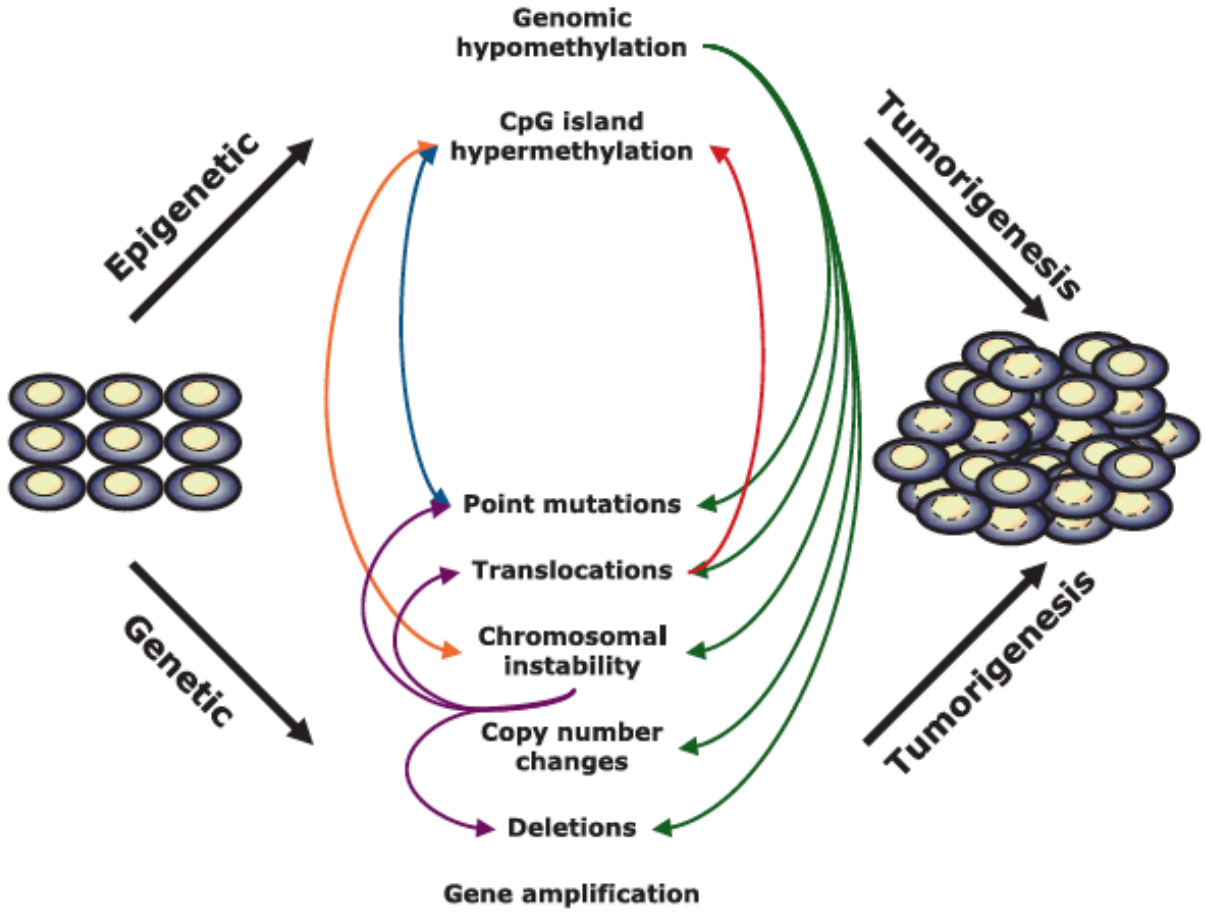


Fig. 15.1 A mechanism-based model of the pathogenesis of human cancer. Data from mouse models of cancer or hereditary human cancer indicate that genetic changes or epigenetic changes alone can initiate tumor formation. Sporadic cancers, which comprise 90–95% of all cancers, almost uniformly exhibit both genetic and epigenetic defects genome-wide, and these mechanisms show substantial interaction (*arrows*). That is, epigenetic events can cause genetic events, and vice versa. Determining the relative contribution of genetic and epigenetic mechanisms to tumor formation is an important goal of current research and should be facilitated by the whole cancer genome and epigenome approaches. Depending on the cancer type, each mechanism can operate early, late, or continuously in the development of the tumor

Epigenetic processes

1- DNA methylation - demethylation

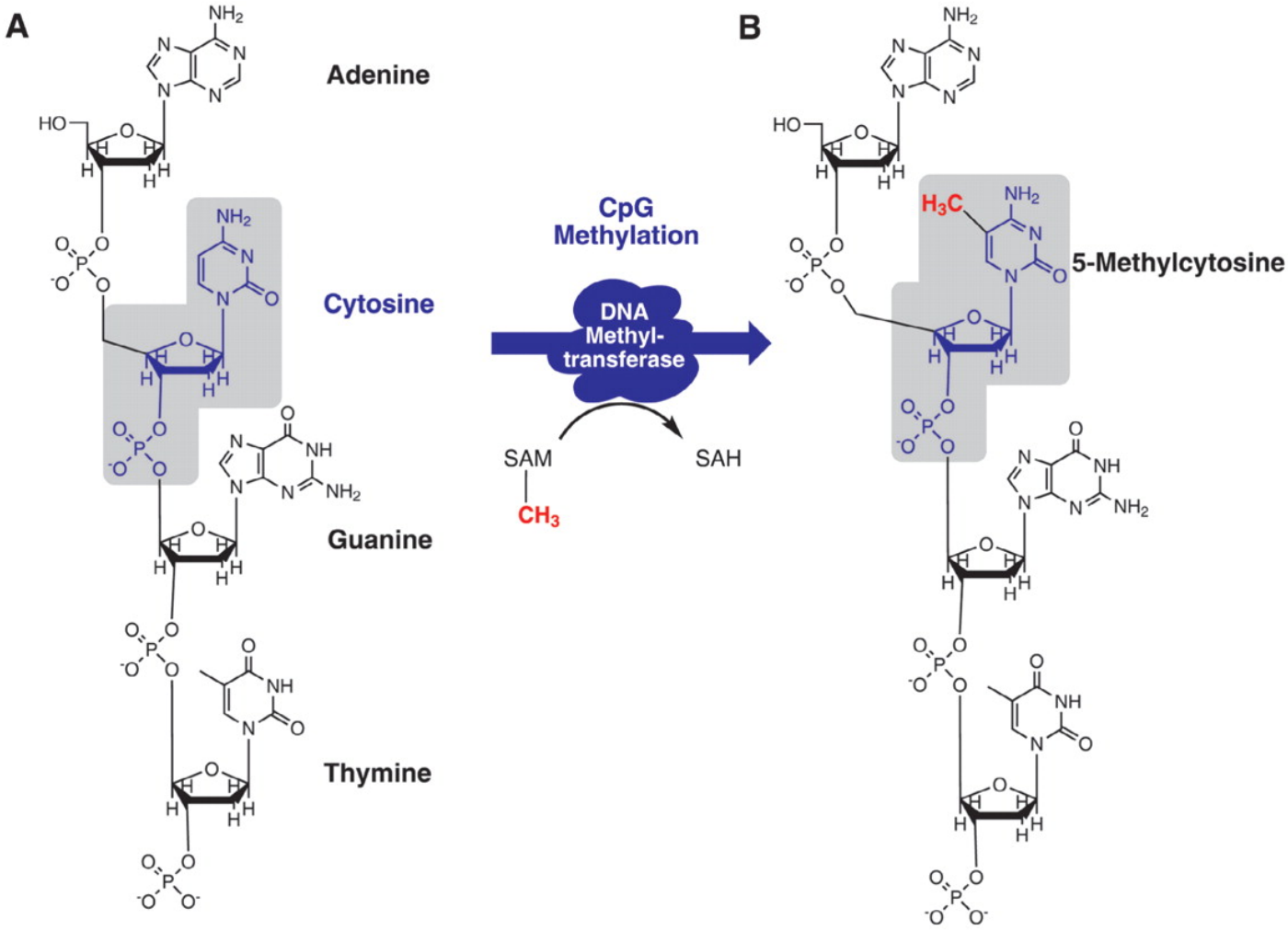
2- Histon modifications

DNA methylation

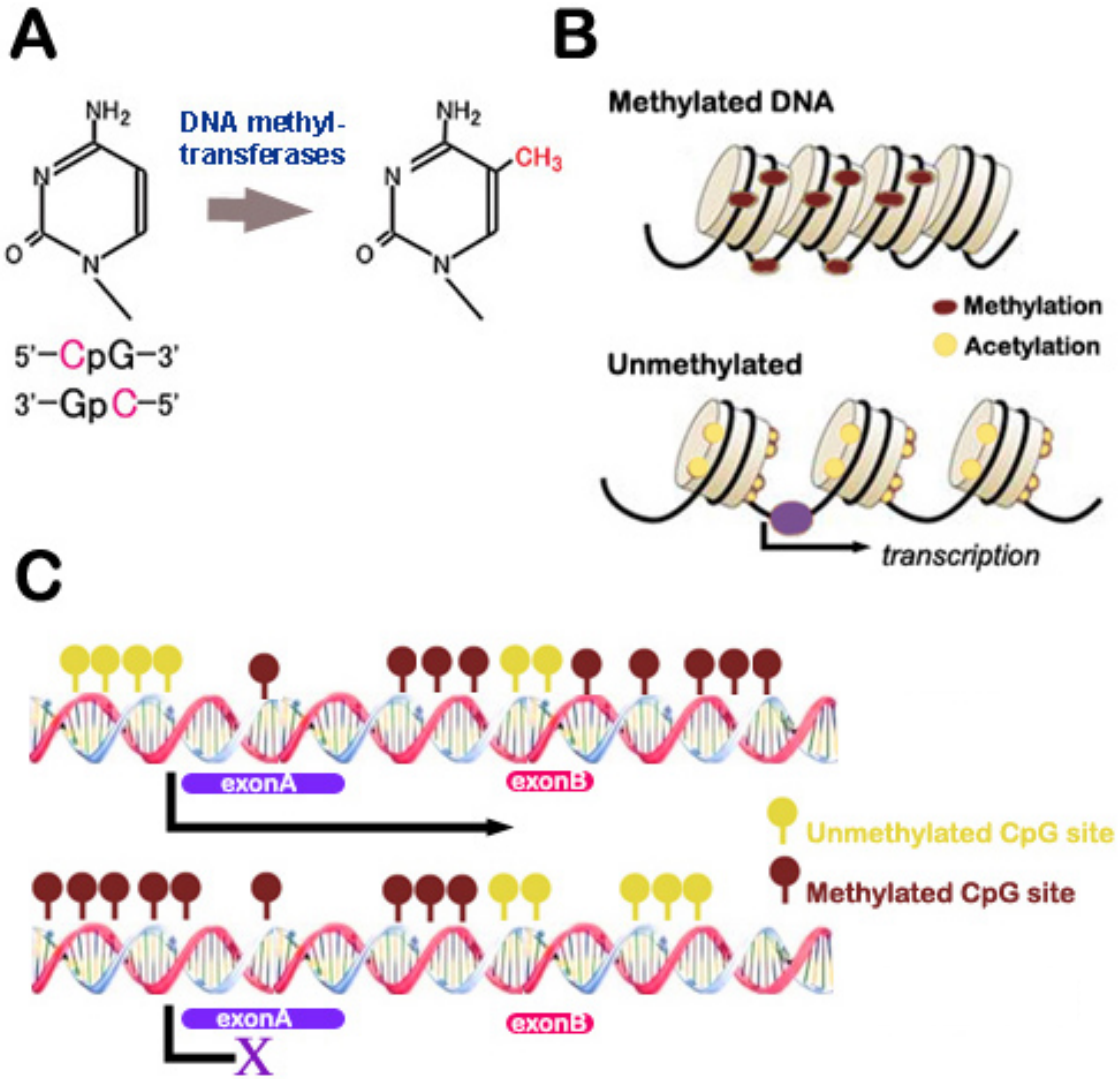
CpG di-nucleotide at cytosine 5^{th} postion covalently binds methyl group. Usually at promoter regions.

S-adenosyl methionine methyl donor

Methly transferase catalyzes the reaction

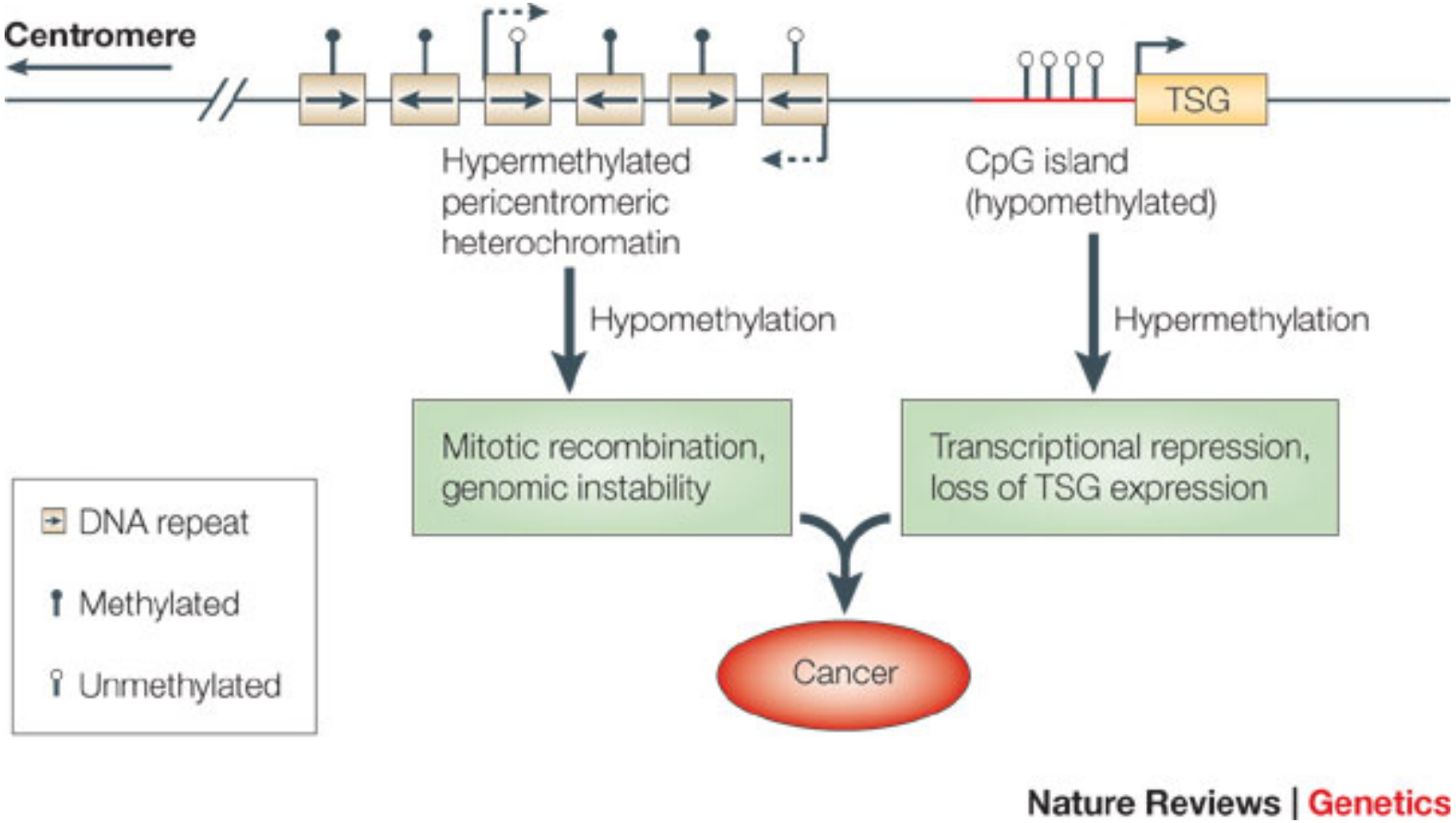

A
Adenine
Cytosine
Guanine
Thymine
CpG
Methylation
DNA
Methyl-
transferase
SAM
SAH
CH3
B
H3C
5-Methylcytosine

DNA Methylation



Hypo
Hyper

DNA Methylation anc Cancer



Methylation of cyclin dependent kinase inhibitors P15/P16

-Abnormal cyclin methylation inhibits **P16INK4a** in various cancers.

-**P15INK4b** hypermethylation in head neck cancers are frequent.

Marker for screening

Epigenetic alterations in Colorectal cancers:

MLH1 promoter hypermethylation

EpCAM: **Ep**itelial **C**ell **A**dhesion Molecule
3’ deletion *MSH2* gene hypermethylation causes inactivation

FAP *APC* inactivation

APC gene mutations act in 80% of colon cancers. APC gene promoter methylation profile may be an important marker at early stages.

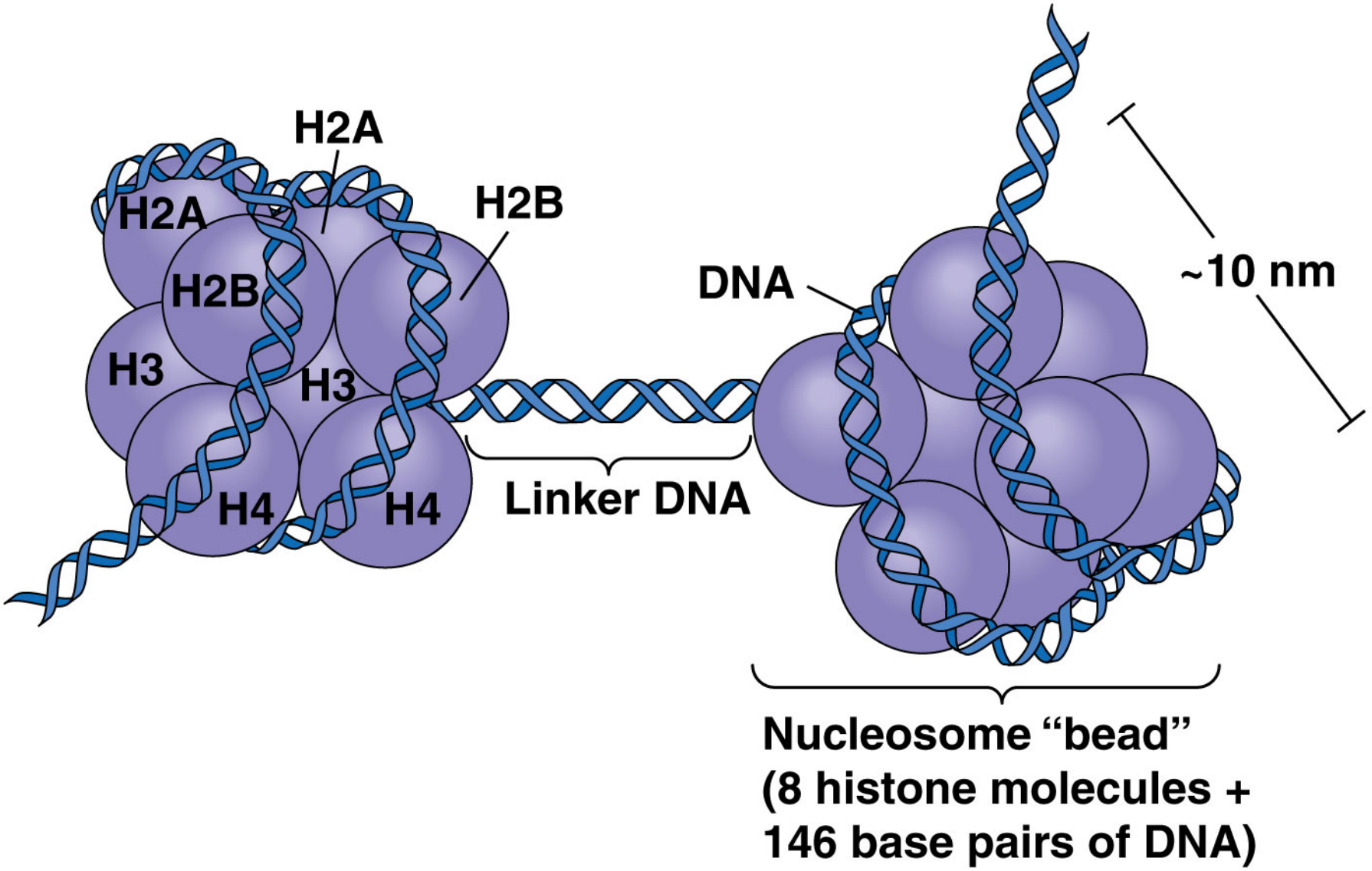
Epigenetic changes in Lung Cancer

Early stage faulty methylation deteceted genes

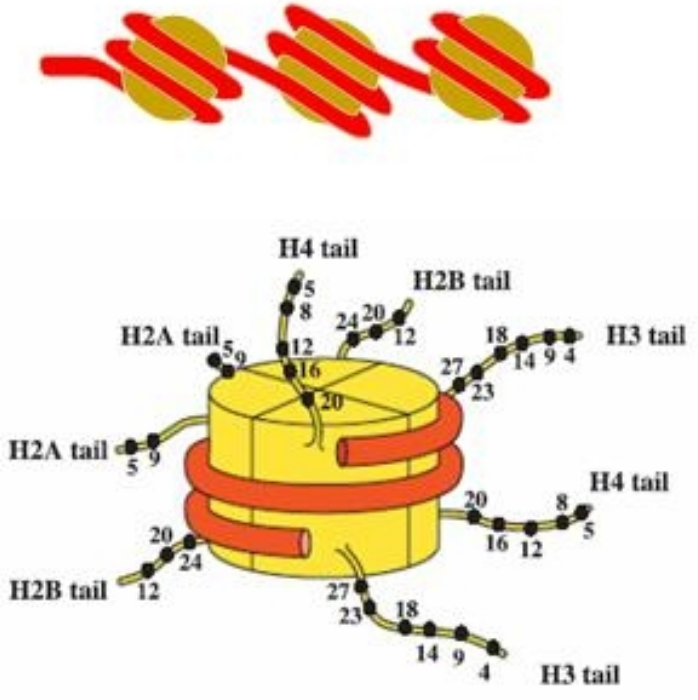
-P 16
-*APC*
-G-ST
-*E-cadehrin*

Breast cancer

BRCA1 CpG island promoter methylation prevents tumor suppressor gene mRNA synthesis.

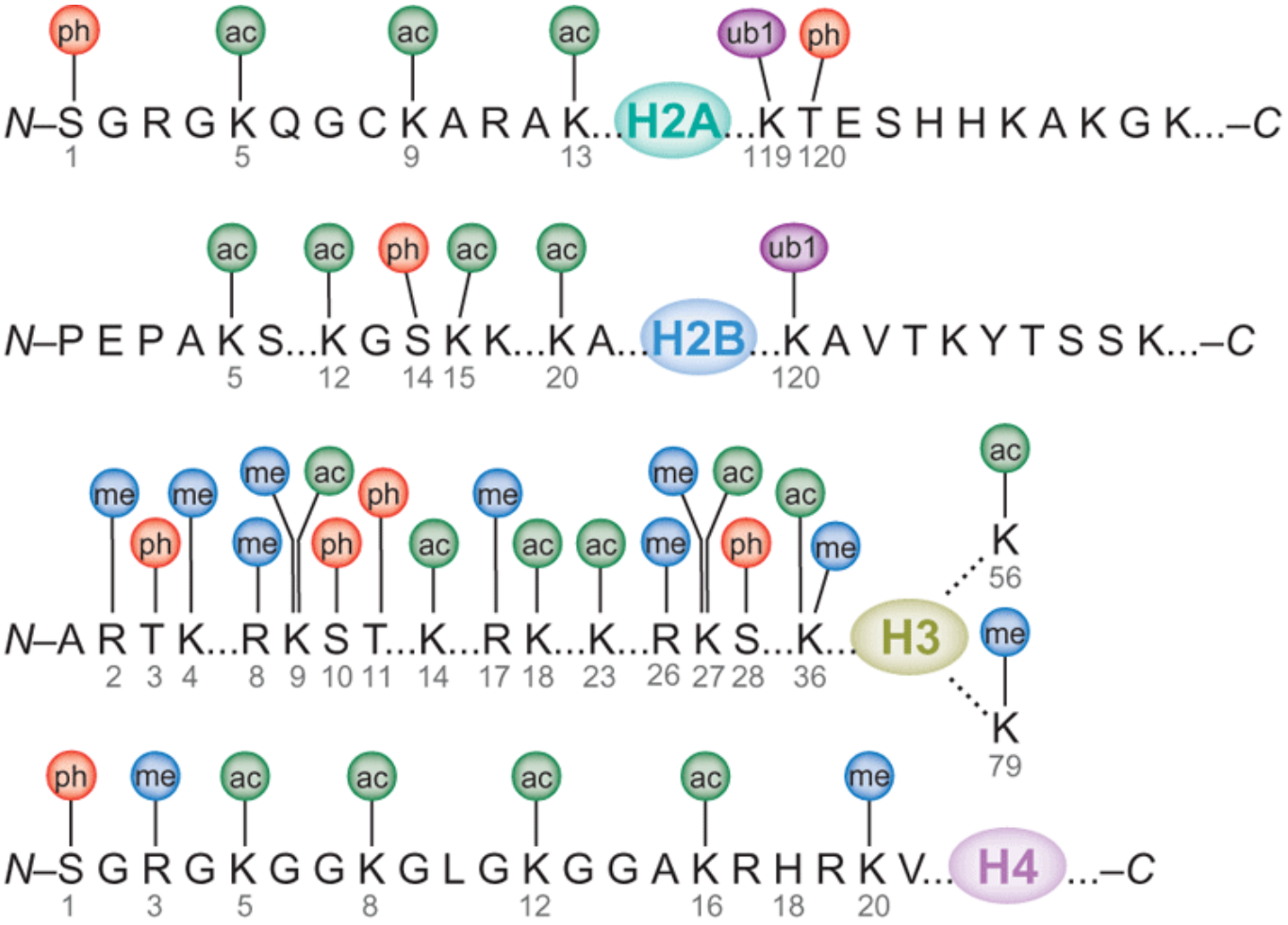


Histon Modifications



- **Ac** acetylation
- **Me** methylation
- **Ub** ubiquination
- **SU** sumoylation
- **P** phosphorylation

Histon Modifications



http://www.nature.com/nsmb/journal/v14/n11/images/nsmb1337-F1.gif

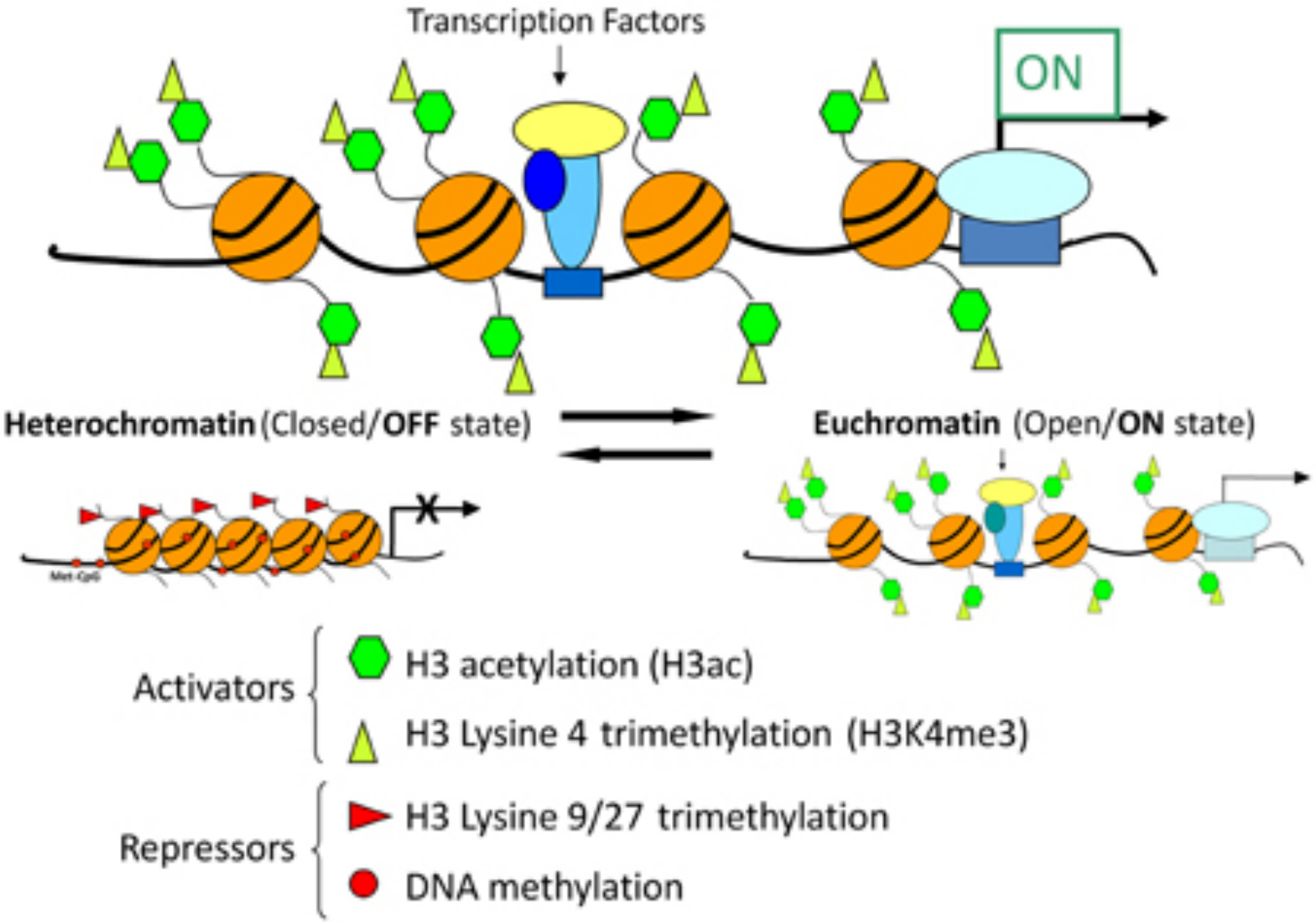
Acetylation

Chromatin remodelling is obtained by acetylation

Especially at H_3(9 ve14.) and H_4 (5, 8, 12, 16.) aminoacids histon asetyl transferase (HAT) lysin acetylation

Acetyl co-enzyme A binds lysines. Histons are neutrolised bearing more negative charges causes transcriptional activity. (HAT)

Histon deasetylases (HDAC) reverse action


Transcription Factors
ON
Heterochromatin (Closed/OFF state)
Euchromatin (Open/ON state)
Activators
H3 acetylation (H3ac)
H3 Lysine 4 trimethylation (H3K4me3)
Repressors
H3 Lysine 9/27 trimethylation
DNA methylation

DNA metilasyon ve histon asetilasyonunu hedefleme

- Decitabine (5-aza-2 deoxycytidine) demethylating agents for ALL and MDS
- Animal models: DNA methyl transferase mRNA can be inhibited by antisense oligos allowing back p16 synthesis stopping tumor growth.
- Histon deasetylase inhibitors (trichostatin) and DNA methytransferase inhibitors (decitabine) combined for sinergistic effect for various repair and suppressor genes to gain back activity

TARGETS

DMTi: 5-azacytidine (DNA metil transferaz inhibitörü)	AZA	İleri solid tümörlerde erlotinib-aracılı etkiyi arttırır
HDACi (histon deasetilaz inhibitörü)	SB939	CRC
	SNDX-275	**HER2-**overexpressing meme Ca hücrelerinde herceptin-mediated etkiyi arttırır
Hipometile edici ajan	SGI-110	Hematolojik ve solid tümörler