Процессы

временные
периодические
постоянные

Молекулярные метки

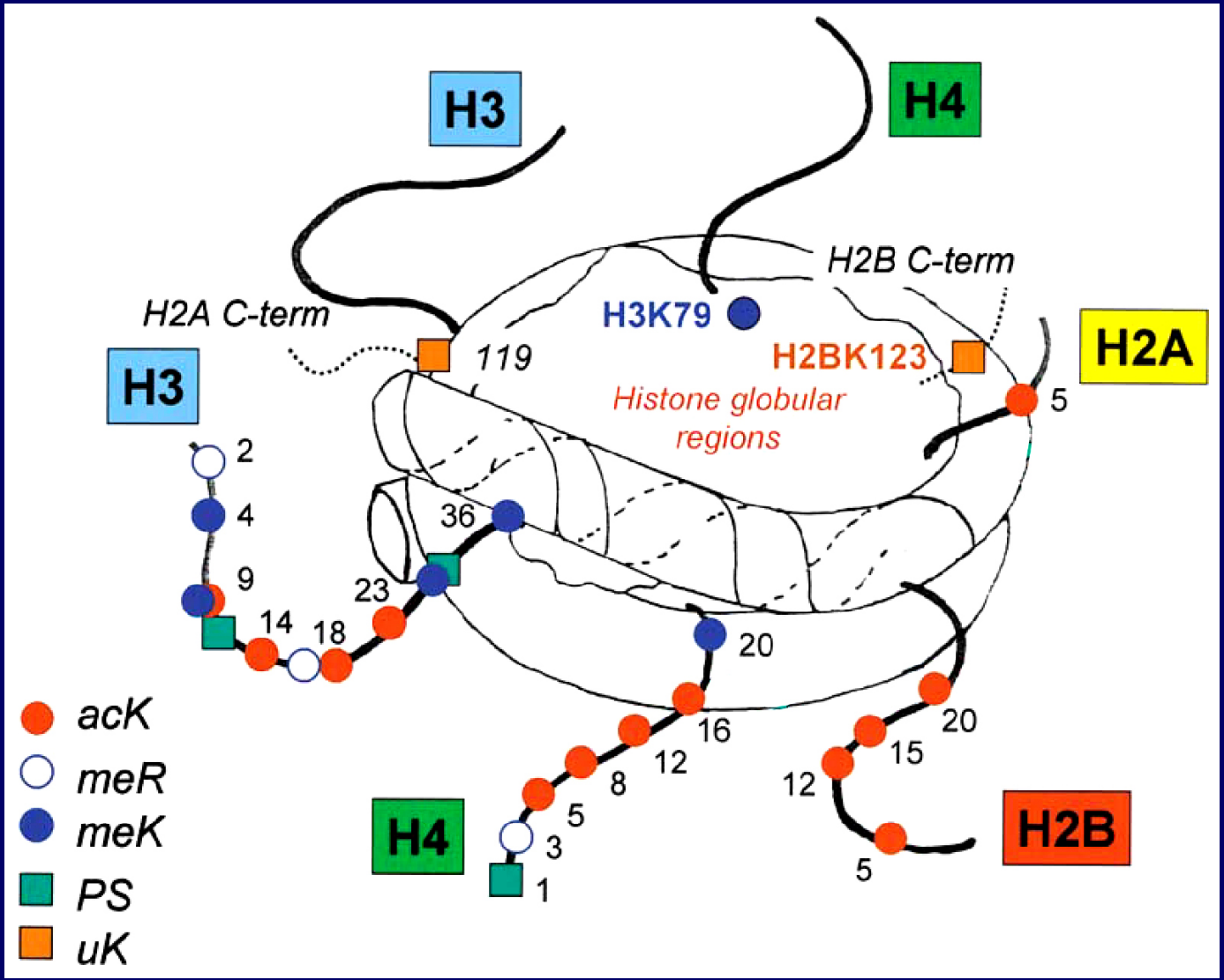
эпигенетические
неэпигенетические

Эпигенетика - раздел генетики, который изучает наследуемые изменения активности генов во время развития организма или деления клеток.

Эпигенетические изменения не сопровождаются изменением в последовательности ДНК

Модификации гистонов и теория “гистонового кода”

Пост-трансляционные модификации гистонов



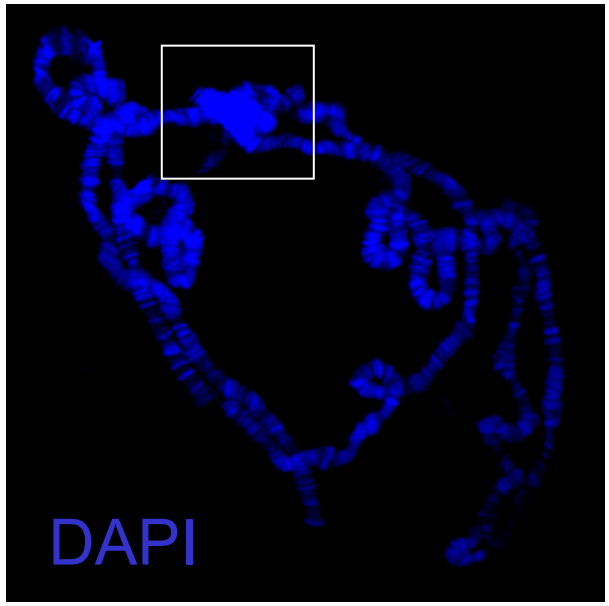
Пост-трансляционные модификации гистонов

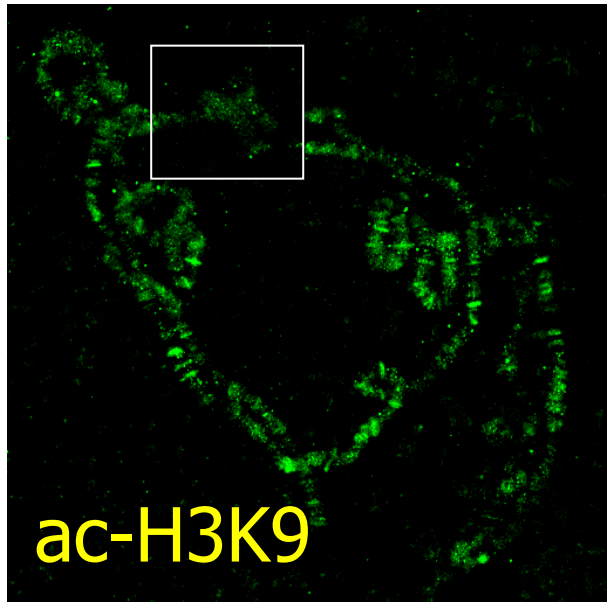
Ацетилирование	лизин (K)
Метилирование	лизин (K) аргинин (R)
Фосфорилирование	серин (S) треонин (T)
Убиквитинилирование	лизин (K)
ADP-рибозилирование	
Сумоилирование	

Пост-трансляционные модификации гистонов

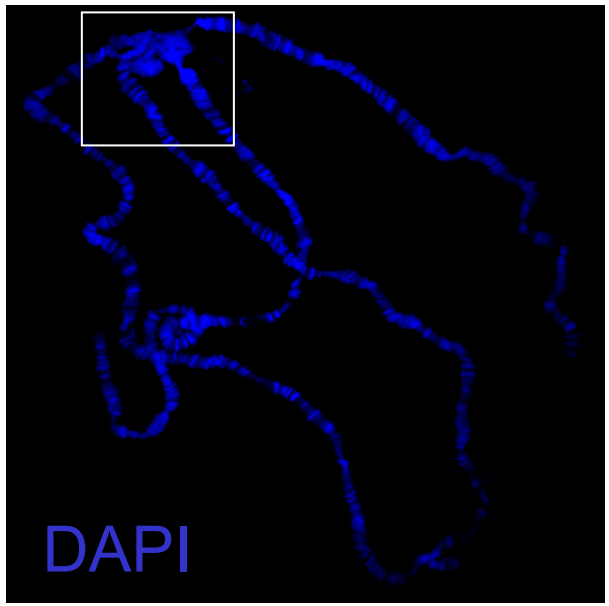
ацетилирование	-	деацетилирование
HAT		HDAC
метилирование	-	деметилирование
HMT		HDM
фосфорилирование	-	дефосфорилирование
kinase		phosphotase
убиквитинилирование	-	деубиквитинилирование
ubiquitin-conjugating emzyme(s)		ubiquitin-removing emzyme(s)
ADP-рибозилирование		
PARP (Poly (ADP-ribose) polymerase)	-	PARG poly(ADP-ribose) glycohydrolase

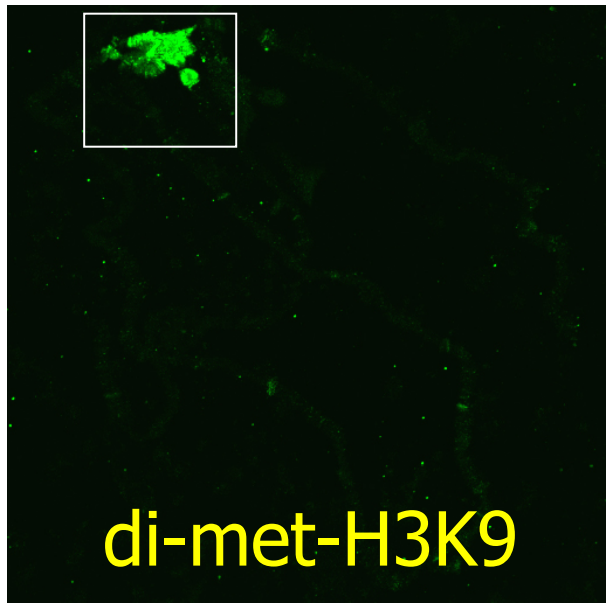
В эухроматине преобладает ацетилированная форма H3K9



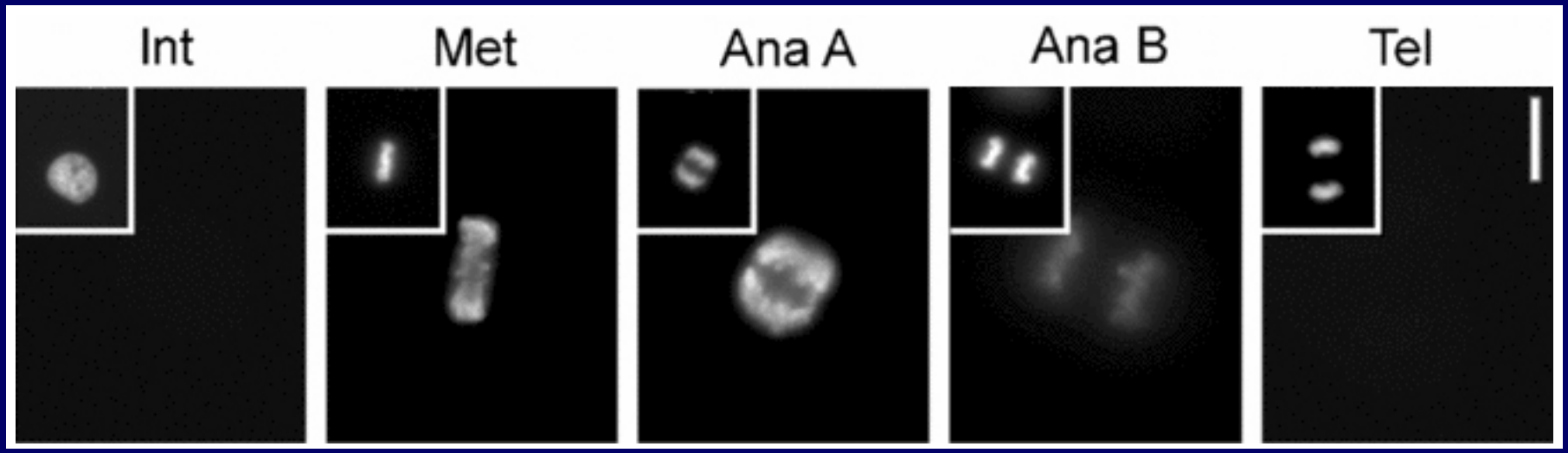


В гетерохроматине преобладают ди- и триметилированные формы H3K9





phos-H3S10

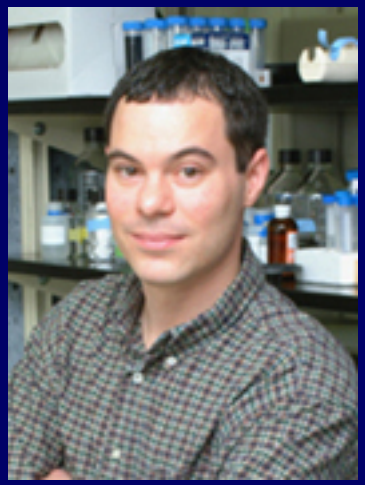


Изменение электростатического взаимодействия между гистонами и ДНК

Молекулярные метки ("Гистоновый код")

Теория “гистонового кода”

Brian Strahl (США)



Charles Allis (США)

Thomas Jenuwein (Австрия)

Nature, 2000

The language of covalent histone modifications

Brian D. Strahl & C. David Allis

Department of Biochemistry and Molecular Genetics, University of Virginia Health Science Center, Charlottesville, Virginia 22908, USA

Histone proteins and the nucleosomes they form with DNA are the fundamental building blocks of eukaryotic chromatin. A diverse array of post-translational modifications that often occur on tail domains of these proteins has been well documented. Although the function of these highly conserved modifications has remained elusive, converging biochemical and genetic evidence suggests functions in several chromatin-based processes. We propose that distinct histone modifications, on one or more tails, act sequentially or in combination to form a ‘histone code’ that is, read by other proteins to bring about distinct downstream events.

How eukaryotic genomes are manipulated within a chromatin environment is a fundamental issue in biology. At the heart of chromatin structure are highly conserved histone proteins (H3, H4, H2A, H2B and H1) that function as building blocks to package eukaryotic DNA into repeating nucleosomal units that are folded into higher-order chromatin fibres[1,2] (Fig. 1). Once thought of as static, non-participating structural elements, it is now clear that histones are integral and dynamic components of the machinery responsible for regulating gene transcription. The same is probably

Transcription-linked acetylation, catalysed by the GCN5 family of HATs, shows a preference for lysine 14 of H3 *in vitro*[17] although an expanded set of lysine residues is likely to be used *in vivo*[18,19]. How is this acetylation site specificity in H3 brought about?

Solution and crystal structure data of various members of the GCN5 HAT family, including co-crystals of the enzyme with H3 tail peptides[20], have begun to yield important insights into the enzymatic mechanisms underlying the site specificity of these HATs[21–25]. One important concept to emerge from these studies is that residues

Science, 2001

REVIEW

Translating the Histone Code

Thomas Jenuwein[1] and C. David Allis[2]

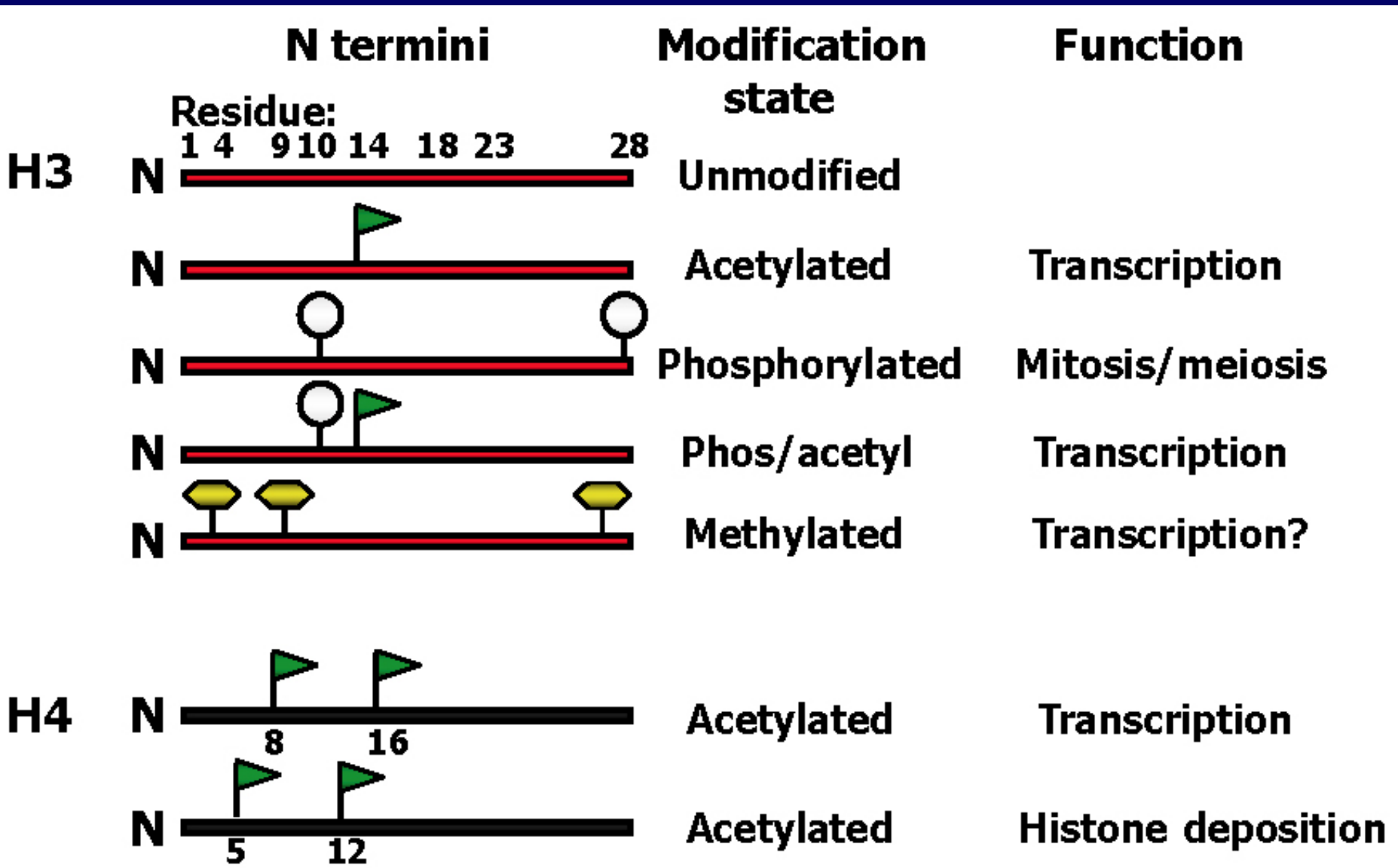
Chromatin, the physiological template of all eukaryotic genetic information, is subject to a diverse array of posttranslational modifications that largely impinge on histone amino termini, thereby regulating access to the underlying DNA. Distinct histone amino-terminal modifications can generate synergistic or antagonistic interaction affinities for chromatin-associated proteins, which in turn dictate dynamic transitions between transcriptionally active or transcriptionally silent chromatin states. The combinatorial nature of histone amino-terminal modifications thus reveals a "histone code" that considerably extends the information potential of the genetic code. We propose that this epigenetic marking system represents a fundamental regulatory mechanism that has an impact on most, if not all, chromatin-templated processes, with far-reaching consequences for cell fate decisions and both normal and pathological development.

Genomic DNA is the ultimate template of our heredity. Yet despite the justifiable excitement over the human genome, many challenges remain in understanding the regulation and transduction of genetic information (*1*). It is unclear, for example, why the number of protein-coding genes in humans, now estimated at ~35,000

nisms for how such a code is "read" and translated into biological functions.

Throughout this review, we have chosen epigenetic phenomena and underlying mechanisms in two general categories: chromatin-based events leading to either gene activation or gene silencing. In particular, we center our dis-

transcriptionally inert are highly condensed in the interphase nucleus and remain cytologically visible as heterochromatic foci or as the "Barr body," which is the inactive X chromosome in female mammalian cells (*2*). The distinct levels of chromatin organization are dependent on the dynamic higher order structuring of nucleosomes, which represent the basic repeating unit of chromatin. In each nucleosome, roughly two superhelical turns of DNA wrap around an octamer of core histone proteins formed by four histone partners: an H3-H4 tetramer and two H2A-H2B dimers (*3*). Histones are small basic proteins consisting of a globular domain and a more flexible and charged NH_2-terminus (histone "tail") that protrudes from the nucleosome. It remains unclear how nucleosomal arrays containing linker histone (H1) then twist and fold this chromatin fiber into increasingly more compacted filaments leading to defined high-


N termini
Modification state
Function
Residue:
1 4 9 10 14 18 23 28
H3
N
Unmodified
N
Acetylated
Transcription
N
Phosphorylated
Mitosis/meiosis
N
Phos/acetyl
Transcription
N
Methylated
Transcription?
H4
N
8 16
Acetylated
Transcription
N
5 12
Acetylated
Histone deposition

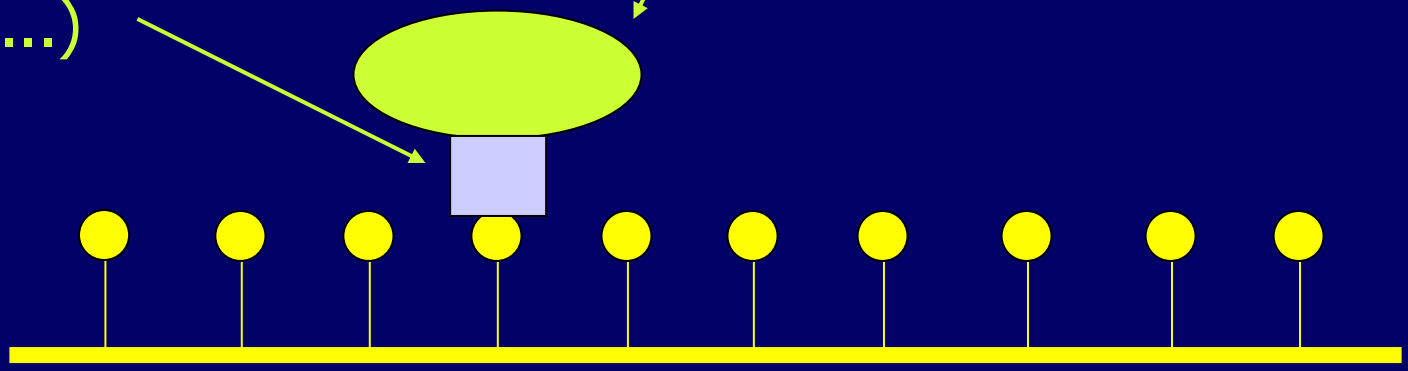
Как работает “гистоновый код”

1. Аминокислотный остаток в гистоне
2. Модифицирующий фермент
3. Белок, который “воспринимает” модификацию

Как работает “гистоновый код”

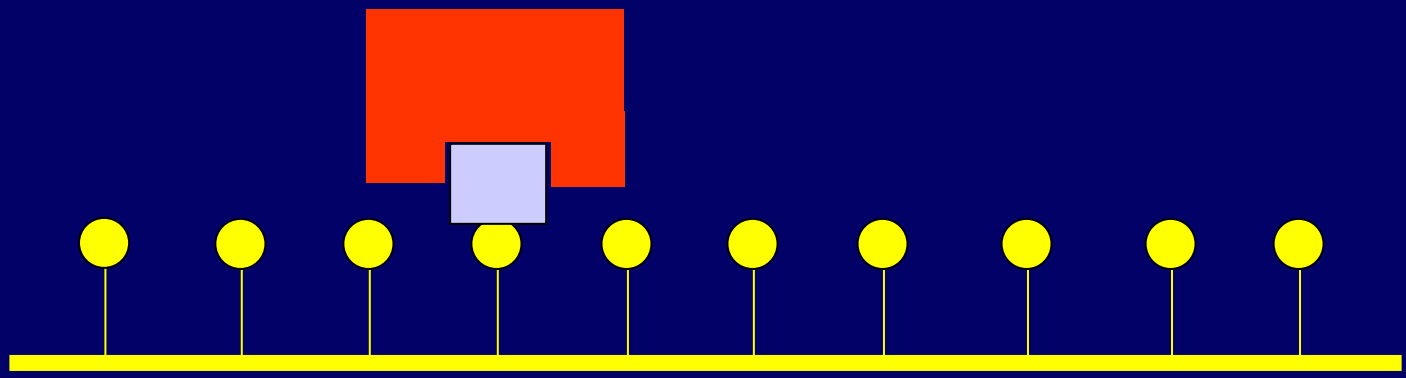
“модификация” (метильная, ацетильная, фосфатная группы...)

Модифицирующий фермент (HAT, HMT...)



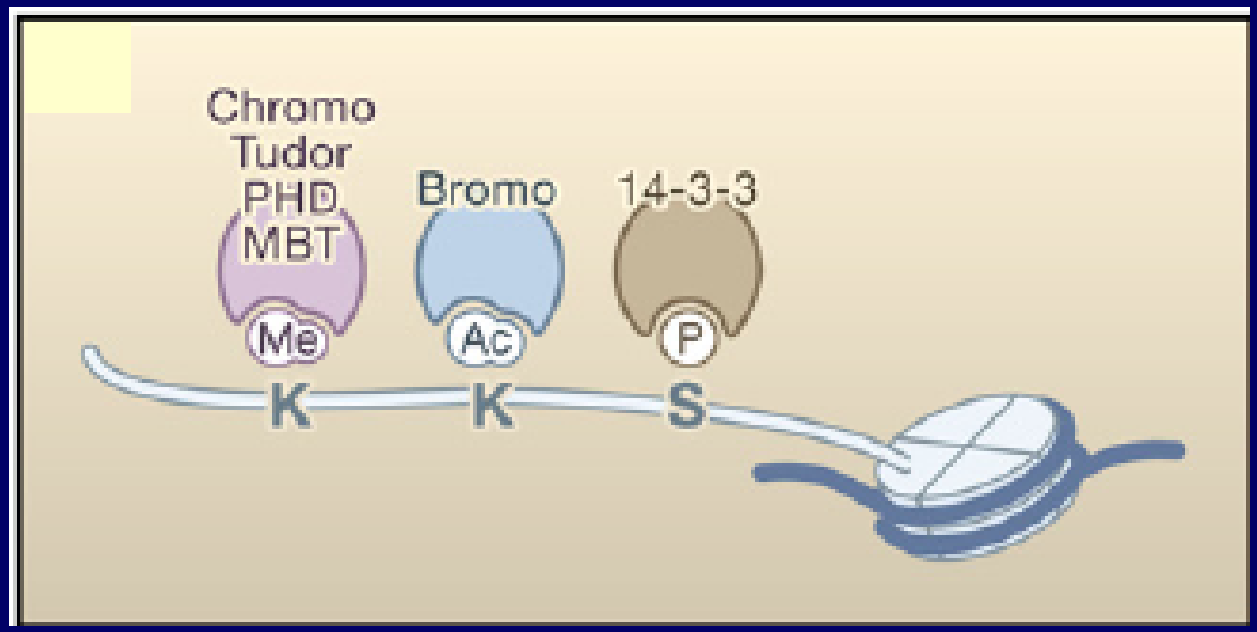
ГИСТОН

Как работает “гистоновый код”



ГИСТОН

Домены белков, распознающие метилированные лизины, ацетилированные лизины, фосфорелированные серины

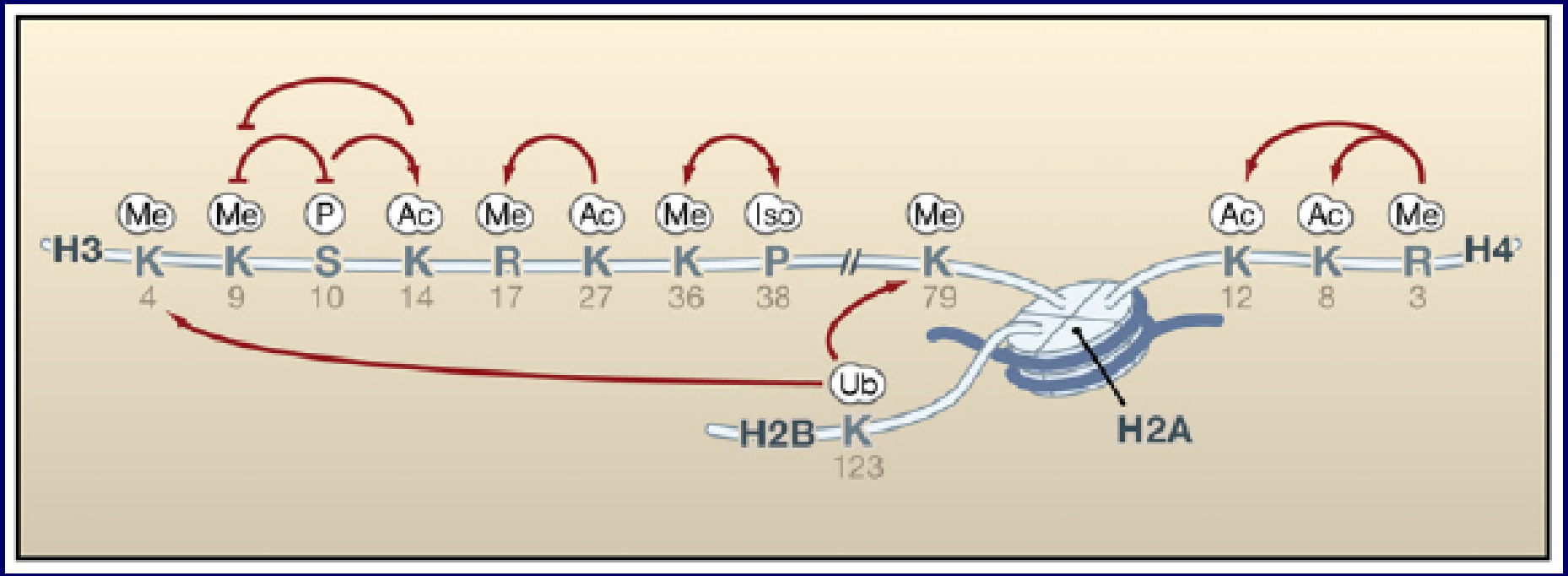


Ацетилированный лизин - bromo-domain

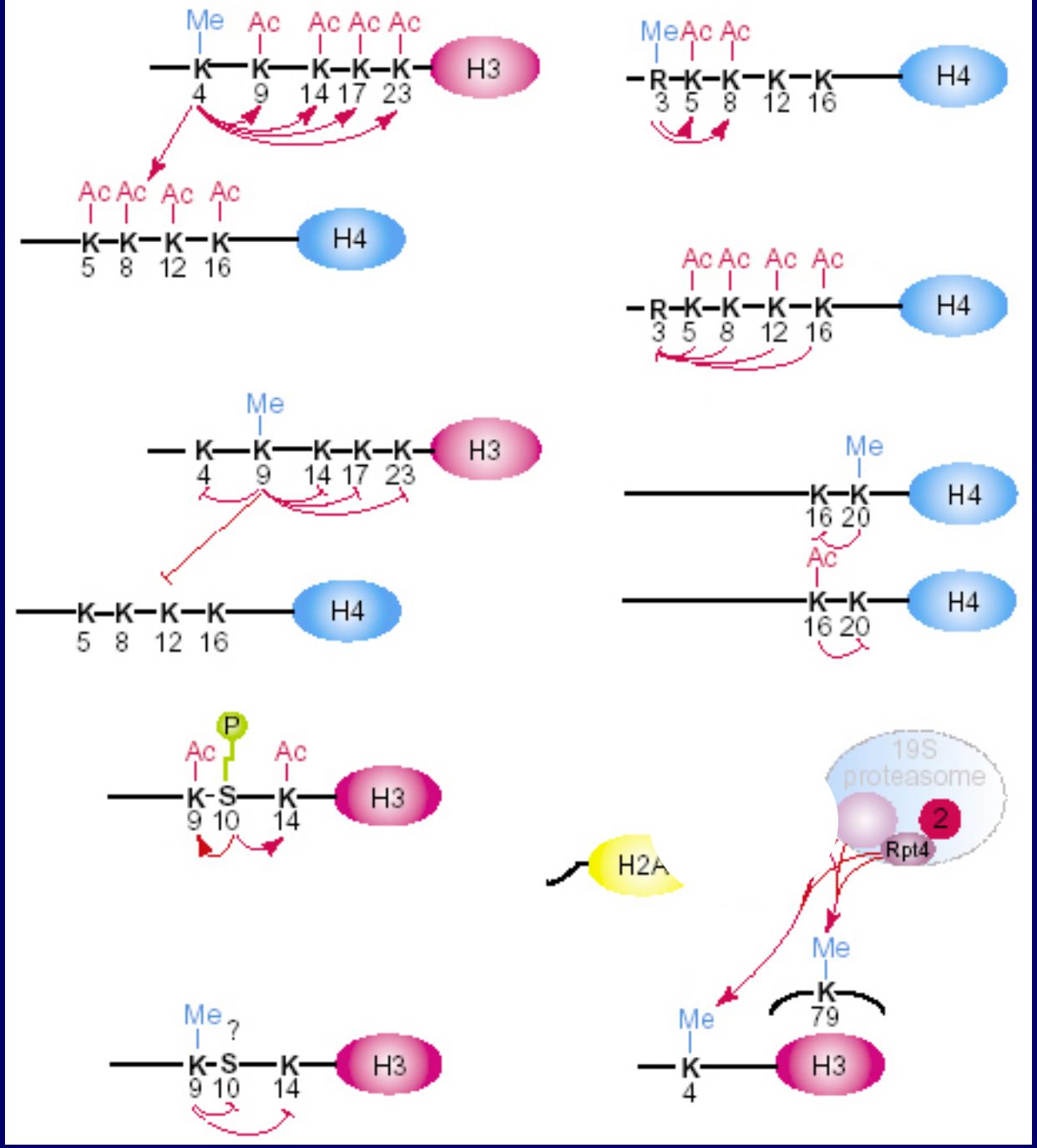
Метилированный лизин - chromo-domain
Tudor-domain

Взаимодействие модификаций гистонов

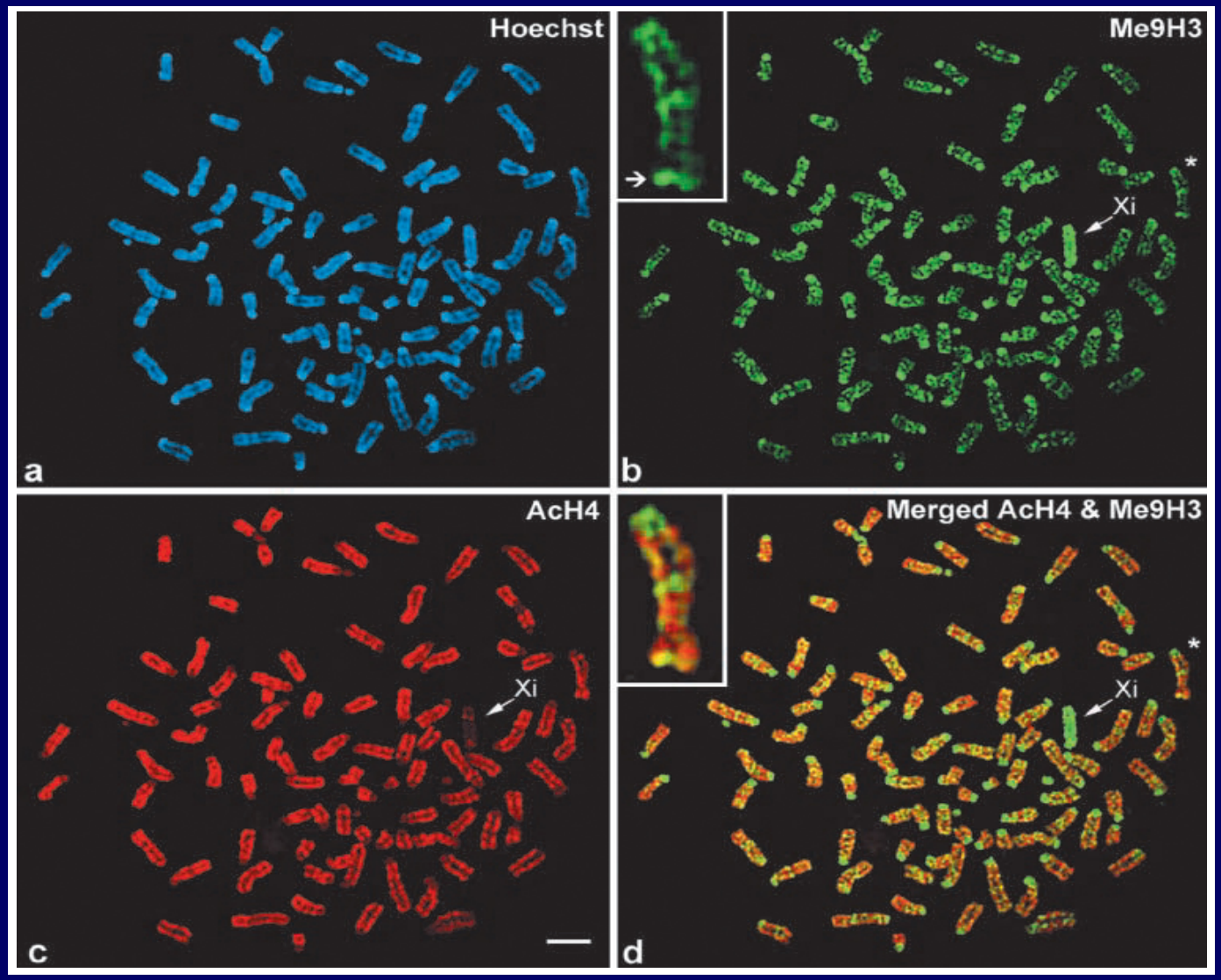
(modifications cross-talk)



Взаимодействие модификаций гистонов



Неперекрывание ацетилированной формы гистона H4 и метилированной по девятому лизину формы гистона H3 (MeH3K9) в хромосомах млекопитающих



S.cerevisiae

Участок гетерохроматина