От организации хроматина к пониманию функционирования геномов эукариот

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кафедра биоинженерии

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МГУ имени М.В.Ломоносова

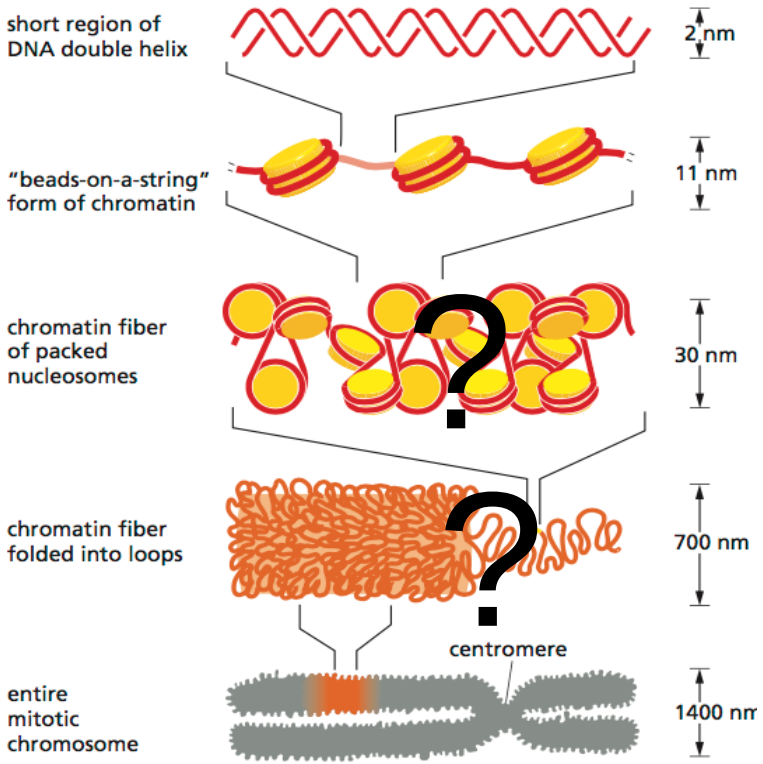
Лекции 4-5.
3Д структура хроматина и эпигенетика.

Апрель 2024

Далее поговорим про устройство ядра и интерфазного хроматина на более больших масштабах

Представления о структуре хроматина

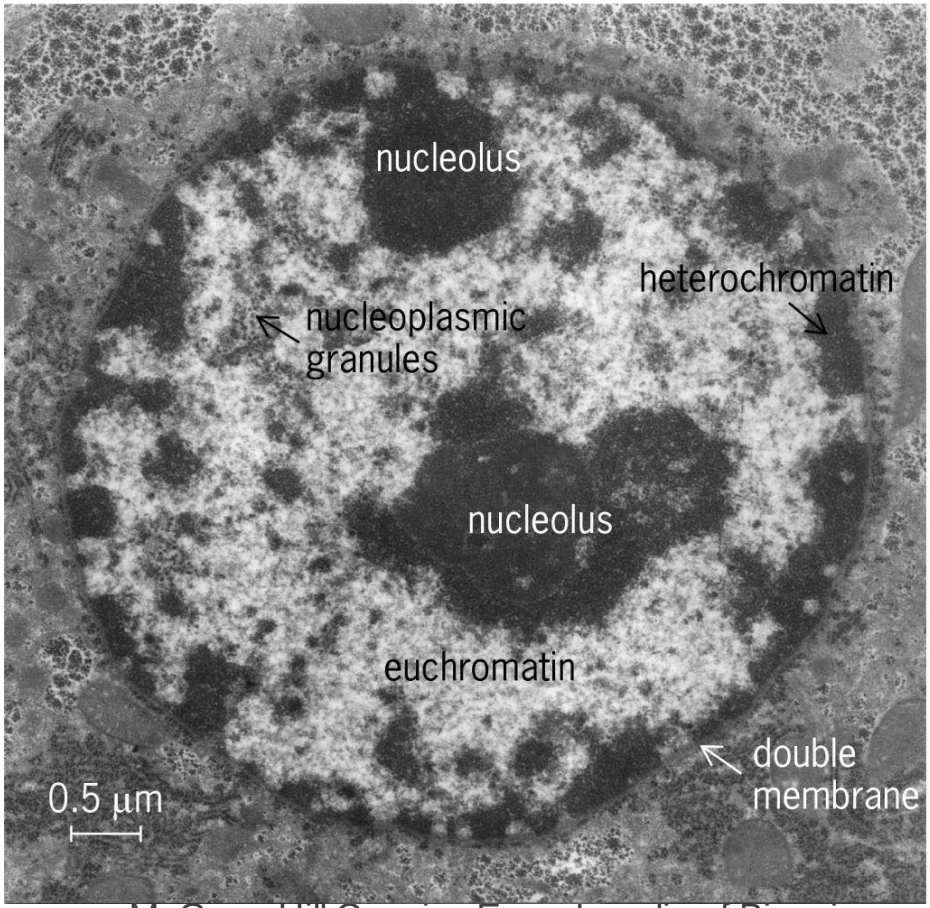
Устаревшее иерархическое представление

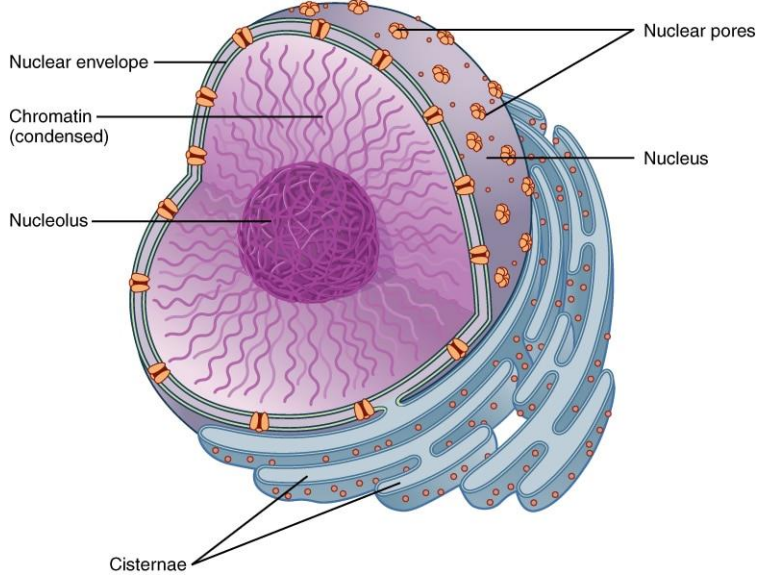


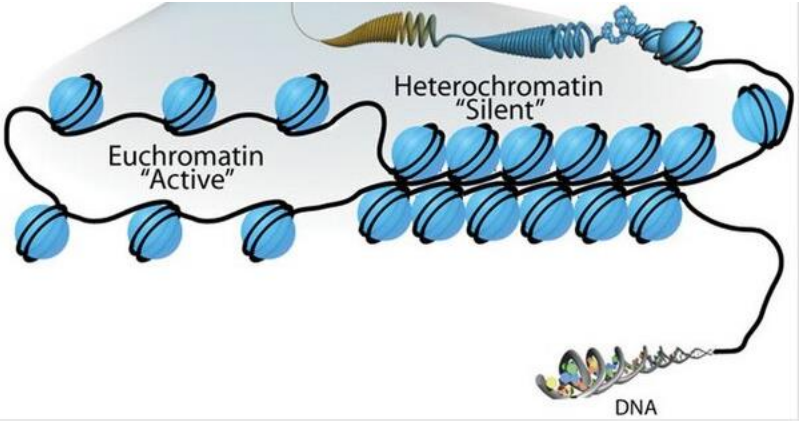
В естественных условиях не существует

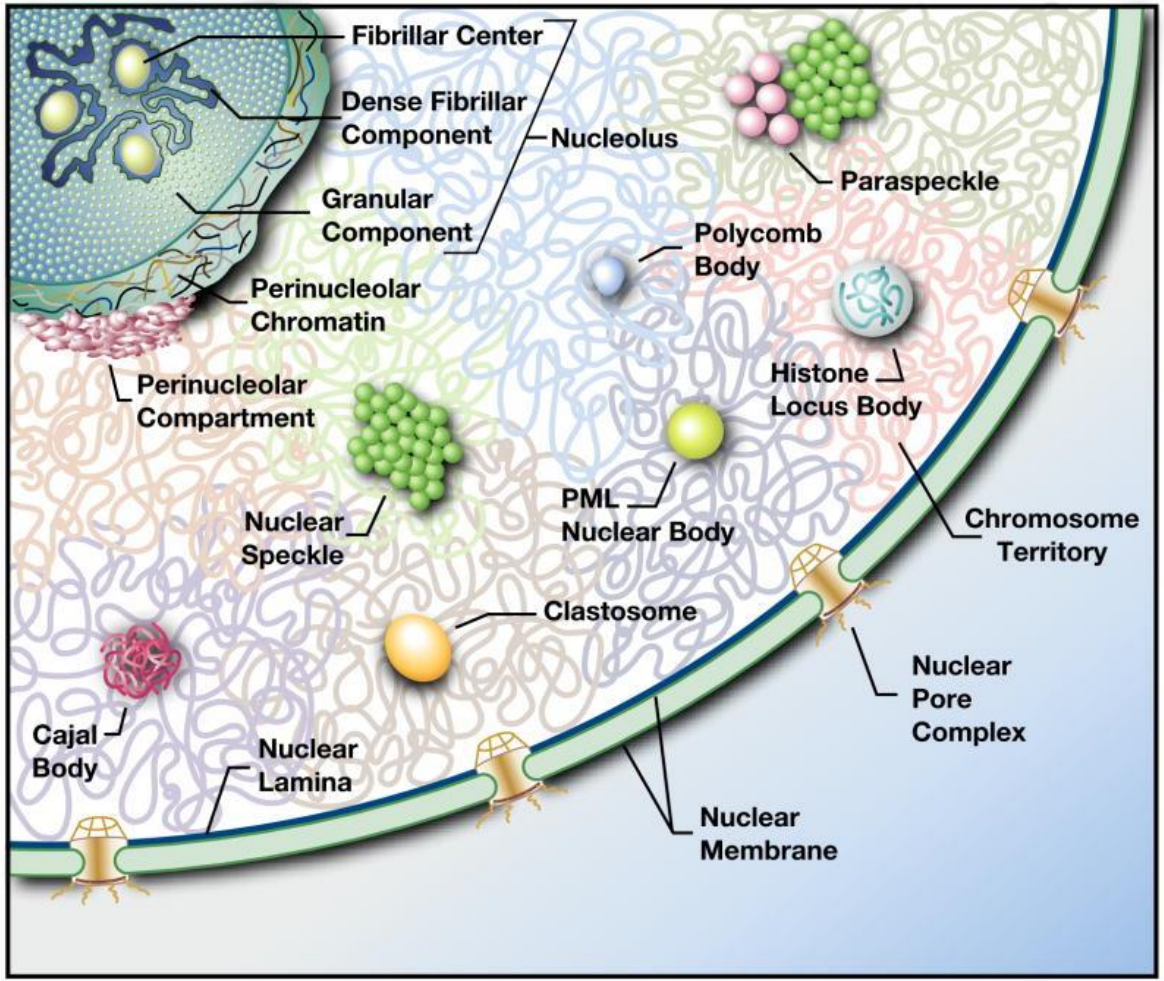
Mol Biol of the CELL, Alberts et al, 2014

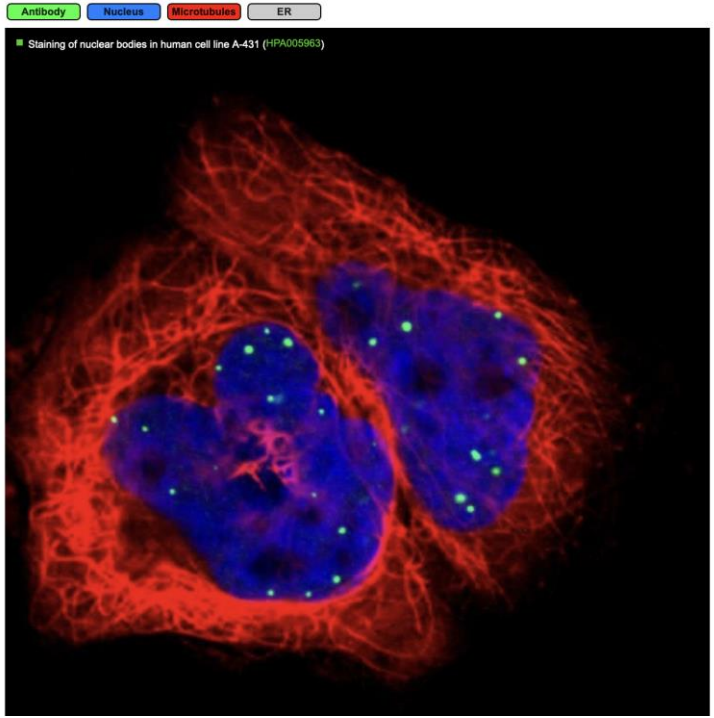
Эу- и гетерохроматин



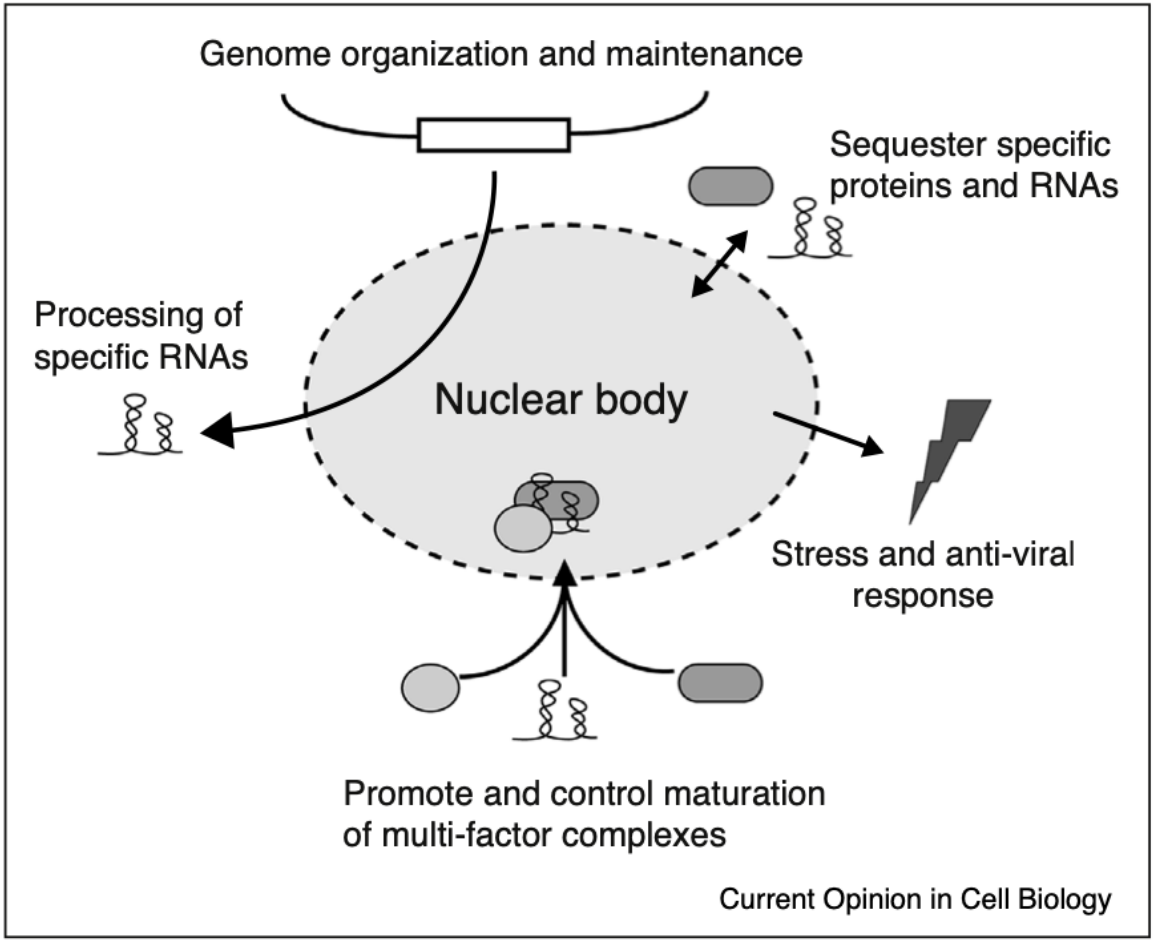




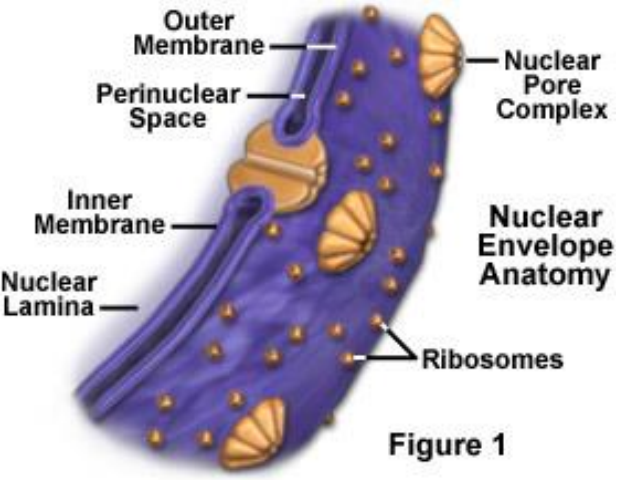




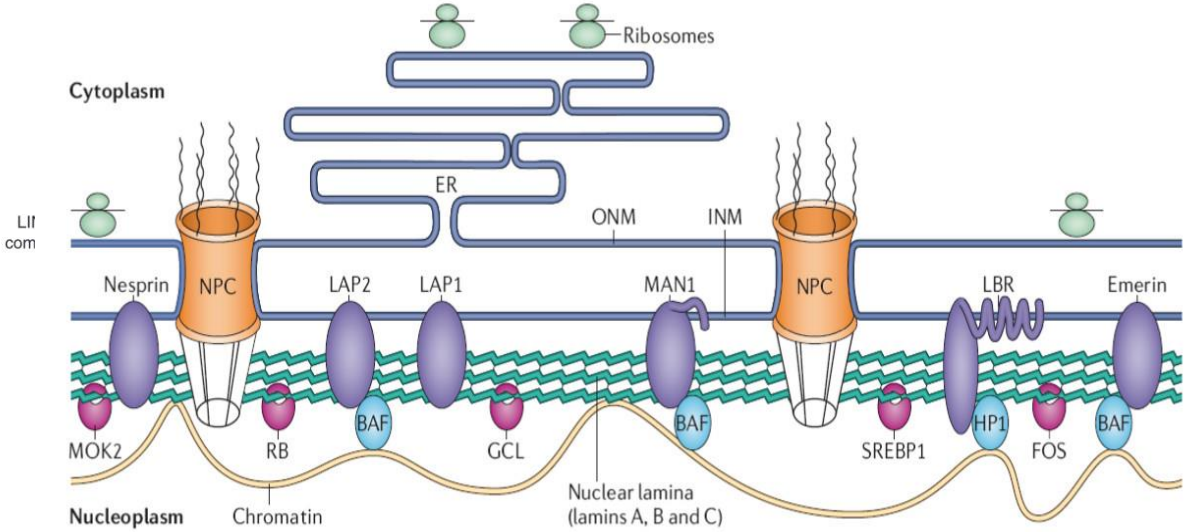
10.1016/j.tig.2011.05.006



definitions of nuclear speckles (NS) are descriptive in nature, typically referring to their physical appearance in microscopy experiments such as '**nuclear domains enriched in pre-mRNA splicing factors, located in the interchromatin region of the nucleoplasm of mammalian cells**'



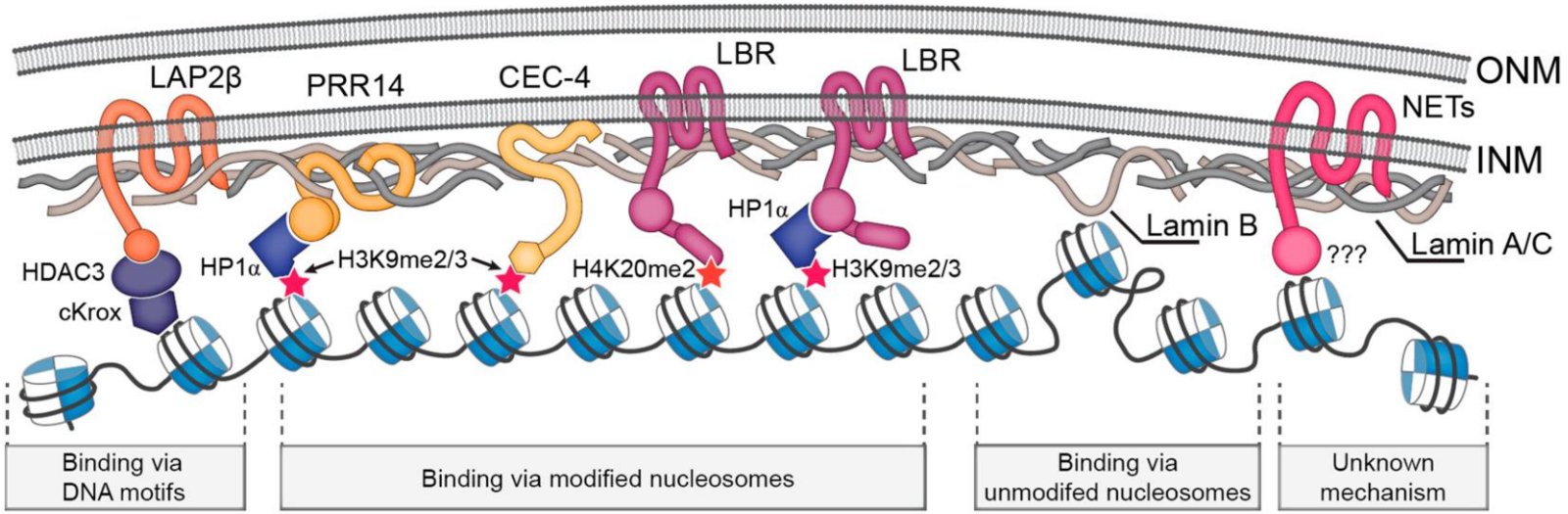
Ядерная мембрана



Ядерная ламина

10.1101/cshperspect.a040113

Концепция:
ядерная ламина и lamina-associated domains

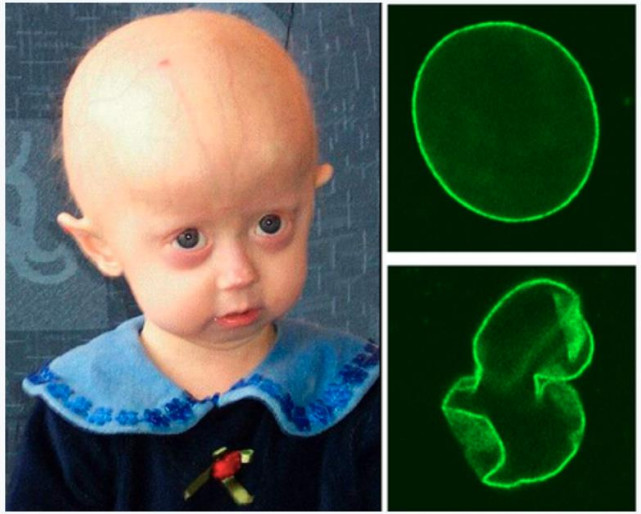


The Nuclear Lamina as an Organizer of Chromosome Architecture

by Yuri Y. Shevelyov [1,*] and Sergey V. Ulianov [2]

Progeria

Other names Hutchinson–Gilford progeria syndrome (HGPS),[1][2] progeria syndrome,[2] Joseph syndrome



A young girl with progeria (left). A healthy cell nucleus (right, top) and a progeric cell nucleus (right, bottom).

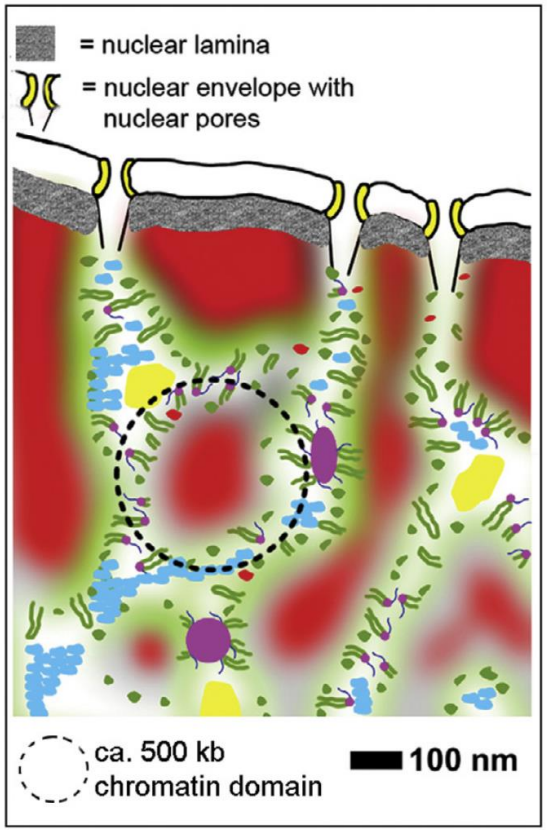
In 2003, the cause of progeria was discovered to be a point mutation in position 1824 of the *LMNA* gene, which replaces a cytosine with thymine

Lamin A Truncation in Hutchinson-Gilford Progeria

Annachiara De Sandre-Giovannoli,[1] Rafaëlle Bernard,[2] Pierre Cau,[1,3] Claire Navarro,[1] Jeanne Amiel,[4] Irène Boccaccio,[1] Stanislas Lyonnet,[4] Colin L. Stewart,[5] Arnold Munnich,[4] Martine Le Merrer,[4] Nicolas Lévy[1,2*]

Концепция:
active compartment/inactive compartment/interchromatin compartment

A



active nuclear compartment

ANC

Transcriptionally competent decondensed chromatin marked by „active“ histone marks

transcriptionally competent chromatin loops,

transcriptionally active chromatin loops

Interchromatin compartment, harboring

Transcription factories,

splicing speckles,

architectural proteins, e.g. CTCF, SAF-A, Matrin

inactive nuclear compartment

INC

Compacted part of chromatin domain clusters (CDCs) marked by repressive histone marks

B

Chromosoma (2014) 123:217–224
DOI 10.1007/s00412-014-0459-8

REVIEW

A requiem to the nuclear matrix: from a controversial concept to 3D organization of the nucleus

S. V. Razin · O. V. Iarovaia · Y. S. Vassetzky

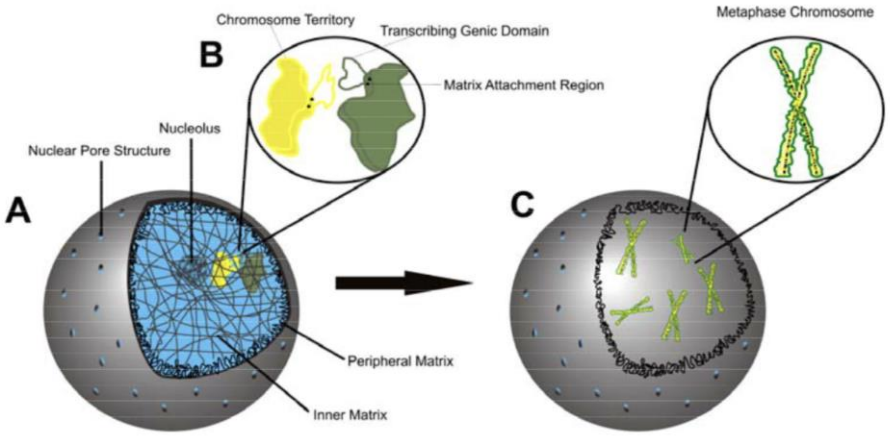


Fig. 1. The nuclear matrix. A - Interphase nucleus. The outer nuclear matrix is

The nuclear lamina is associated with the inner face of the inner nuclear membrane of the nuclear envelope, whereas the outer face of the outer nuclear membrane is continuous with the endoplasmic reticulum.[1] The nuclear lamina is similar in structure to the nuclear matrix, that extends throughout the nucleoplasm.

10.2478/s11658-006-0016-4

Концепция: Хромосомные территории

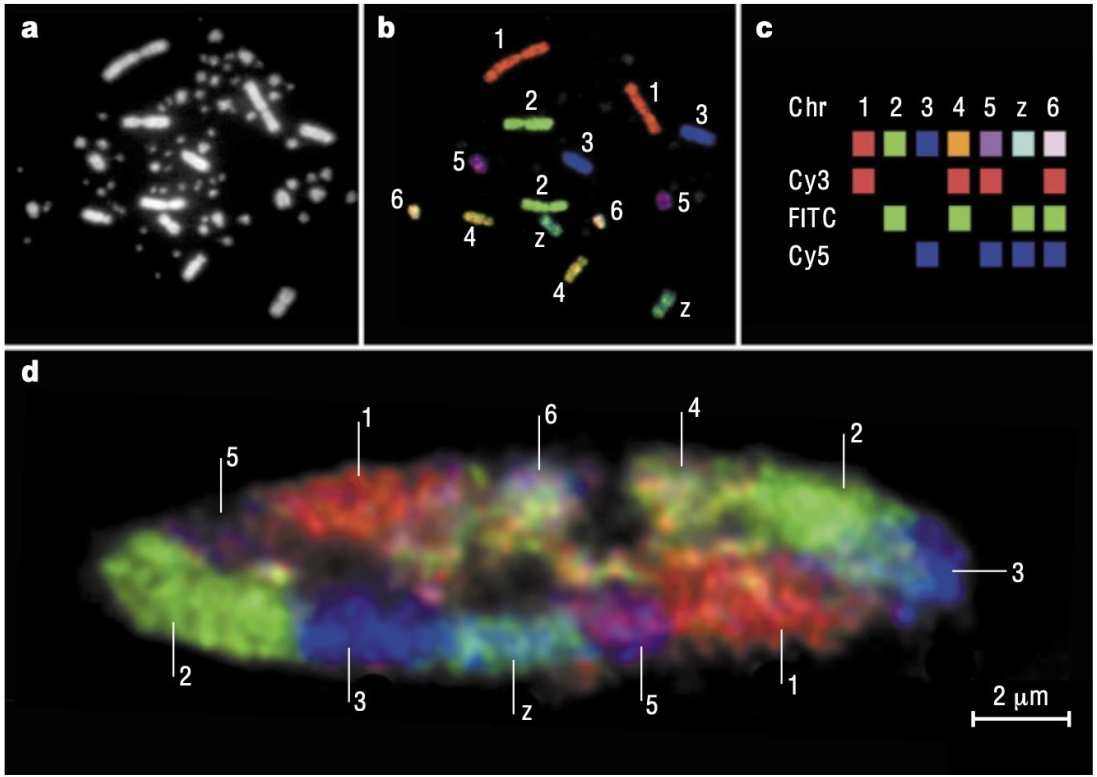


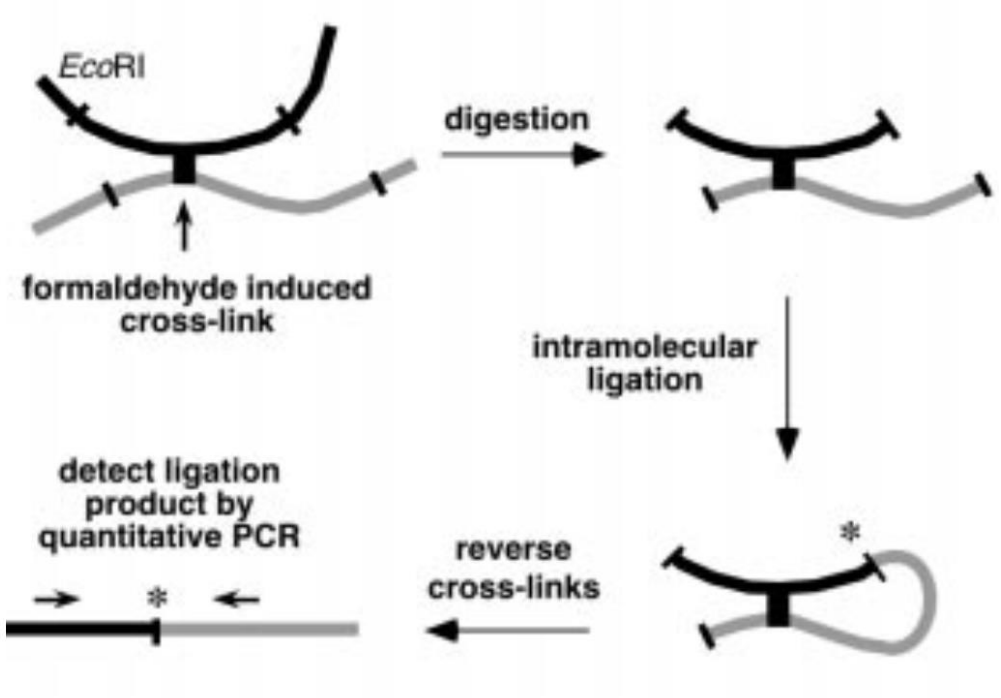
Figure 2 | **Chromosome territories in the chicken. a** | 4,6-diamidino-2-phenylindole (DAPI)-stained, diploid, chicken metaphase spread with macro- and microchromosomes. **b** | The same metaphase spread after multicolour fluorescence *in situ* hybridization with pseudocoloured chromosomes. Chicken chromosome paint probes (image courtesy of Johannes Wienberg) were labelled by a combinatorial scheme with oestradiol (1, 4, 5, 6),

Cremer, T.; Cremer, C. (2001). . Nature Reviews Genetics, 2(4), 292–301. doi:10.1038/35066075

Capturing Chromosome Conformation

Job Dekker,[1]* Karsten Rippe,[2] Martijn Dekker,[3] Nancy Kleckner[1]

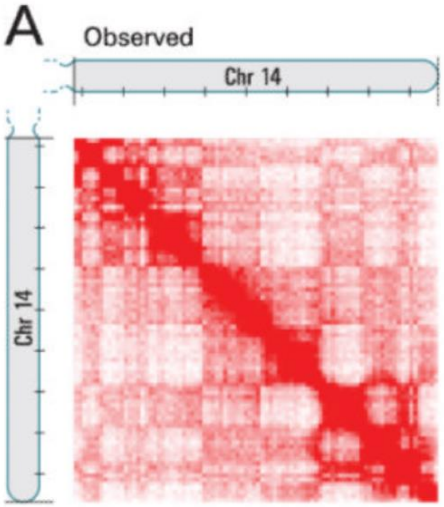
15 FEBRUARY 2002 VOL 295 SCIENCE

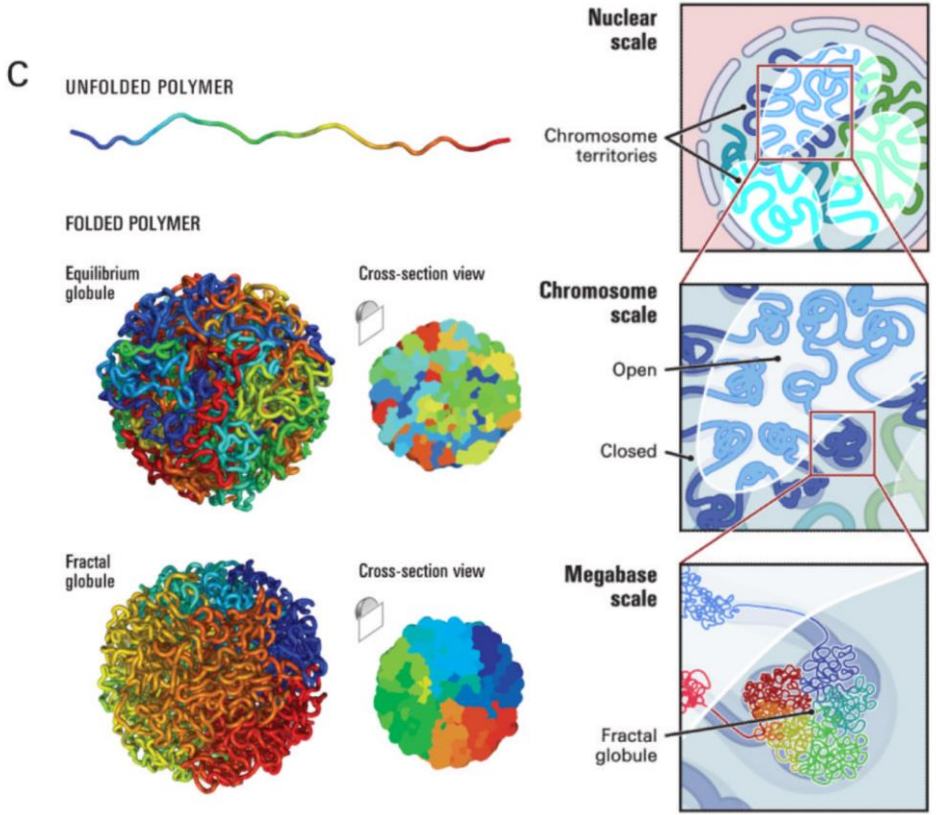


Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome

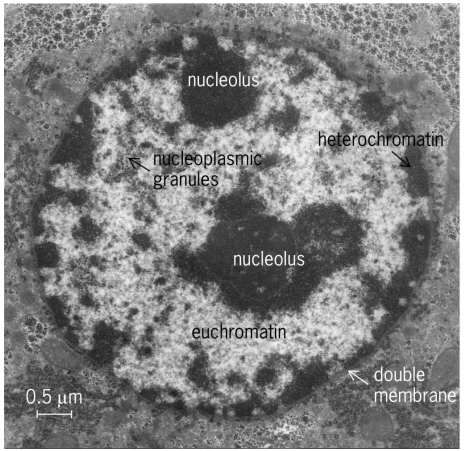
Erez Lieberman-Aiden,[1,2,3,4]* Nynke L. van Berkum,[5]* Louise Williams,[1] Maxim Imakaev,[2] Tobias Ragoczy,[6,7] Agnes Telling,[6,7] Ido Amit,[1] Bryan R. Lajoie,[5] Peter J. Sabo,[8] Michael O. Dorschner,[8] Richard Sandstrom,[8] Bradley Bernstein,[1,9] M. A. Bender,[10] Mark Groudine,[6,7] Andreas Gnirke,[1] John Stamatoyannopoulos,[8] Leonid A. Mirny,[2,11] Eric S. Lander,[1,12,13]† Job Dekker[5]†

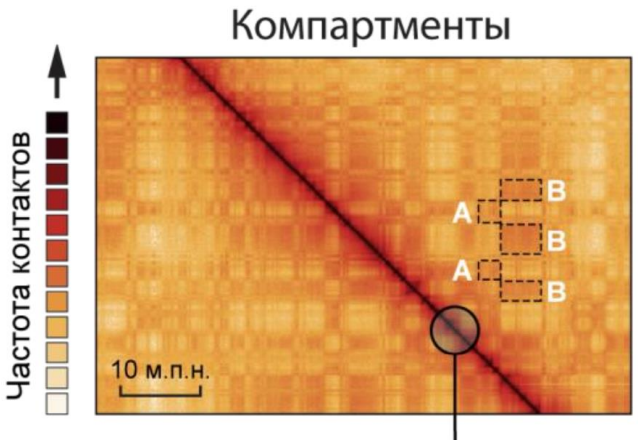
www.sciencemag.org **SCIENCE** VOL 326 9 OCTOBER 2009

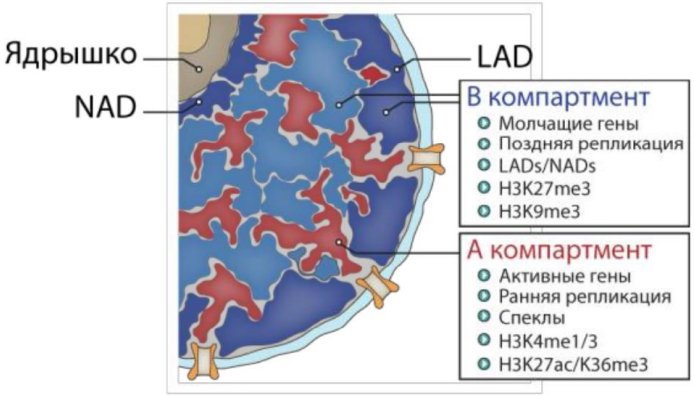




Концепция : Эу/гетерохроматин, A/B – компартменты





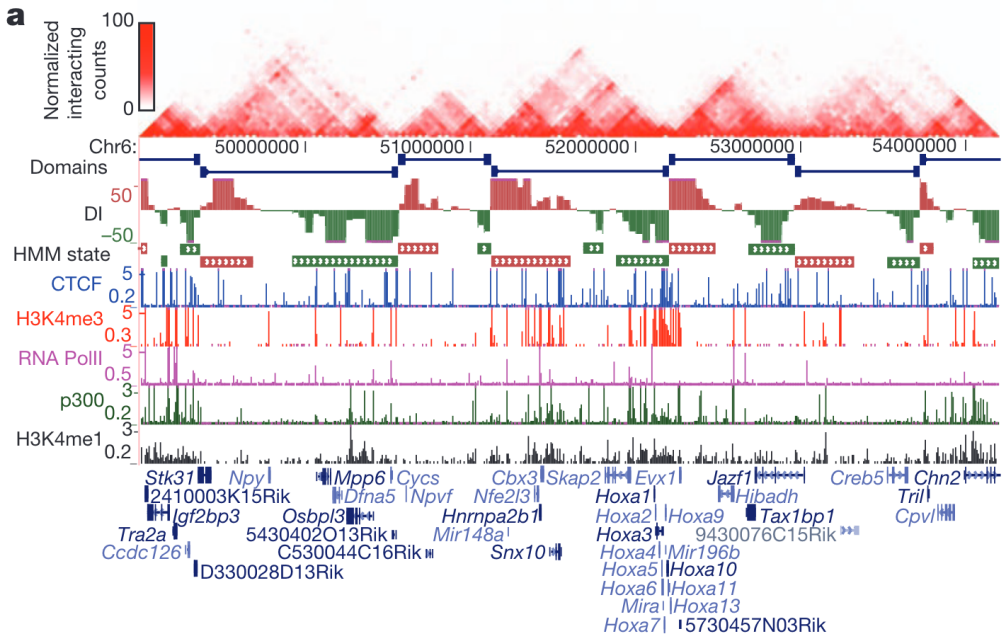


С.В. Ульянов – докторская диссертация 2023 г.

Topological domains in mammalian genomes identified by analysis of chromatin interactions

Jesse R. Dixon[1,2,3], Siddarth Selvaraj[1,4], Feng Yue[1], Audrey Kim[1], Yan Li[1], Yin Shen[1], Ming Hu[5], Jun S. Liu[5] & Bing Ren[1,6]

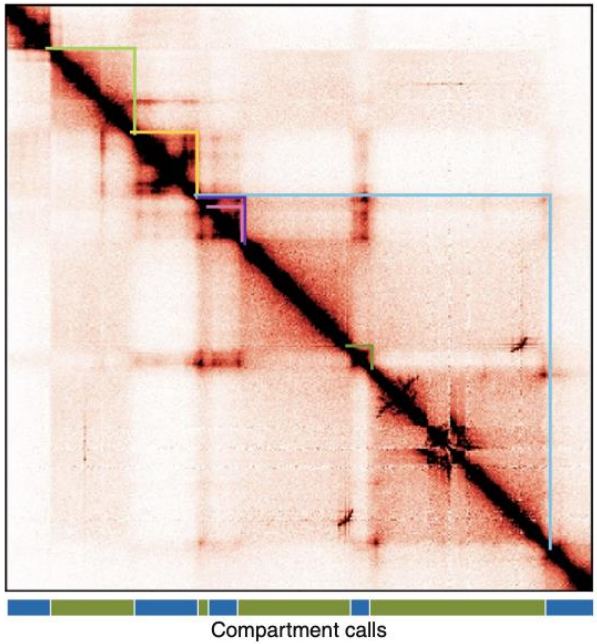
376 | NATURE | VOL 485 | 17 MAY 2012



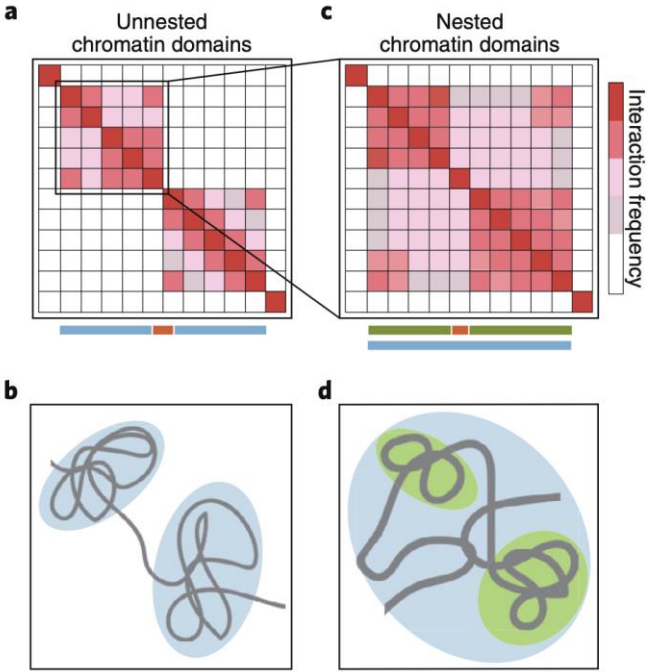
Топологически ассоциированные домены

topologically associating domain

Концепция 3: ТАДы – топологически ассоциирующие домены



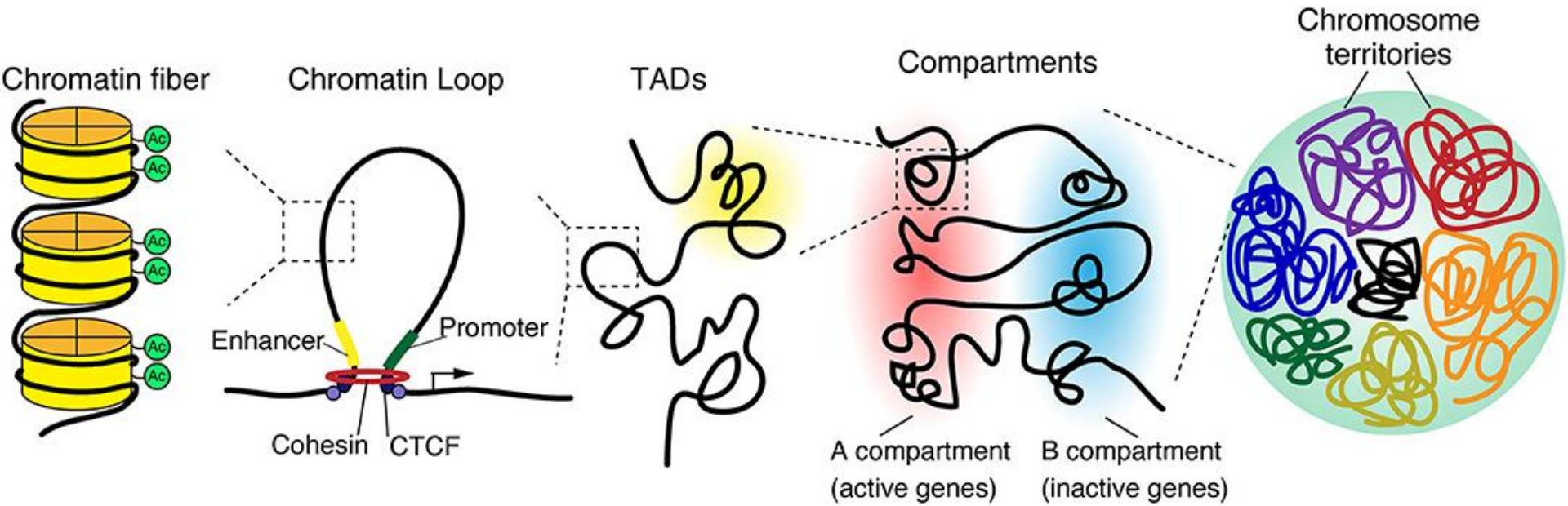
Карта контактов вдоль генома (метод Hi-C)



10.1038/s41588-019-0561-1

Представления о структуре хроматина

Более современное представление



https://www.frontiersin.org/articles/10.3389/fcell.2020.626541/full

Концепция 5: Loop extrusion – экструзия петель

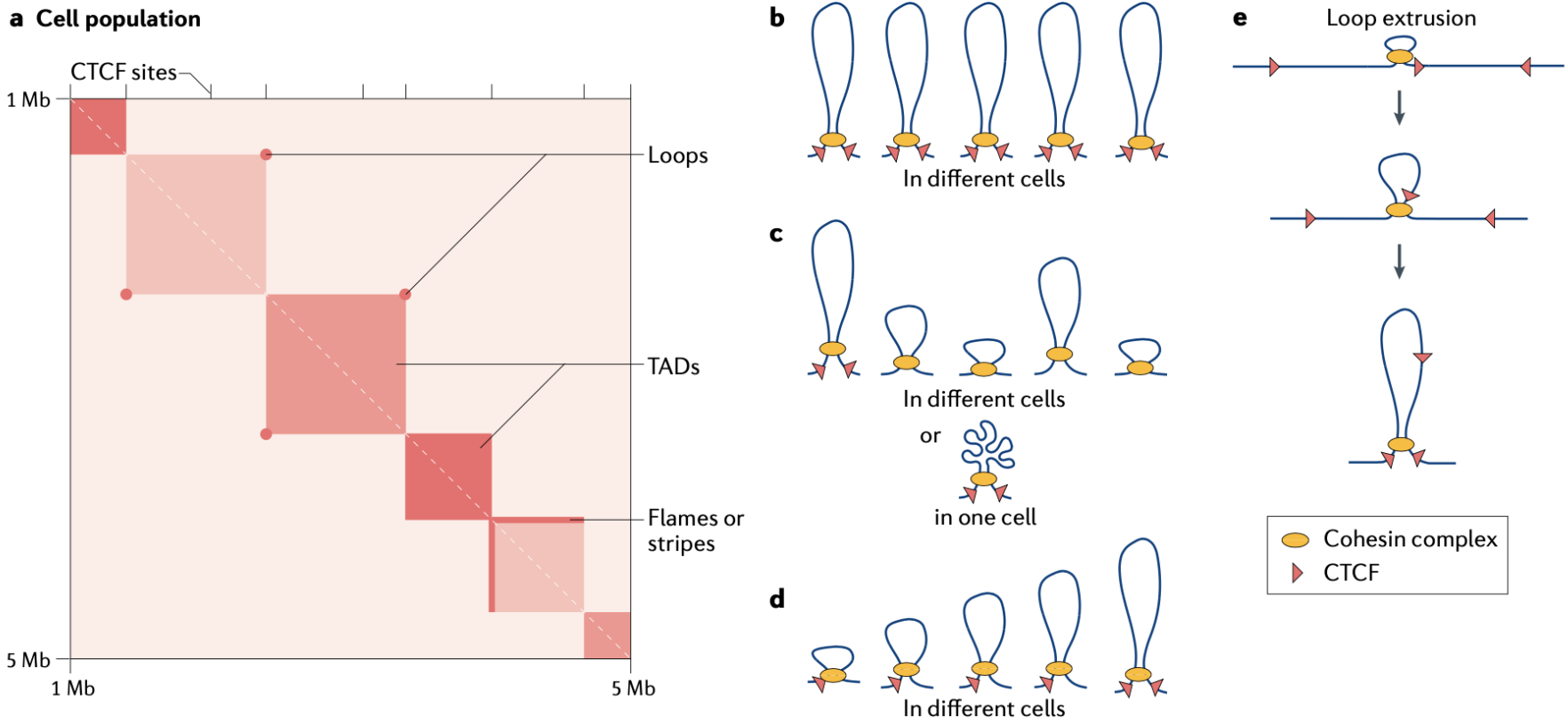
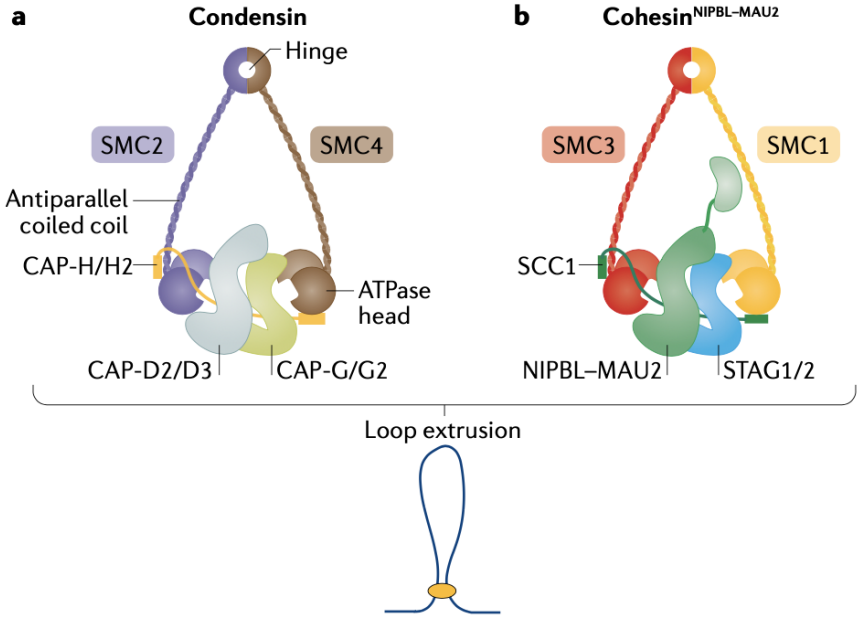


Fig. 1 | **Interphase genome organization. a** | Schematic representation of a Hi-C map depicting the organization, across

Концепция: Loop extrusion – экструзия петель



10.1126/science.aar7831

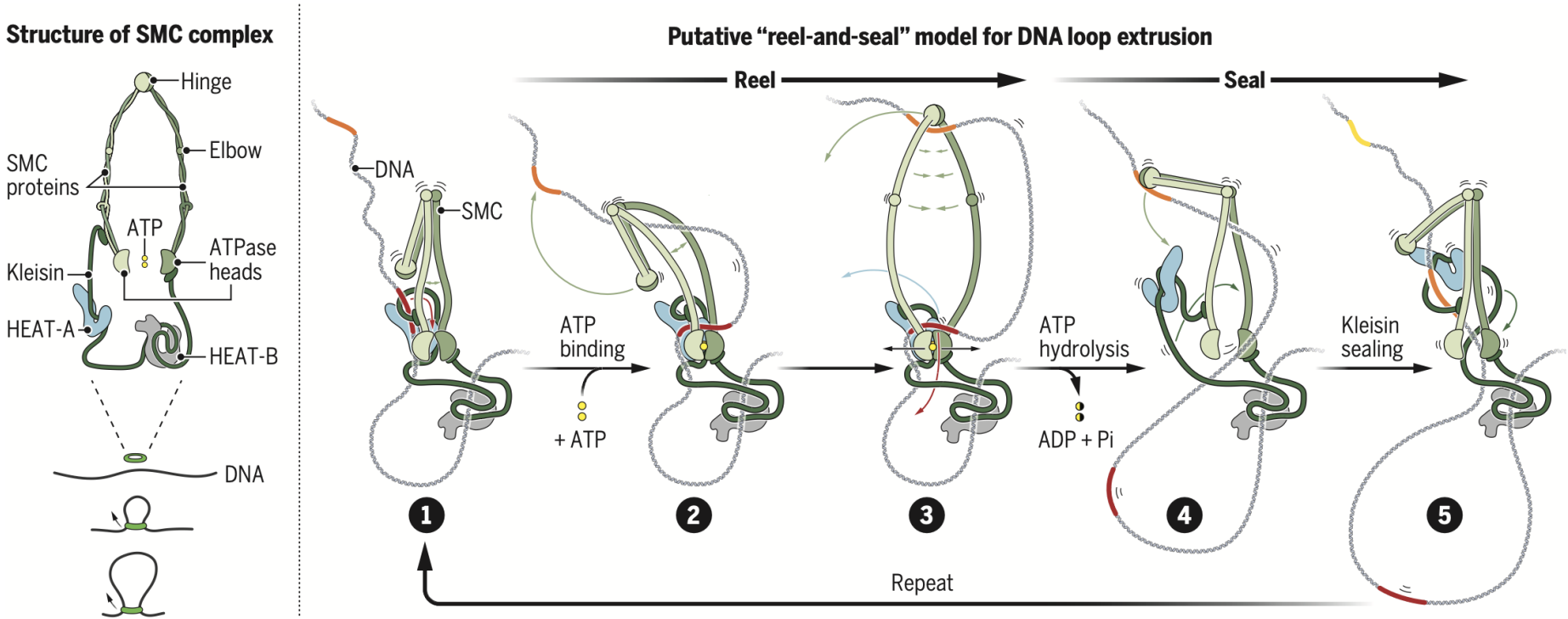
PERSPECTIVE | HYPOTHESIS

How do molecular motors fold the genome?

A potential mechanism of DNA loop extrusion by molecular motors is discussed

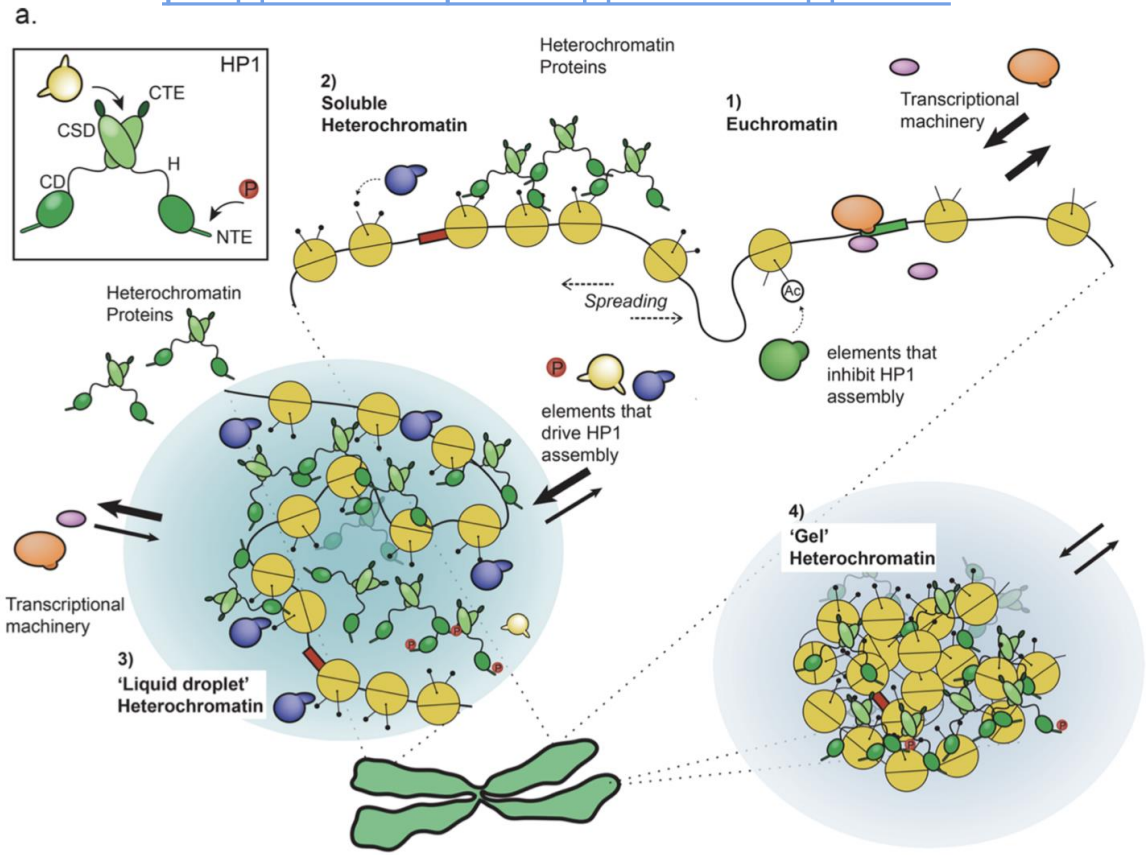
CEES DEKKER , CHRISTIAN H. HAERING , JAN-MICHAEL PETERS , AND BENJAMIN D. ROWLAND Authors Info & Affiliations

SCIENCE · 9 Nov 2023 · Vol 382, Issue 6671 · pp. 646-648 · DOI: 10.1126/science.adi8308



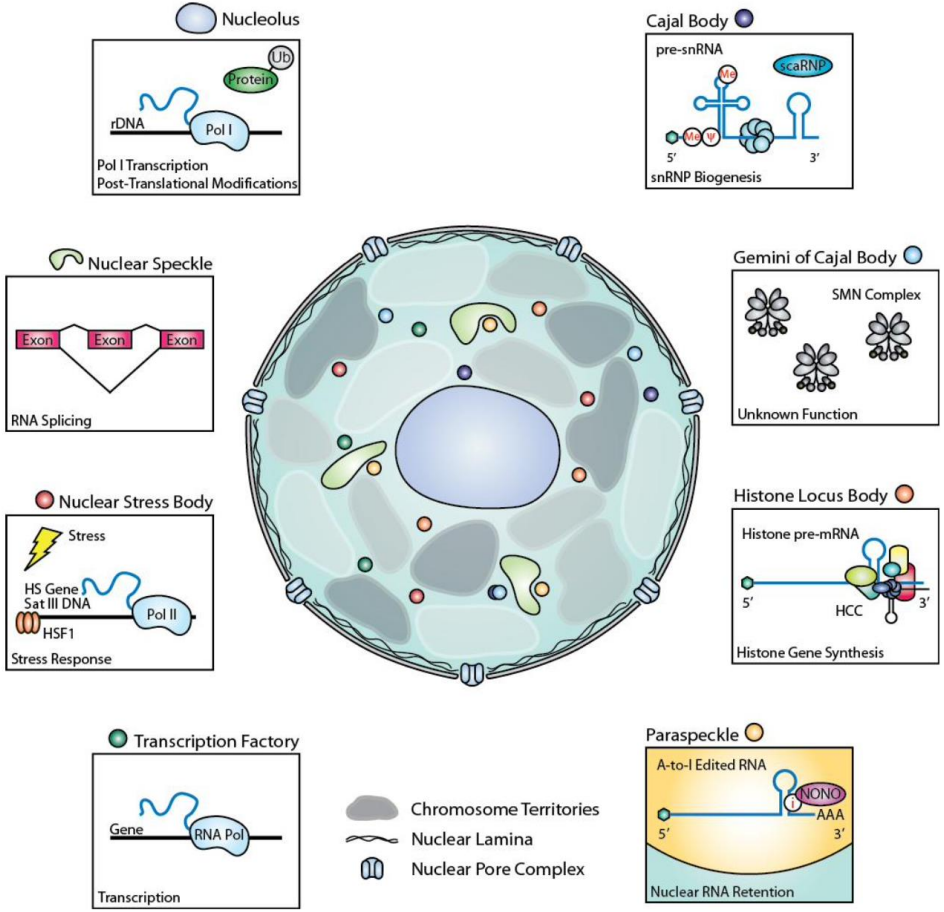
ADP, adenosine diphosphate; ATP, adenosine triphosphate; NCAPD2, non-SMC condensin subunit D2; NCAPD3, non-SMC condensin subunit D3; NCAPG, non-SMC condensin subunit G; NCAPG2, non-SMC condensin subunit G2; NIPBL, nipped-B-like protein; Pi, inorganic phosphate; SMC, structural maintenance of chromosomes complex; STAG1, cohesin subunit SA-1; STAG2, cohesin subunit SA-2.

Концепция 2: ”Жидкие капли” разделение фаз жидкость-жидкость

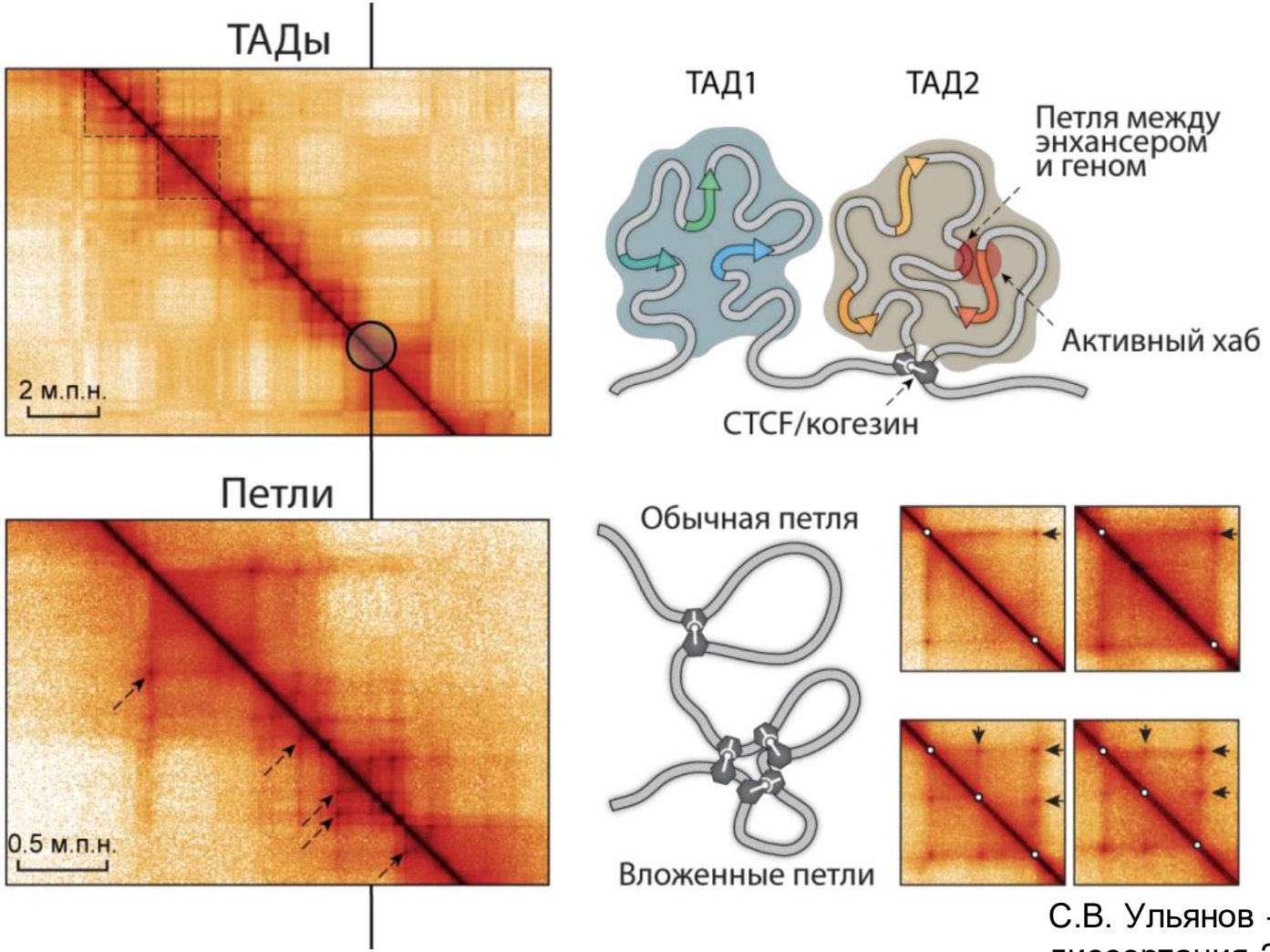


Larson AG, Narlikar GJ. 2018. Biochemistry 57: 2540–2548.

В формировании немембранных органелл важную роль играют статистические физические взаимодействия (разделение фаз)



https://www.mdpi.com/2079-7737/2/3/976



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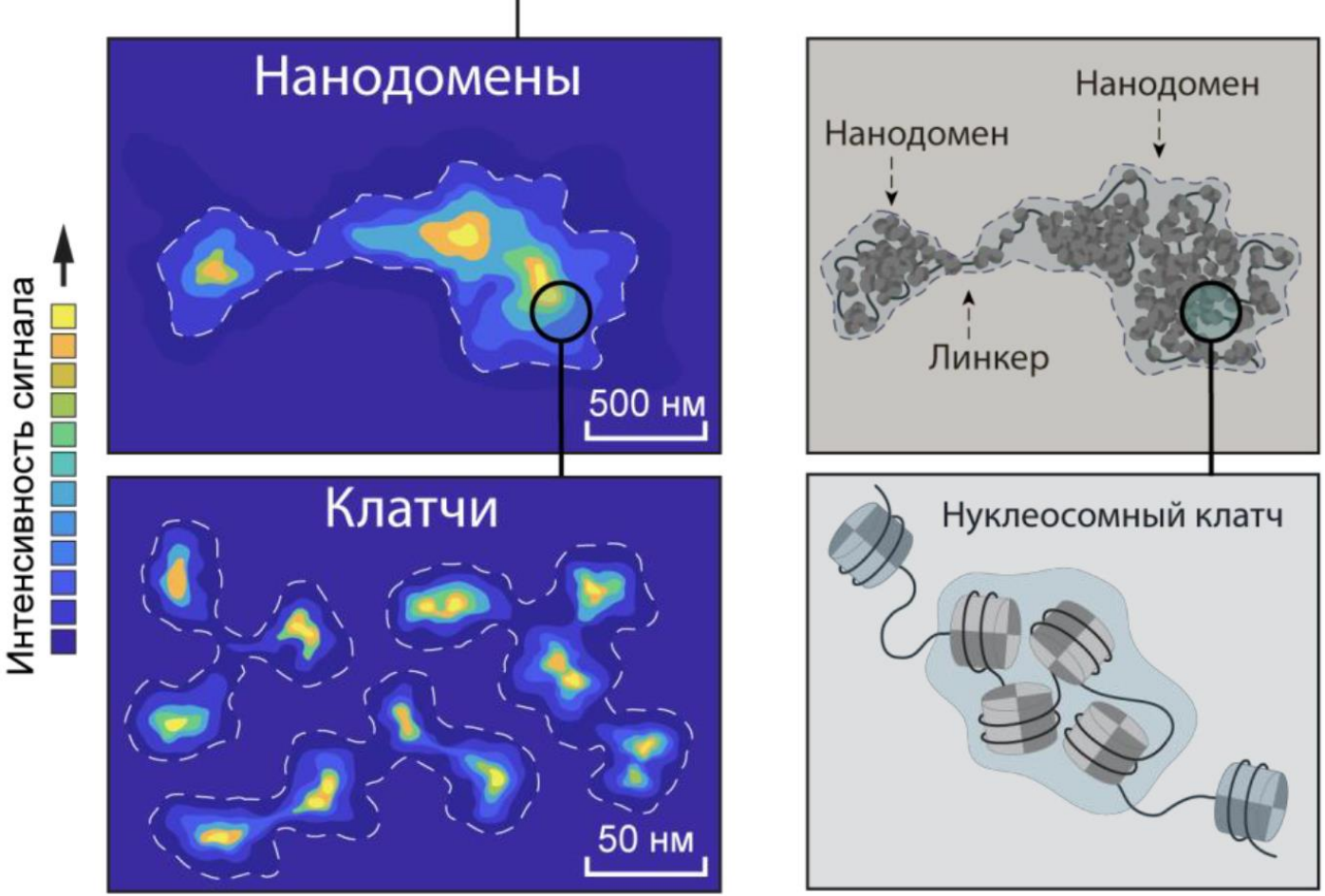

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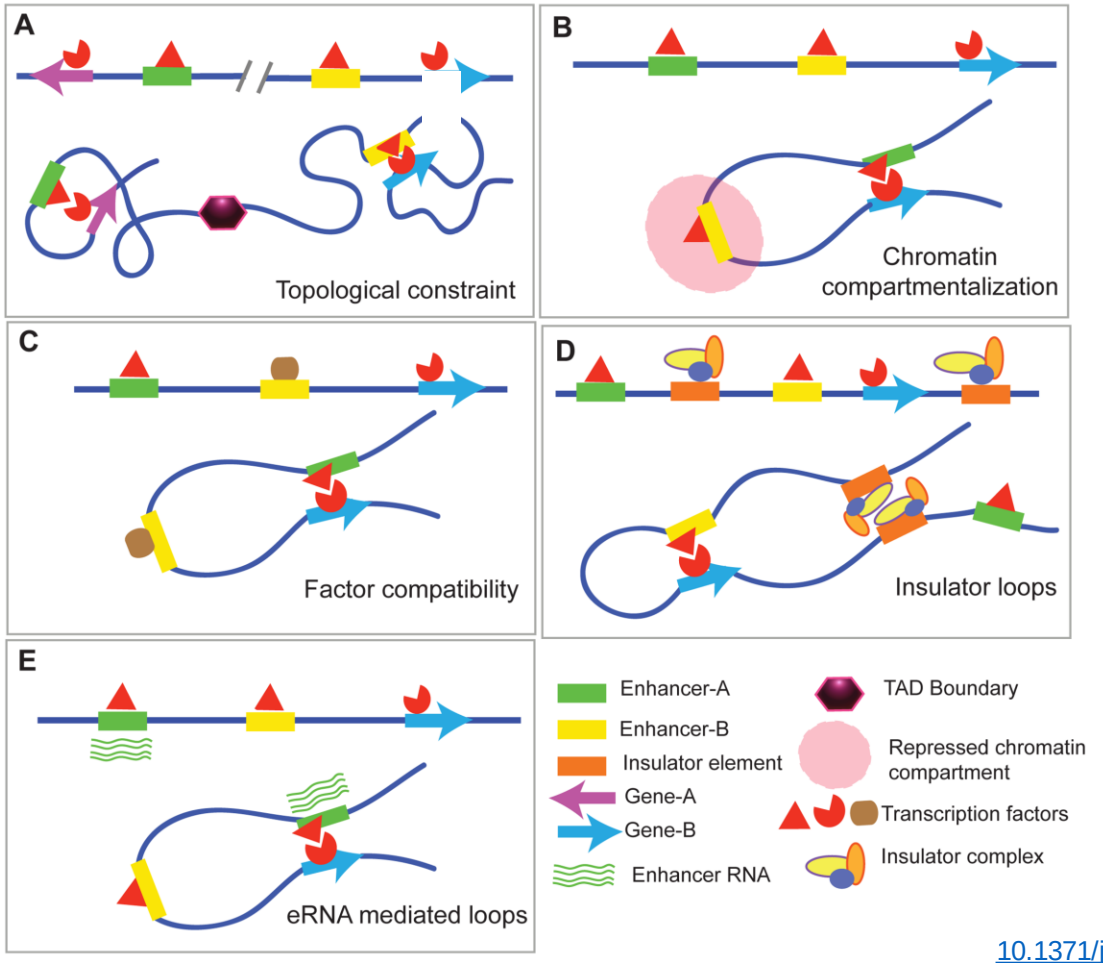
Концепция: ”Петли”, топология и взаимодействия элементов вдоль ДНК



10.1371/journal.pgen.1005640.g002

Эпигенетика и ее механизмы

Содержание лекции

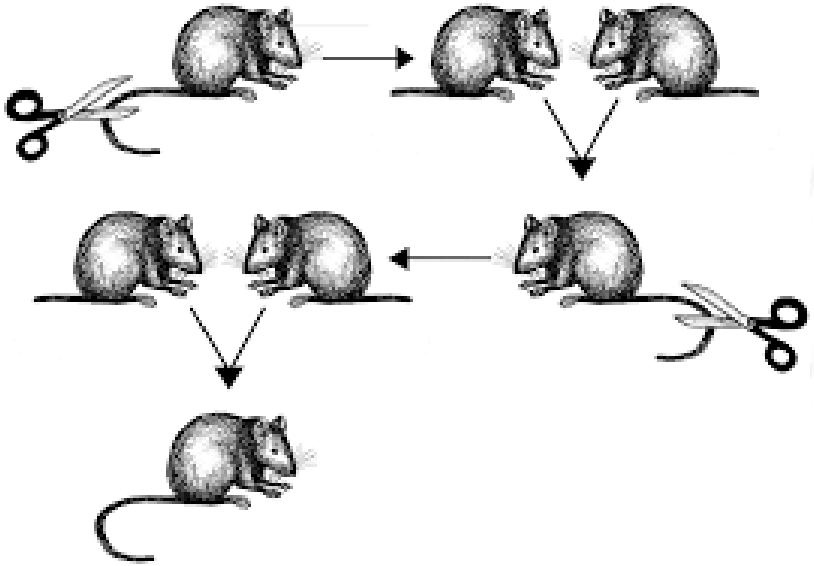
- История вопроса. К. Уаддингтон.
- ДНК метилирование. Эффекты. Ферменты. Промотеры и CpG островки. Мутации. Наследование. Импринтинг.
- ПТМ гистонов. Цвета хроматина.
- Ацетилирование, метилирование. Ингибиторы.
- Шапероны гистонов.
- Ремоделлеры. pBAF.
- Сопряжение меток и метилирования. CoREST?
- Спрэддинг гетерохроматина. Границы.
- Расположение нуклеосом. +1 нуклеосомы.

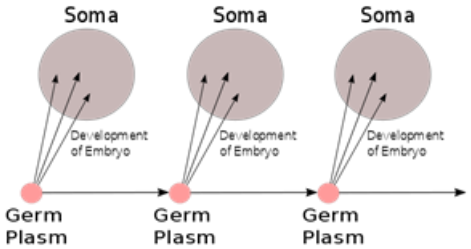
Эпигенетика

- Epigenetics (also sometimes called epigenomics) is a field of study focused on changes in DNA that do not involve alterations to the underlying sequence. The DNA letters and the proteins that interact with DNA can have chemical modifications that change the degrees to which genes are turned on and off. Certain epigenetic modifications may be passed on from parent cell to daughter cell during cell division or from one generation to the next. The collection of all epigenetic changes in a genome is called an epigenome. (NHGRI)

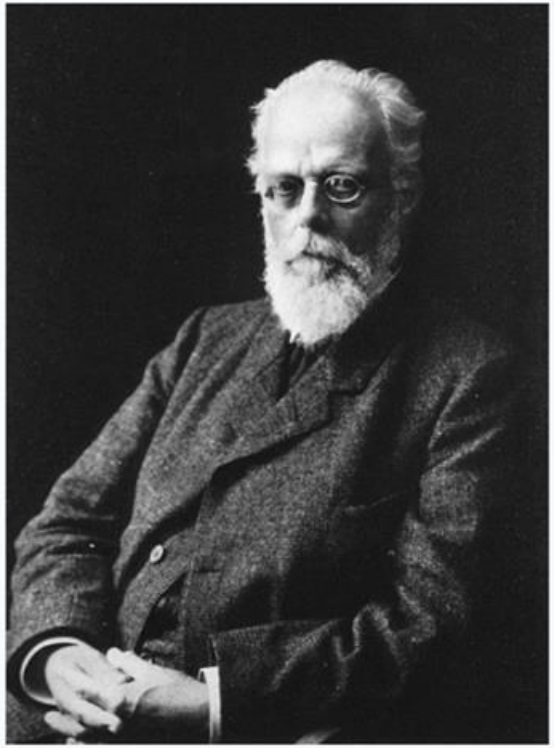
др.-греч. ἐπι- — приставка, обозначающая пребывание на чём-либо или помещение на что-либо

История вопроса



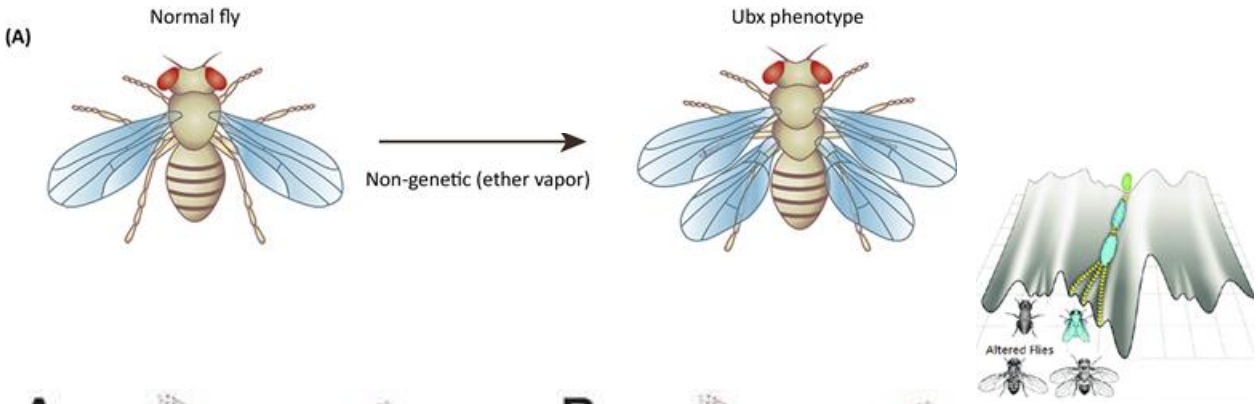


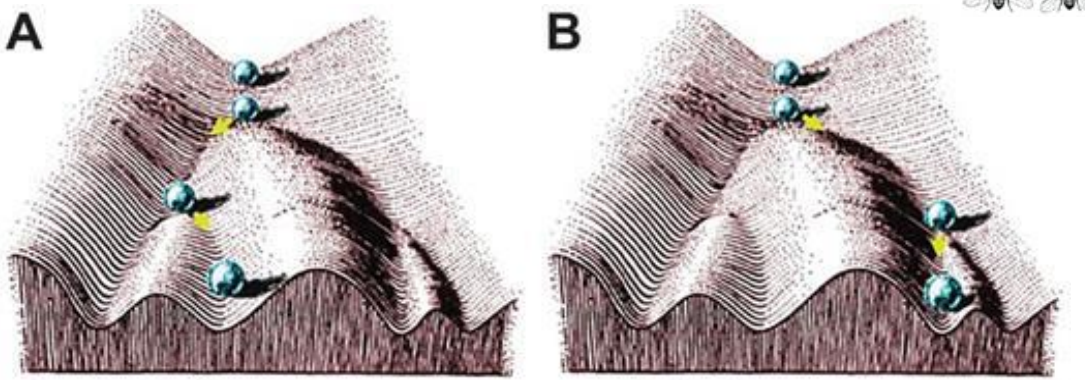
August Weismann



Born	17 January 1834 Frankfurt am Main, Germany
Died	5 November 1914 (aged 80) Freiburg, Germany
Known for	germ plasm theory

История вопроса





Conrad Hal Waddington

CBE FRS FRSE

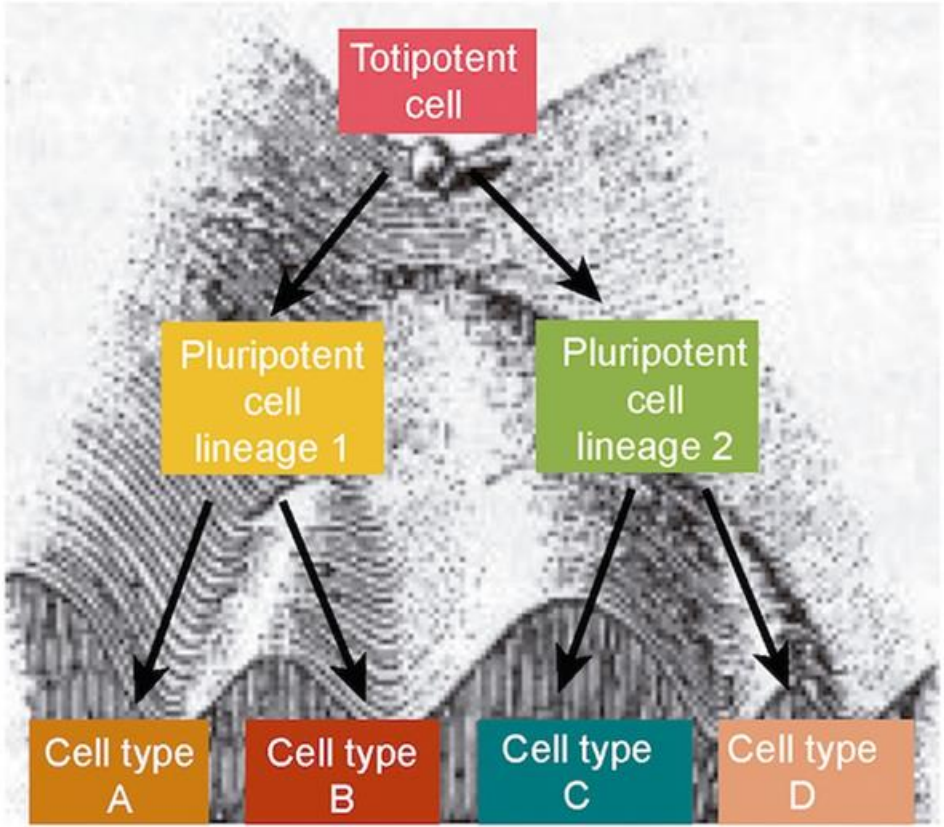
Conrad Hal Waddington in 1934

Born	8 November 1905 Evesham, Worcestershire, England
Died	26 September 1975 (aged 69) Edinburgh, Scotland

Понятие эпигенетического ландшафта развития, фенотипической пластичности, эпигенетического наследования, генетической ассимиляции

10.1242/jeb.120071

Multicellular eukaryote



10.3389/fmicb.2021.685080

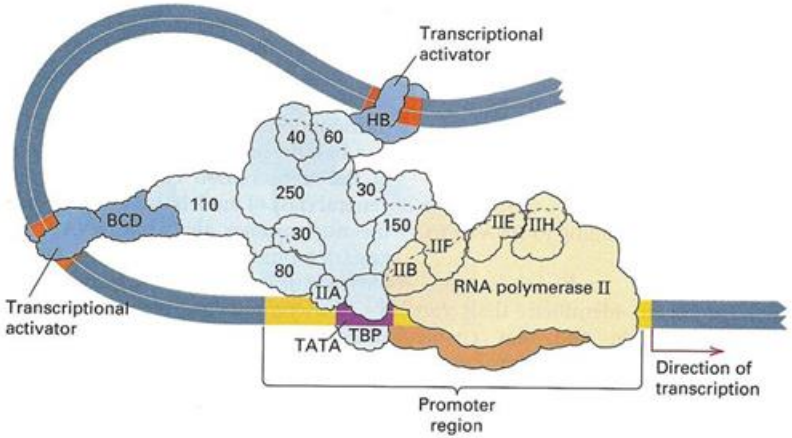
Открыта мемориальная доска памяти сотрудников факультета, пострадавших за свои научные убеждения в 1948 году

24 ноября на биологическом факультете состоялось большое событие. Торжественно была открыта мемориальная доска памяти сотрудников факультета, пострадавших за свои научные убеждения в 1948 году.

Молекулярные механизмы эпигенетики

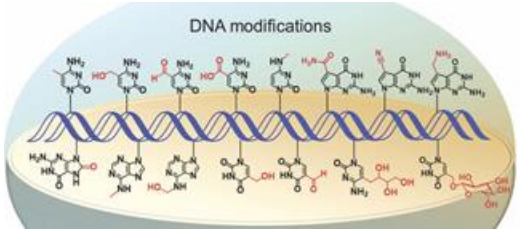
Что влияет на транскрипцию генов?

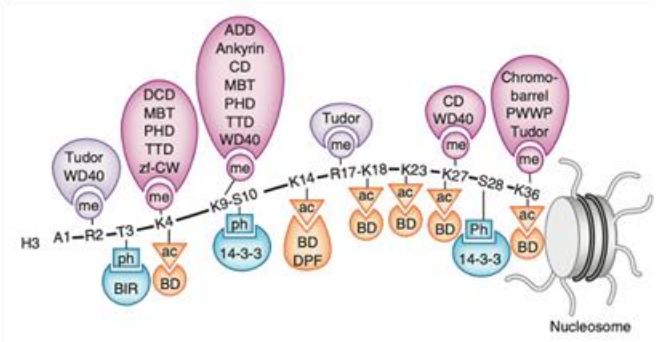
Эффективность инициации транскрипции, эффективность элонгации

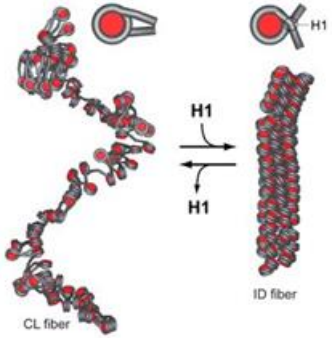


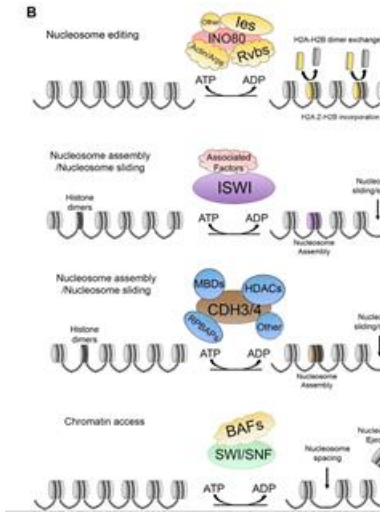
1) Доступностью ДНК для связывания (расположение нуклеосом, компактность хроматина)
2) Легкостью транскрипции через нуклеосомы
3) Легкостью формирования петель
4) Модификациями ДНК помогающими или затрудняющими связывания факторов
5) Модификациями гистонов помогающими или затрудняющими связывания факторов

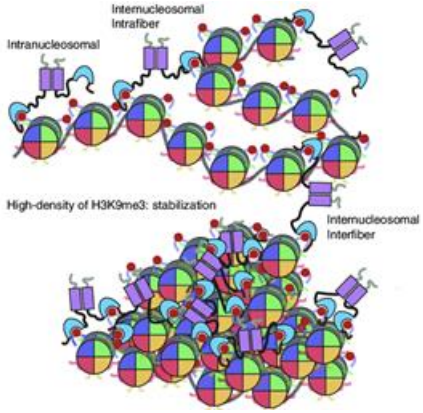
http://www.discoveryandinnovation.com/BIOL202/notes/lecture19.html

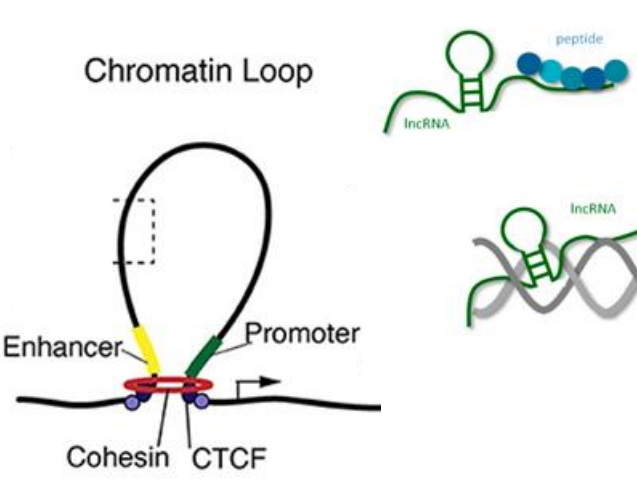

DNA modifications


ADD
Ankyrin
CD
MBT
PHD
TTD
WD40
DCD
MBT
PHD
TTD
zf-CW
Tudor
WD40
Tudor
CD
WD40
Chromo-
barrel
PWWP
Tudor
me
ac
ph
BD
BIR
DPF
14-3-3
H3
A1–R2–T3–K4–K9–S10–K14–R17–K18–K23–K27–S28–K36
Nucleosome

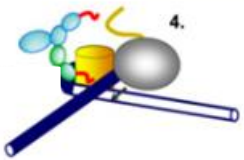

H1
H1
H1
CL fiber
ID fiber

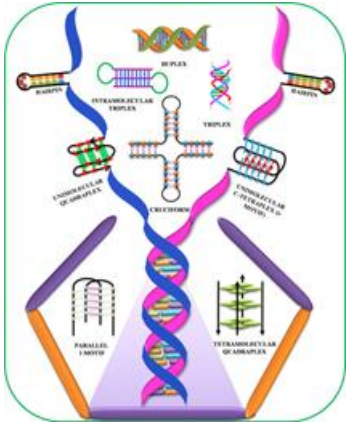

B
Nucleosome editing
INO80
Ies
Rvb5
ATP
ADP
Nucleosome assembly
/Nucleosome sliding
Associated
Factors
ISWI
Histone
dimers
Nucleosome
Assembly
Nucleosome assembly
/Nucleosome sliding
MBDs
HDACs
CDH3/4
RPBAP5
Other
Chromatin access
BAFs
SWI/SNF
Nucleosome
spacing

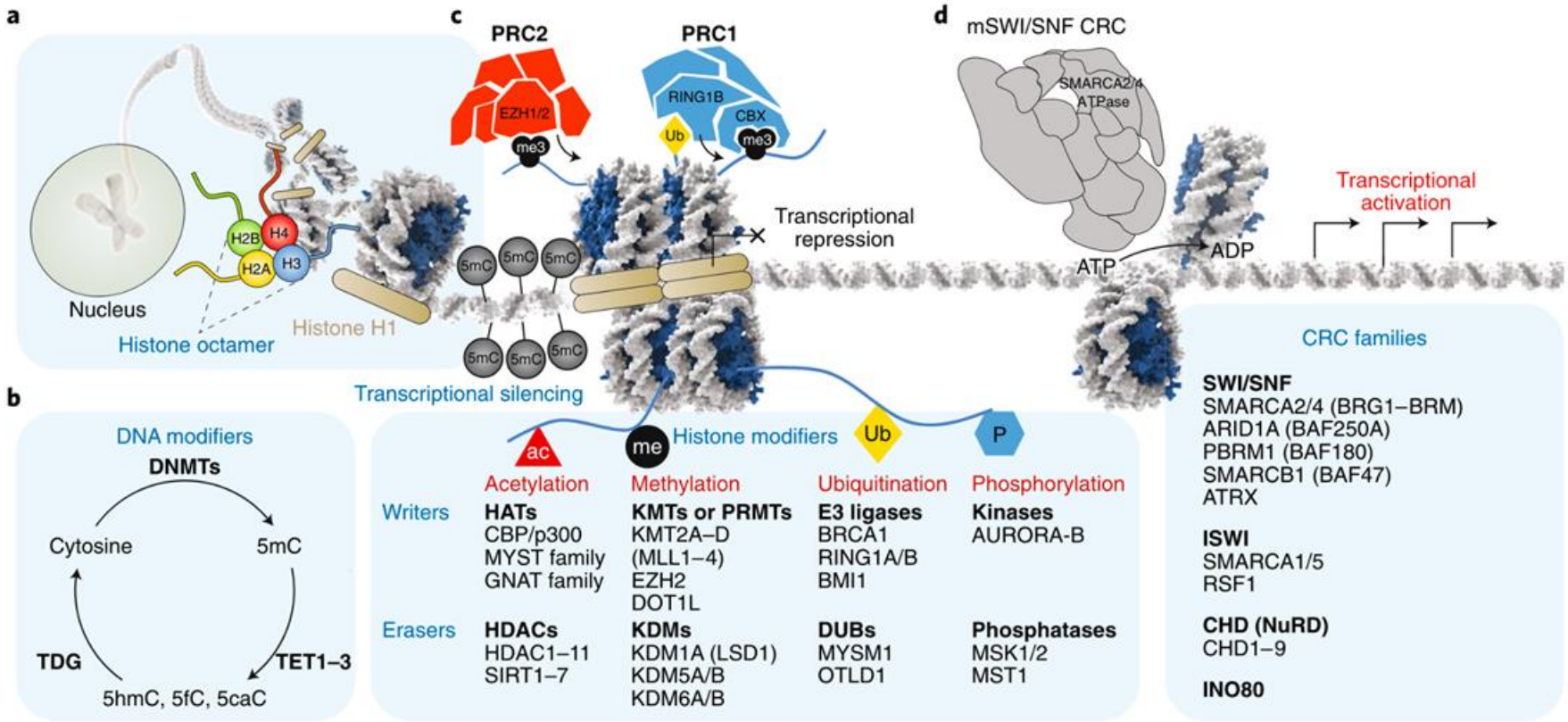

Internucleosomal
Intrafiber
Intranucleosomal
High-density of H3K9me3: stabilization
Internucleosomal
Interfiber


Chromatin Loop
Enhancer
Promoter
Cohesin
CTCF
peptide
lncRNA
lncRNA
interactome
lncRNA
DNA


Spt16
SSRP1
hFACT
- Histone octamer


4.

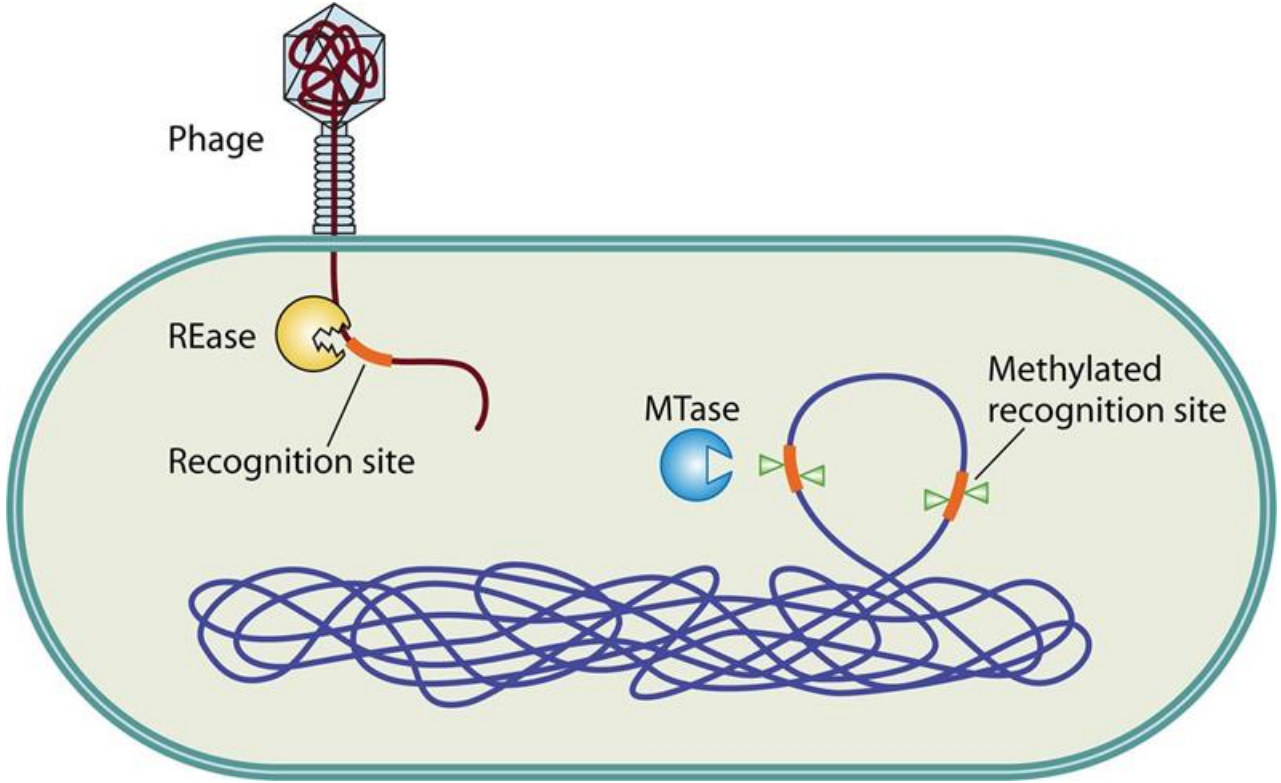




. 1 | Chromatin regulatory processes in mammalian cells. a, DNA is wrapped around a histone octamer containing two copies each of histones H2A,

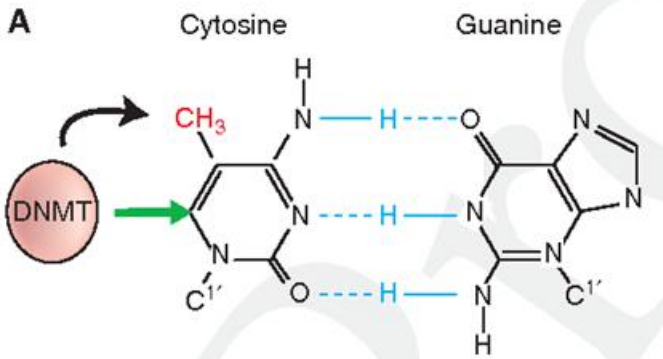
10.1038/s41556-018-0258-1

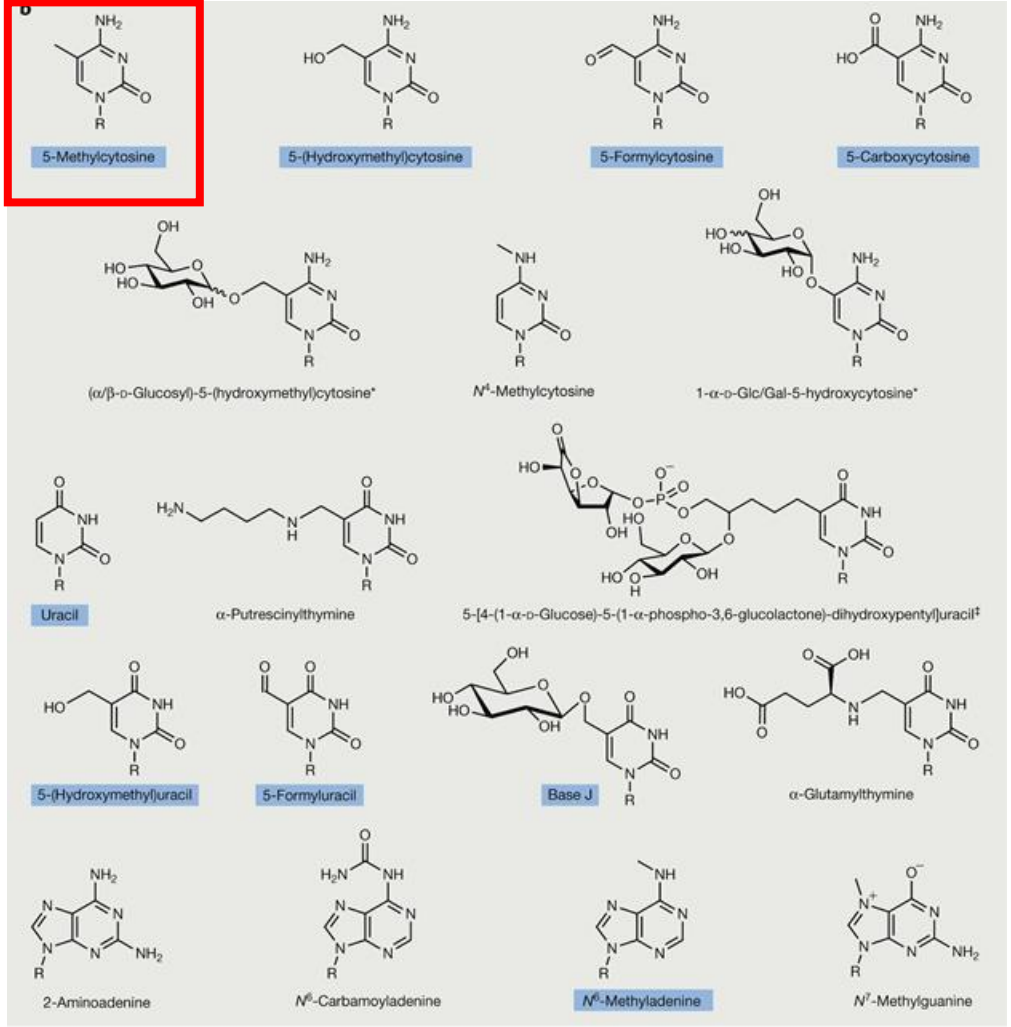
Системы рестрикции-модификации в бактериях



1960-ые годы

Метилирование ДНК



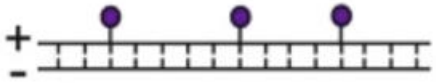


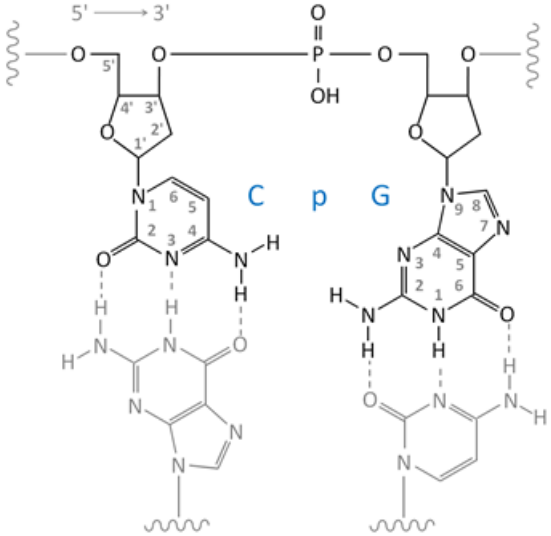
Метилирование ДНК у млекопитающих -- история

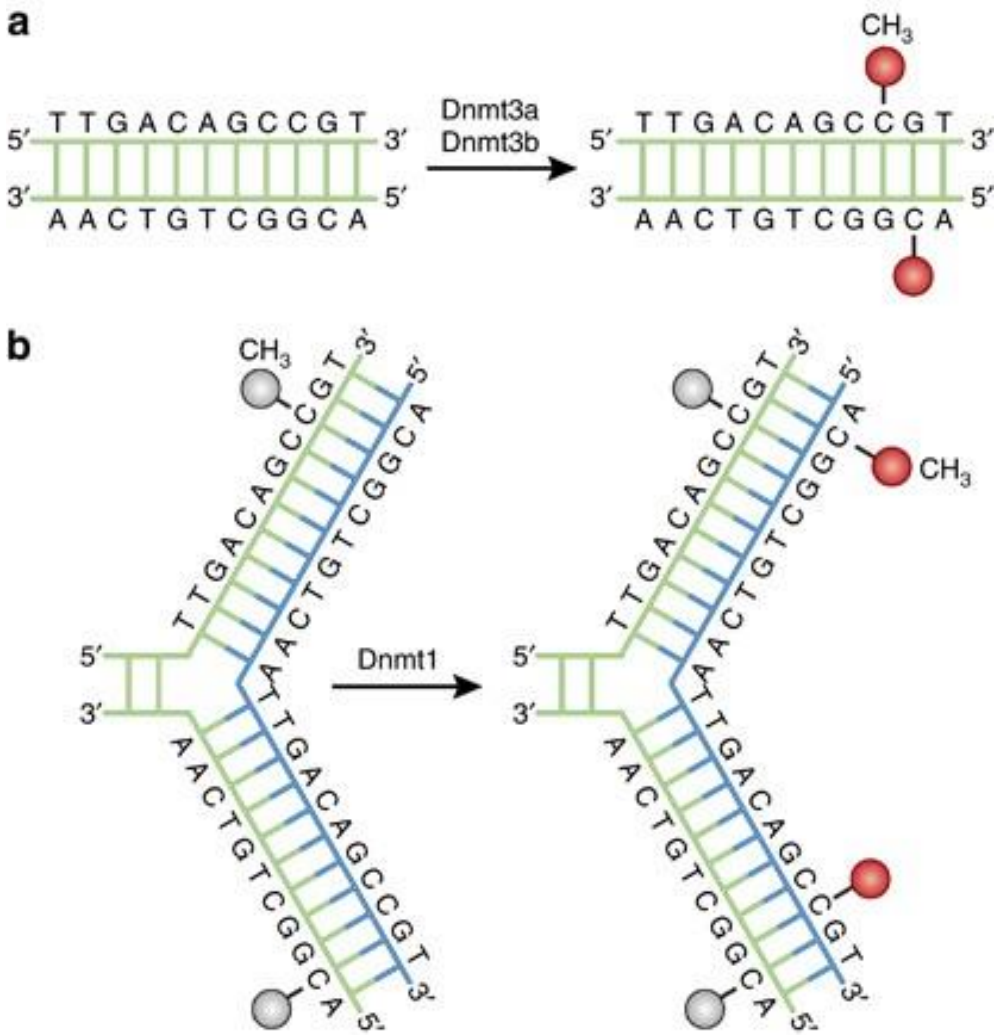
- 1970-ые: Метилирование распределено неравномерно по геному, разное в разных тканях, мешает транскрипции генов
- 1980-ые: метилирование идет в контексте CpG, они распределены неравномерно, существуют островки CpG, открыты ферменты – метилтрансферазы. Метилирование промотеров подавляет транскрипцию.
- 1990-ые: открыты белки узнающие метилированную ДНК, открыты де ново метил трансферазы
- 2000-ые: Большинство промотеров не регулируется посредством метилирования – для понимания регуляции генов необходимо рассматривать метилирование во взаимодействии с модификациями гистонов. Транспозоны активно регулируются метилированием ДНК.

CpG

- Метилирование у млекопитающих идет в контексте CpG






a
CH3
5′ T T G A C A G C C G T 3′
3′ A A C T G T C G G C A 5′
Dnmt3a
Dnmt3b
5′ T T G A C A G C C G T 3′
3′ A A C T G T C G G C A 5′
CH3
b
CH3
Dnmt1
CH3

ДНК метилтрансферазы

m6A - those that generate N6-methyladenine EC 2.1.1.72

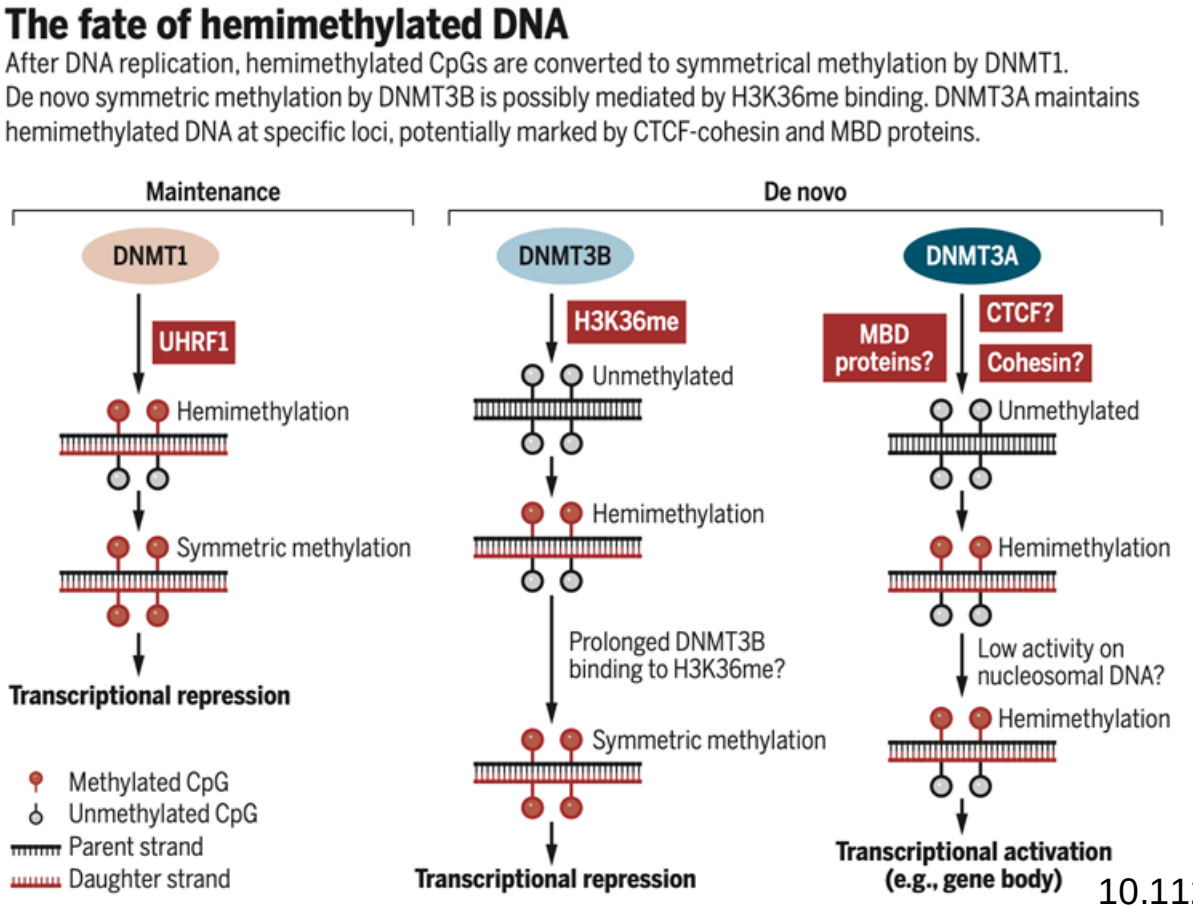
m4C - those that generate N4-methylcytosine EC 2.1.1.113

m5C - those that generate C5-methylcytosine EC 2.1.1.37

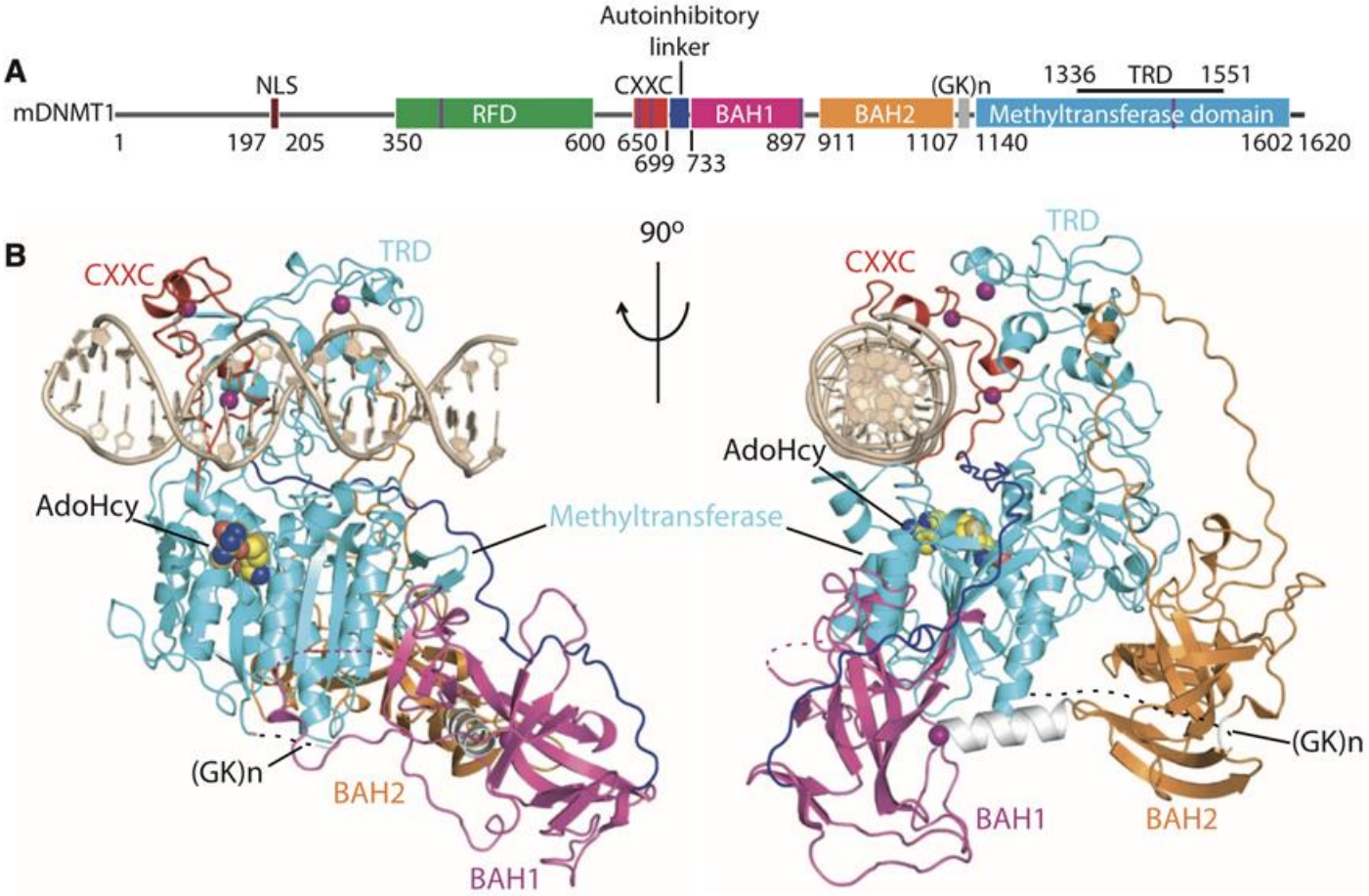
mC5 ДНК метилтрансферазы человека:

1. DNMT1
2. DNMT3a1, DNMT3a2
3. DNMT3b
4. DNMT3c (в половых клетках?)
5. DNMT3L (вспомогательная функция к DNMT3a)

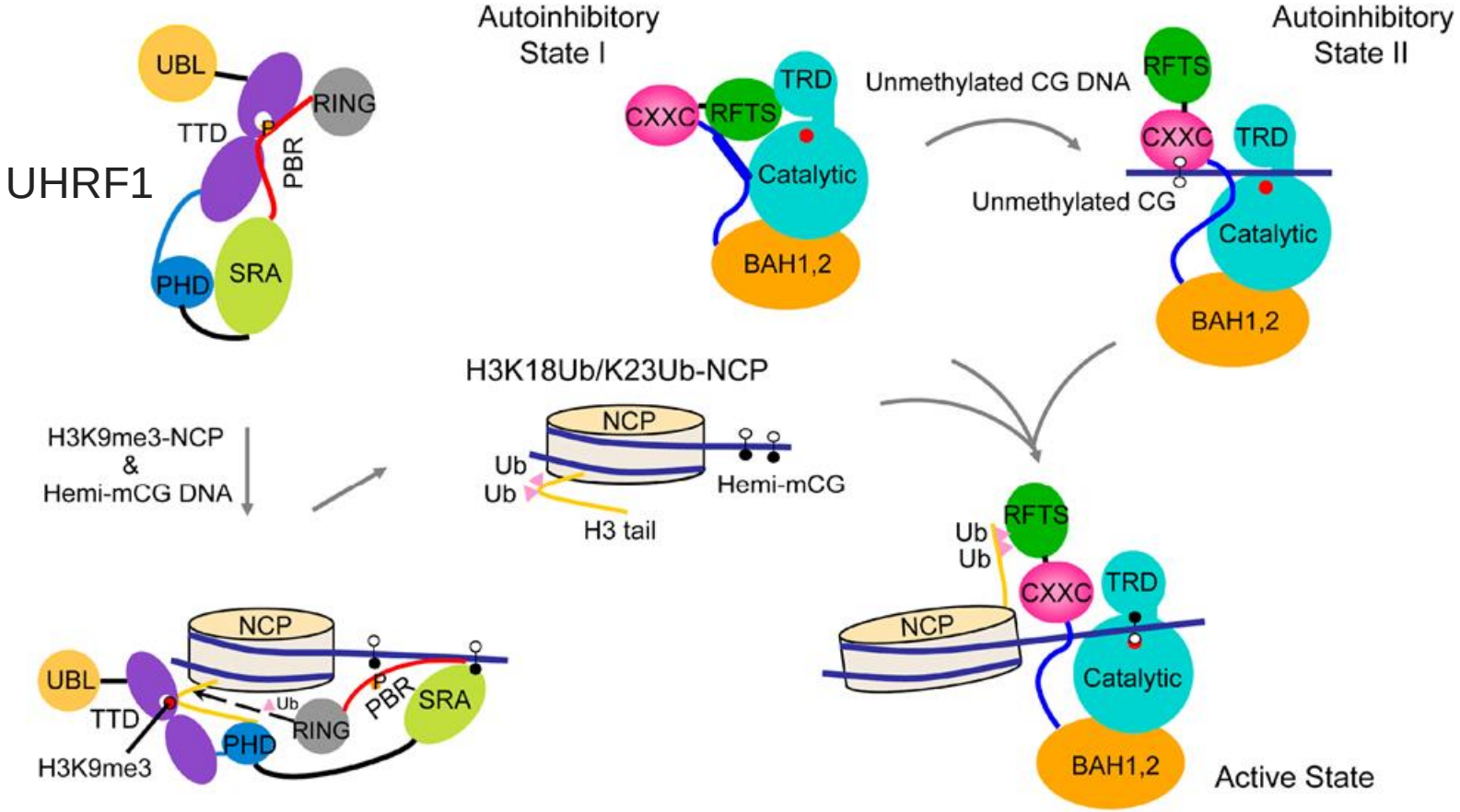
ДНК метилтрансферазы



10.1126/science.aat0789



doi/10.1126/science.1195380

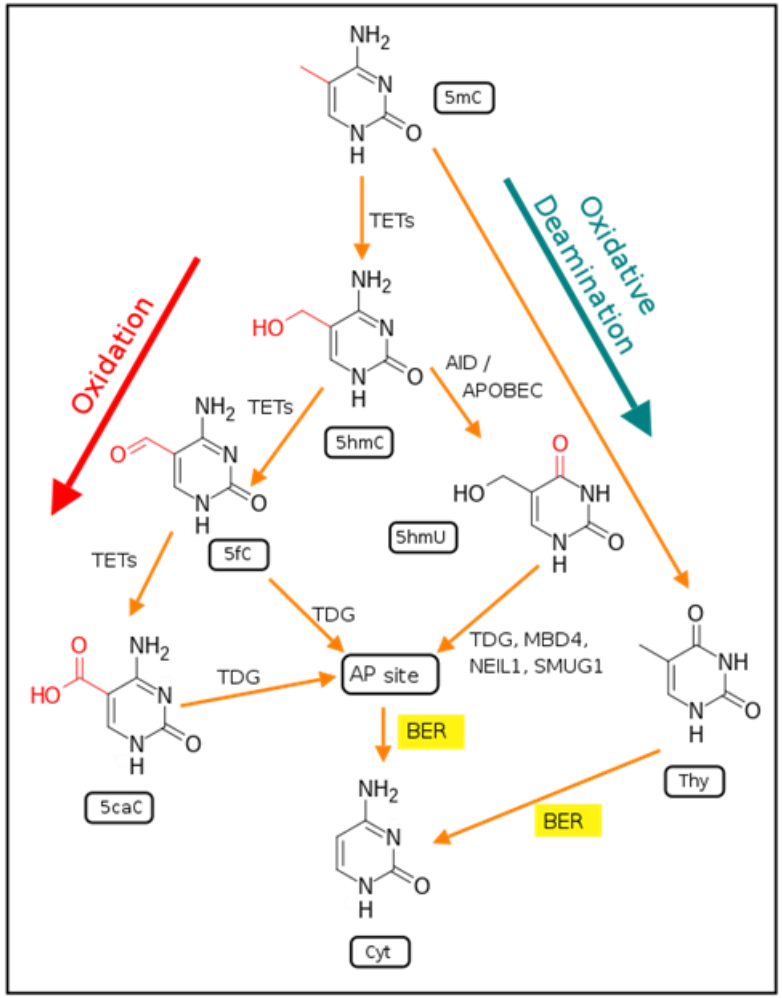


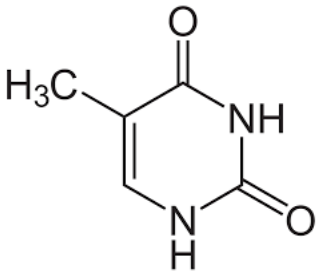
10.3390/genes9120620

Деметилирование

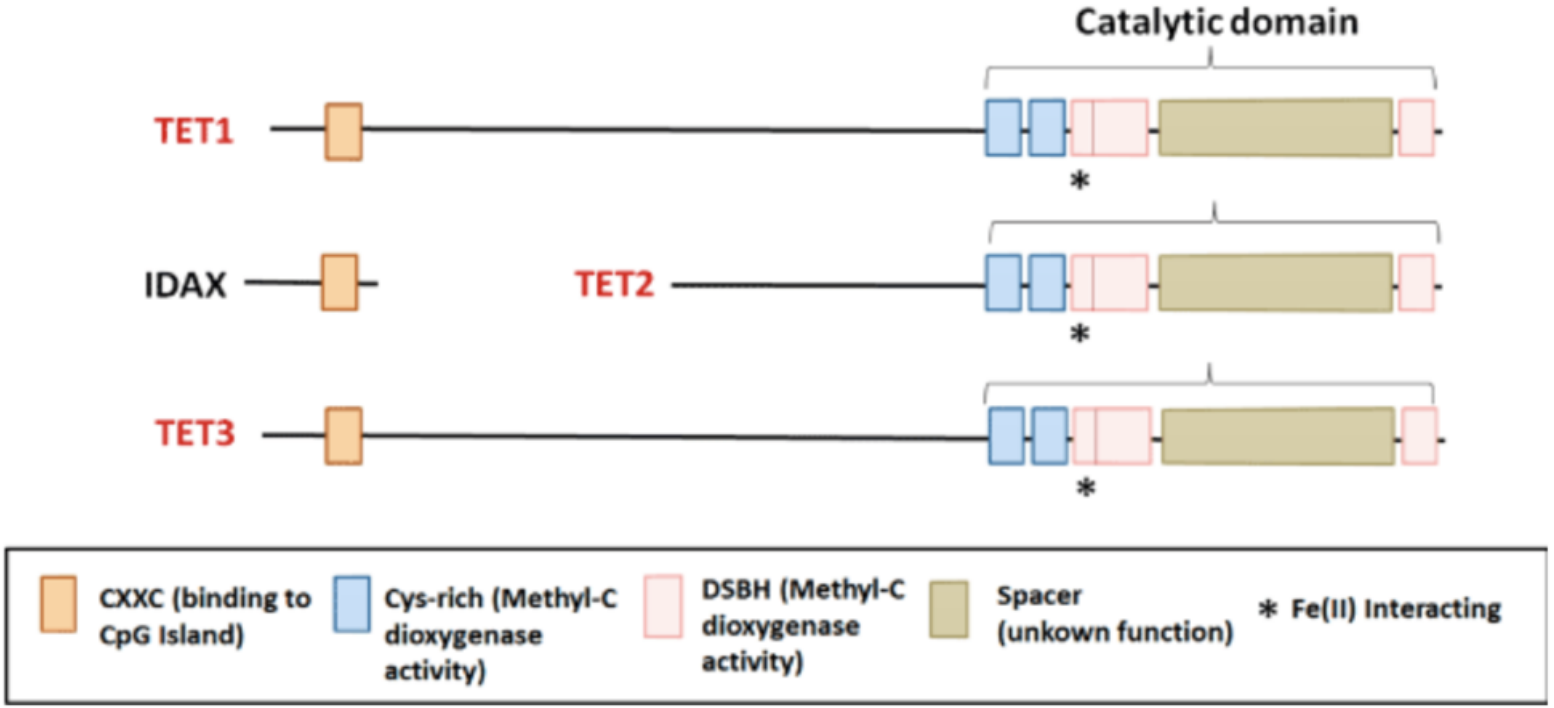
Ten-eleven translocation (Tet) proteins catalyze 5-methylcytosine (5 mC) conversion to 5-hydroxymethylcytosine (5 hmC)

Thymine-DNA glycosylase (TDG)

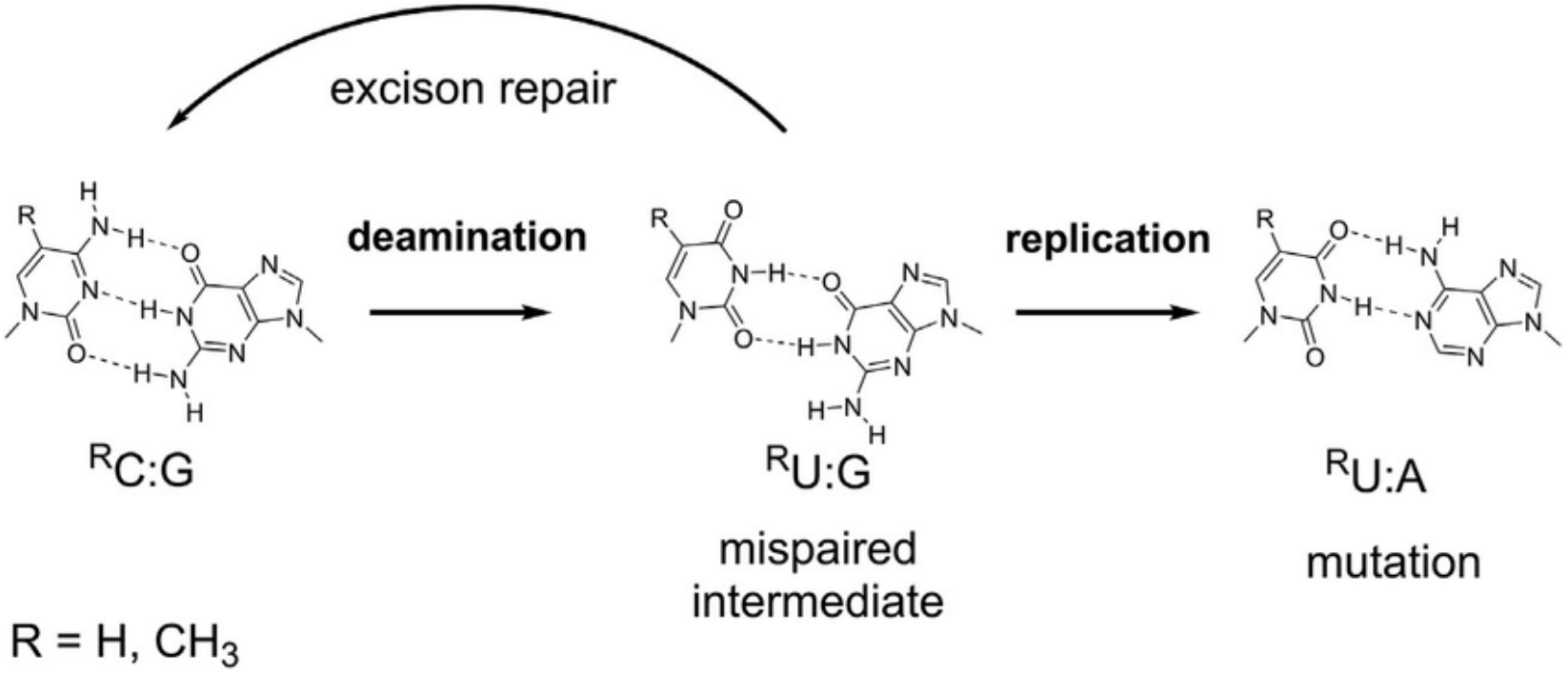




thymine


Catalytic domain
TET1
IDAX
TET2
TET3
*
CXXC (binding to CpG Island)
Cys-rich (Methyl-C dioxygenase activity)
DSBH (Methyl-C dioxygenase activity)
Spacer (unkown function)
* Fe(II) Interacting

CpG и мутации (C>T)

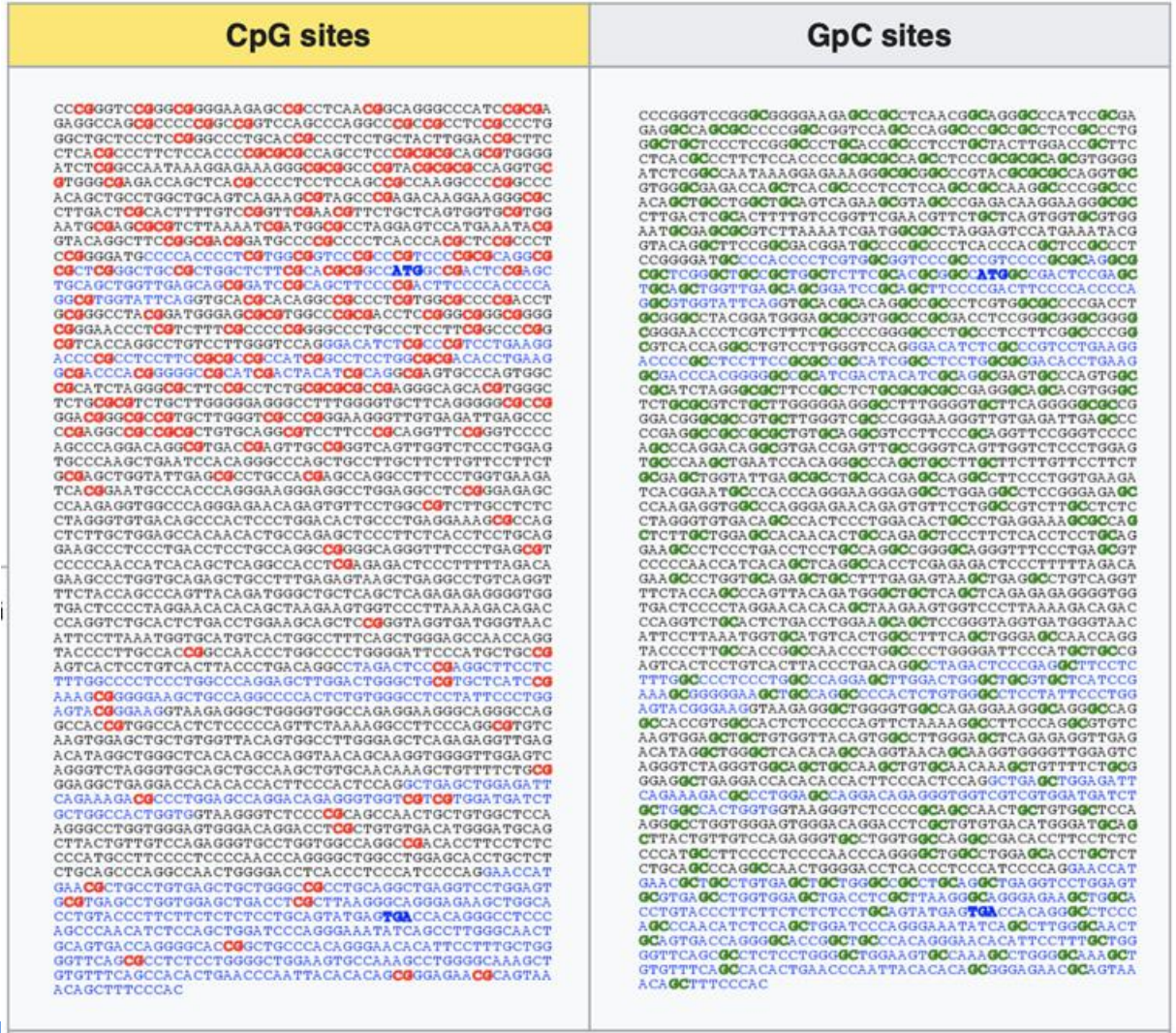


Распределение CpG

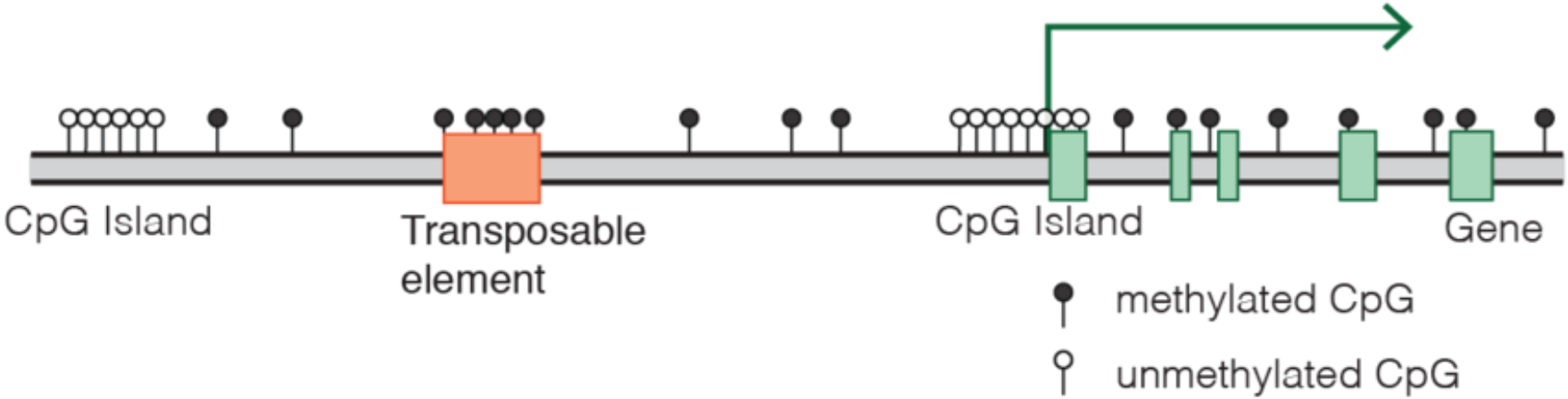
- У человека GC-состав ~40%. Теоретическая вероятность CpG 0.2*0.2=0.04
- Реальная встречаемость CpG 1%.
- У млекопитающих, 70% - 80% CpG сайтов метилировано
- У человека около 70% промотеров, расположенных около сайта начала транскрипции содержат CpG островки (island).

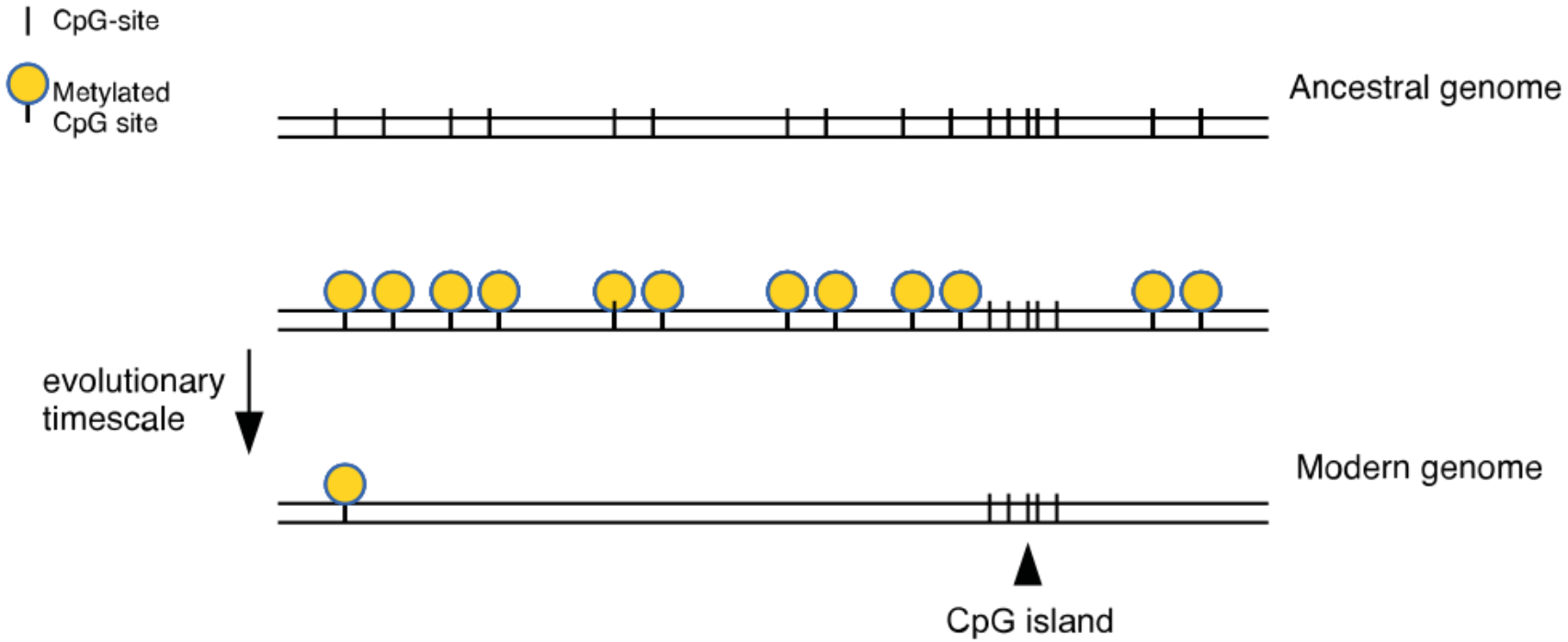
CpG-островки

- Регион длиной около 200 п.н.
- GC состав более 50%
- Наблюдаемое количество CpG по отношению к ожидаемому при случайном перемешивании последовательности более 60%
- Часто располагаются вблизи начала гена в районе промотеров.


CpG sites
GpC sites

Typical mammalian DNA methylation landscape

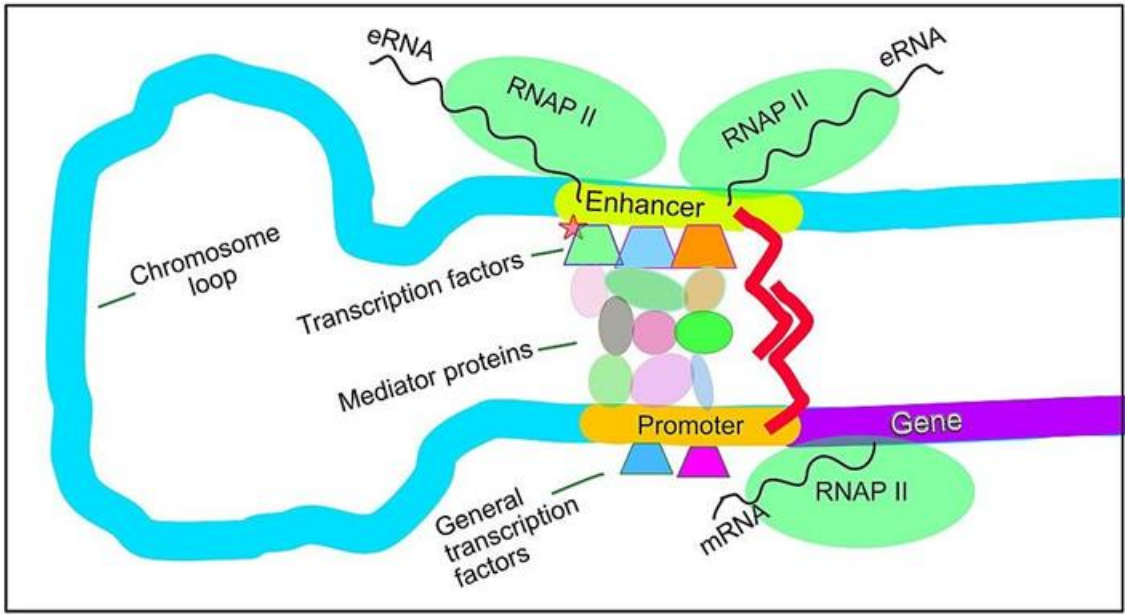



CpG-site
Metylated CpG site
Ancestral genome
evolutionary timescale
Modern genome
CpG island

Функциональная роль метилирования

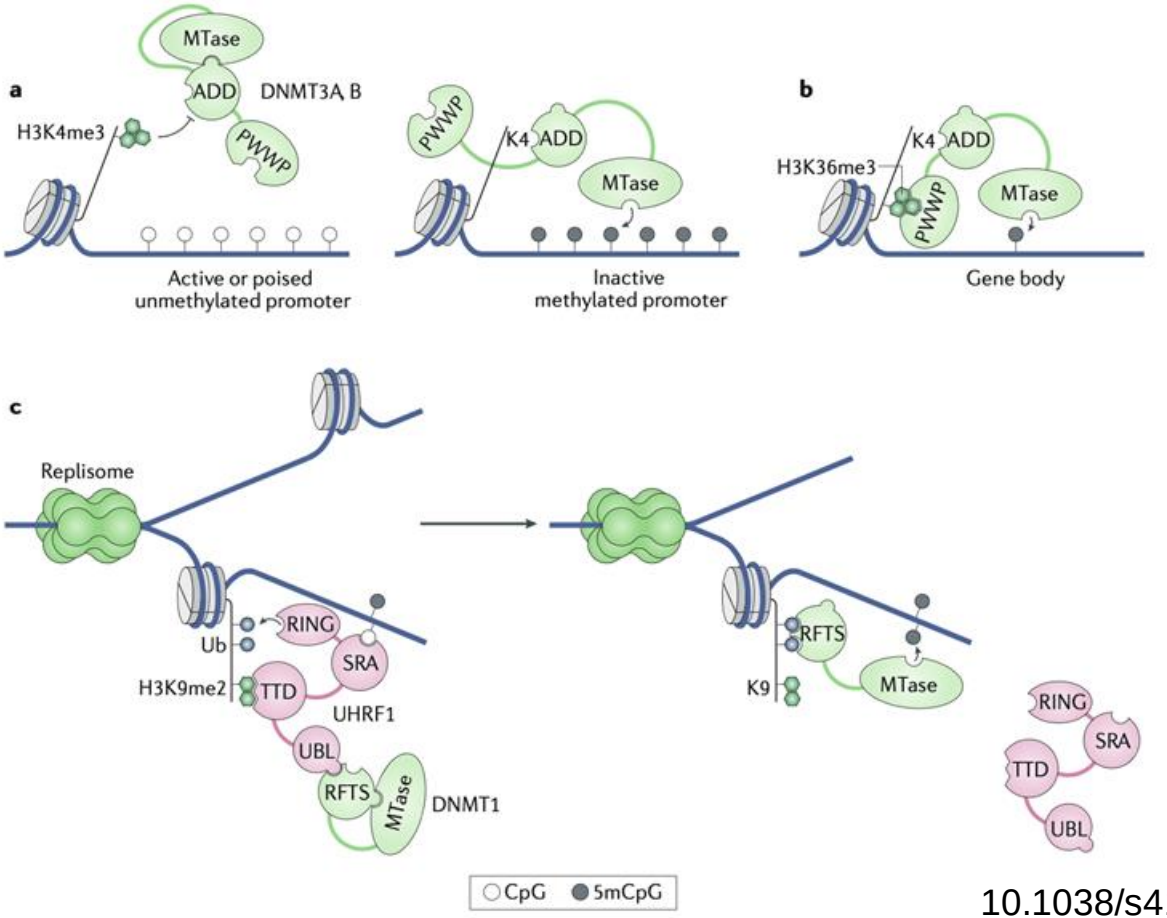
- Метилирование CpG-островков вблизи промотеров коррелирует с репрессией транскрипции.
- Однако, оно не обязательно для репрессии.
- В теле активно транскрибируемых генов наблюдается высокий уровень метилирования ДНК.

Каким образом метилирование ДНК управляет экспрессией генов?



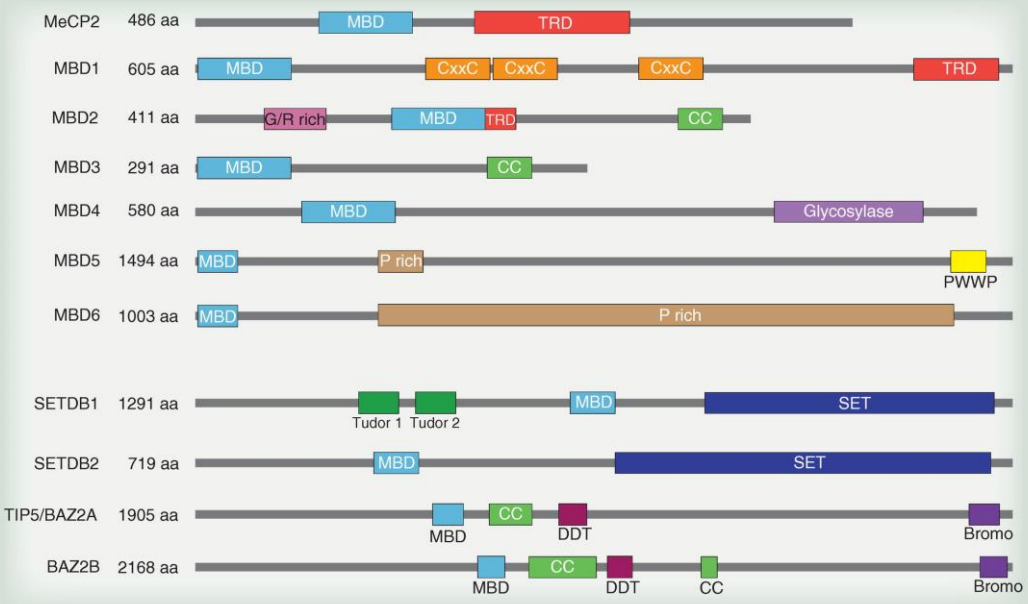
1. Мешает связыванию белков с ДНК
2. Привлекает регуляторные белковые комплексы
3. Стабилизирует нуклеосомы (?)

Примеры молекулярных механизмов (репрессия)

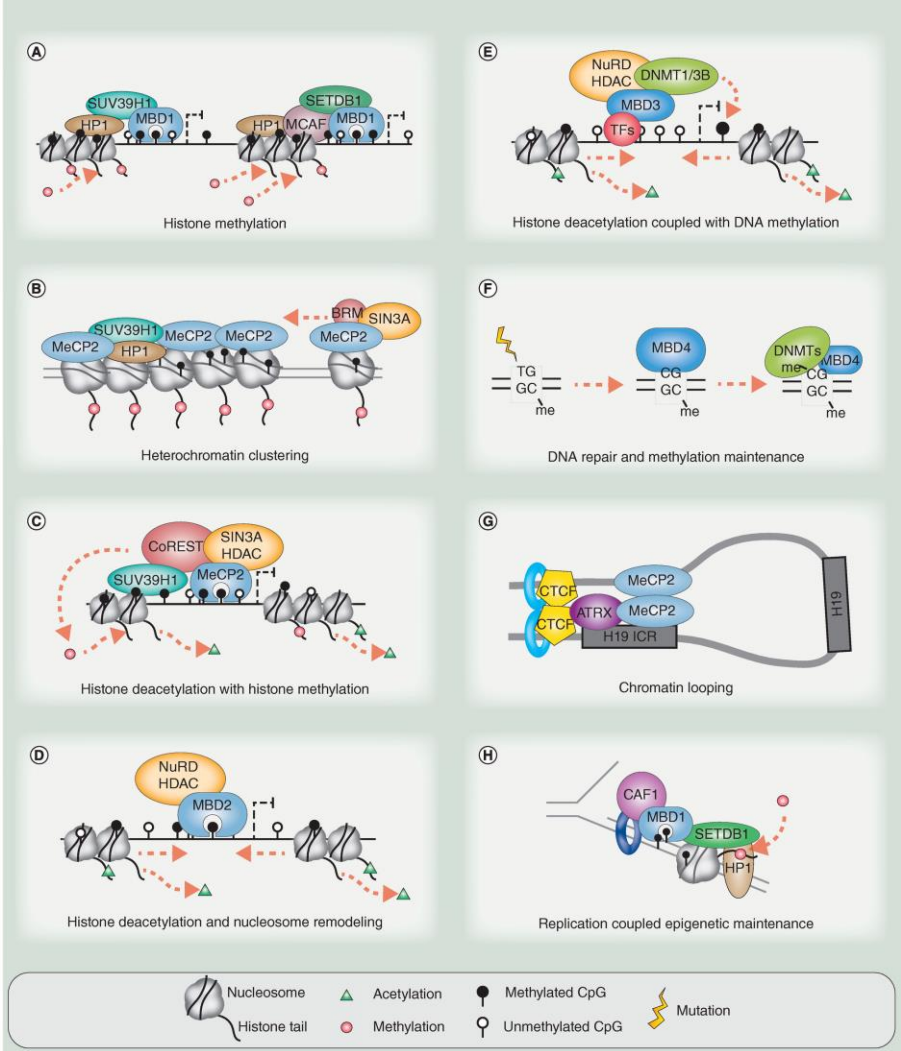


10.1038/s41580-019-0159-6

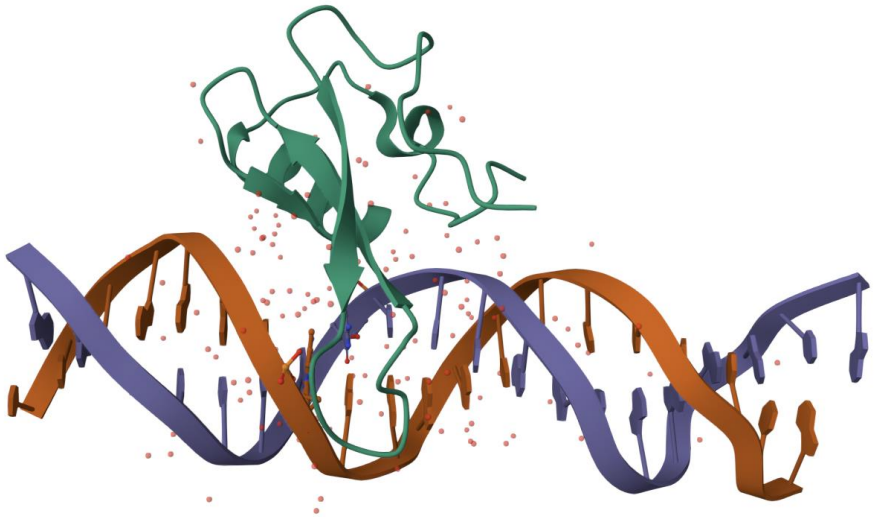
methyl-CpG-binding domain (MBD) protein family



10.2217/epi.15.39


A
SUV39H1
HP1
MBD1
SETDB1
HP1
MCAF
MBD1
Histone methylation
B
BRM
SIN3A
SUV39H1
MeCP2
MeCP2
MeCP2
MeCP2
HP1
Heterochromatin clustering
C
CoREST
SIN3A
HDAC
SUV39H1
MeCP2
Histone deacetylation with histone methylation
D
NuRD
HDAC
MBD2
Histone deacetylation and nucleosome remodeling
E
NuRD
HDAC
DNMT1/3B
MBD3
TFs
Histone deacetylation coupled with DNA methylation
F
TG
GC
me
MBD4
CG
GC
me
DNMTs
me
MBD4
CG
GC
me
DNA repair and methylation maintenance
G
CTCF
CTCF
ATRX
MeCP2
MeCP2
H19 ICR
H19
Chromatin looping
H
CAF1
MBD1
SETDB1
HP1
Replication coupled epigenetic maintenance
Nucleosome
Histone tail
Acetylation
Methylation
Methylated CpG
Unmethylated CpG
Mutation

MeCP2 – вовлечен в развитие нейронов



Rett syndrome

Other names Cerebroatrophic hyperammonemia (*obsolete*),[1] [2] dementia, ataxia, and loss of purposeful hand use syndrome[3]

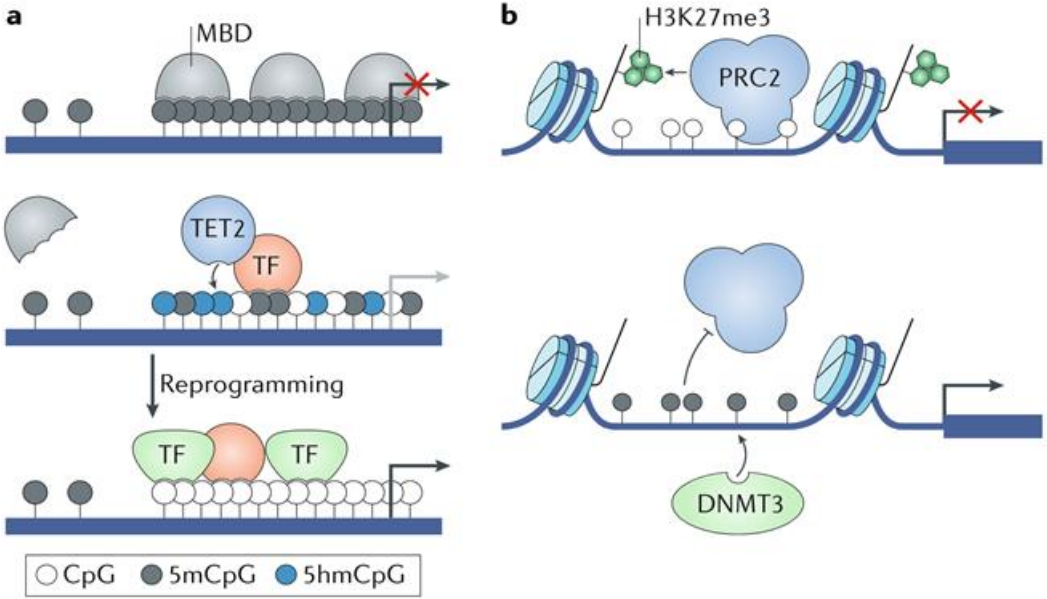
A girl with Rett Syndrome smiling at the camera

Specialty Psychiatry, Clinical Psychology, pediatrics, neurology

Symptoms Impairments in language and coordination, and repetitive movements, slower growth, smaller head[4]

Примеры молекулярных механизмов, активирующих транскрипцию через метилирование ДНК

cell pluripotency factors KLF4 and OCt4, the homeobox proteins HOXB13, NKX neural patterning factors



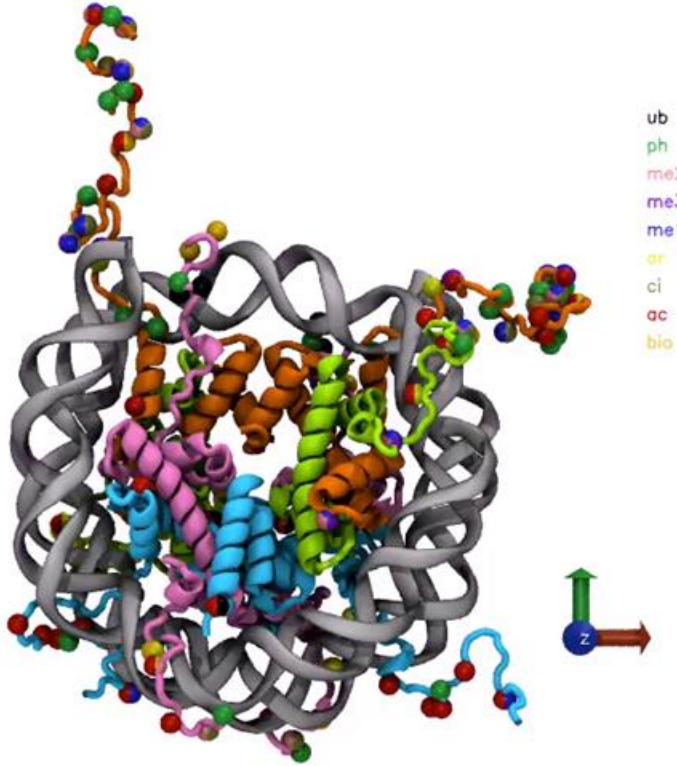
DNA methylation-mediated transcription activation

10.1038/s41580-019-0159-6

Пост-трансляционные модификации гистонов

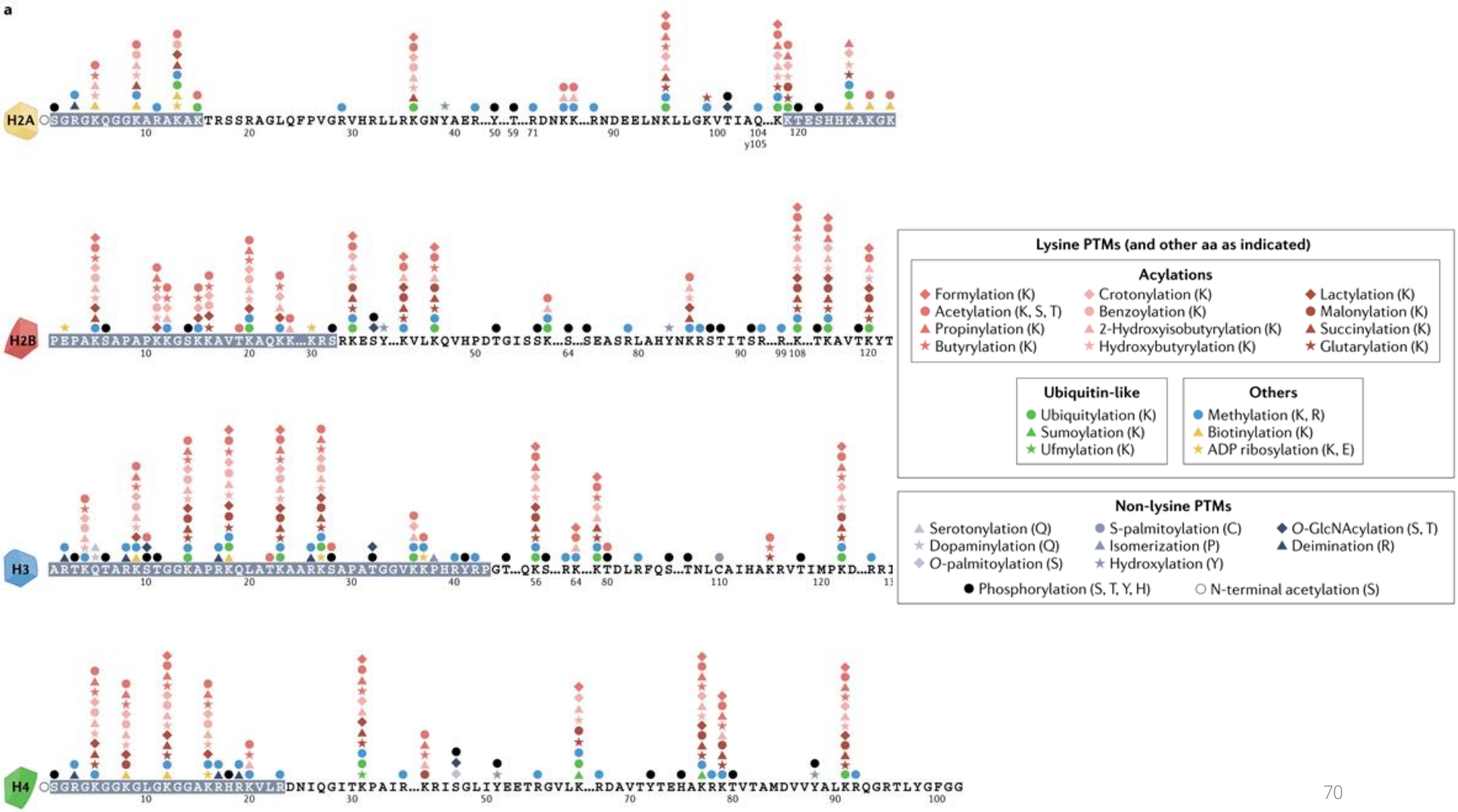
Histone post-translational modifications

Nucleosome structure (1KX5)

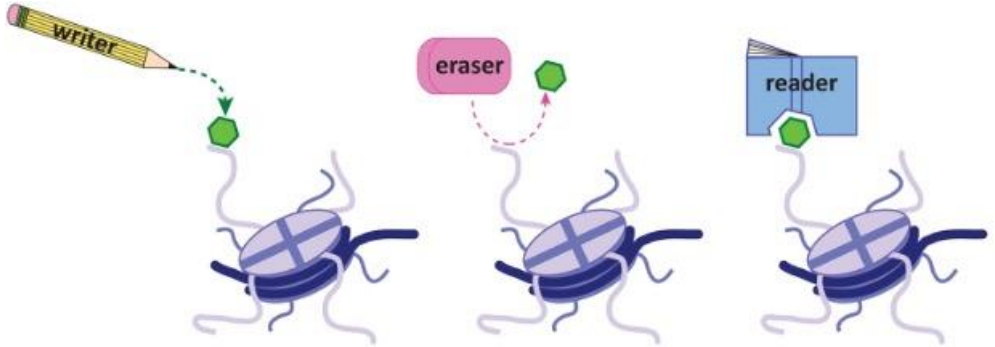


ub
ph
me2
me3
me1
ar
ci
ac
bio

H2A	H2B	H3	H4
H2AS1ph	H2BK5ac	H3R2me1	H4S1ph
H2AR3me2	H2BK5me1	H3R2me2	H4R3me1
H2AR3ci	H2BK12ac	H3R2ci	H4R3me2
H2AK5ac	H2BS14ph	H3T3ph	H4R3ci
H2AK9ac	H2BK15ac	H3K4ac	H4K5ac
H2AK9bio	H2BK16ac	H3K4me1	H4K8ac
H2AK13bio	H2BK20ac	H3K4me2	H4K8bio
H2AK13ar	H2BK30ar	H3K4me3	H4K12ac
H2AK119ub	H2BK46ac	H3S6ph	H4K12bio
H2AT120ph	H2BK120ac	H3T6ph	H4K16ac
H2AK121ub	H2BK120ub	H3R8ci	H4K16ar
H2AK125bio		H3K9ac	H4K20me1
H2AK127bio		H3K9me1	H4K20me2
H2AK129bio		H3K9me2	H4K20me3
H2AS137ph		H3K9me3	H4K91ac
H2AS139ph		H3K9bio	H4K91ub
H2AY142ph		H3S10ph	
		H3T11ph	
		H3K14ac	
		H3R17me1	
		H3R17me2	
		H3R17ci	
		H3K18ac	
		H3K18bio	
		H3K23ac	
		H3R26me1	
		H3R26ci	
		H3K27ac	
		H3K27me1	
		H3K27me2	
		H3K27me3	
		H3K27ar	
		H3S28ph	
		H3S31ph	
		H3K36ac	
		H3K36me3	
		H3K36me1	
		H3K36me2	
		H3K37ar	
		H3Y41ph	
		H3T45ph	
		H3K56ac	
		H3K79me1	
		H3K79me2	


a
H2A
SGRGKQGGKARAKAKTRSSRAGLQFPVGRVHRLLRKGNYAER...Y...T...RDNKK...RNDEELNKLLGKVTIAQ...KKTESHHKAKGK
10 20 30 40 50 59 71 90 100 104 120
y105
H2B
PEPAKSAPAPKKGSKKAVTKAQKK...KRSRKESY...KVLKQVHPDTGISSK...S...SEASRLAHYNKRSTITSR...R..K...TKAVTKYT
10 20 30 50 64 80 90 99 108 120
H3
ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVKKPHRYRPGT...QKS...RK...KTDLRFQS...TNLCAIHAKRVTIMPKD...RR
10 20 30 40 56 64 80 110 120
H4
SGRGKGGKGLGKGGAKRHRKVLRDNIQGITKPAIR...KRISGLIYEETRGVLK...RDAVTYTEHAKRKTVTAMDVVYALKRQGRTLYGFGG
10 20 30 50 70 80 90 100
Lysine PTMs (and other aa as indicated)
Acylations
Formylation (K)
Acetylation (K, S, T)
Propinylation (K)
Butyrylation (K)
Crotonylation (K)
Benzoylation (K)
2-Hydroxyisobutyrylation (K)
Hydroxybutyrylation (K)
Lactylation (K)
Malonylation (K)
Succinylation (K)
Glutarylation (K)
Ubiquitin-like
Ubiquitylation (K)
Sumoylation (K)
Ufmylation (K)
Others
Methylation (K, R)
Biotinylation (K)
ADP ribosylation (K, E)
Non-lysine PTMs
Serotonylation (Q)
Dopaminylation (Q)
O-palmitoylation (S)
S-palmitoylation (C)
Isomerization (P)
Hydroxylation (Y)
O-GlcNAcylation (S, T)
Deimination (R)
Phosphorylation (S, T, Y, H)
N-terminal acetylation (S)

Brno nomenclature



Писатели, стиратели, читатели

ENCODE ChIP-seq Experiment Matrix *hg19*

search for: tracks files

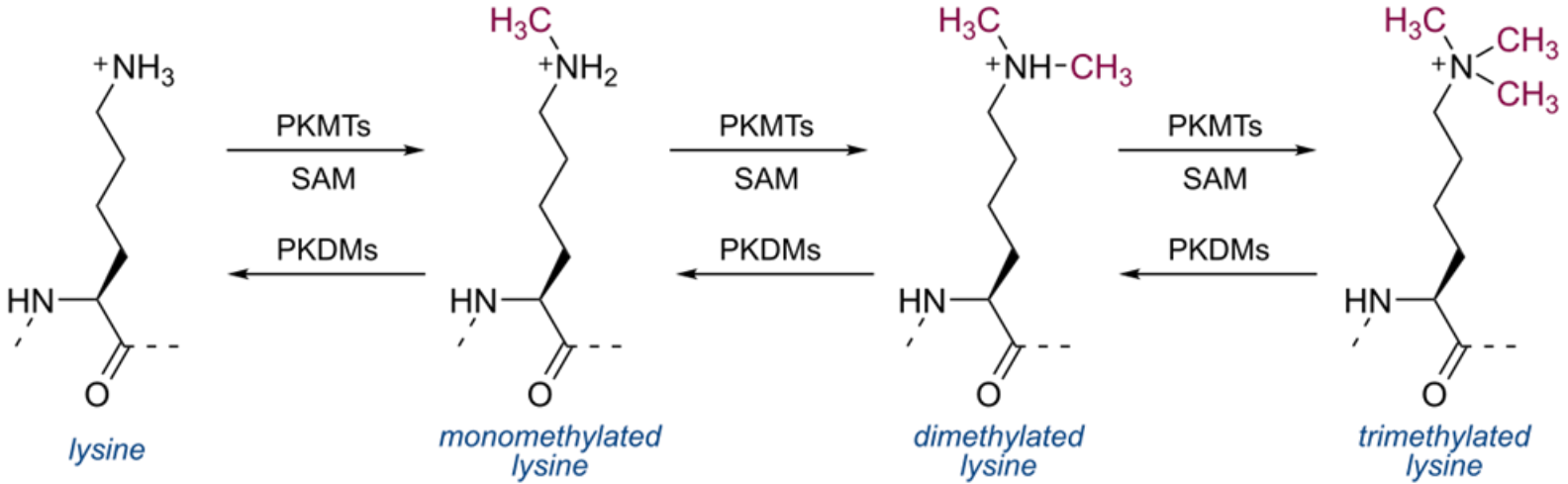
Antibody Targets

Cell Types

Cell Types	Histone Modification: H2AFZ	H3K27ac	H3K27me3	H3K36me3	H3K4me1	H3K4me2	H3K4me3	H3K79me2	H3K9ac	H3K9me1	H3K9me3	H4K20me1
Tier 1												
GM12878	1	1	2	2	1	1	2	1	1		1	1
H1-hESC	1	1	1	1	1	1	1	1	1		1	1
K562	1	1	3	2	2	1	8	1	2	1	1	1

H3K4me1 + H3K27me3	repressed enhancers in stem cells
H3K4me1	enhancer
H3K4me3	active promoter regions
H3K4me2	Marks promoters and enhancers. Most CpG islands are marked by H3K4me2 in primary cells. May be associated also with poised promoters.
H3K4me1 + H3K27ac	active enhancer
H3K27Ac	Enhancers, promoters
H3K36me3	Gene body - [H3K36me2 (which is distributed broadly in intergenic regions and weakly transcribed regions, for moderate levels of DNA methylation); H3K36me3, which essentially marks the actively transcribed regions, for high levels of methylation.]
H3K9me3	конститутивный гетерохроматин
H3K27me3	факультативный гетерохроматин
H3K79me2	H3K79me2 is a mark of the transcriptional transition region - the region between the initiation marks (K4me3, etc) and the elongation marks (K36me3).
H4K20me1	Is associated with active and accessible regions. In mammals, PR-Set7 specifically catalyzes H4K20 monomethylation. NOTE CONTRAST to H3K20me3 which is associated with heterochromatin and DNA repair.

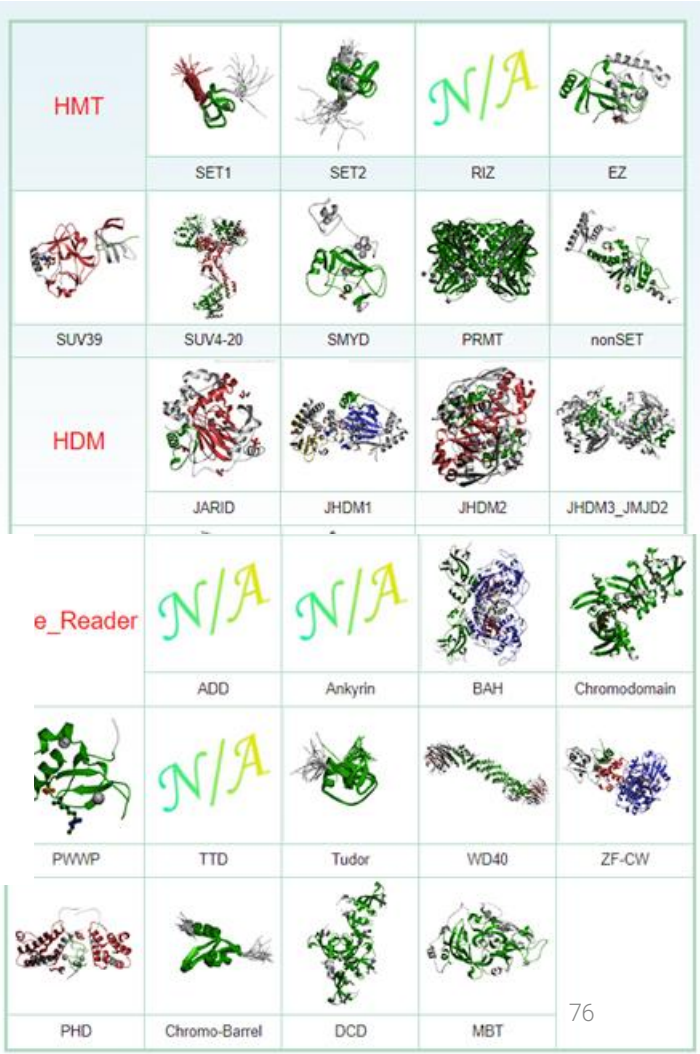
Метилирование лизинов



Protein lysine methyltransferases (**PKMTs**)
Заряд +1 не меняется

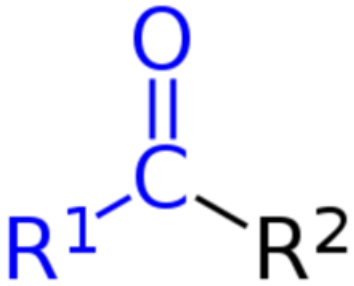
Histone Methylation Domains

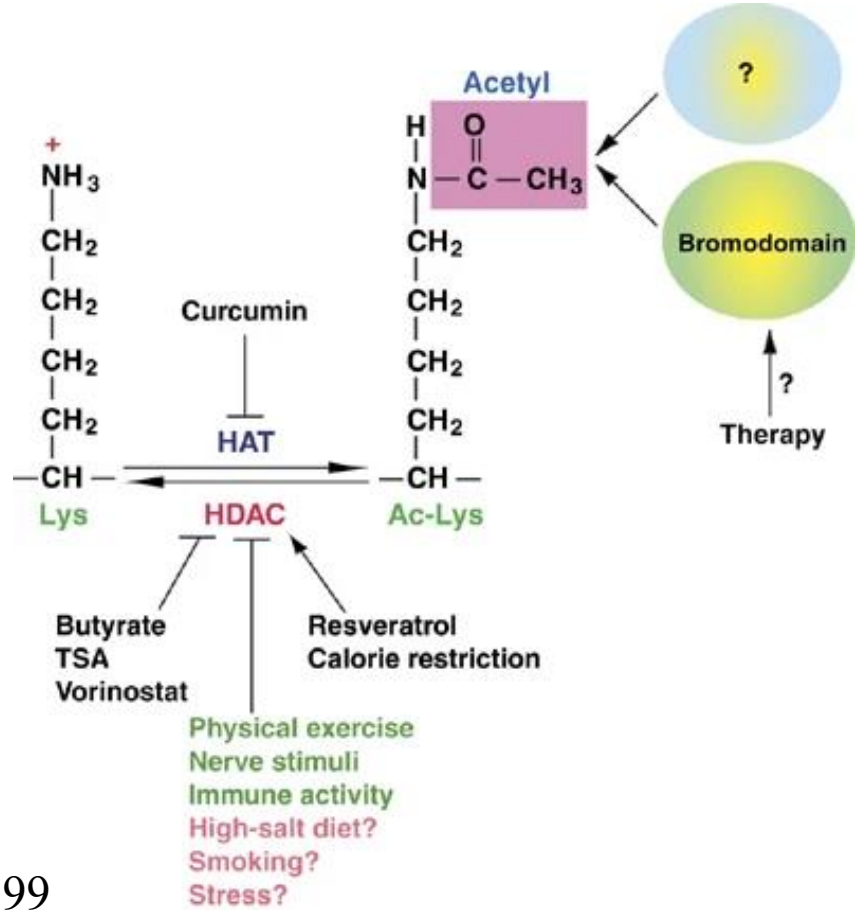
- Histone Methyltransferase (HMT)
  - nonSET
  - PRMT
  - SET1
  - SET2
  - RIZ
  - EZ
  - SUV39
  - SUV4-20
  - SMYD
  - HMT_other
- Histone Demethylase (HDM)
  - LSD1_KDM1
  - JARID
  - JHDM1
  - JHDM2
  - JHDM3_JMJD2
  - PHF2_PHF8
  - UTX_UTY
  - JmjC_only
- Histone Methylation Reader (Me_Reader)
  - ADD
  - Ankyrin
  - BAH
  - Chromodomain
  - PWWP
  - TTD
  - Tudor
  - WD40
  - ZF-CW
  - PHD
  - Chromo-Barrel
  - DCD
  - MBT
  - Me_Reader_other



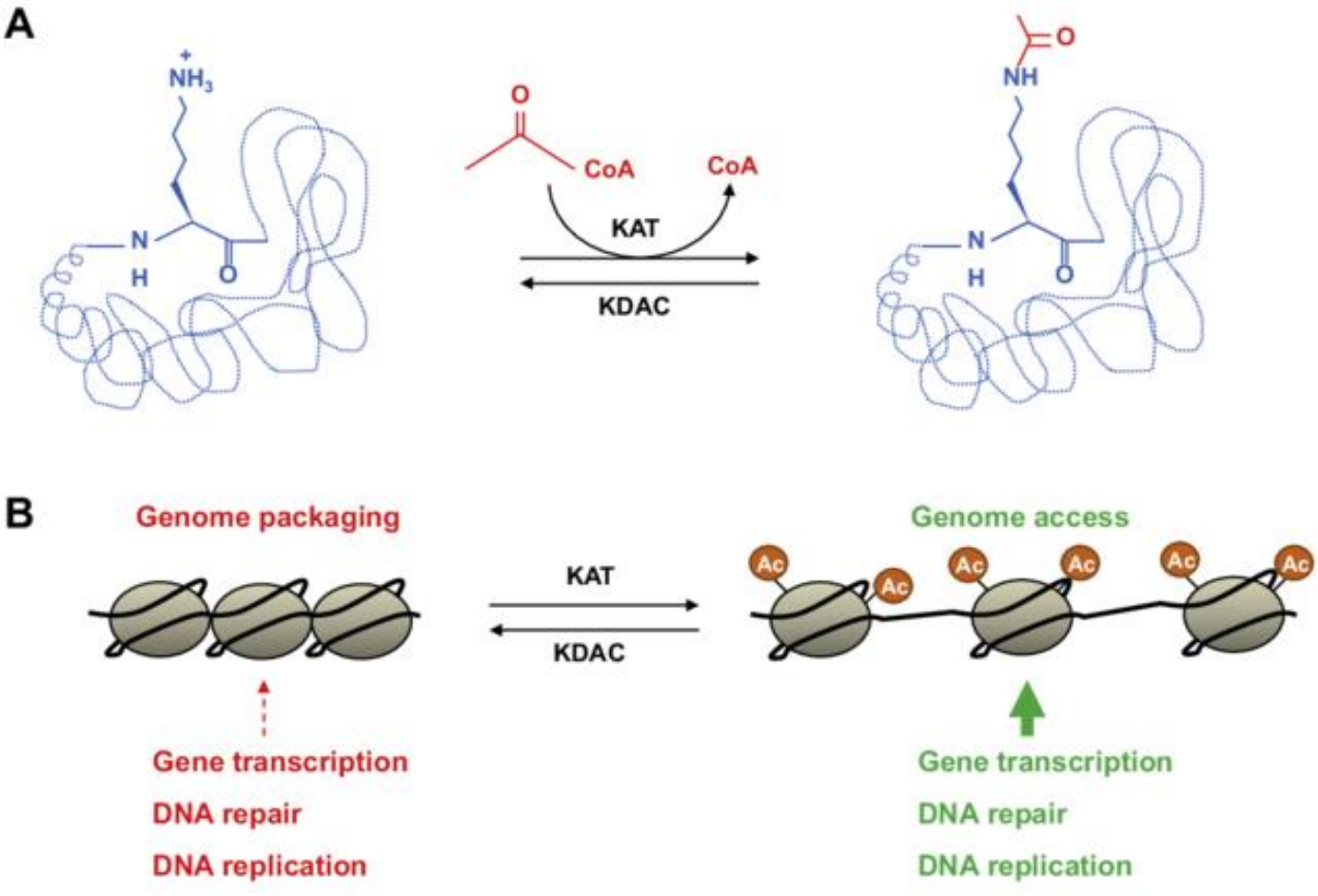
http://weram.biocuckoo.org

Ацилирование (ацетилирование)



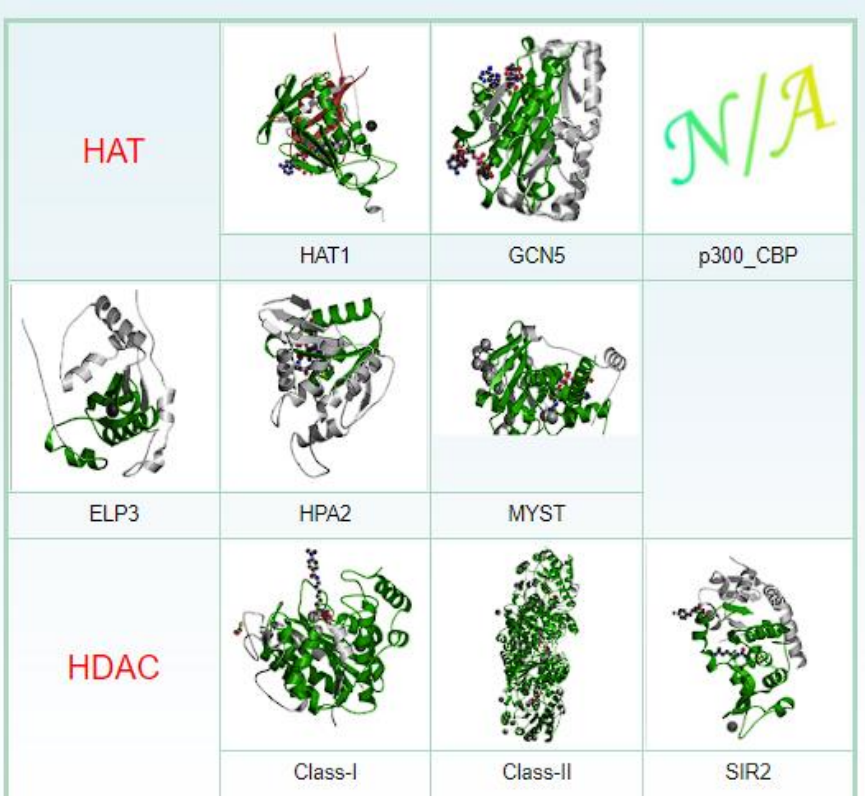


10.1038/sj.onc.1210599


A
NH3
N
H
O
O
CoA
CoA
KAT
KDAC
O
NH
N
H
O
B
Genome packaging
KAT
KDAC
Genome access
Ac
Ac
Ac
Ac
Ac
Ac
Gene transcription
DNA repair
DNA replication
Gene transcription
DNA repair
DNA replication

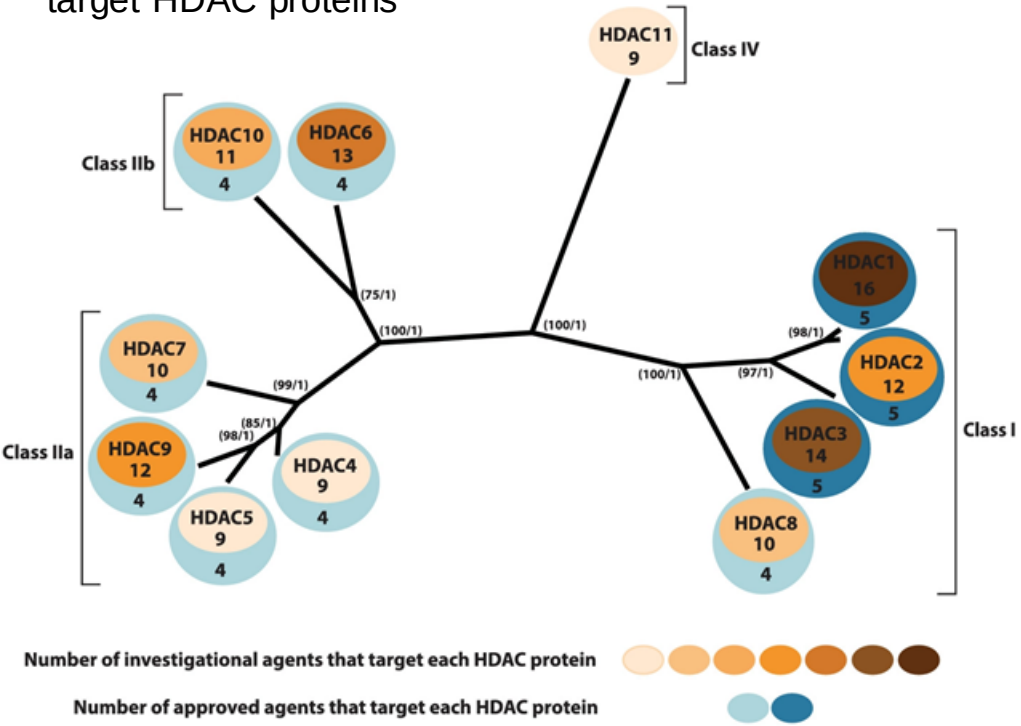
Histone Acetylation Domains

- Histone Acetyltransferase (HAT)
  - p300_CBP
  - MYST
  - HAT_other
  - GCN5
  - HAT1
  - HPA2
  - ELP3
  - GNAT_other
- Histone Deacetylase (HDAC)
  - Class-I
  - Class-II
  - SIR2
  - Class-IV
  - HD2
- Histone Acetylation Reader (Ac_Reader)
  - Bromodomain
  - Tandem-PHD

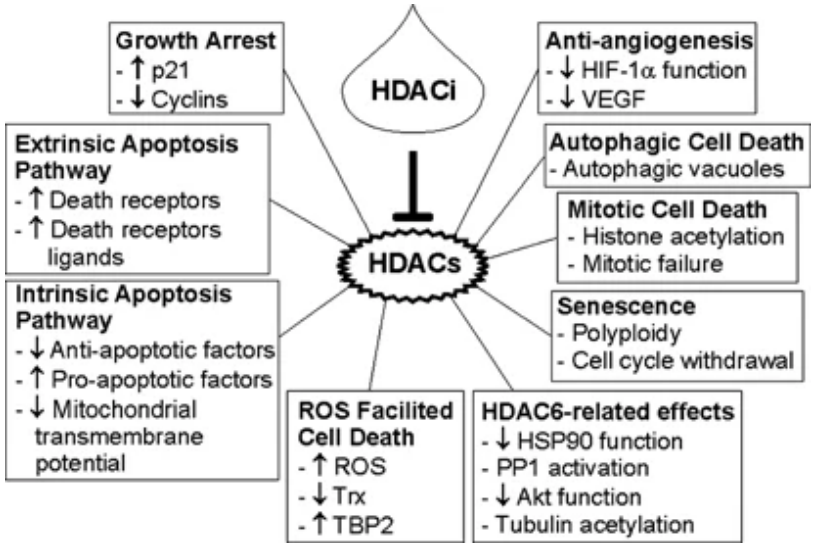


HDAC/HAC inhibitors

Number of investigational and approved agents that target HDAC proteins



Multiple HDACi-activated antitumor pathways



https://doi.org/10.1038/sj.onc.1210620, https://doi.org/10.1111/bcp.14889

Вориностат - ингибитор [гистондеацетилаз](), использующийся в качестве лекарственного средства при терапии Т-клеточной лимфомы

HDACi

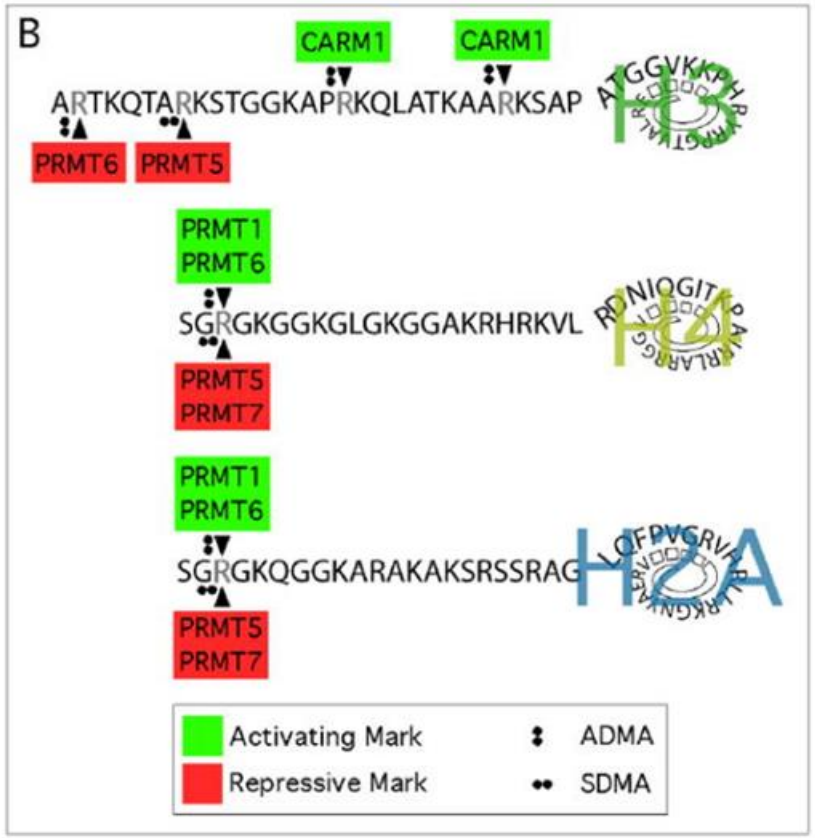
Drug name	Enzyme specificity	Indications investigated	Highest CT phase
Abexinostat	HDAC 1, 2, 3, 6, 10	DLBCL, MCL, AML, ALL, FL, RCC, MDS, sarcoma, skin cancers, NSCLC	Phase 3
Fimepinostat (CUDC-907)	HDAC 1, 2, 3, 10	Lymphomas, brain tumours	Phase 1/2
Quisinostat (JNJ26481585)	HDAC 1, 6, 9	Ovarian cancer, CTCL, NSCLC	Phase 2
Ricolinostat (ACY-1215)	HDAC 6	MM, DNP, lymphomas, BC, gynaecological cancers, CLL	Phase 2
Trichostatin A	HDAC 7, 8	Haematological cancers	Phase 1
Nanatinostat (VRx-3996)	HDAC 9	EBv-associated malignancies	Phase 1/2
CG200745	HDAC 9, 11	MDS, pancreatic cancer	Phase 1/2
Pracinostat	Pan-HDAC	MDS, AML, MF, PC, sarcoma	Phase 3
Resminostat	Pan-HDAC	CTCL, HCC, HL, CRC, pancreatic cancer, NSCLC	Phase 2
CUDC-101	Pan-HDAC	Advanced solid tumours	Phase 1 (discontinued)
MPT0E028	Pan-HDAC	Advanced solid tumours	Phase 1

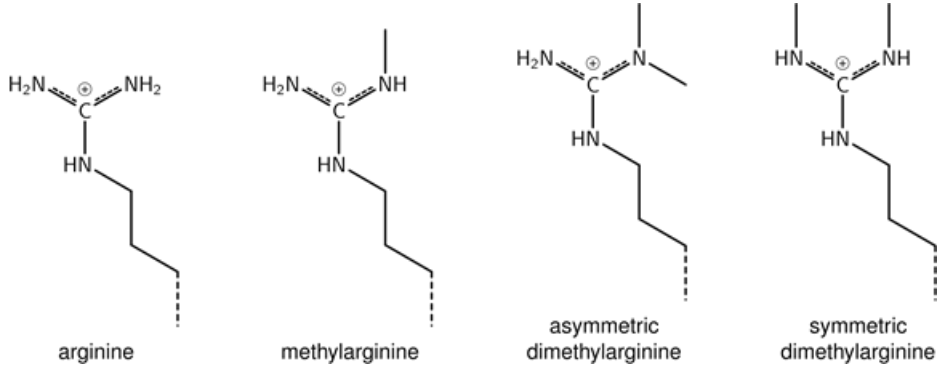
Drug name	Chemical class	Enzyme specificity	Indications investigated	Highest CT phase
Tacedinaline (CI-994)	Benzamide	HDAC 1	Solid and haematological cancers	Phase 3 (discontinued)
Entinostat	Benzamide	Class 1 HDACs	PC, BC, BlC, AML, CRC, LL, RCC, melanoma, NSCLC, gynaecological cancers, CNS tumours, MDS, pancreatic cancer, NE tumours	Phase 2
Domatinostat	Benzamide	Class 1 HDACs	CTCL	Phase 1
RG2833	Benzamide	HDAC 3	Friedreich's ataxia	Phase 1
Givinostat	Benzamide	Pan-HDAC	MDs, PV, JIA	Phase 2
KA2507	Cyclic peptide	HDAC 6	Melanoma	Phase 1
Mocetinostat	Benzamide	Pan-HDAC	UC, NSLC, HL, DLBCL, FL, leiomyosarcoma, melanoma	Phase 2
OBP-801	Cyclic peptide	Pan-HDAC	LC, lymphoma, RC, glaucoma	Phase 1a
AR-42	Benzamide	Pan-HDAC	RCC, sarcoma, meningioma, VS, AML	Phase 1

.....

https://doi.org/10.1111/bcp.14889

Метилирование аргининов



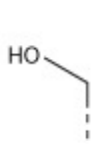


(A) Arginine residues in the tails of histones can be **monomethylarginines (MMA), asymmetric dimethylarginines (ADMA), and symmetric dimethylarginines (SDMA)**. The MMA form of arginine is generally regarded as an intermediate on its way to the dimethylated state and is not depicted here. (B) The known sites of histone H3, H4, and H2A arginine dimethylation are shown. Red denotes transcriptional repressor activity and green denotes transcriptional activator activity.

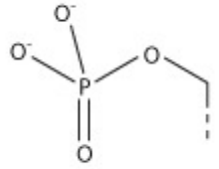
https://doi.org/10.1016%2Fj.febslet.2010.11.010

Фосфорилирование

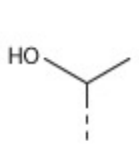
Histone	Phosphorylated residue	Kinases	Role
H2A	S1	?	Mitosis
	S16	RSK2	EGF signaling
	S122*(Sc)/T120(Hs)	Bub1, NHK-1 (Dm)	DNA repair/Mitosis/Meiosis
	S129* (Sc)/S139(Hs,H2AX)	Mec1, Tel1 (Sc) / ATM, ATR, DNA-PK (Hs)	DNA repair
	Y142 (H2AX)	Mst1 WSTF	Apoptosis DNA repair
H2B	S10 (Sc)/S14 (Hs)	Ste20 (Sc)/Mst1 (Hs) (Ipl1?)	Apoptosis Meiosis
	S32	RSK2	EGF signaling
	S36	AMPK	Transcription
H4	S1	CKII Sps1	DNA repair, Transcription Meiosis, Transcription
	S47	PAK2	(H3.3-H4) Deposition
H1	S/T	CDK2	Mitosis Transcription



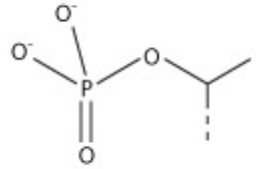
serine



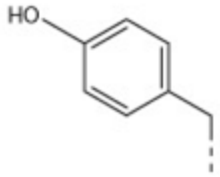
phosphoserine



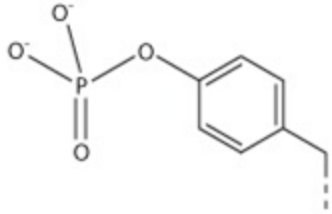
threonine



phosphothreonine



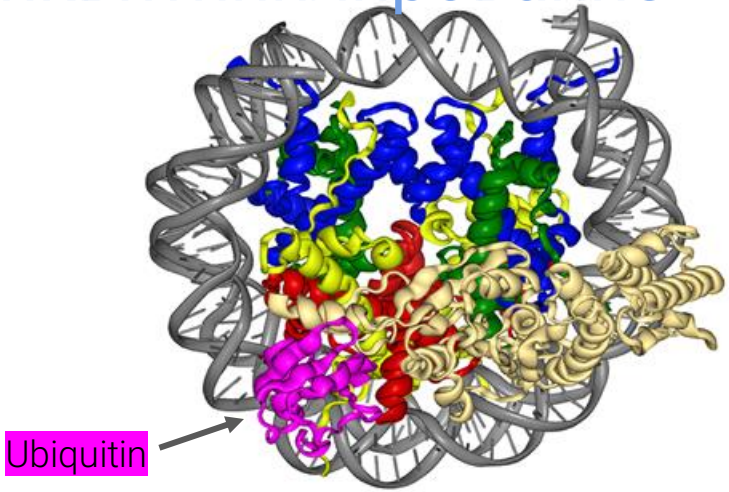
tyrosine



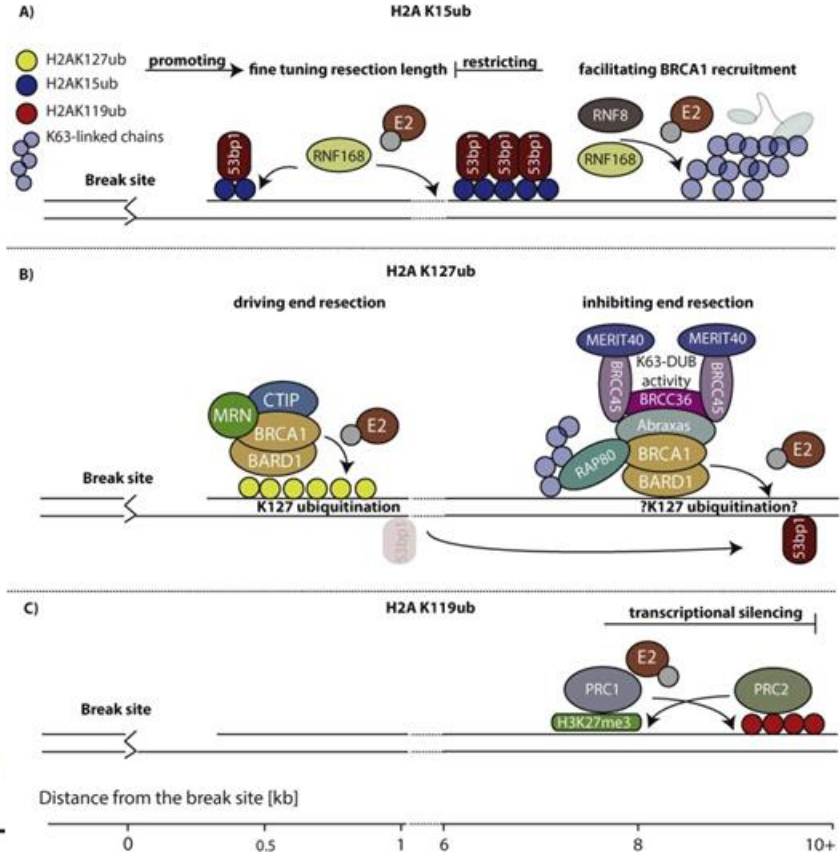
phosphotyrosine

H3	T3	Haspin	Mitosis
	T6	PKCβ	Transcription
	S10	Ipl1 (Sc) / AuroraB (Hs), RSK2, MSK1, ERK1, p38, Fyn, Chk1, PRK1	Transcription, Chromatin condensation, UVB response
	T11	Mek1 (Sc)/ Dlk (Hs, ?) PRK1, PKM2 Chk1	Meiosis (Sc), Mitosis (Hs) Transcription DNA damage response
	S28	AuroraB, ERK1/2, p38 MLTK-α, JNK1/2, MSK1	Meiosis Mitosis, Transcription
	Y41	JAK2	Transcription
	T45	PK-Cδ	Apoptosis

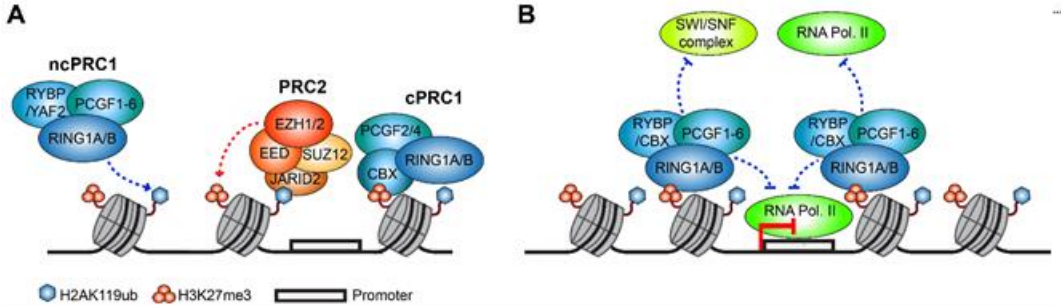
Юбиквитинилирование



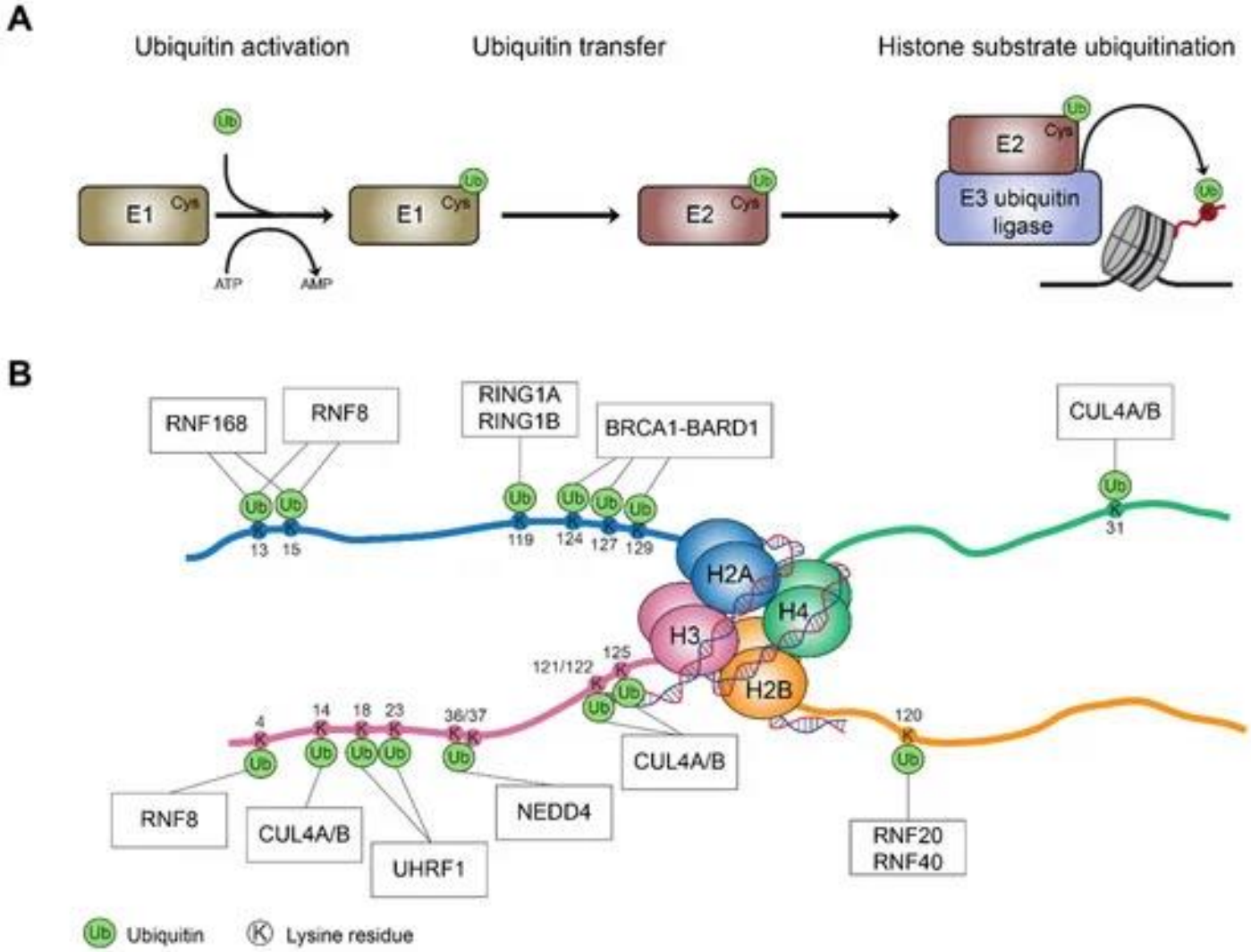
Model of site-specific ubiquitination in the DNA damage response



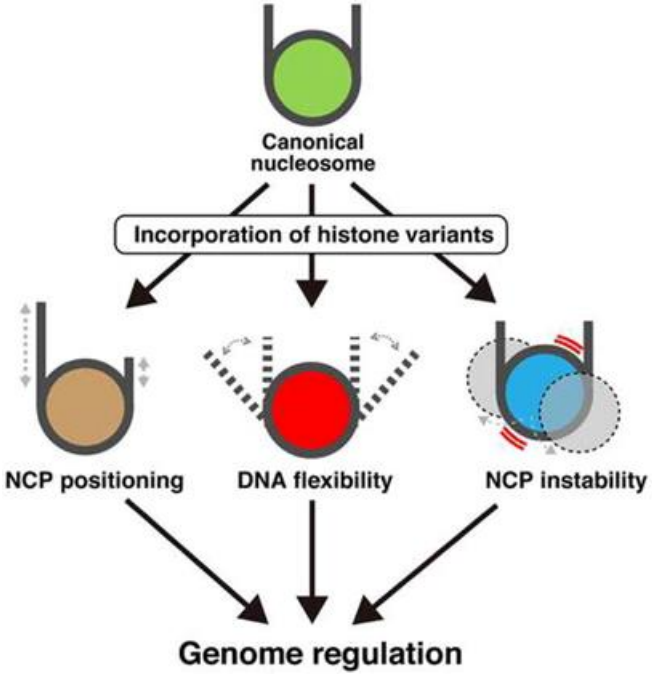
Transcriptional regulation by PRC1-mediated H2AK119ub

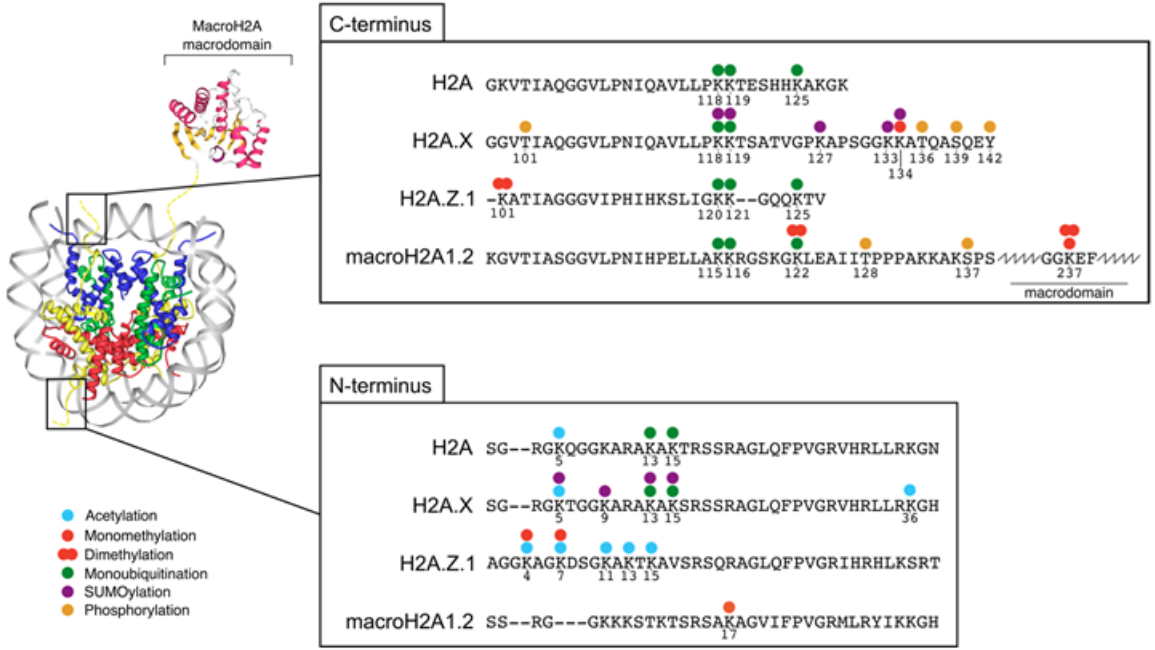


https://doi.org/10.3390/cells11152404, https://doi.org/10.1016/j.dnarep.2017.06.011


A
Ubiquitin activation
Ubiquitin transfer
Histone substrate ubiquitination
Ub
E1
Cys
ATP
AMP
E2
E3 ubiquitin ligase
B
RNF168
RNF8
RING1A
RING1B
BRCA1-BARD1
CUL4A/B
13
15
119
124
127
129
31
H2A
H4
H3
H2B
121/122
125
4
14
18
23
36/37
120
RNF8
CUL4A/B
UHRF1
NEDD4
RNF20
RNF40
Ubiquitin
Lysine residue

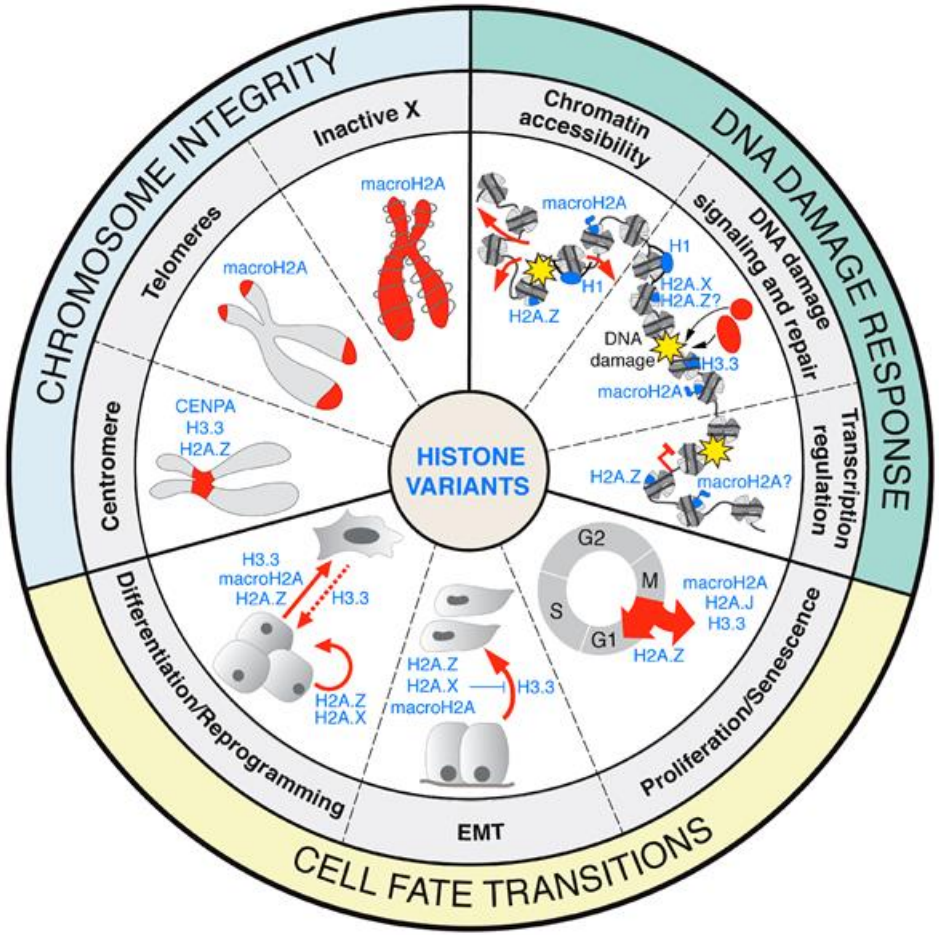
Гистоновые варианты и регуляция транскрипции





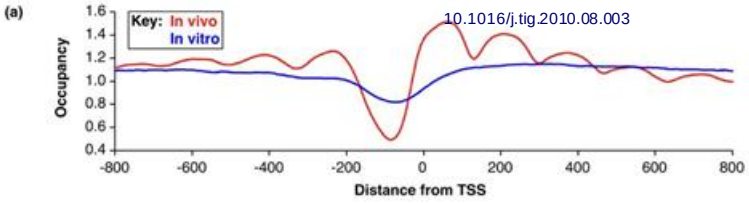
10.1016/j.jmb.2020.10.012

10.3390/cancers10030059

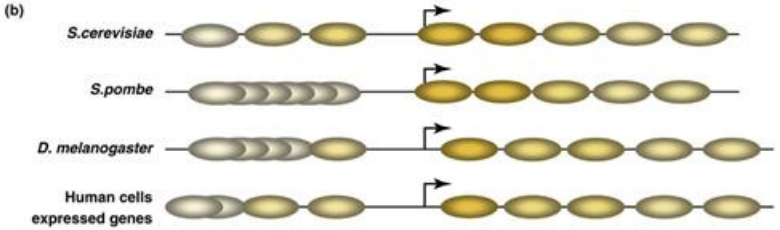


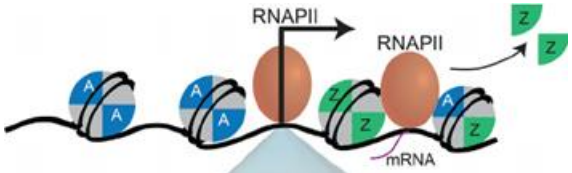
10.3390/cells9112424

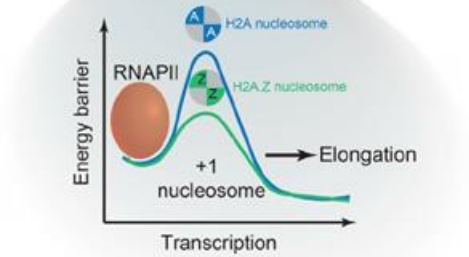
Структура преинициационного комплекса с +1 нуклеосомой

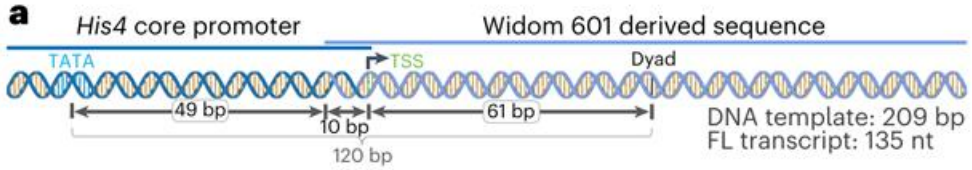


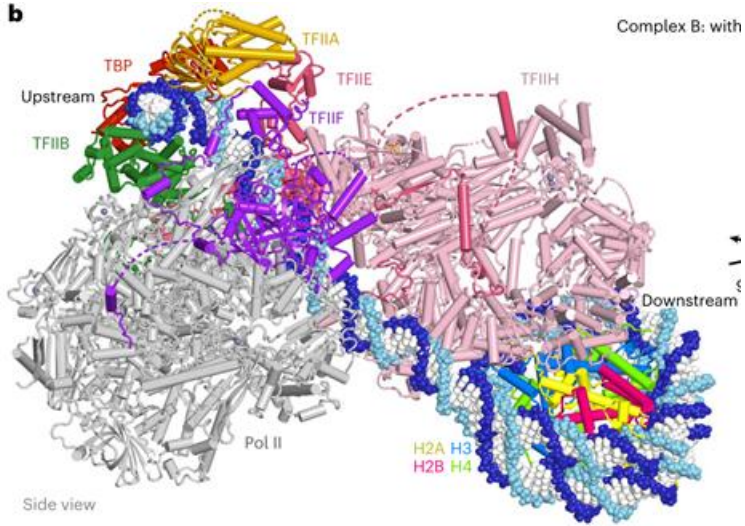
10.1016/j.tig.2010.08.003











10.1038/s41594-022-00865-w

10.12703/P7-01

Ремоделирование хроматина (Chromatin remodeling)

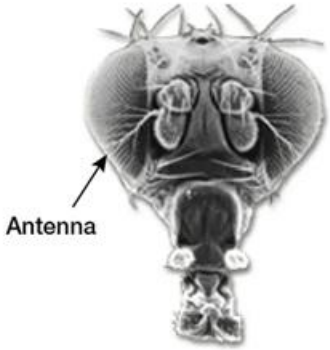
Ремоделирование хроматина - это динамическая модификация архитектуры хроматина, обеспечивающая доступ белков к конденсированной геномной ДНК и тем самым контролирующая экспрессию генов. Такое ремоделирование в основном осуществляется путем

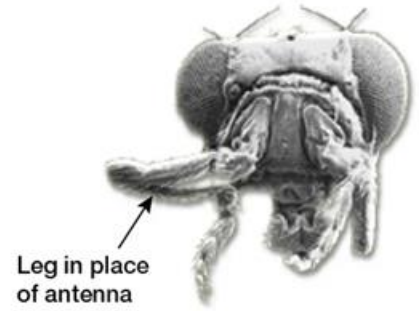
1) ковалентных модификаций гистонов специфическими ферментами, например гистонацетилтрансферазами (HATs), деацетилазами, метилтрансферазами и киназами, и

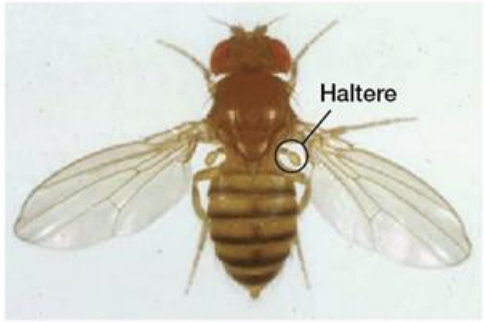
2) АТФ-зависимыми комплексами ремоделирования хроматина, которые либо перемещают, выбрасывают, либо реструктурируют нуклеосомы.

Практические примеры

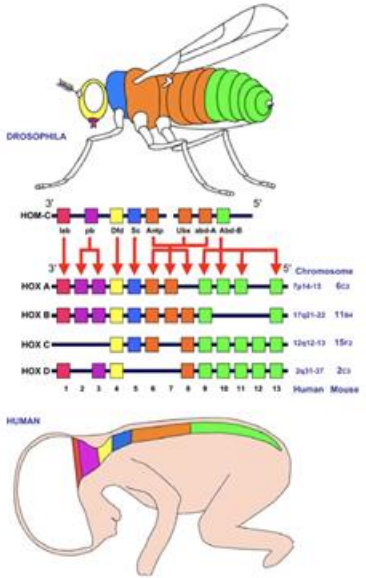
- Мутации в HOX-генах



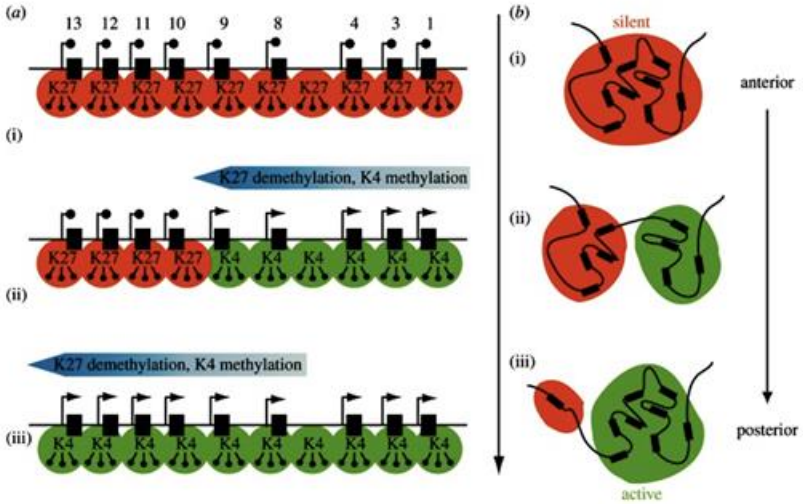




- Контроль развития организма вдоль оси голова-хвост

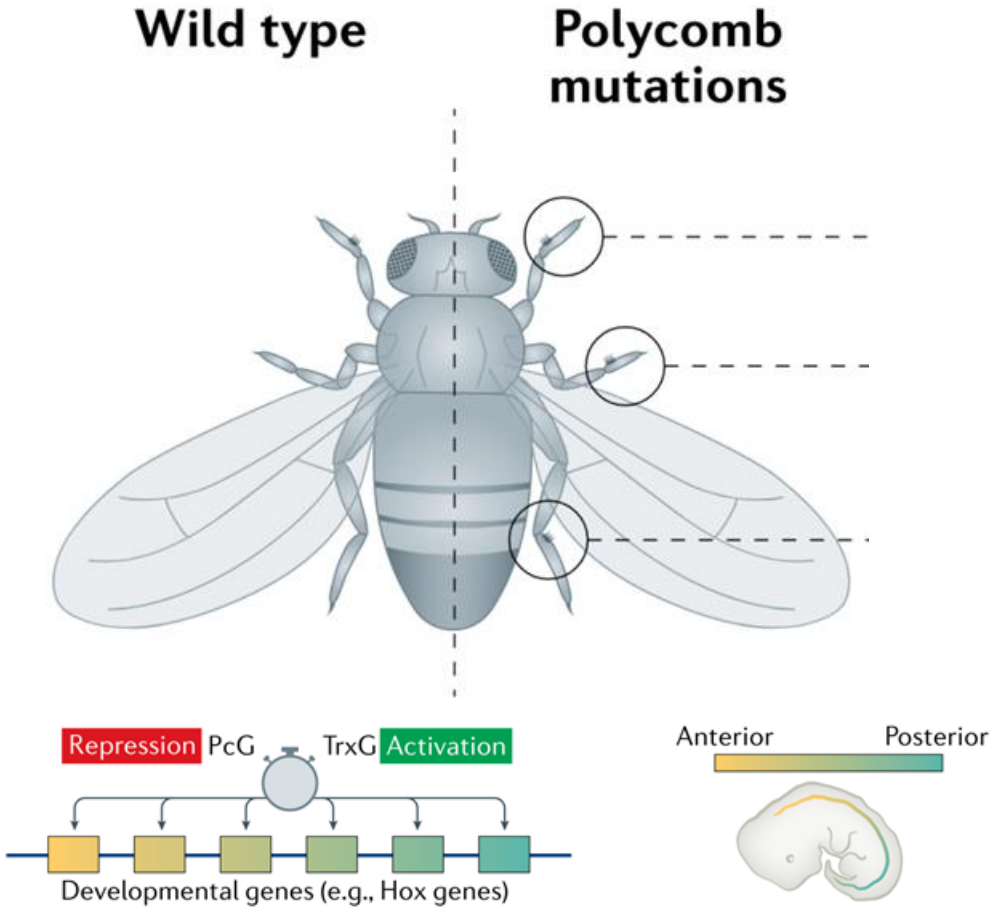


Нох-гены

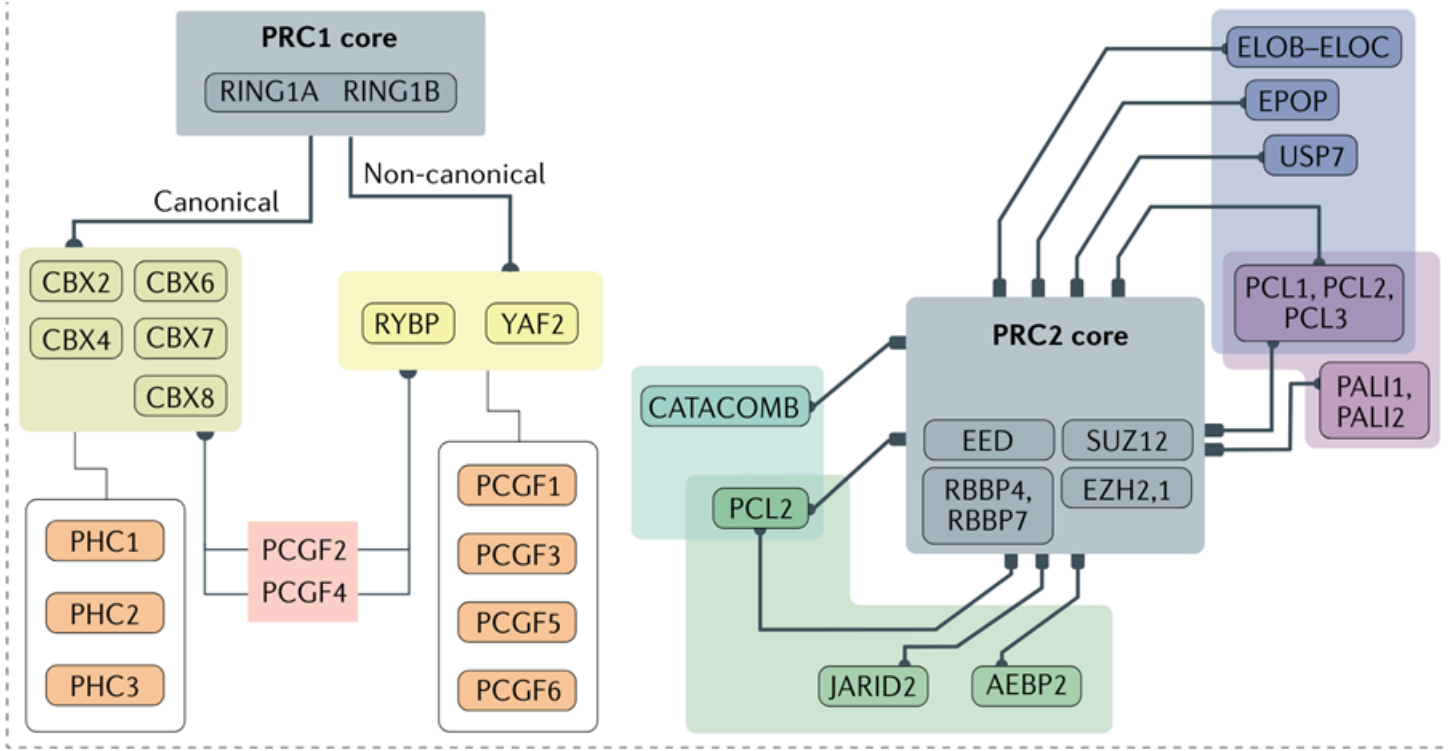


«Колинеарность» – гены, расположенные вдоль ДНК, последовательно активируются в сегментах тела от головы к хвосту

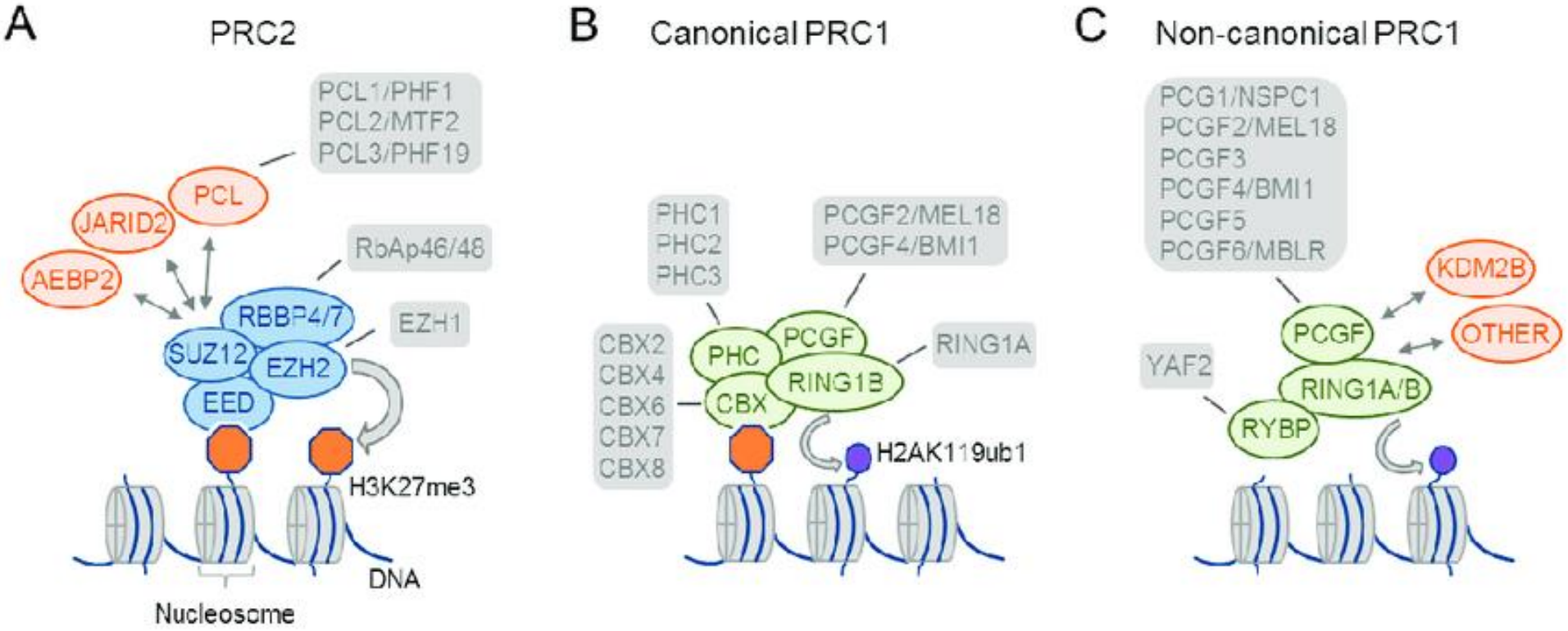
Polycomb repressor group proteins



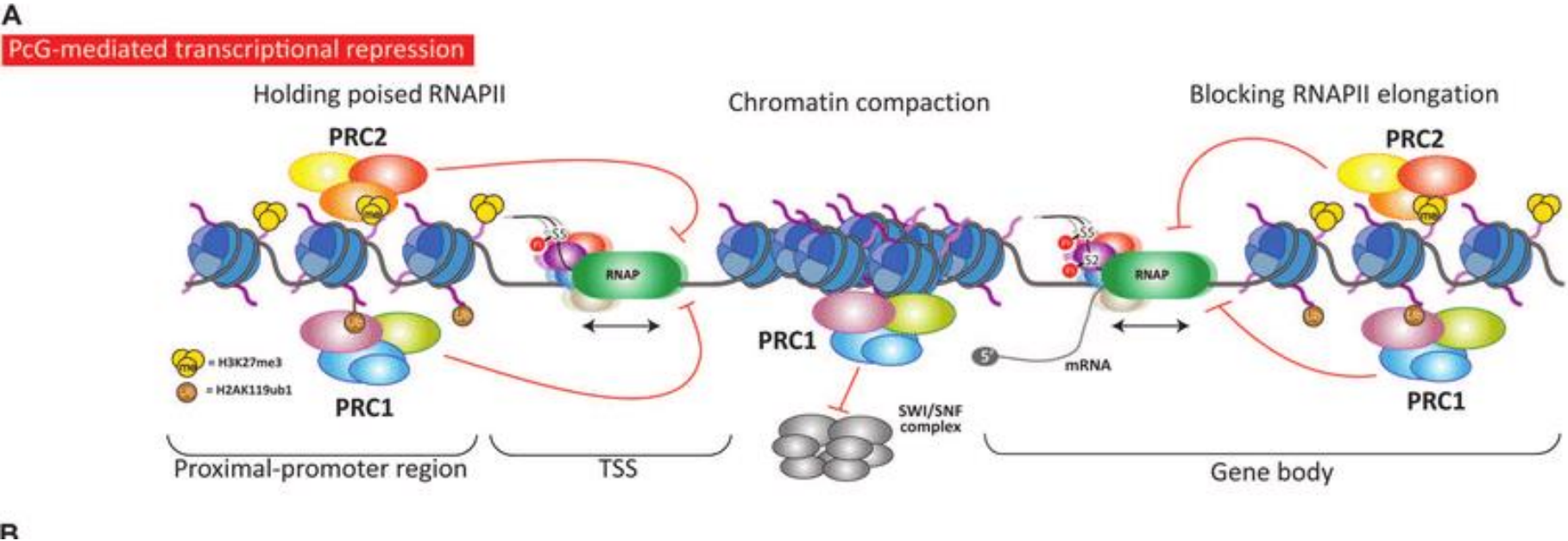
Polycomb repressor group proteins



involved in stable and heritable transcriptional silencing



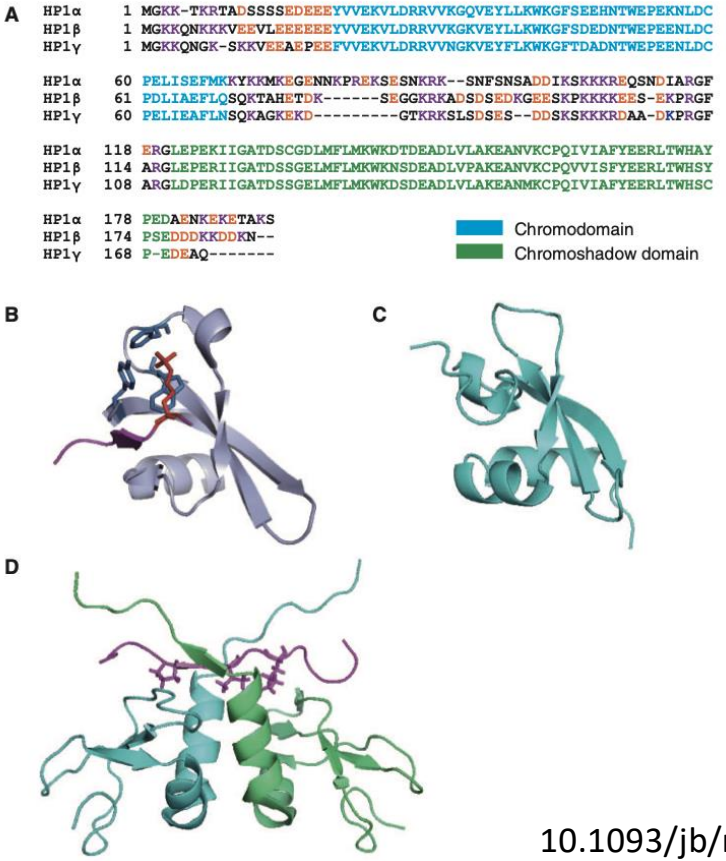
10.3390/epigenomes1030021



10.1126/sciadv.1500737

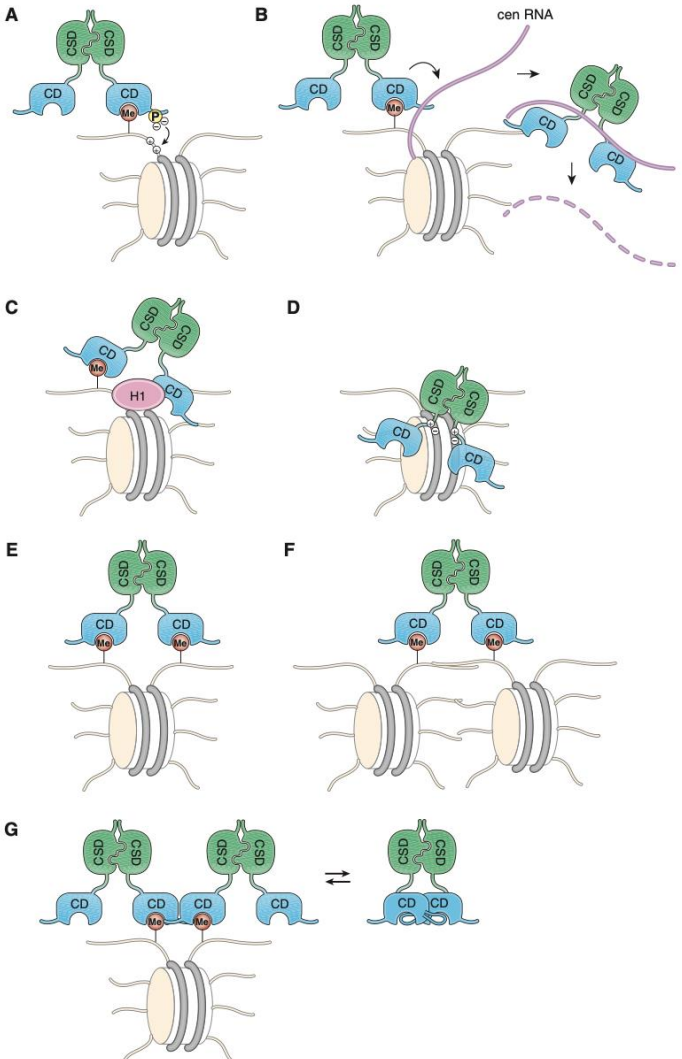
Heterochromatin protein 1 (HP1)

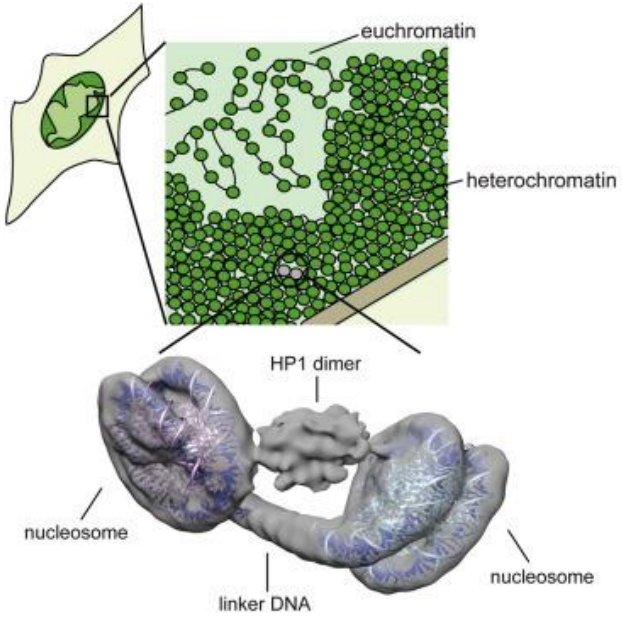
Heterochromatin protein 1 (HP1) is an evolutionarily conserved chromosomal protein that binds lysine 9-methylated histone H3 (H3K9me), a hallmark of het- erochromatin, and plays a crucial role in forming higher-order chromatin structures. HP1 has an N-ter- minal chromodomain and a C-terminal chromo shadow domain, linked by an unstructured hinge region



A series of in vitro biochemical analyses demon- strated that HP1 CD preferentially binds H3K9me3 over H3K9me2 or H3K9me1, and that each HP1 iso- form's CD displays a different binding affinity for H3K9me3

10.1093/jb/mvu032


A
B
cen RNA
C
D
E
F
G
CSD
CD
Me
P
H1


euchromatin
heterochromatin
HP1 dimer
nucleosome
linker DNA
nucleosome

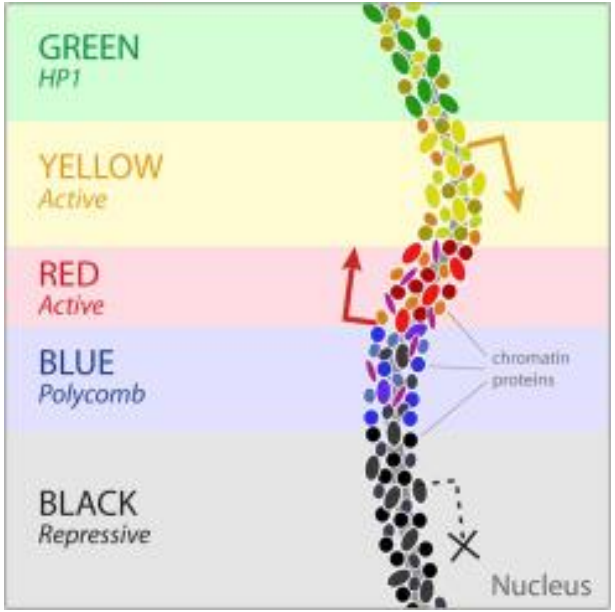
Цвета хроматина

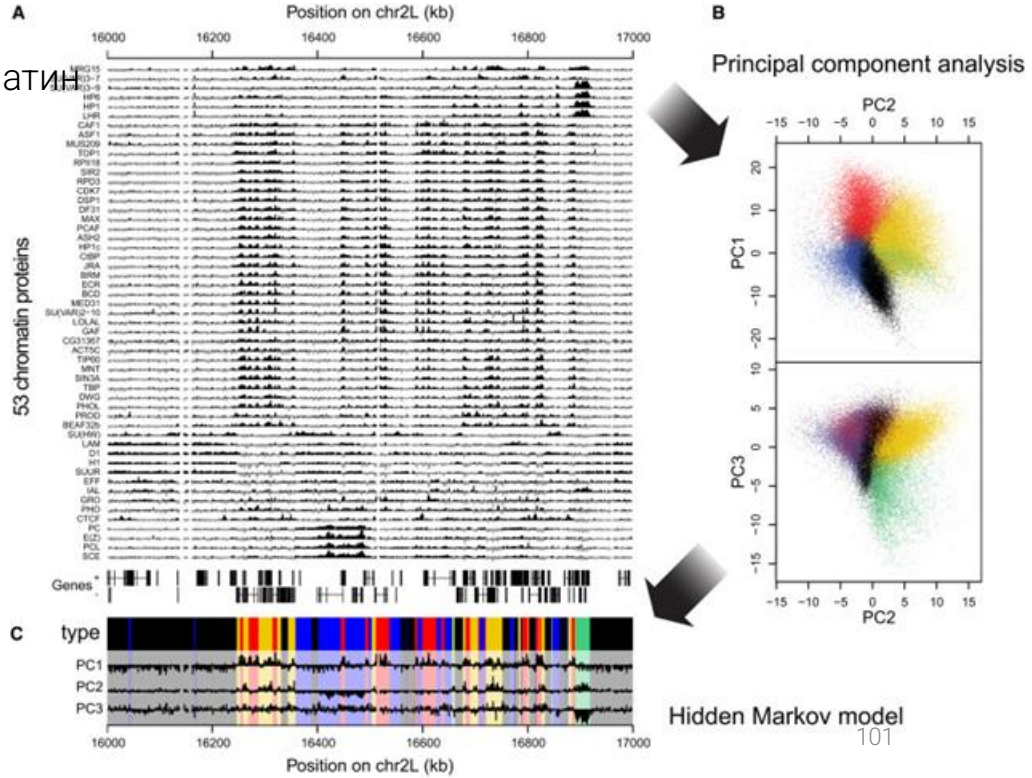
Systematic Protein Location Mapping Reveals Five Principal Chromatin Types in *Drosophila* Cells

Guillaume J. Filion,[1,5] Joke G. van Bemmel,[1,5] Ulrich Braunschweig,[1,5] Wendy Talhout,[1] Jop Kind,[1] Lucas D. Ward,[3,4,6] Wim Brugman,[2] Inês J. de Castro,[1,7] Ron M. Kerkhoven,[2] Harmen J. Bussemaker,[3,4] and Bas van Steensel[1,*]

53 профиля белков на хроматине после Dam-метилирования (идентификация ДНК-аденин-метилирования) объединены в цвета хроматина:

- красный, желтый - активный хроматин,
- зеленый, синий, черный - неактивный хроматин





BLUE and GREEN Chromatin Correspond to Known Heterochromatin Types

GREEN chromatin corresponds to classic heterochromatin that is marked by SU(VAR)3-9, HP1, and the HP1-interacting proteins LHR and HP6.

BLUE chromatin corresponds to PcG chromatin, as shown by the extensive binding by the PcG proteins PC, E(Z), PCL, and SCE.

BLACK Chromatin Is the Prevalent Type of Repressive Chromatin

BLACK chromatin is overall relatively gene poor

BLACK chromatin is almost universally marked by four of the 53 mapped proteins: histone H1, D1, IAL, and SUUR, whereas SU(HW), LAM, and EFF are also frequently present

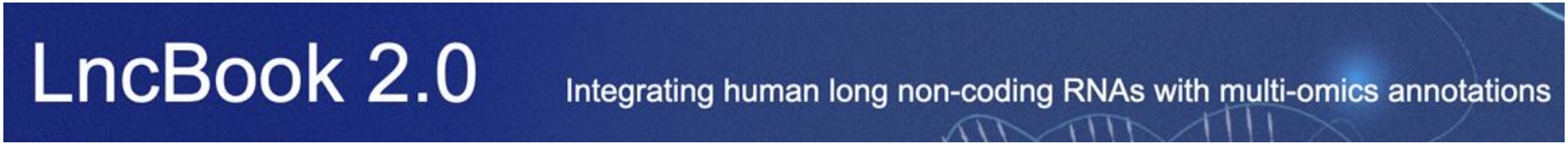
YELLOW and RED Chromatin Are Two Distinct Types of Euchromatin

Genes with universal cellular functions such as ‘‘ribosome,’’ ‘‘DNA repair,’’ and ‘‘nucleic acid metabolic process’’ are almost exclusively found in YELLOW chromatin (Figure 6B), whereas genes in RED chromatin are linked to more specific processes such as ‘‘receptor binding,’’ ‘‘defense response,’’ ‘‘transcription factor activity,’’ and ‘‘signal transduction’’

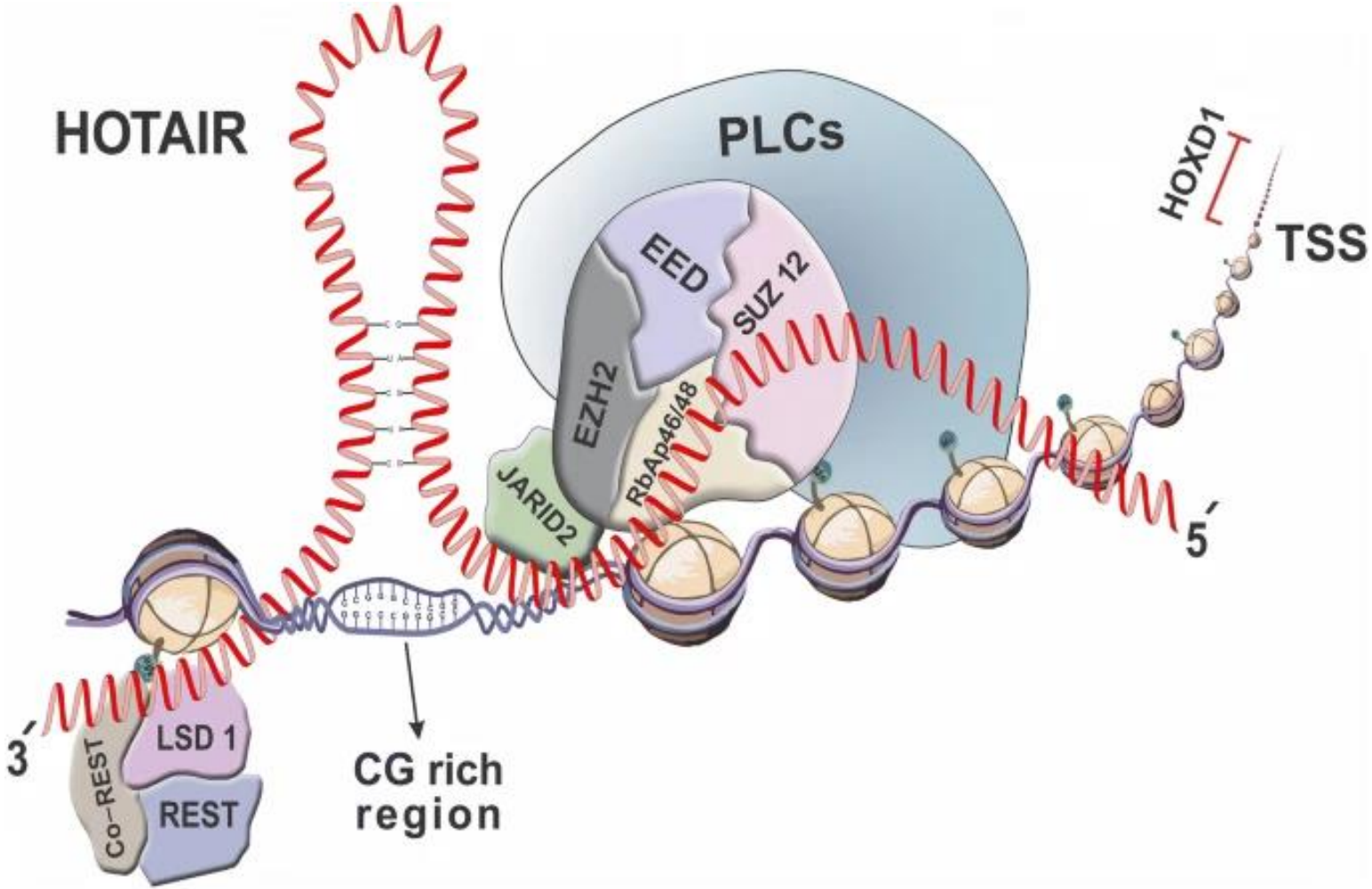
Спасибо за внимание!

Роль длинных некодирующих РНК

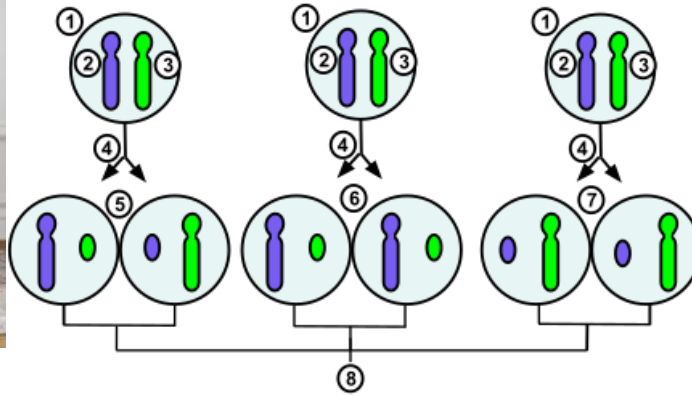
Длинные некодирующие РНК (днкРНК, lncRNAs) — некодирующие РНК, которые как правило имеют длину более 200 нуклеотидов, и расположены в ядре или в цитоплазме.



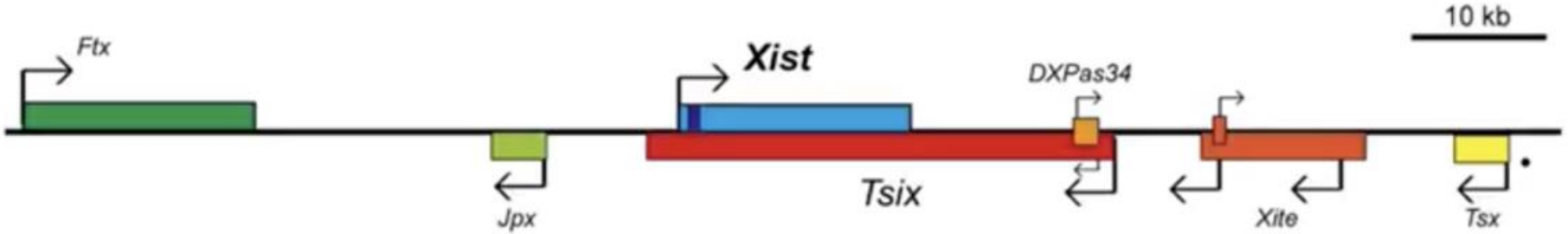
LncBook accommodates a high-quality collection of 95,243 human lncRNA genes and 323,950 lncRNA transcripts, and incorporates their abundant annotations at different omics levels, thereby enabling users to decipher functional signatures of lncRNAs in human diseases and different biological contexts.


HOTAIR
PLCs
HOXD1
TSS
EED
SUZ 12
EZH2
RbAp46/48
JARID2
5´
3´
LSD 1
Co-REST
REST
CG rich
region

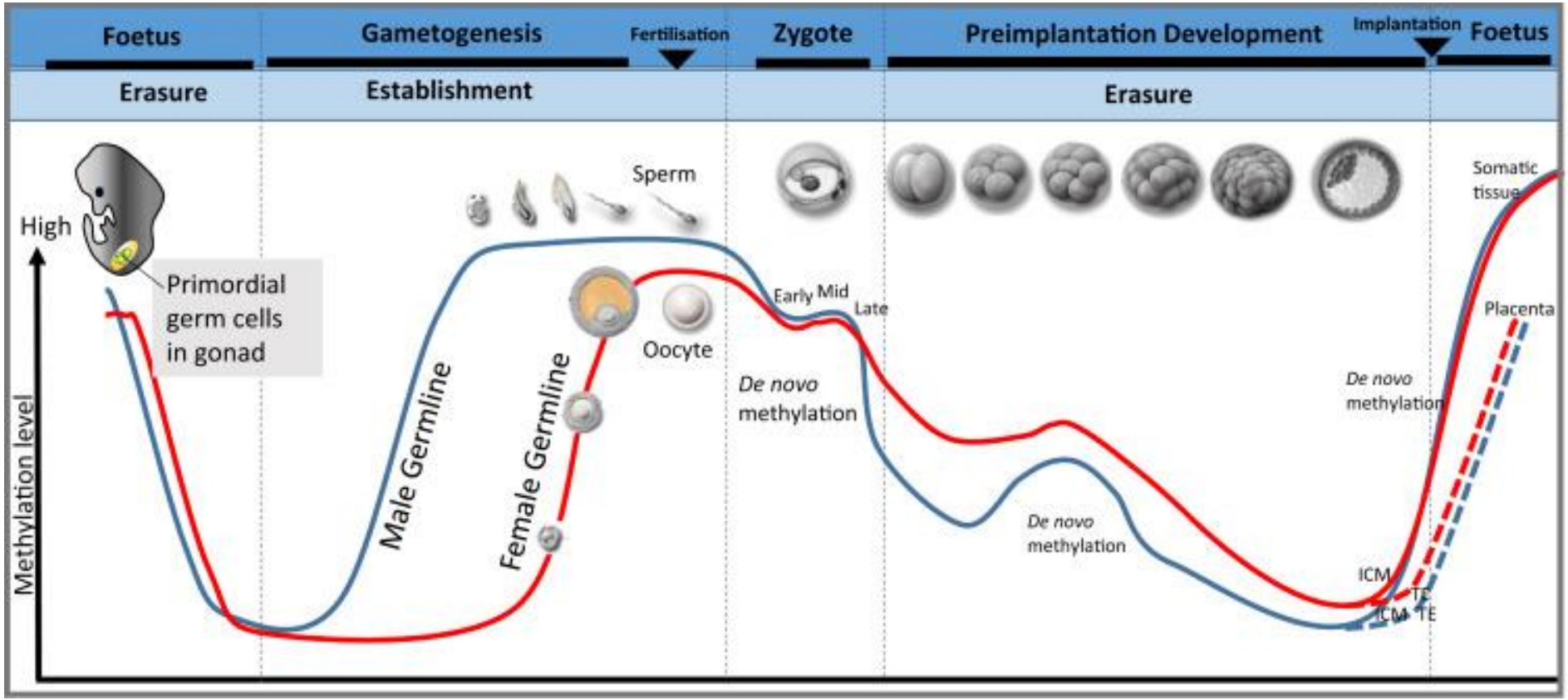
Xist (X-inactive specific transcript)



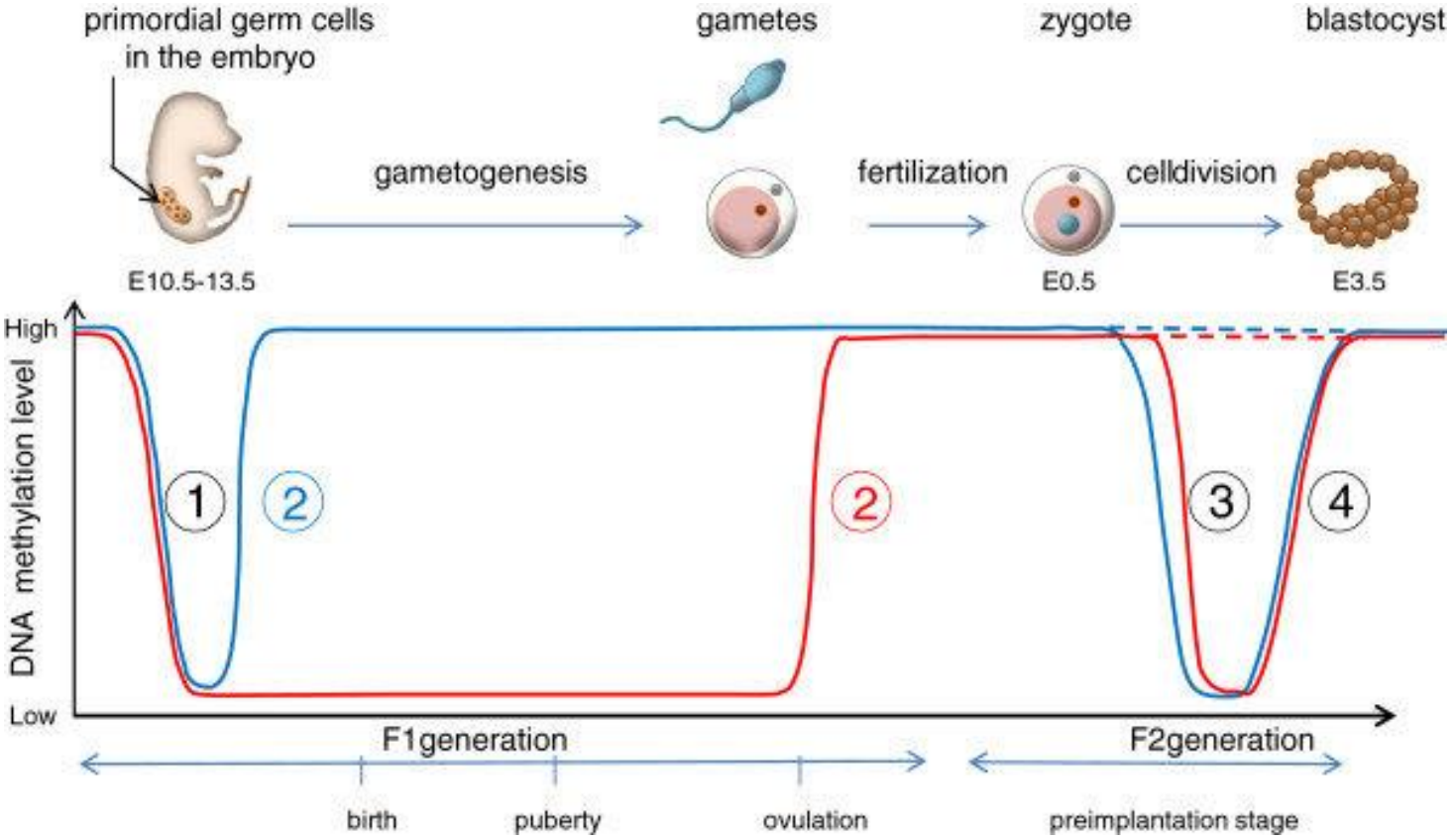
X inactivation centre (XIC)



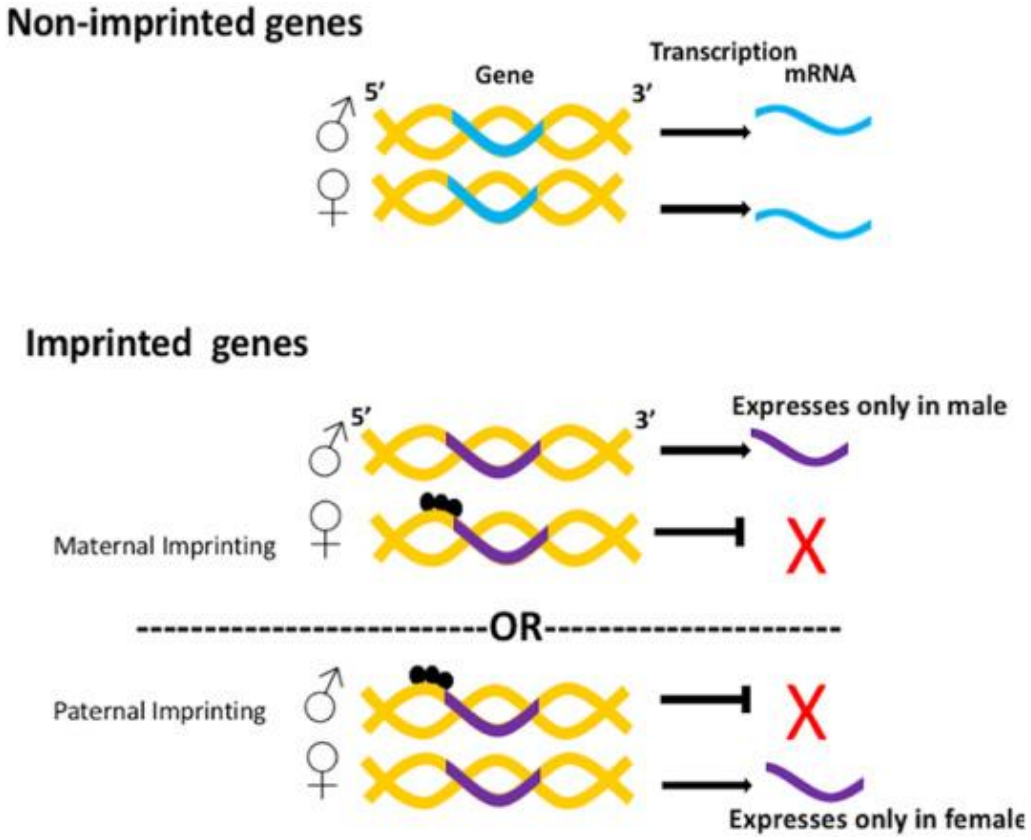
Epigenetic genome wide reprogramming



Epigenetic genome wide reprogramming



Импринтинг


Non-imprinted genes
Transcription
Gene
mRNA
5′
3′
Imprinted genes
5′
3′
Expresses only in male
Maternal Imprinting
X
----------OR----------
Paternal Imprinting
X
Expresses only in female

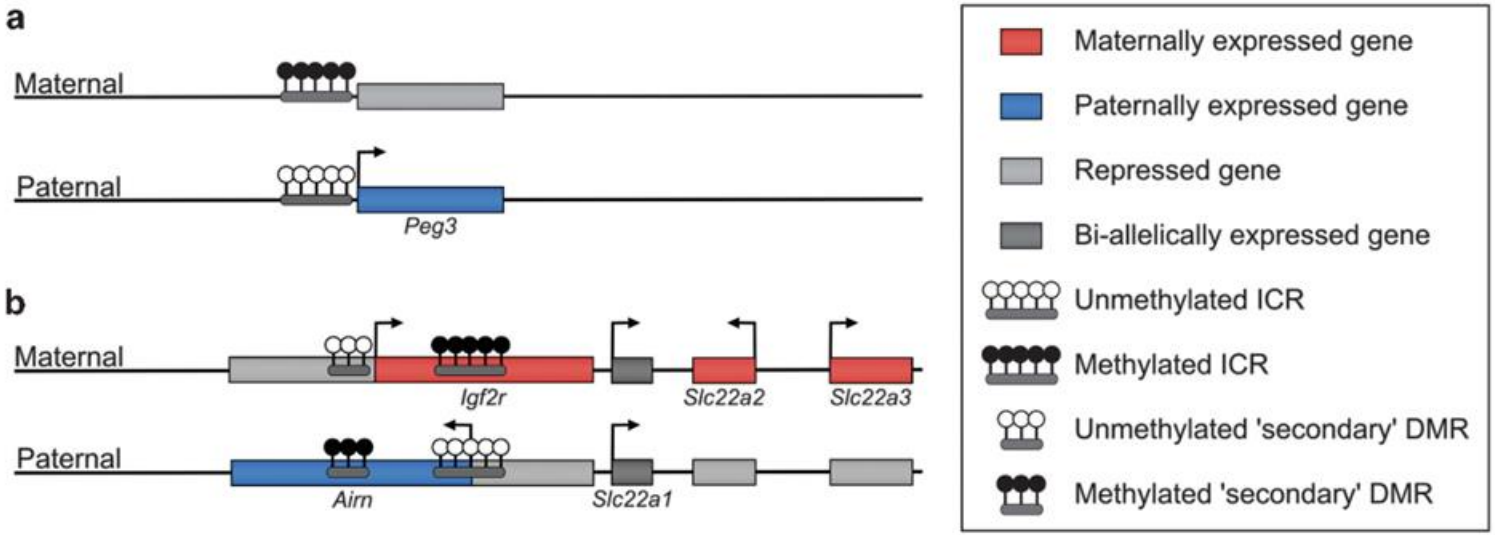
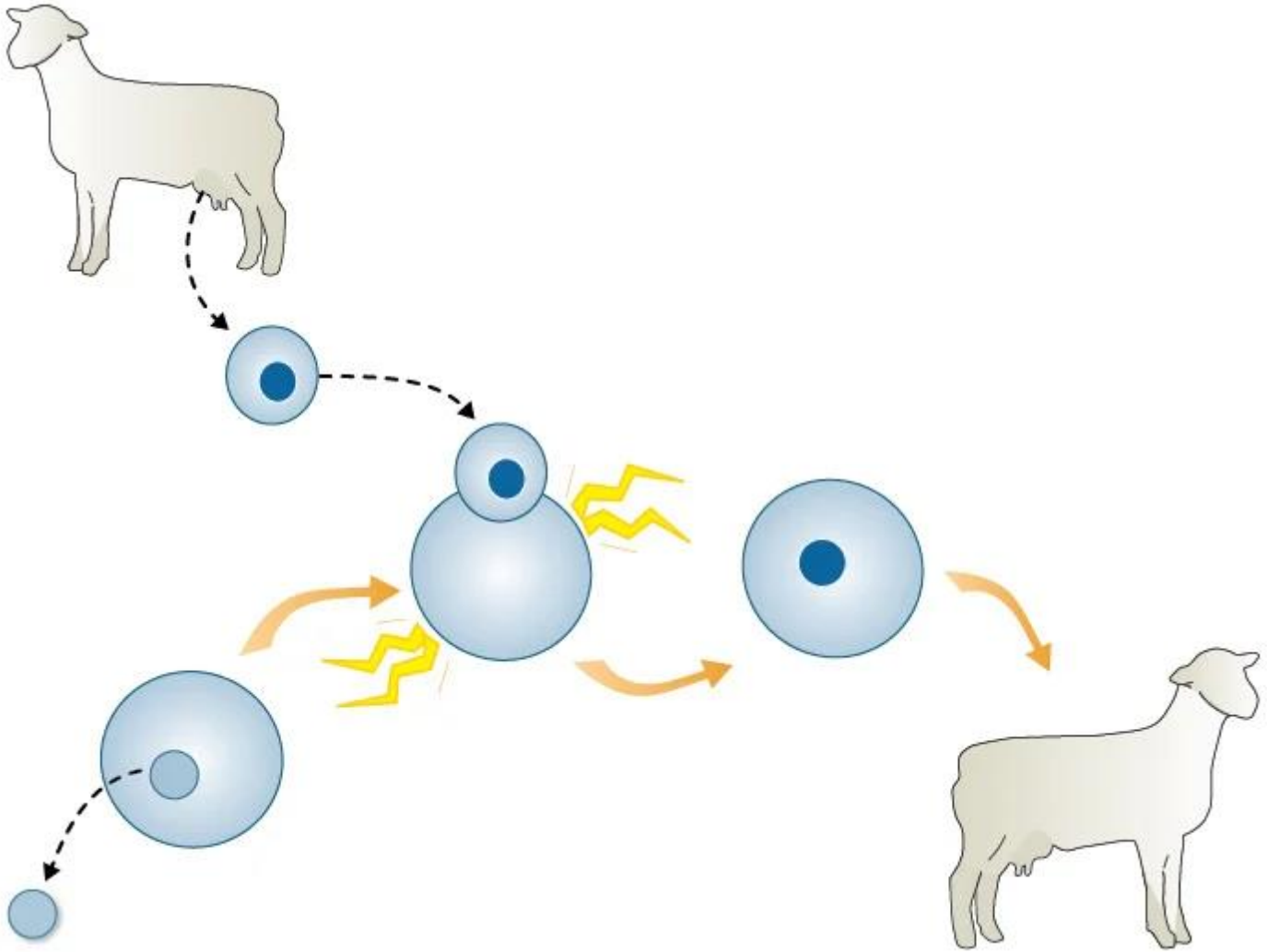
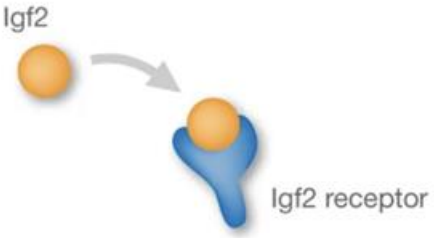


Figure 1 Examples of directly and indirectly regulated imprinted regions. Schematic representation of the (**a**) *Peg3* imprinted gene on chromosome 7 and (**b**) the *Igf2r* imprinted cluster on chromosome 17. The expression status of the genes on the maternal and paternal alleles is illustrated; active promoters are represented by horizontal arrows. (**a**) The differentially methylated ICR established during germ cell development is located at the promoter of the *Peg3* gene and directly regulates the monoallelic transcription of this gene. (**b**) The maternally methylated ICR indirectly regulates the monoallelic expression of the adjacent genes at this locus, partially mediated by the monoallelic methylation acquired at the nearby secondary DMR at the *Igf2r* promoter.

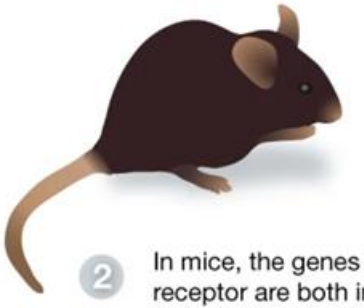
10.1038/hdy.2014.54



AN EXAMPLE OF IMPRINTING



1 In mammals, the growth factor Igf2 interacts with the Igf2 receptor.



Genes from mom:
Igf2 receptor - ON
Igf2 - OFF

Genes from dad:
Igf2 receptor - OFF
Igf2 - ON

2 In mice, the genes for Igf2 and the Igf2 receptor are both imprinted.

Deleting the mother's Igf2 receptor gene produces overly large offspring.

Deleting the father's Igf2 gene produces dwarf offspring.

Deleting the mother's Igf2 receptor gene AND the father's Igf2 gene produces normally sized offspring.

3 The imprints on the Igf2 and Igf2 receptor genes normally cancel each other out. Changing the imprint on one copy of the gene has a dramatic effect on the size of the offspring. This result supports the genetic conflict hypothesis