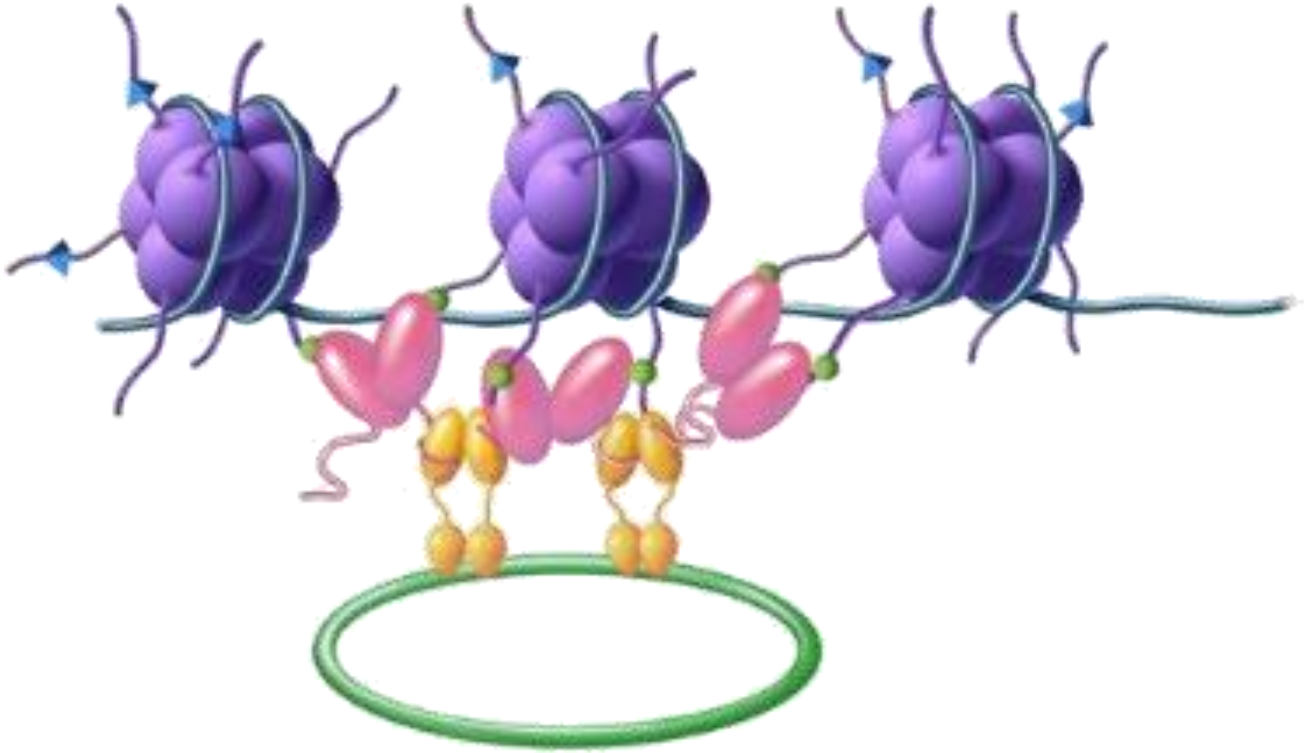


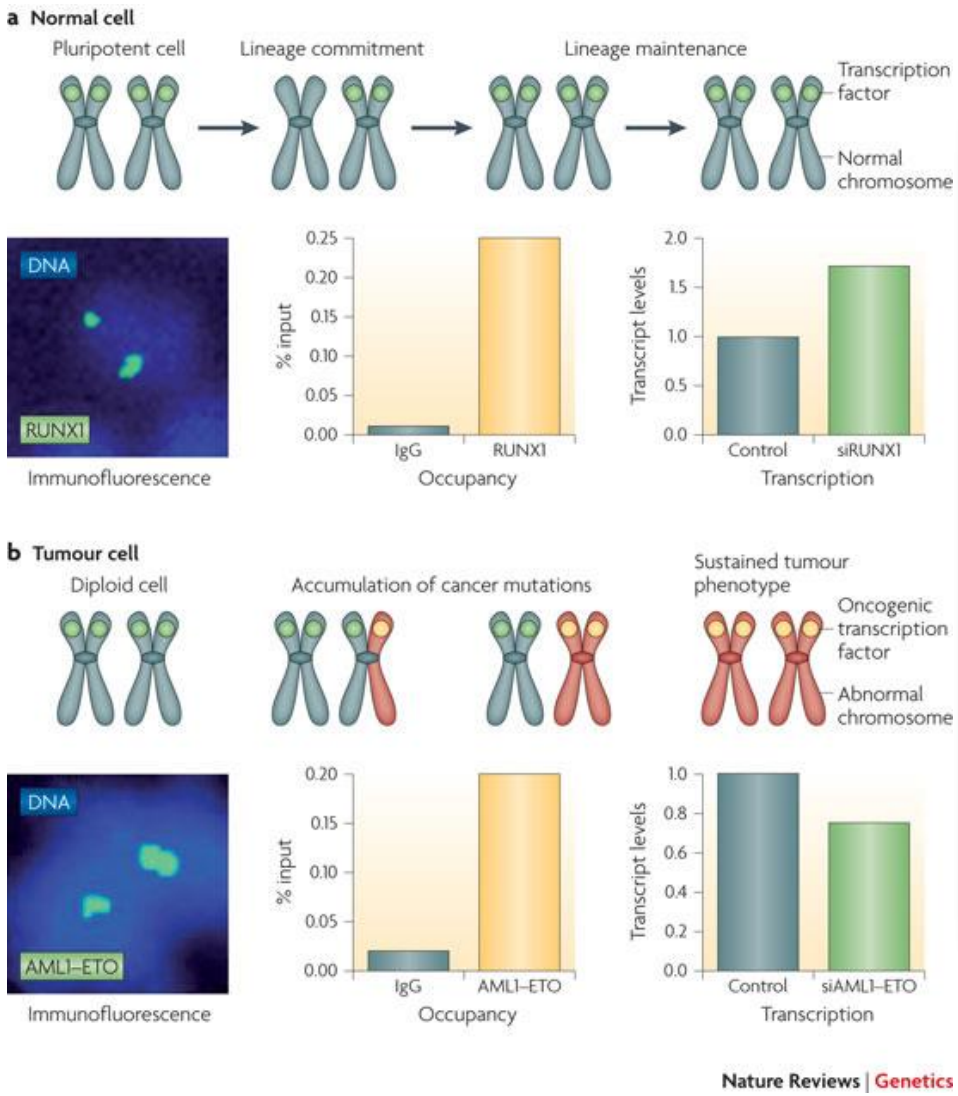
Mitotikus könyvjelzés

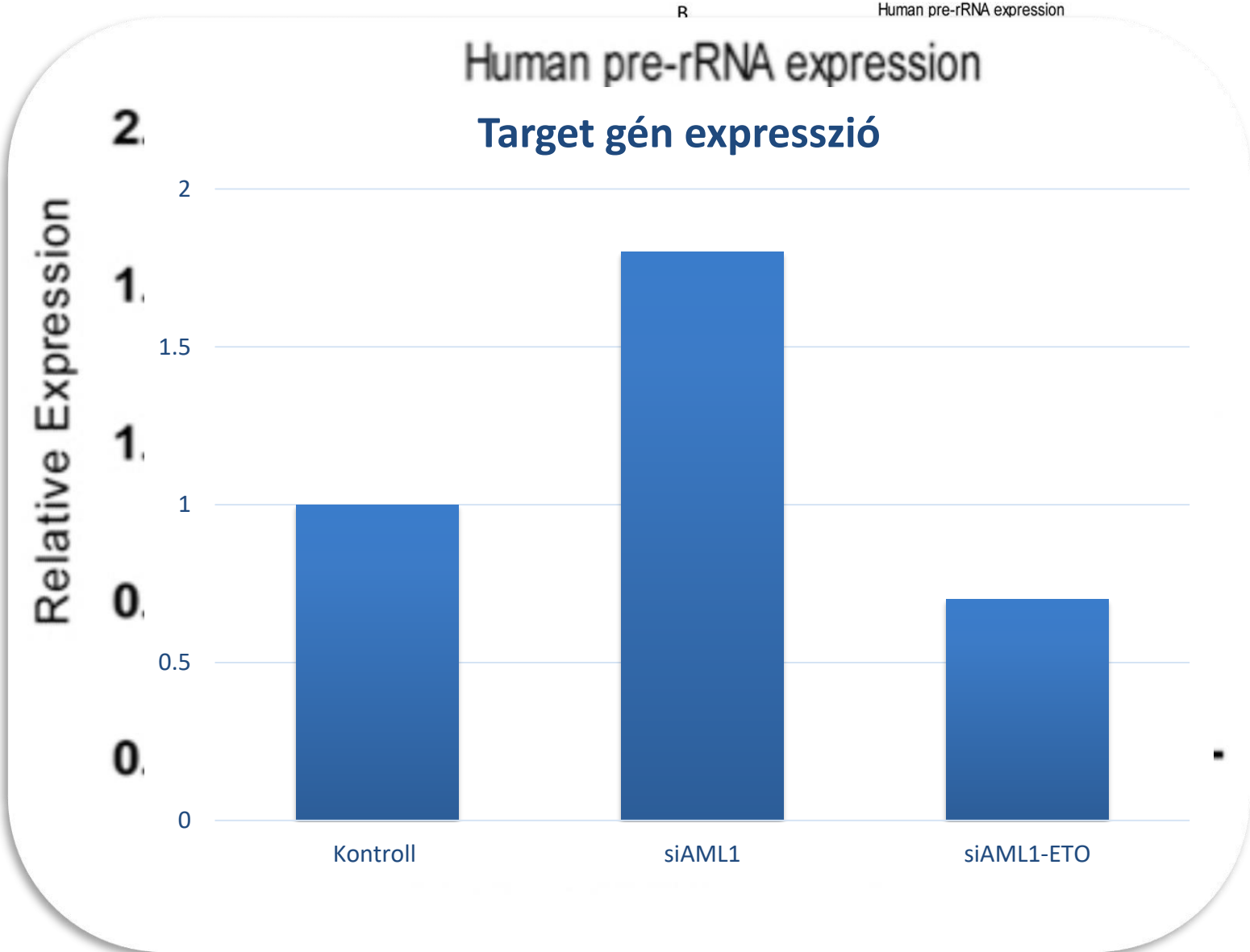
Dr. Kovács Árpád Ferenc

2015.10.13

DRARPAD

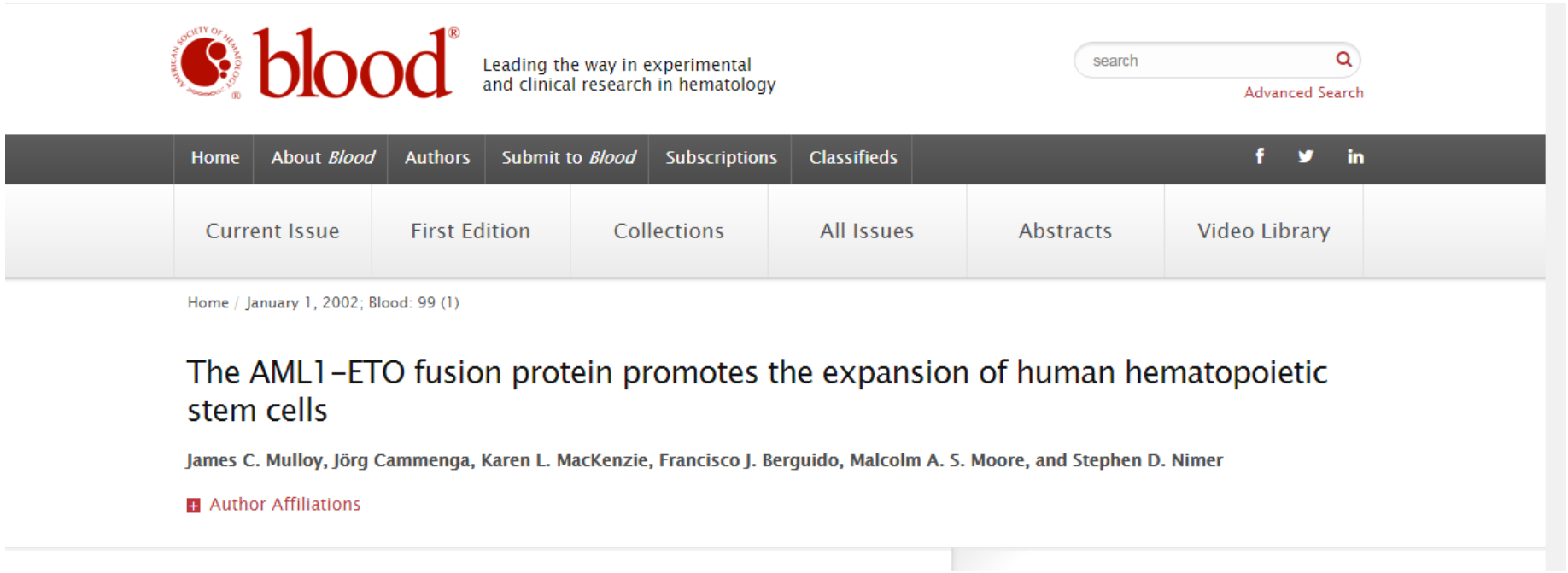
Nature Reviews Genetics **11**, 583-589 (August 2010) | doi:10.1038/nrg2827





Hogyan csökken a gén kifejeződés?

Válasz (1)



"AML1-ETO interferes with the function of the AML1 (RUNX1) transcription factor in a **dominant-negative fashion** and **represses transcription by binding** its consensus DNA–binding site and **via protein-protein interactions with other transcription factors**."

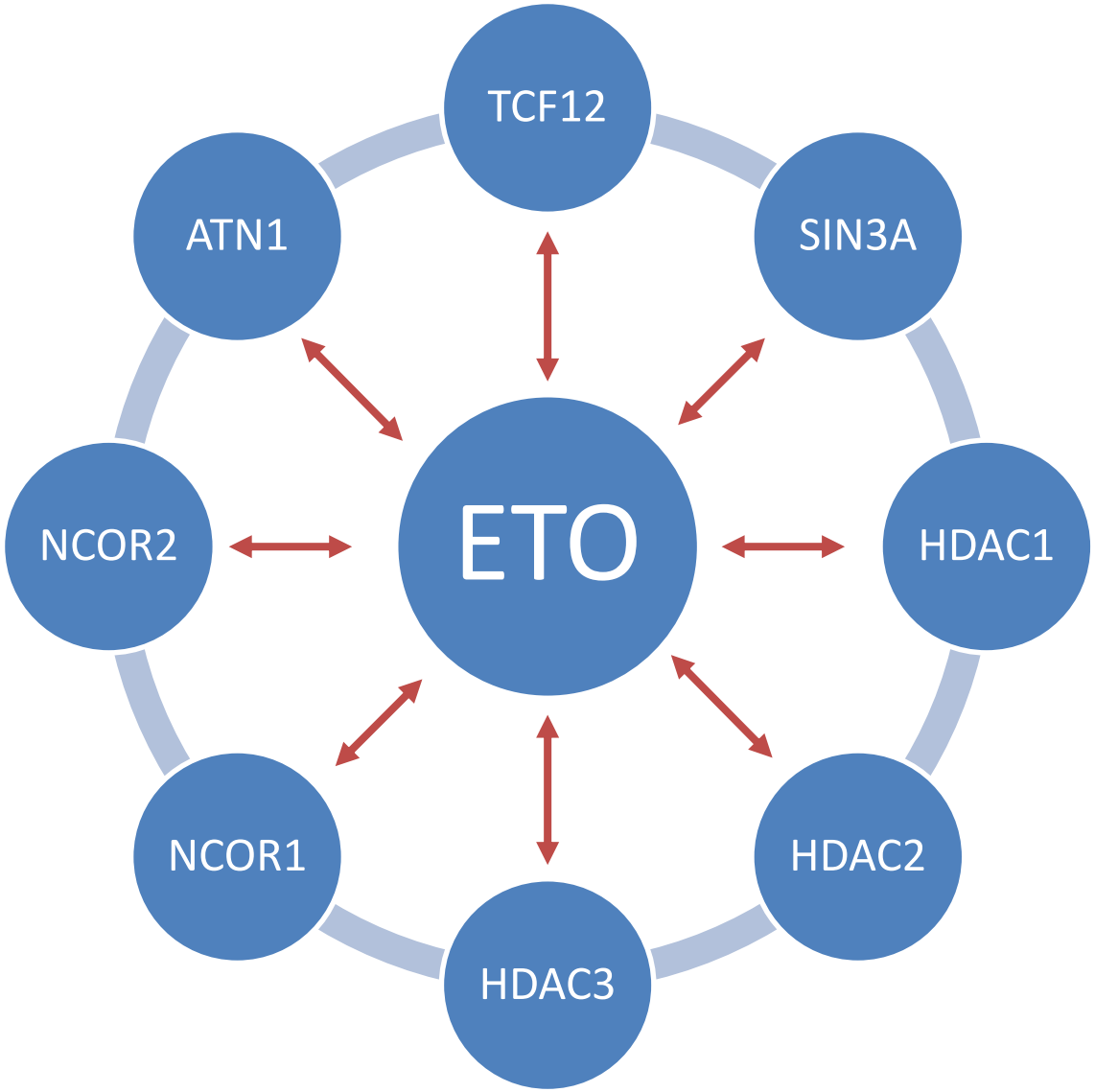
Válasz (2)

AML1 — N terminális | DNS-kötő domén | Szabályzó domén | C terminális

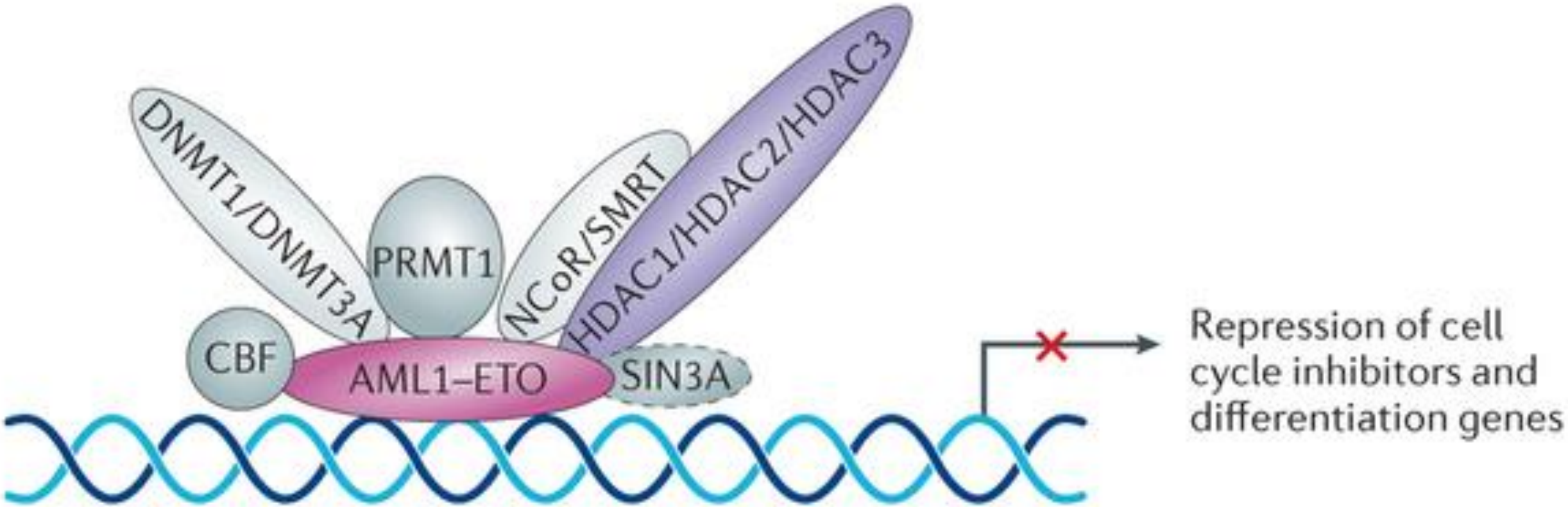
ETO — N terminális | Szabályzó domén | C terminális

AML1-ETO — N terminális | DNS-kötő domén | Szabályzó domén | C terminális

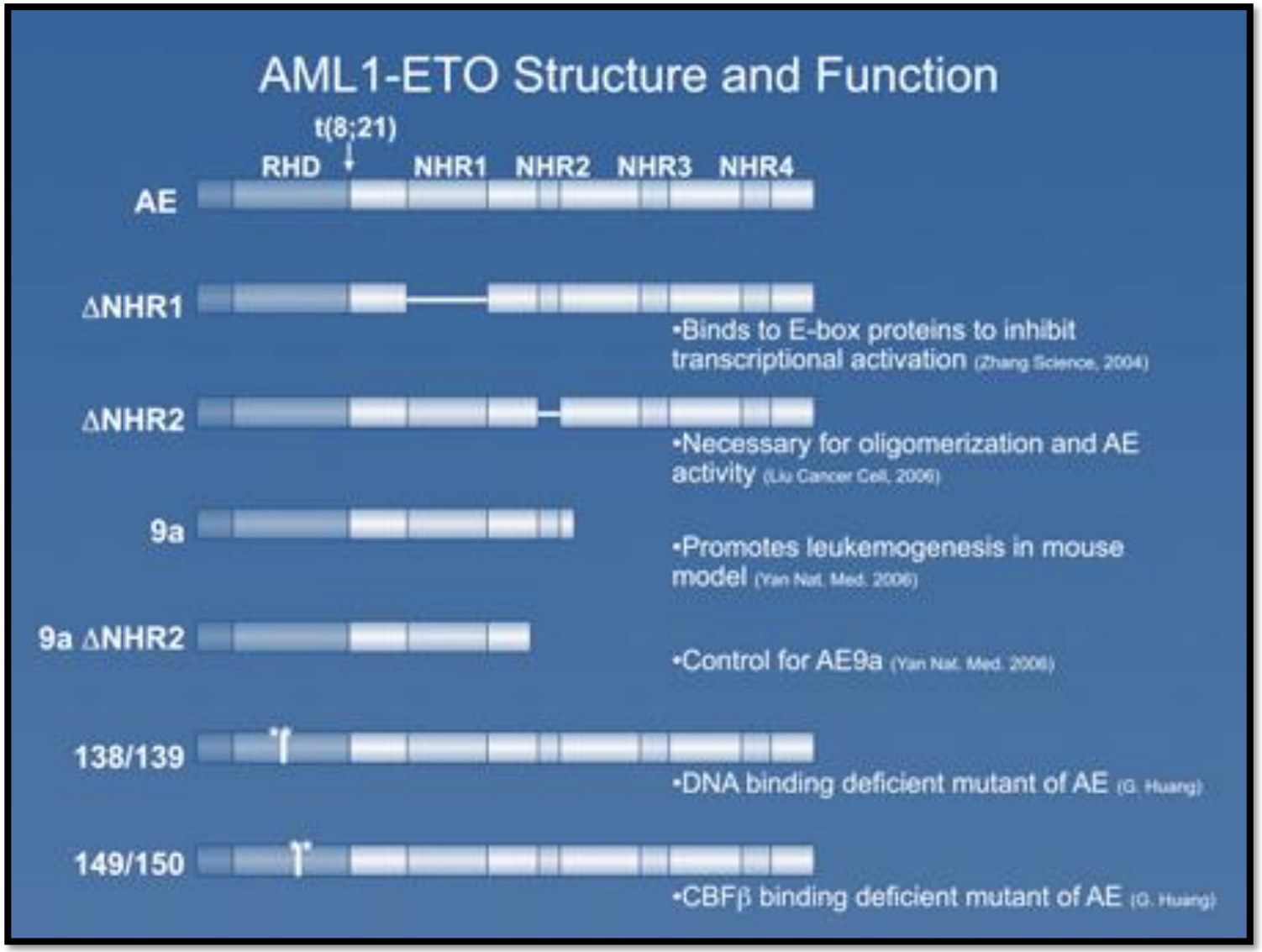
Válasz (3)



Válasz (4)


DNMT1/DNMT3A
PRMT1
NCoR/SMRT
HDAC1/HDAC2/HDAC3
CBF
AML1–ETO
SIN3A
Repression of cell cycle inhibitors and differentiation genes

Válasz (5)

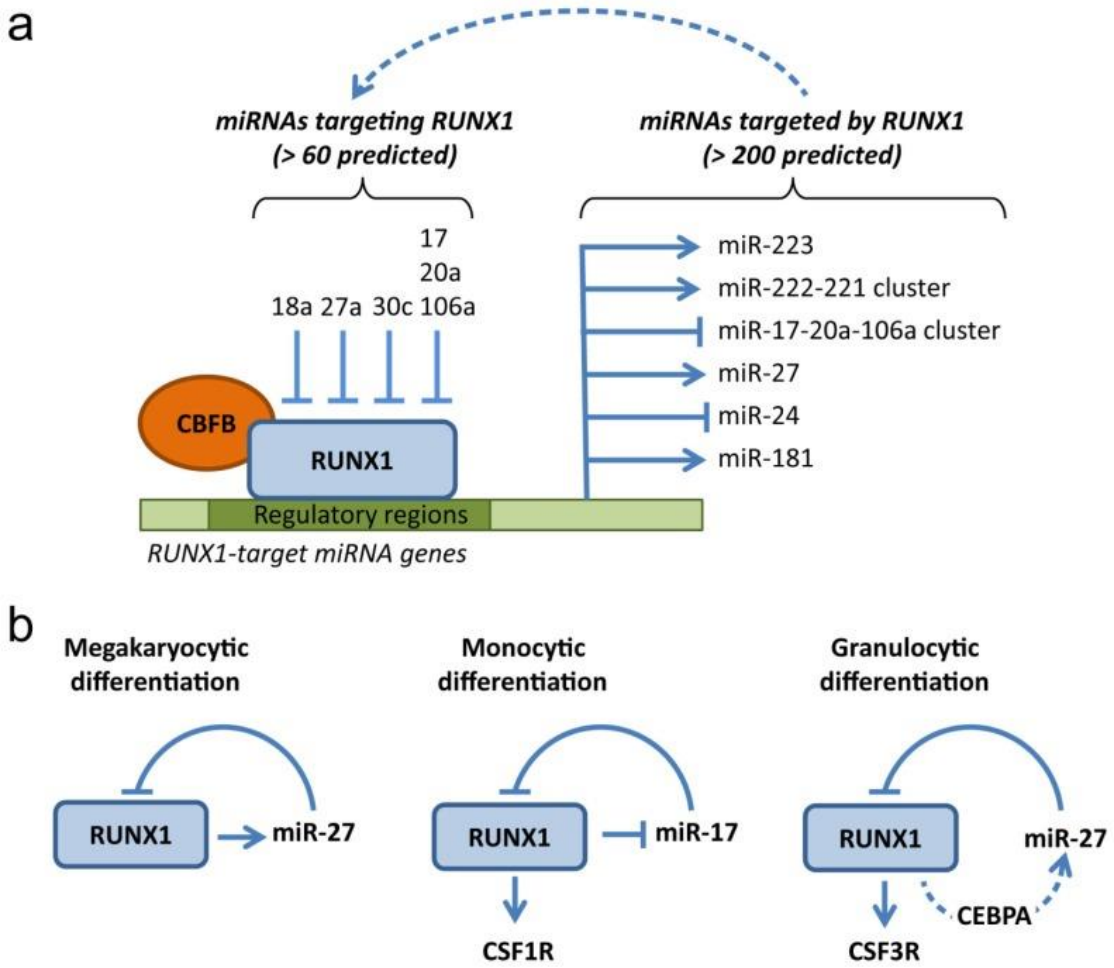


Alternatív splicing

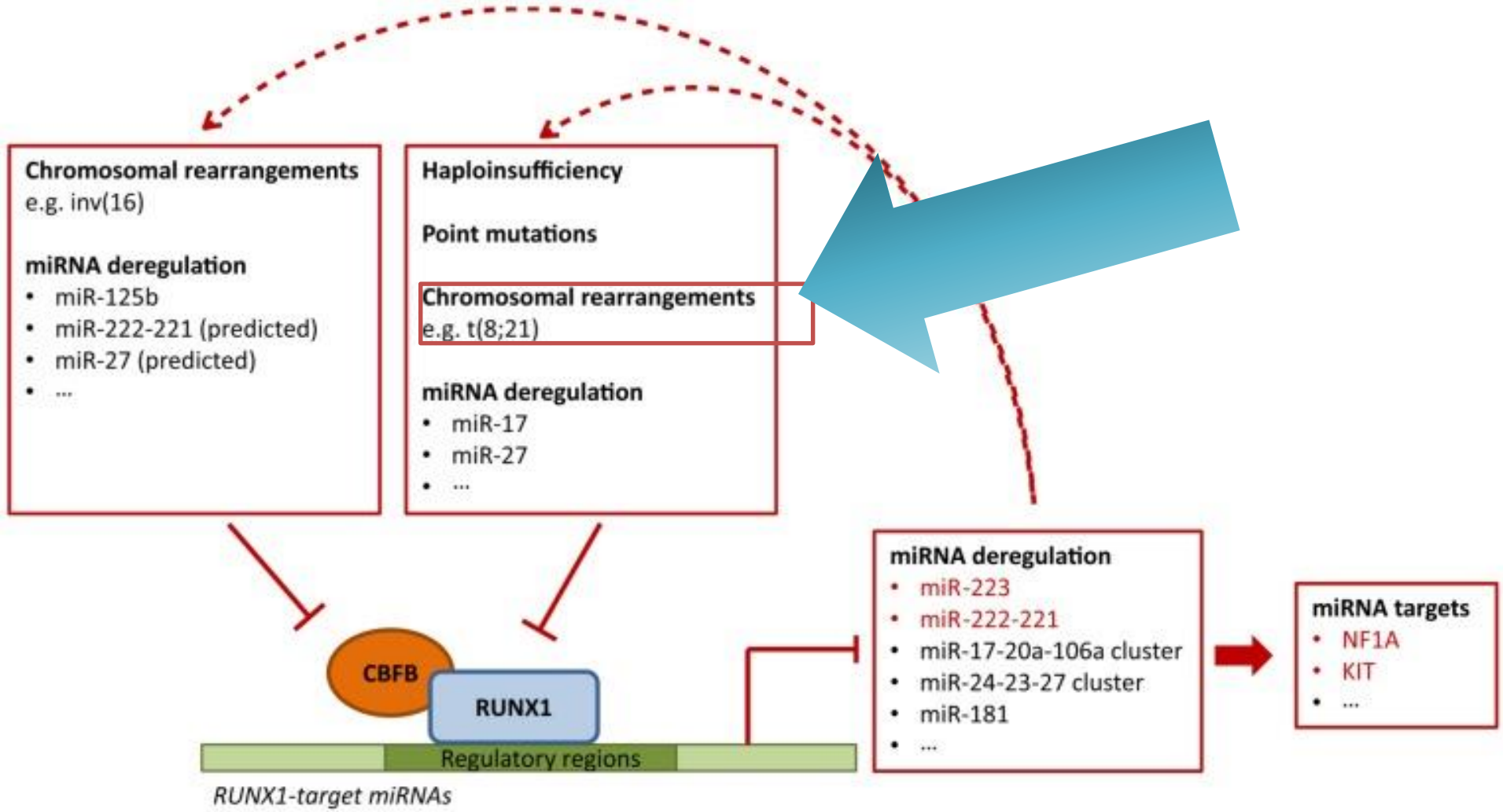
19 izoforma

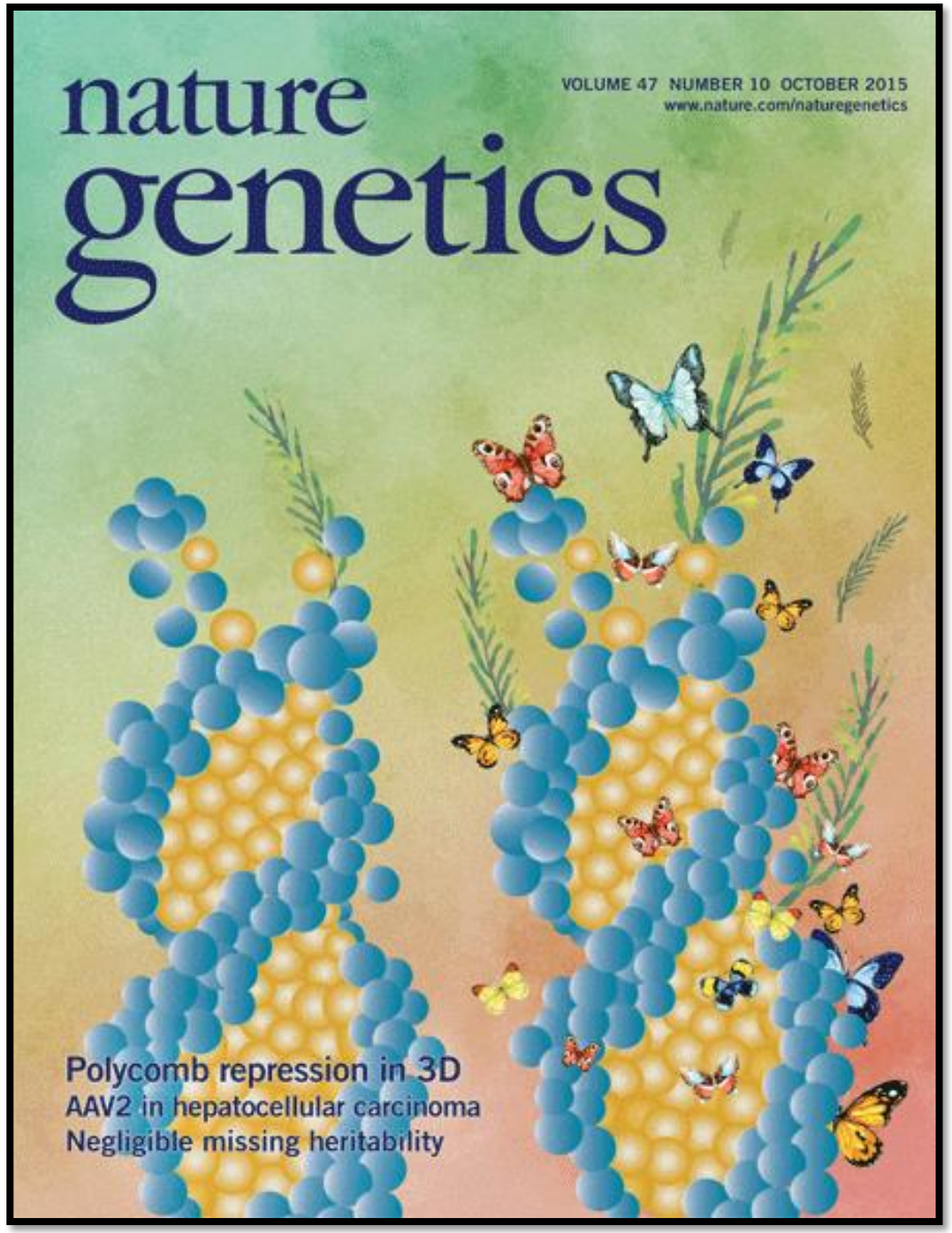
Válasz (6)

RUNX1 szabályzó kör és miRNS-ek

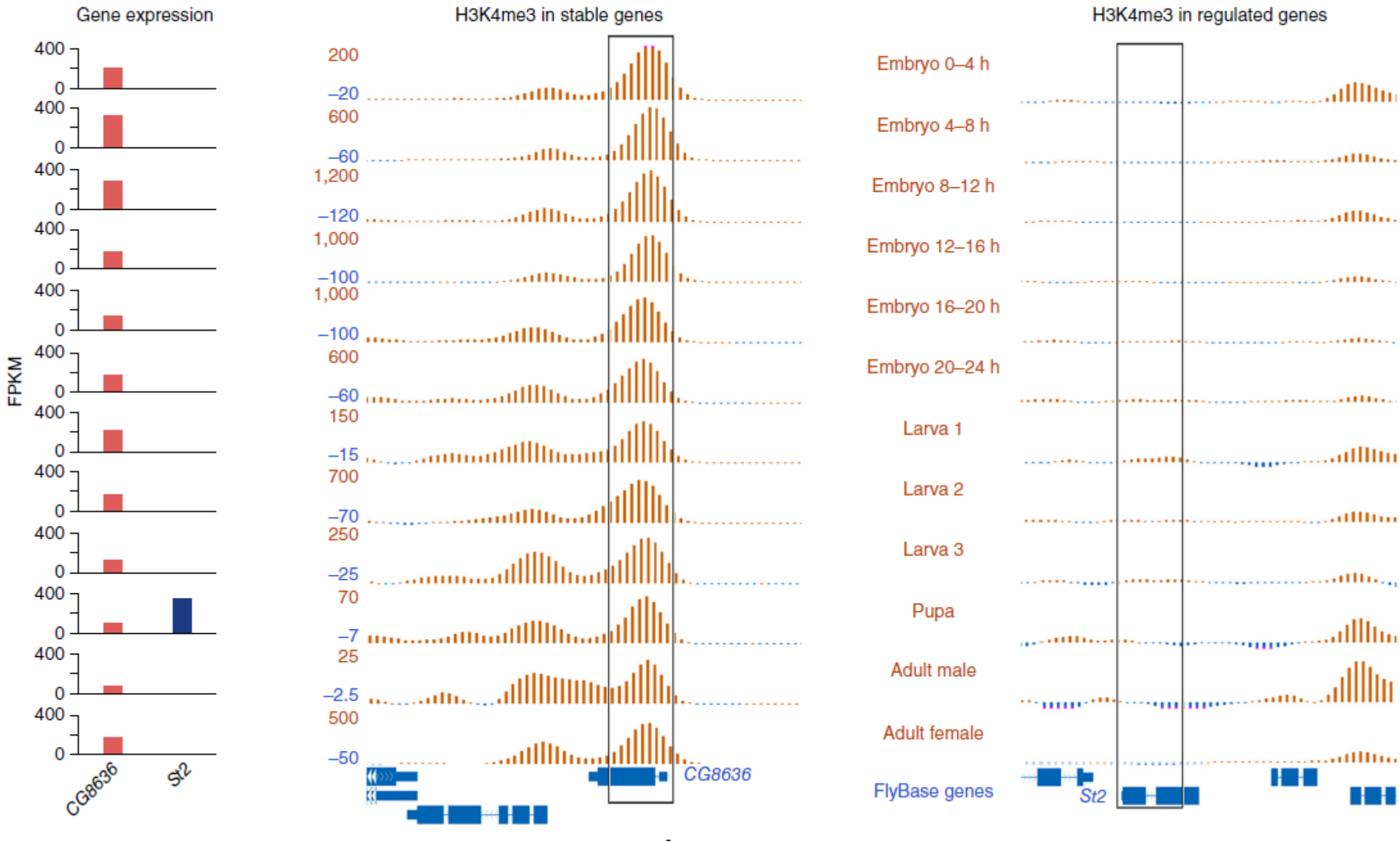


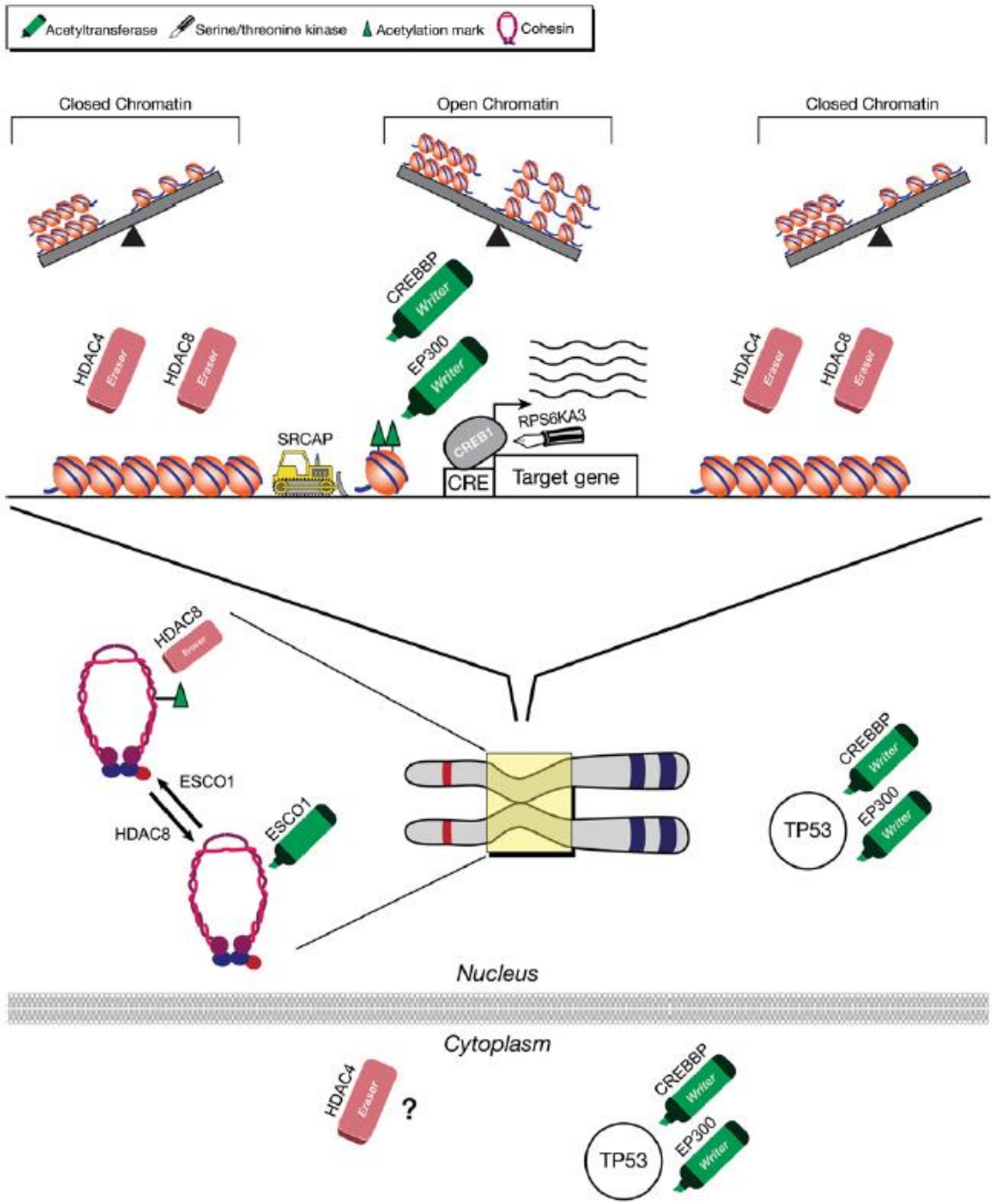
Válasz (7)

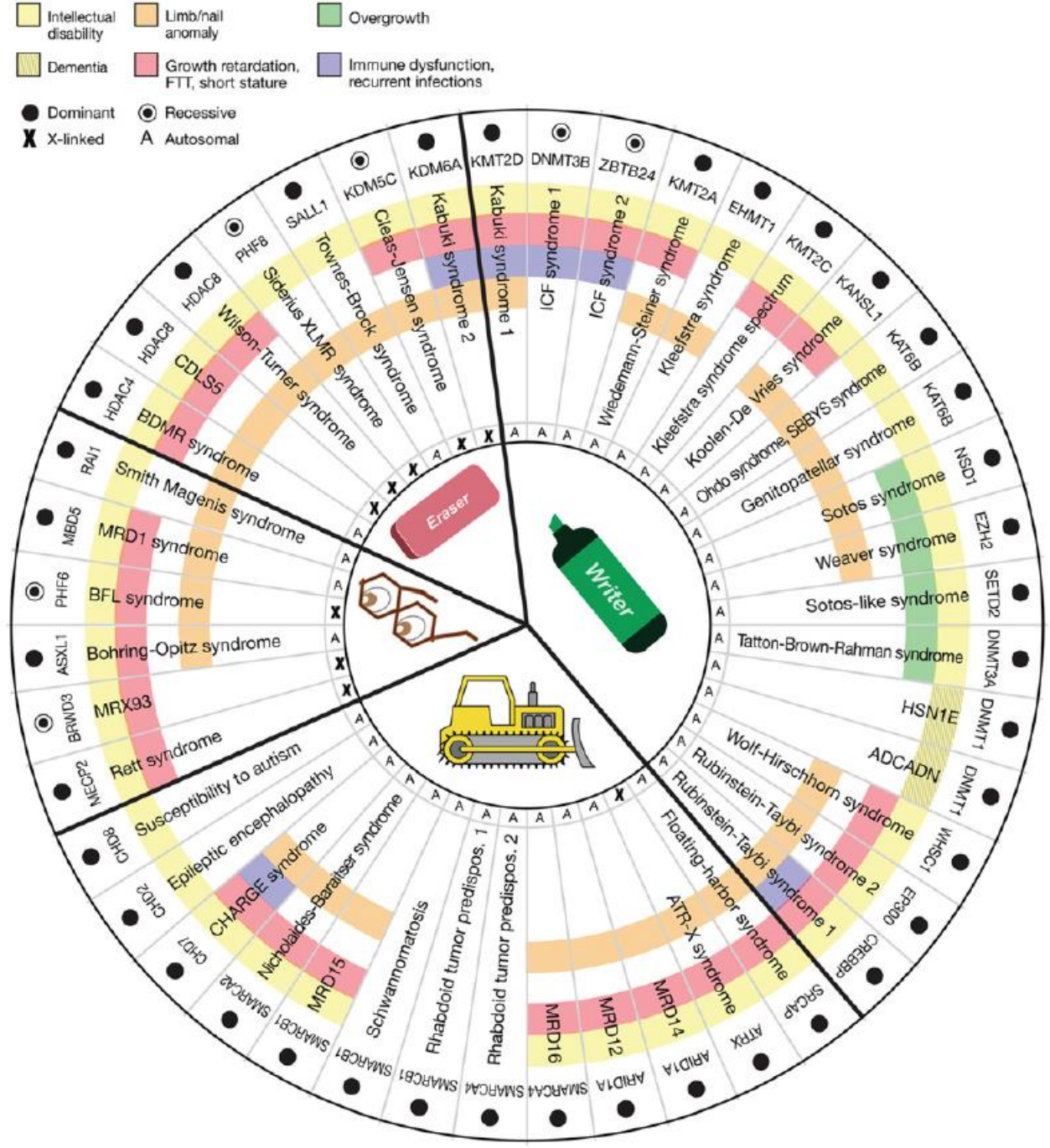

Chromosomal rearrangements
e.g. inv(16)
miRNA deregulation
• miR-125b
• miR-222-221 (predicted)
• miR-27 (predicted)
• ...
Haploinsufficiency
Point mutations
Chromosomal rearrangements
e.g. t(8;21)
miRNA deregulation
• miR-17
• miR-27
• ...
CBFB
RUNX1
Regulatory regions
RUNX1-target miRNAs
miRNA deregulation
• miR-223
• miR-222-221
• miR-17-20a-106a cluster
• miR-24-23-27 cluster
• miR-181
• ...
miRNA targets
• NF1A
• KIT
• ...



The **chromatin marks are irrelevant** for regulating genes that are expressed in a punctual manner during development. The results of this study contrast sharply with the generally accepted view of the key roles that these epigenetic marks play in regulating gene expression


Gene expression
FPKM
400
0
CG8636
St2
H3K4me3 in stable genes
200
–20
600
–60
1,200
–120
1,000
–100
1,000
–100
600
–60
150
–15
700
–70
250
–25
70
–7
25
–2.5
500
–50
CG8636
H3K4me3 in regulated genes
Embryo 0–4 h
Embryo 4–8 h
Embryo 8–12 h
Embryo 12–16 h
Embryo 16–20 h
Embryo 20–24 h
Larva 1
Larva 2
Larva 3
Pupa
Adult male
Adult female
FlyBase genes
St2


Acetyltransferase
Serine/threonine kinase
Acetylation mark
Cohesin
Closed Chromatin
Open Chromatin
Closed Chromatin
CREBBP
Writer
EP300
Writer
HDAC4
Eraser
HDAC8
Eraser
SRCAP
CREB1
RPS6KA3
CRE
Target gene
HDAC8
Eraser
ESCO1
HDAC8
ESCO1
CREBBP
Writer
TP53
EP300
Writer
Nucleus
Cytoplasm
HDAC4
Eraser
?
CREBBP
Writer
TP53
EP300
Writer


Intellectual disability
Limb/nail anomaly
Overgrowth
Dementia
Growth retardation, FTT, short stature
Immune dysfunction, recurrent infections
Dominant
Recessive
X-linked
A Autosomal
Eraser
Writer
Kabuki syndrome 1
ICF syndrome 1
ICF syndrome 2
Wiedemann-Steiner syndrome
Kleefstra syndrome
Kleefstra syndrome spectrum
Koolen-De Vries syndrome
Ohdo syndrome, SBBYS syndrome
Genitopatellar syndrome
Sotos syndrome
Weaver syndrome
Sotos-like syndrome
Tatton-Brown-Rahman syndrome
HSN1E
ADCADN
Wolf-Hirschhorn syndrome
Rubinstein-Taybi syndrome 2
Rubinstein-Taybi syndrome 1
Floating-harbor syndrome
ATR-X syndrome
MRD14
MRD12
MRD16
Rhabdoid tumor predispos. 2
Rhabdoid tumor predispos. 1
Schwannomatosis
MRD15
Nicolaides-Baraitser syndrome
CHARGE syndrome
Epileptic encephalopathy
Susceptibility to autism
Rett syndrome
MRX93
Bohring-Opitz syndrome
BFL syndrome
MRD1 syndrome
Smith Magenis syndrome
BDMR syndrome
CDLS5
Wilson-Turner syndrome
Siderius XLMR syndrome
Townes-Brock syndrome
Cleas-Jensen syndrome
Kabuki syndrome 2
KMT2D
DNMT3B
ZBTB24
KMT2A
EHMT1
KMT2C
KANSL1
KAT6B
KAT6B
NSD1
EZH2
SETD2
DNMT3A
DNMT1
DNMT1
WHSC1
EP300
CREBBP
SRCAP
ATRX
ARID1A
ARID1A
SMARCA4
SMARCA4
SMARCB1
SMARCB1
SMARCA2
CHD7
CHD2
CHD8
MECP2
BRWD3
ASXL1
PHF6
MBD5
RAI1
HDAC4
HDAC8
HDAC8
PHF8
SALL1
KDM5C
KDM6A

a PcG and TrxG group proteins

PRC1

Subunit	Molecular function
Pc (CBX)	Chromodomain binds H3K27me3
Psc (BMI1 and MEL18)	Binds DNA and compacts chromatin
Ph (PH)	SAM domain self-associates
Sce (RING1A and RING1B)	Ubiquitylates H2AK118 (K119 in vertebrates), compacts chromatin

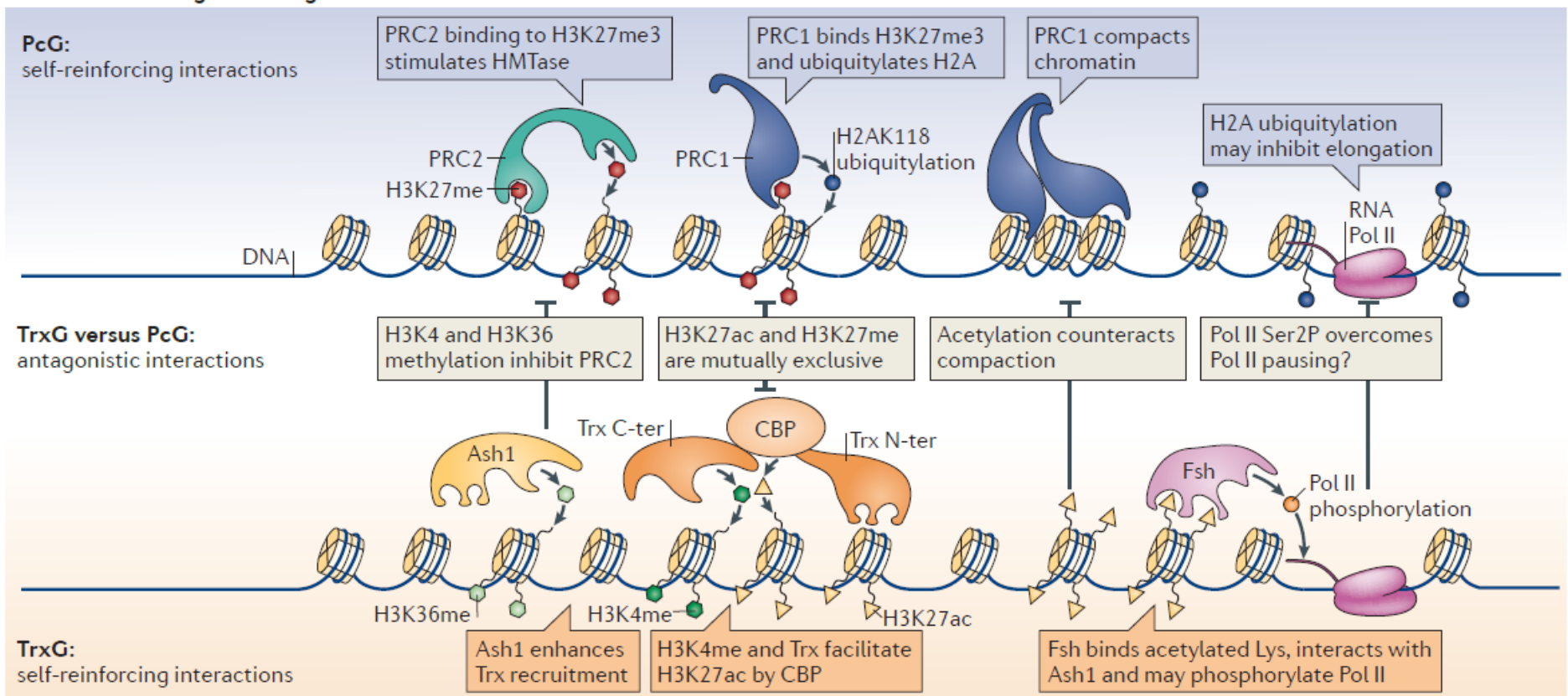
PRC2

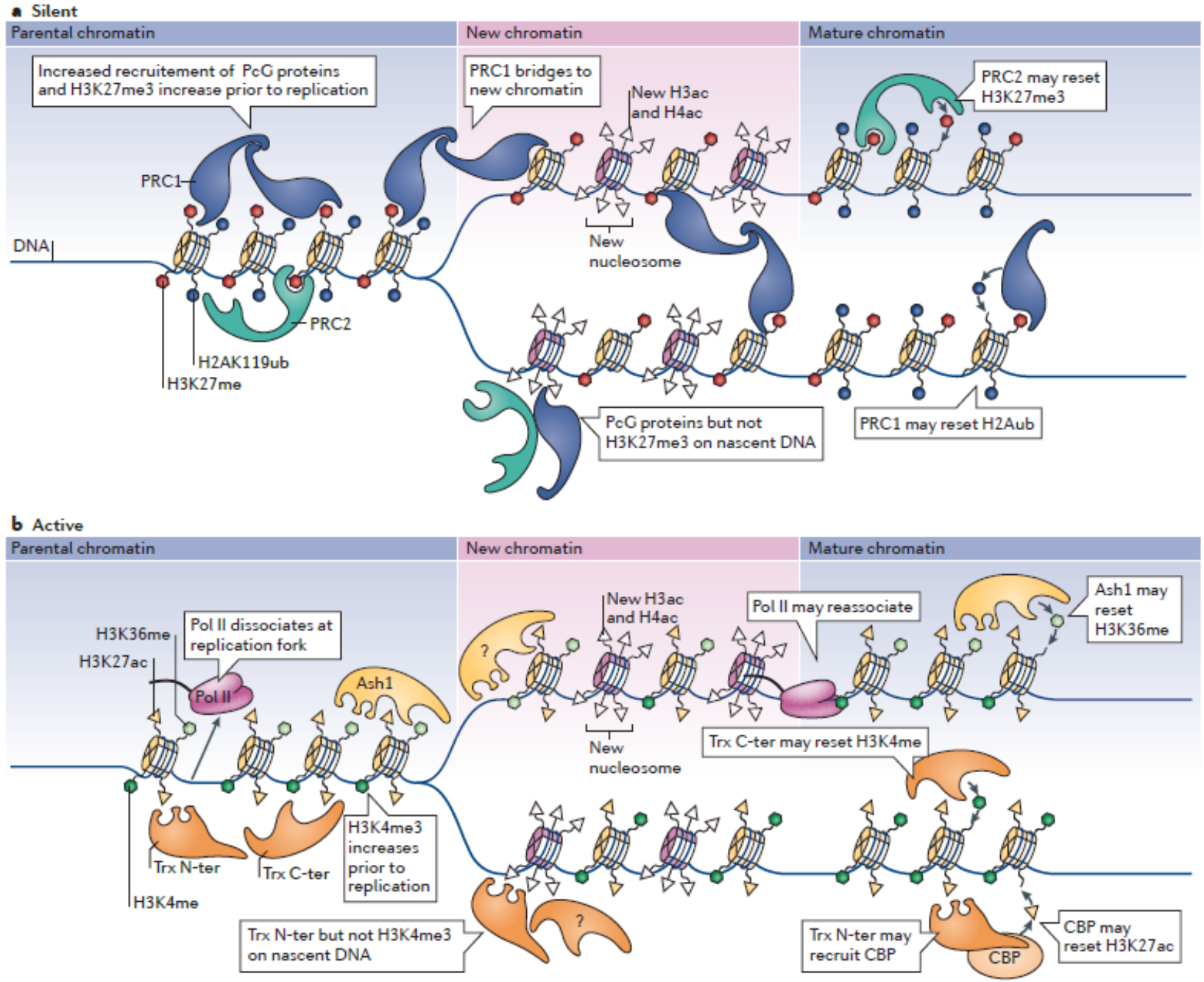
Subunit	Molecular function
E(z) (EZH2)	SET domain methylates H3K27
Su(z)12 (SUZ12)	Enhances E(z) HMTase activity
Esc (EED)	Enhances E(z) HMTase activity and binds H3K27me3
Nurf55 (RbAp46 and RbAp48)	Binds histones and SU(z)12

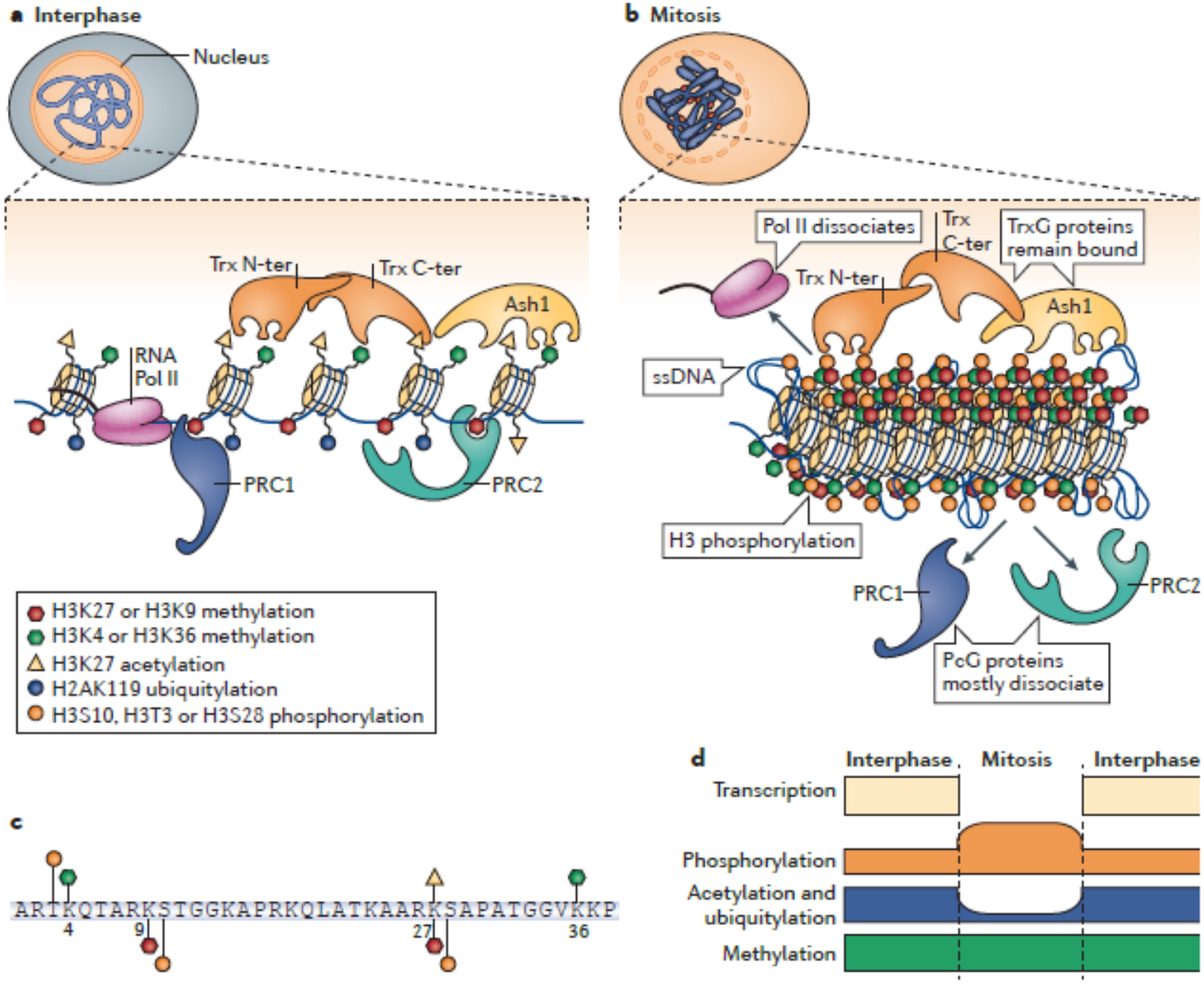
TrxG

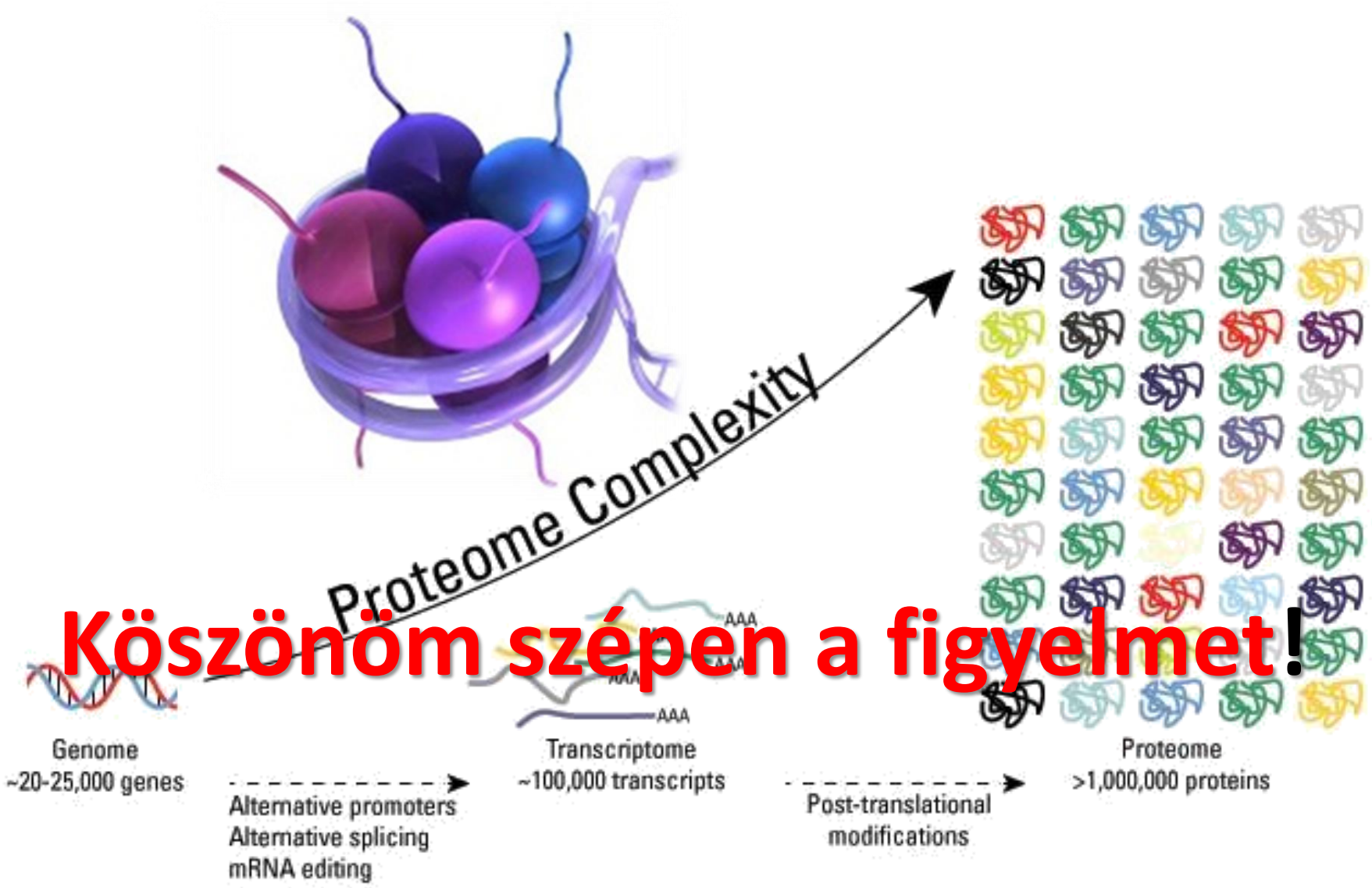
Subunit	Molecular function
Ash1 (ASH1L)	SET domain methylates H3K36
Trx C-ter (MLL C-ter)	SET domain methylates H3K4
Trx N-ter (MLL N-ter)	Required for H3K27 acetylation by CBP
Fsh (BRD4)	Bromodomains bind acetylated Lys BRD4 phosphorylates Pol II CTD at Ser2

b Self-reinforcing and antagonstic interactions




a Silent
Parental chromatin
New chromatin
Mature chromatin
Increased recruitement of PcG proteins and H3K27me3 increase prior to replication
PRC1 bridges to new chromatin
New H3ac and H4ac
PRC2 may reset H3K27me3
PRC1
DNA
New nucleosome
PRC2
H2AK119ub
H3K27me
PcG proteins but not H3K27me3 on nascent DNA
PRC1 may reset H2Aub
b Active
Parental chromatin
New chromatin
Mature chromatin
H3K36me
H3K27ac
Pol II dissociates at replication fork
Pol II
Ash1
New H3ac and H4ac
Pol II may reassociate
Ash1 may reset H3K36me
?
New nucleosome
Trx C-ter may reset H3K4me
Trx N-ter
Trx C-ter
H3K4me3 increases prior to replication
H3K4me
Trx N-ter but not H3K4me3 on nascent DNA
?
Trx N-ter may recruit CBP
CBP
CBP may reset H3K27ac


a Interphase
Nucleus
Trx N-ter
Trx C-ter
Ash1
RNA
Pol II
PRC1
PRC2
H3K27 or H3K9 methylation
H3K4 or H3K36 methylation
H3K27 acetylation
H2AK119 ubiquitylation
H3S10, H3T3 or H3S28 phosphorylation
b Mitosis
Pol II dissociates
Trx
C-ter
TrxG proteins
remain bound
Trx N-ter
Ash1
ssDNA
H3 phosphorylation
PRC1
PRC2
PcG proteins
mostly dissociate
c
ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVKKP
4
9
27
36
d
Interphase
Mitosis
Interphase
Transcription
Phosphorylation
Acetylation and
ubiquitylation
Methylation



Köszönöm szépen a figyelmet!

DRARPAD