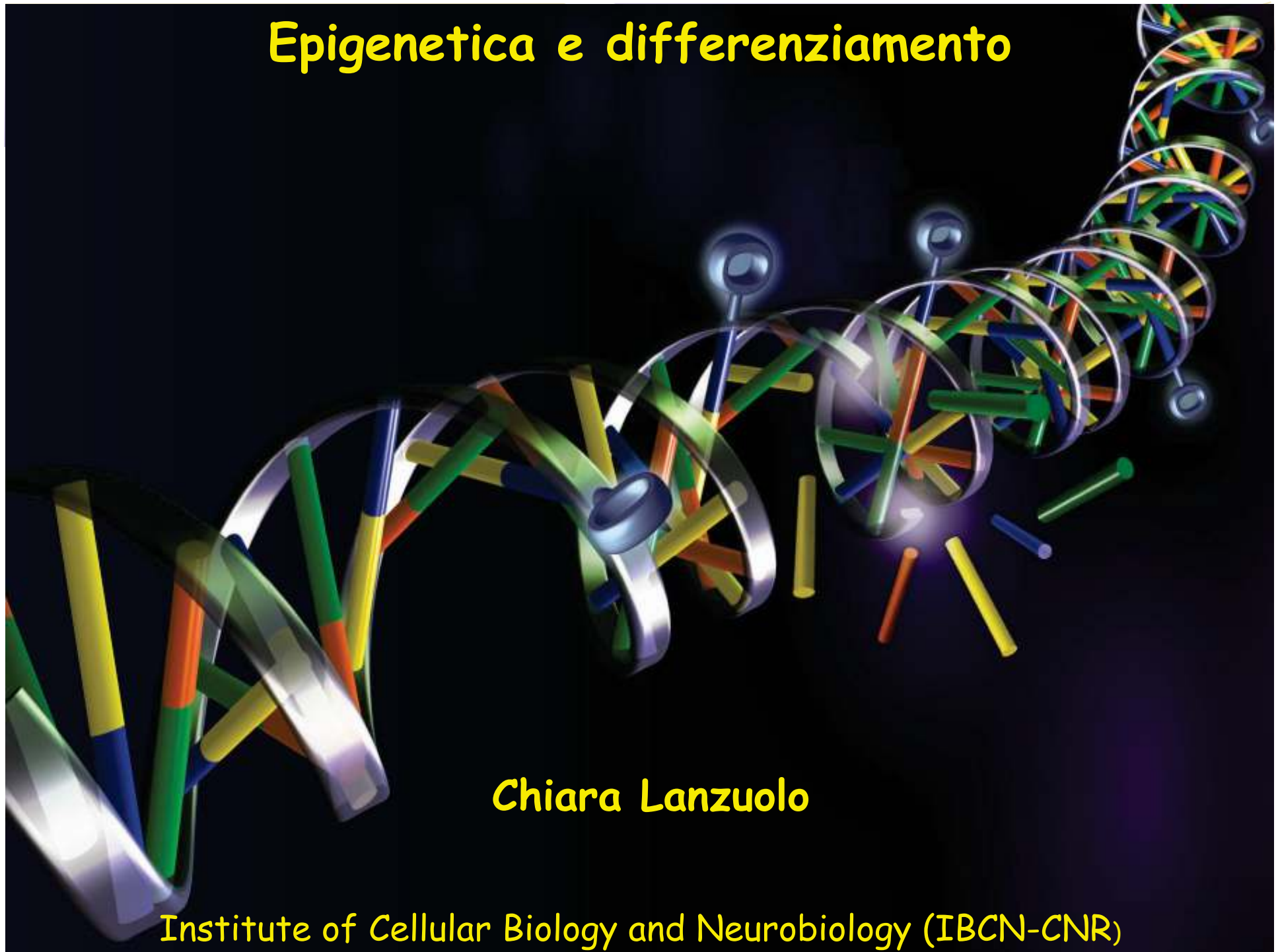


Epigenetica e differenziamento



Chiara Lanzuolo

Institute of Cellular Biology and Neurobiology (IBCN-CNR)

Epigenetica

Conrad Waddington, 1942: Epigenetica: epigenesi + genetica



Conrad Waddington
Nature Reviews | Genetics

“The branch of Biology which studies the causal interactions genes and their products, bringing the phenotype into being”

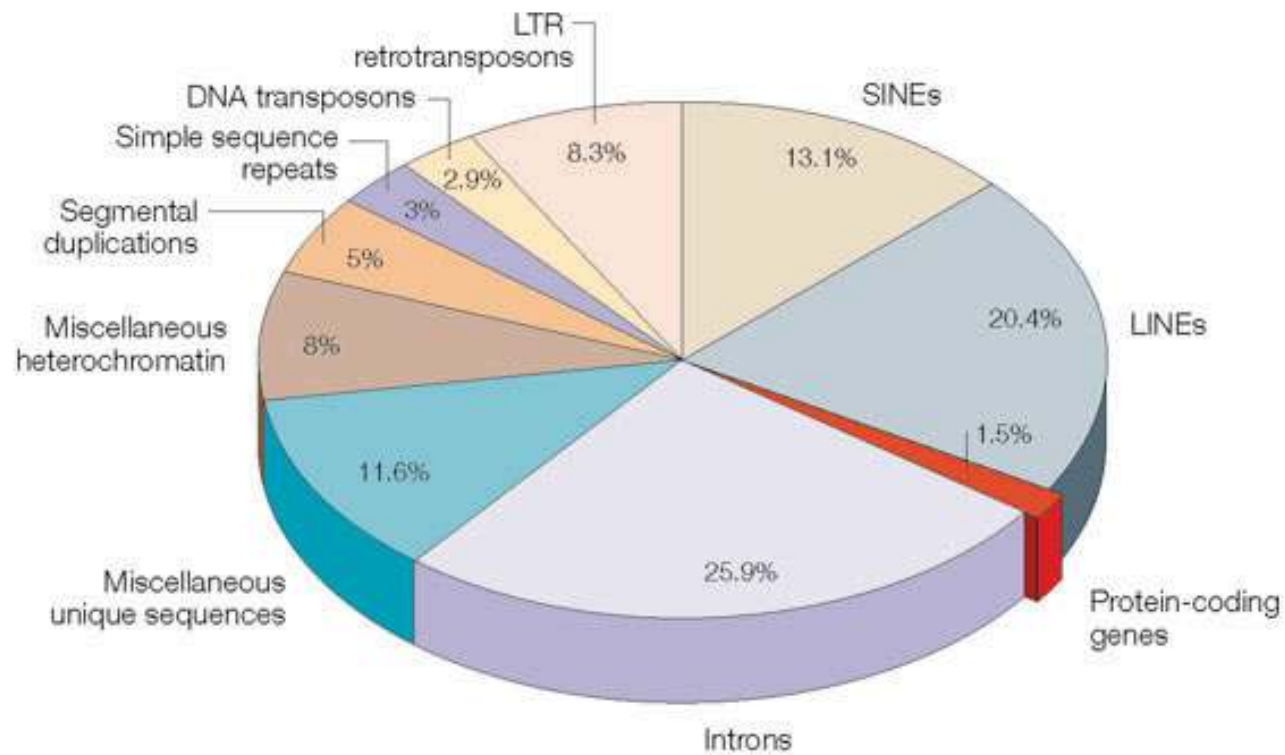
Il codice genetico definisce l'organismo



Pur avendo lo stesso DNA gli individui possono sembrare molto diversi



Il genoma umano è formato al 98% da sequenze non codificanti

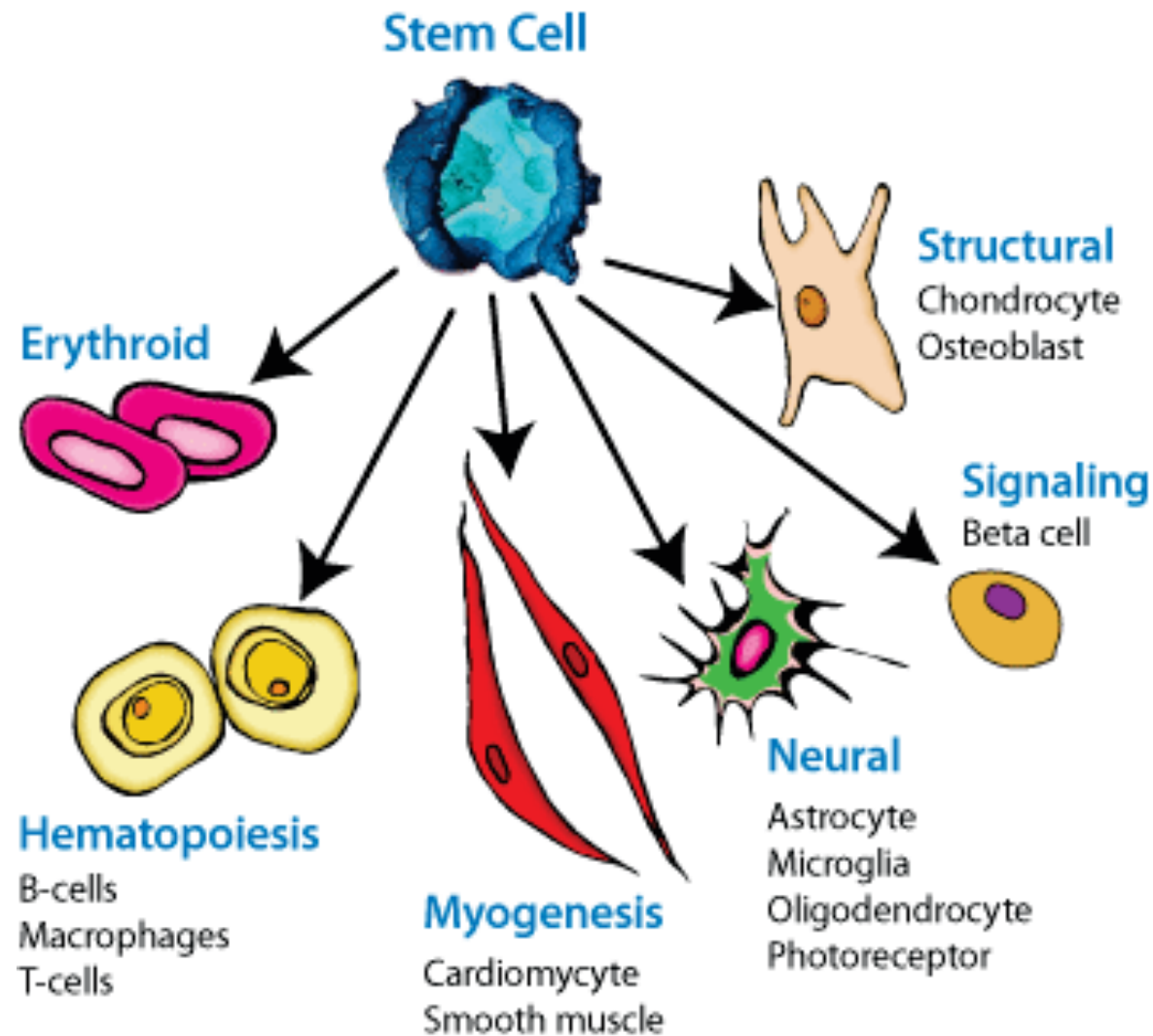


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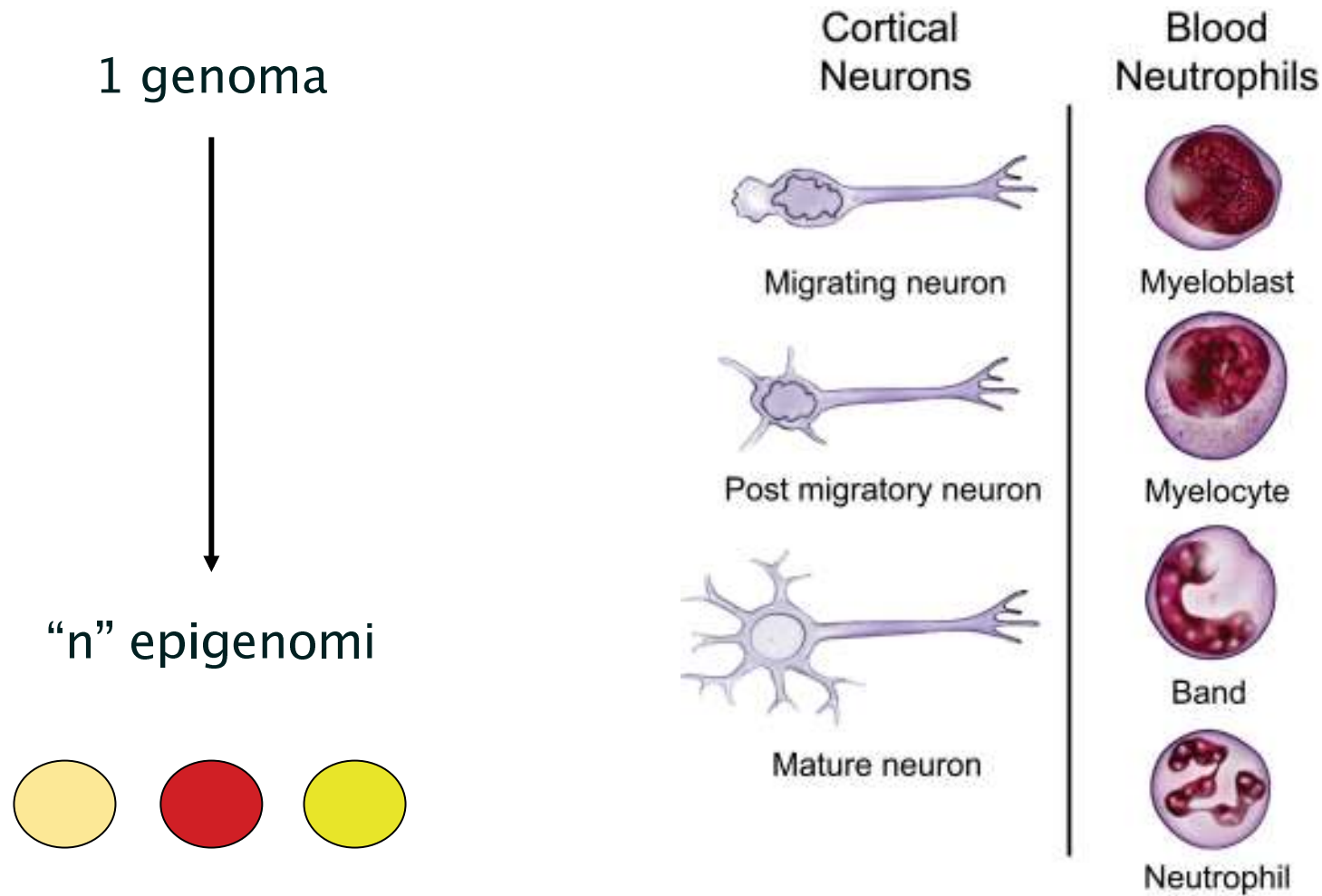
Clonare un genoma non è sufficiente per avere un fenotipo identico



*Tutte le cellule di un organismo sono uguali perché hanno lo stesso genoma
Tuttavia, differiscono l'una dall'altra perché hanno un epigenoma diverso*



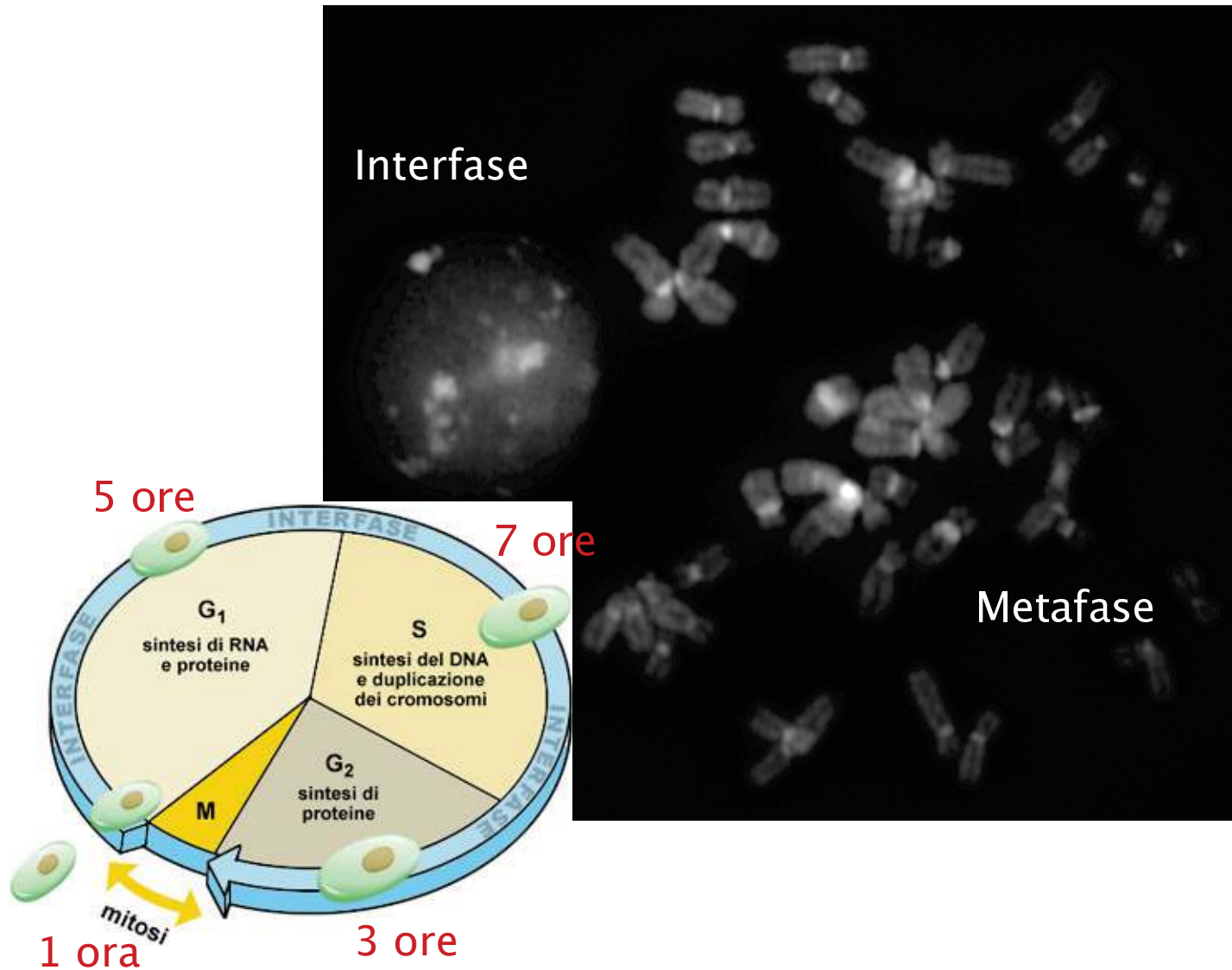
Durante il differenziamento le cellule acquisiscono fenotipi e funzioni diverse mediante la determinazione di programmi trascrizionali specifici



I meccanismi epigenetici fissano nel tempo e nello spazio i programmi trascrizionali

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Organizzazione spaziale del genoma nel tempo

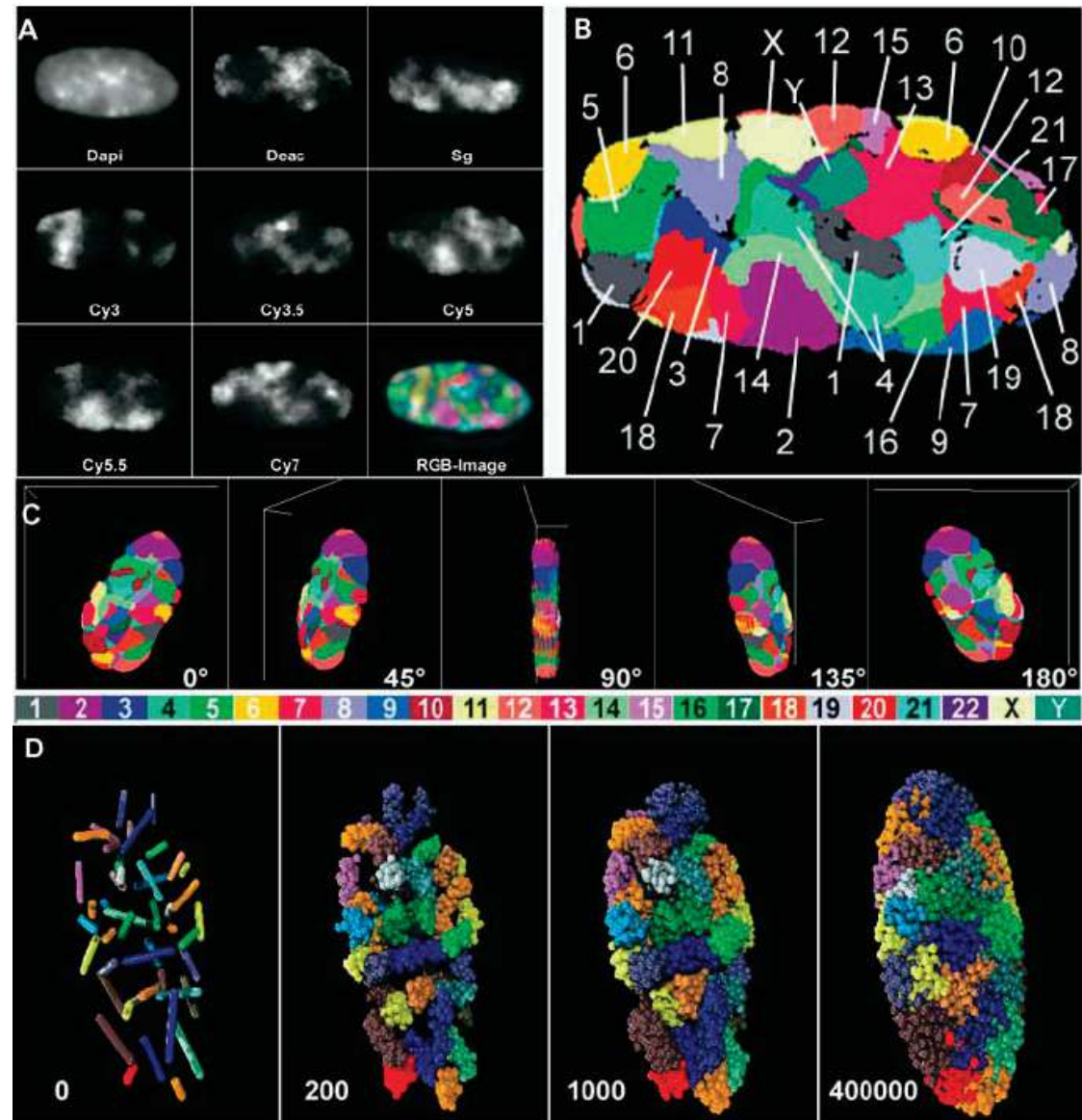


Organizzazione spaziale del genoma in interfase

*Topologia nucleare interfase
ed architettura genomica*

*I cromosomi occupano sempre
lo stesso spazio di un nucleo.*

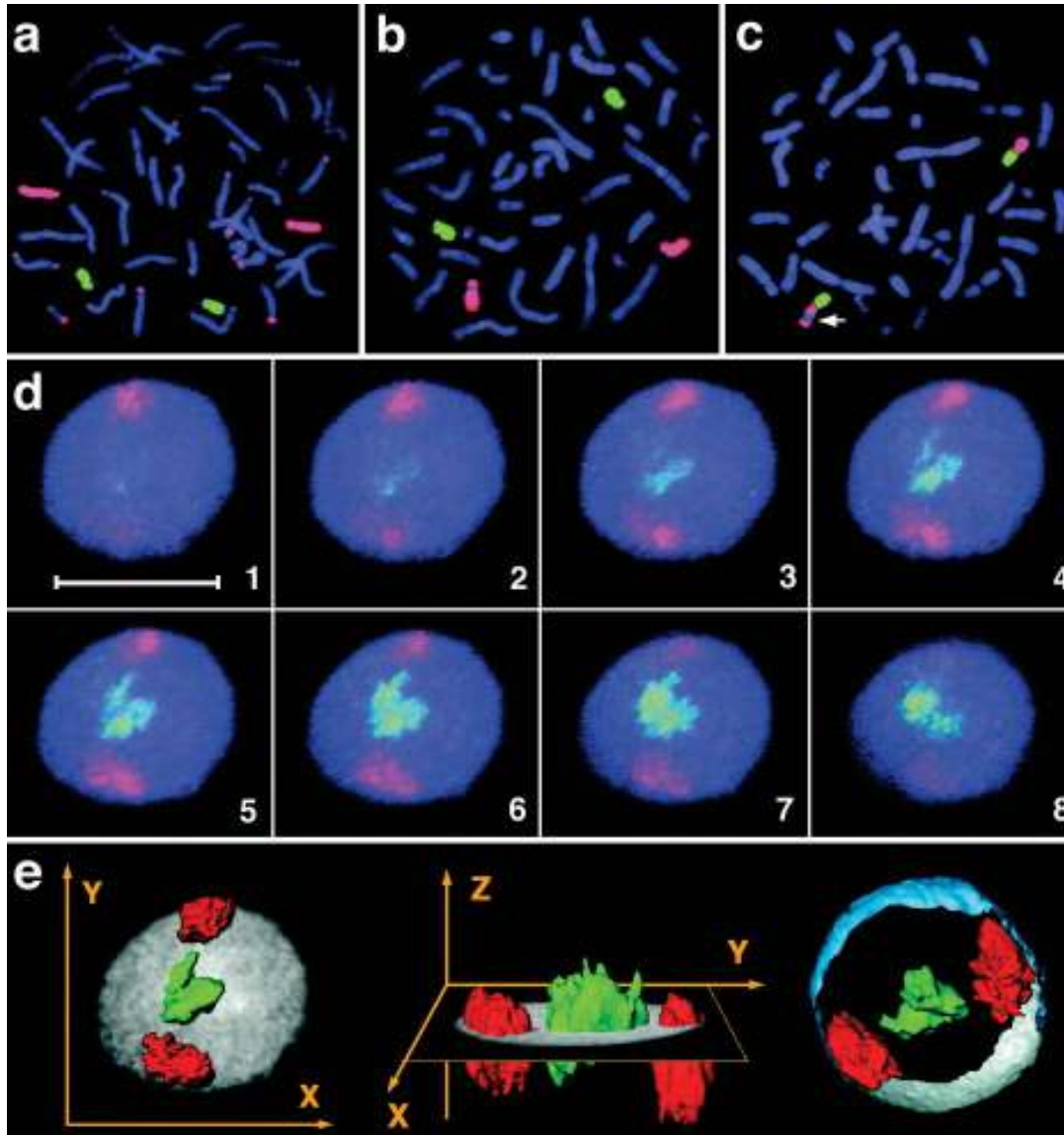
*I territori cromosomici sono
conservati nell'evoluzione*



(Bolzer. et al., PLoS Biol. 2005)

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Organizzazione spaziale del genoma in interfase



Cromosomi con un alto numero di geni attivi sono posizionati centralmente nel nucleo.

Cromosomi con pochi geni o repressi sono posizionati alla periferia nucleare.

(Tanabe. et al., PNAS 2002)

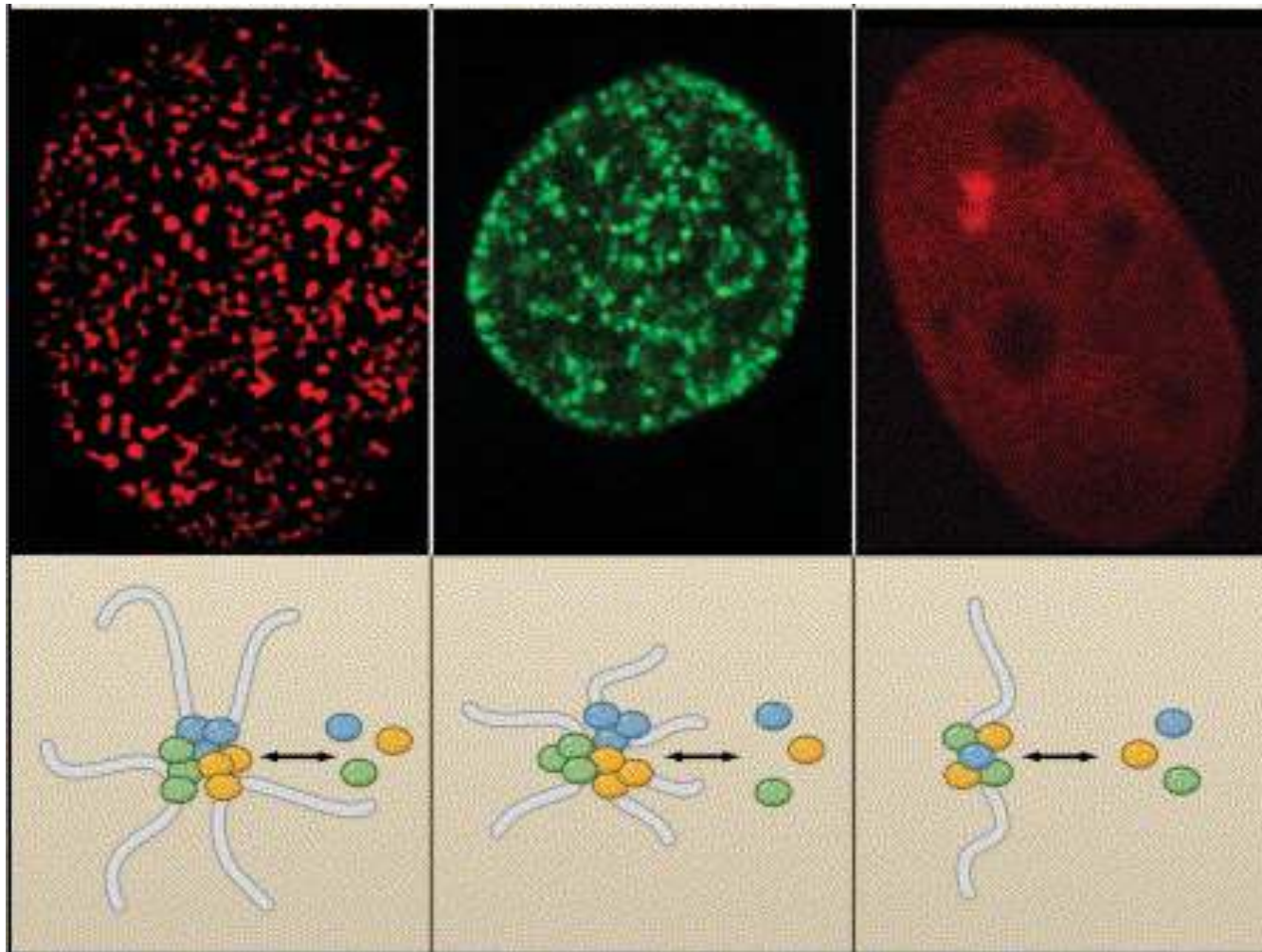
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Compartimentalizzazione dei processi nucleari

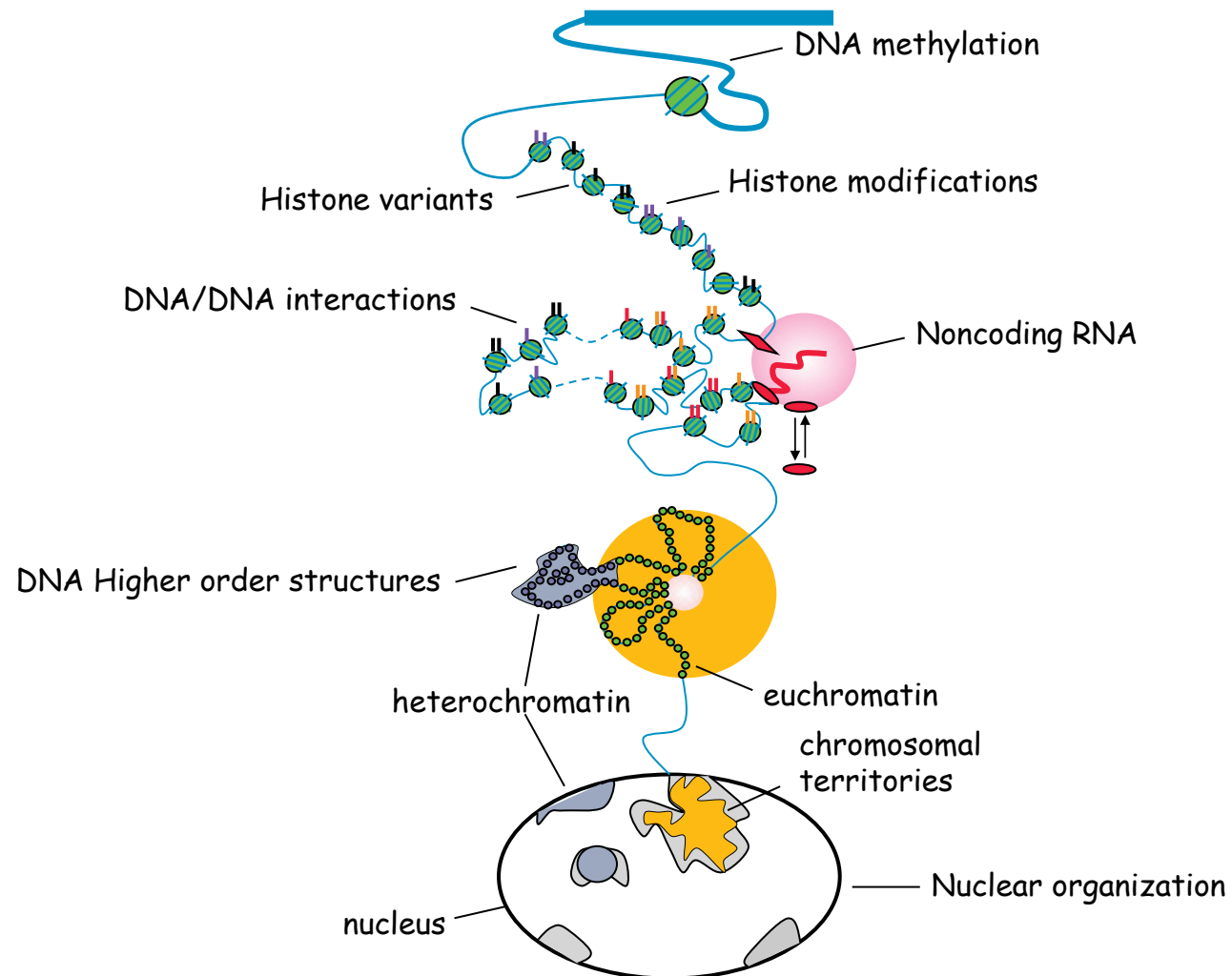
TRASCRIZIONE

REPLICAZIONE

RIPARO DEL DNA



I meccanismi epigenetici controllano la struttura del DNA agendo a diversi livelli



Il genoma viene metilato sulla citosina del dinucleotide CG



Addition of a methyl group to a cytosine within C-G dinucleotides which are frequently located in the regulatory regions of genes.

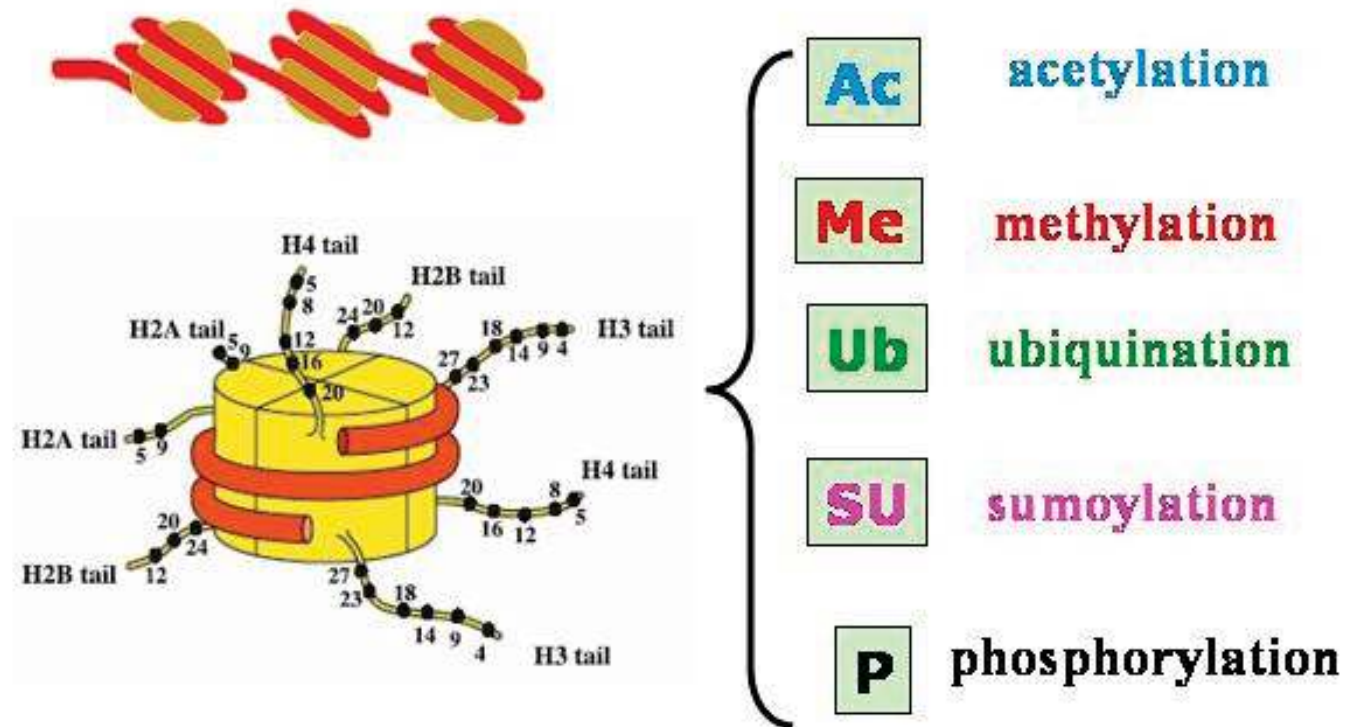
A mechanism for gene silencing:

- ⇒ preventing binding of regulatory factors
- ⇒ affecting chromatin status

○ Unmethylated
● Methylated

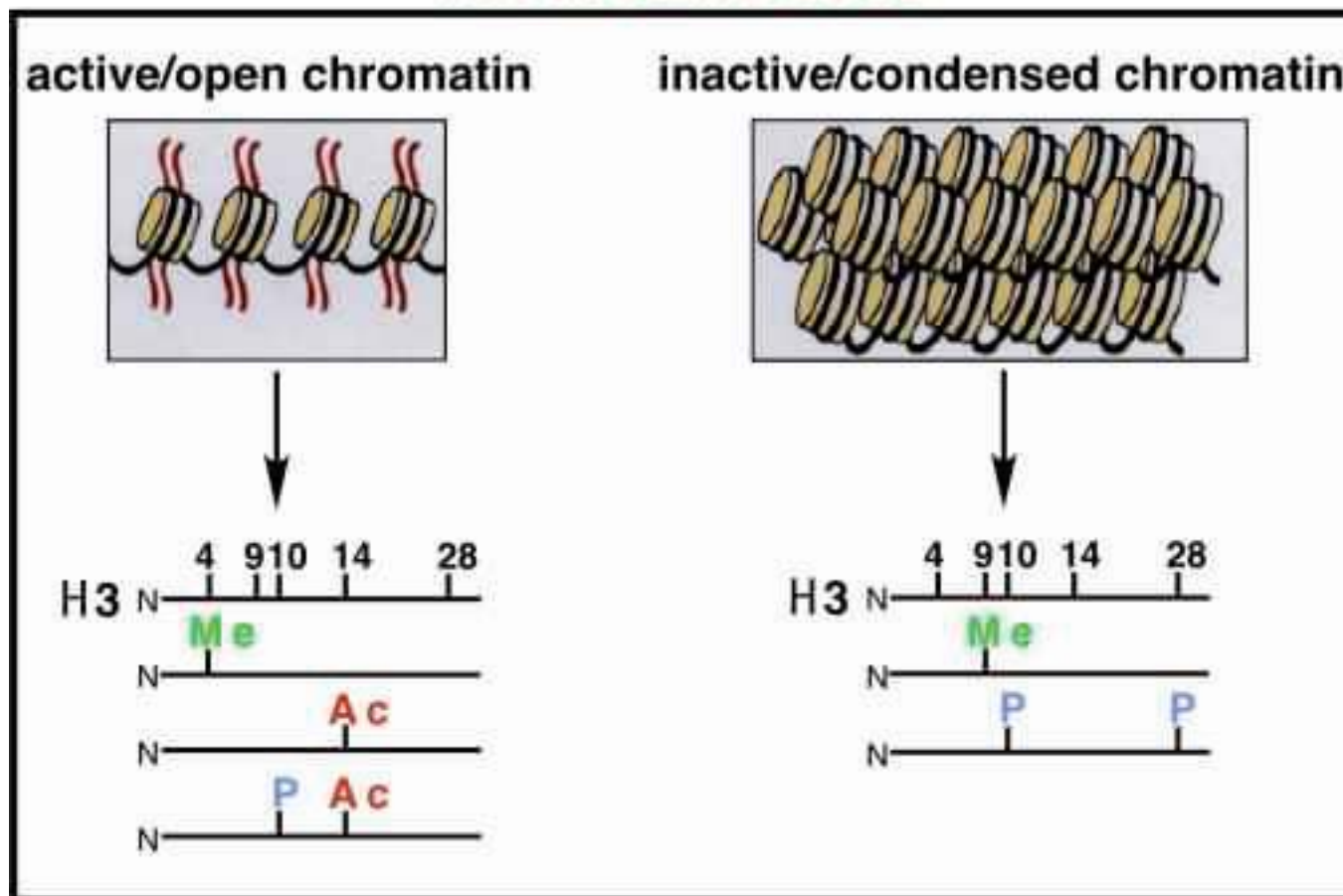


Le proteine istoniche possono essere modificate

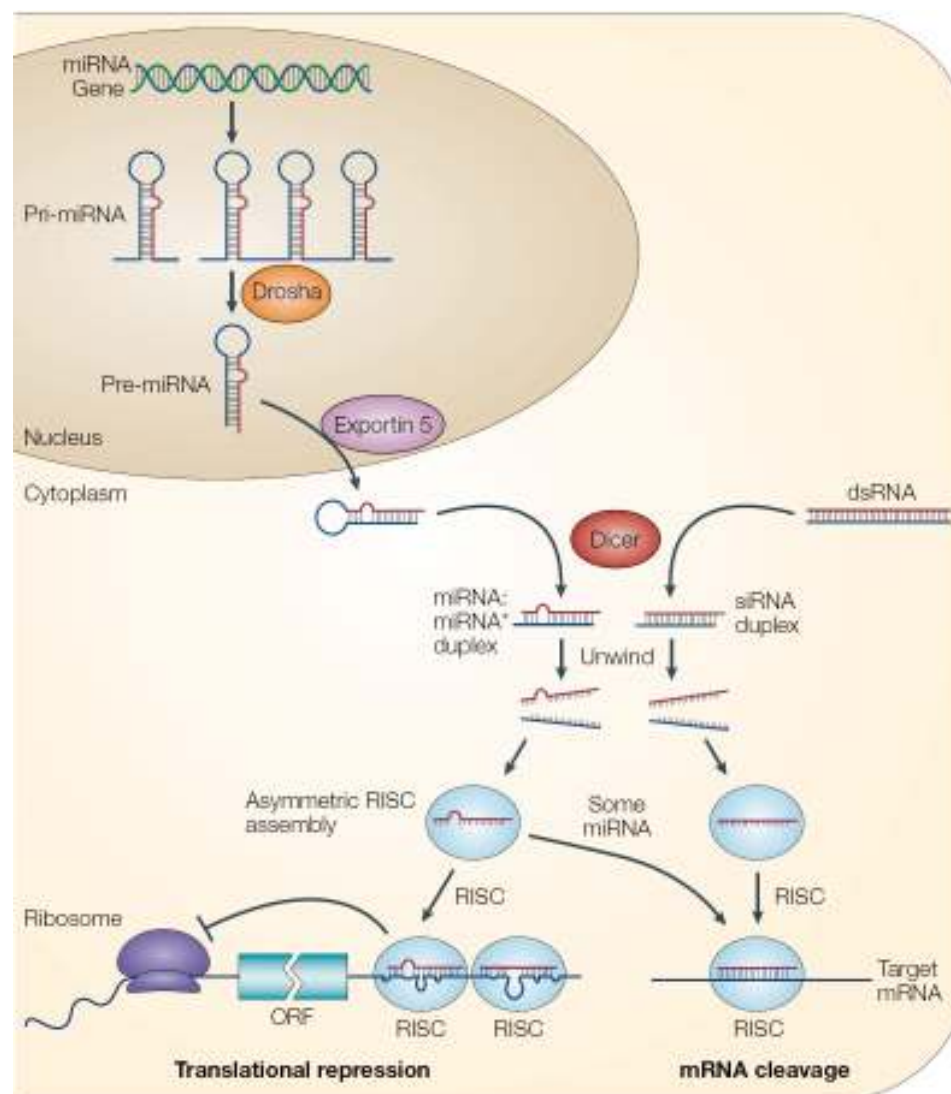


*Le modifiche istoniche formano un codice istonico che
riflette stati trascrizionali specifici*

The Histone Code

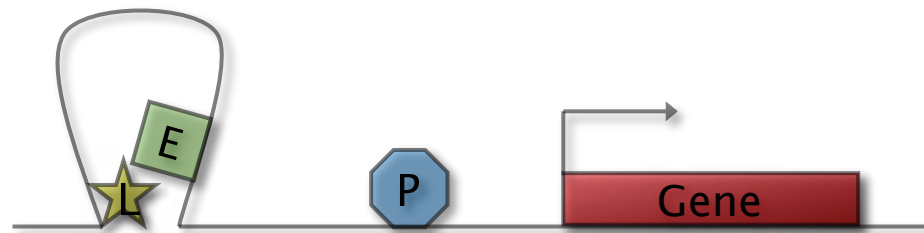


L'RNA non codificante regola i livelli di proteina

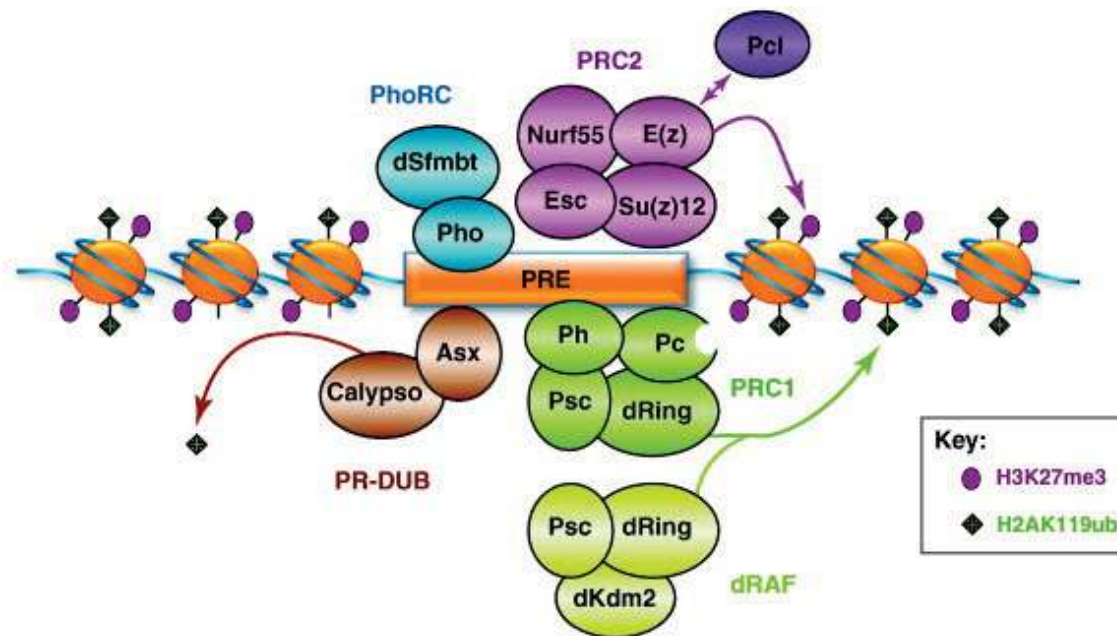


Sequenze contigue ma distanti possono avere effetto sulla regolazione di un gene

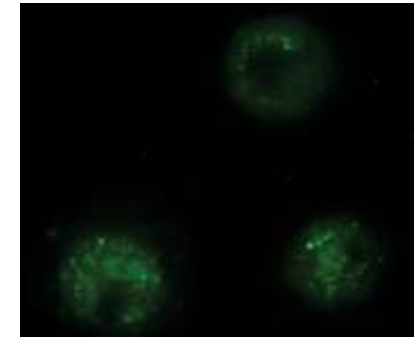
Looping model



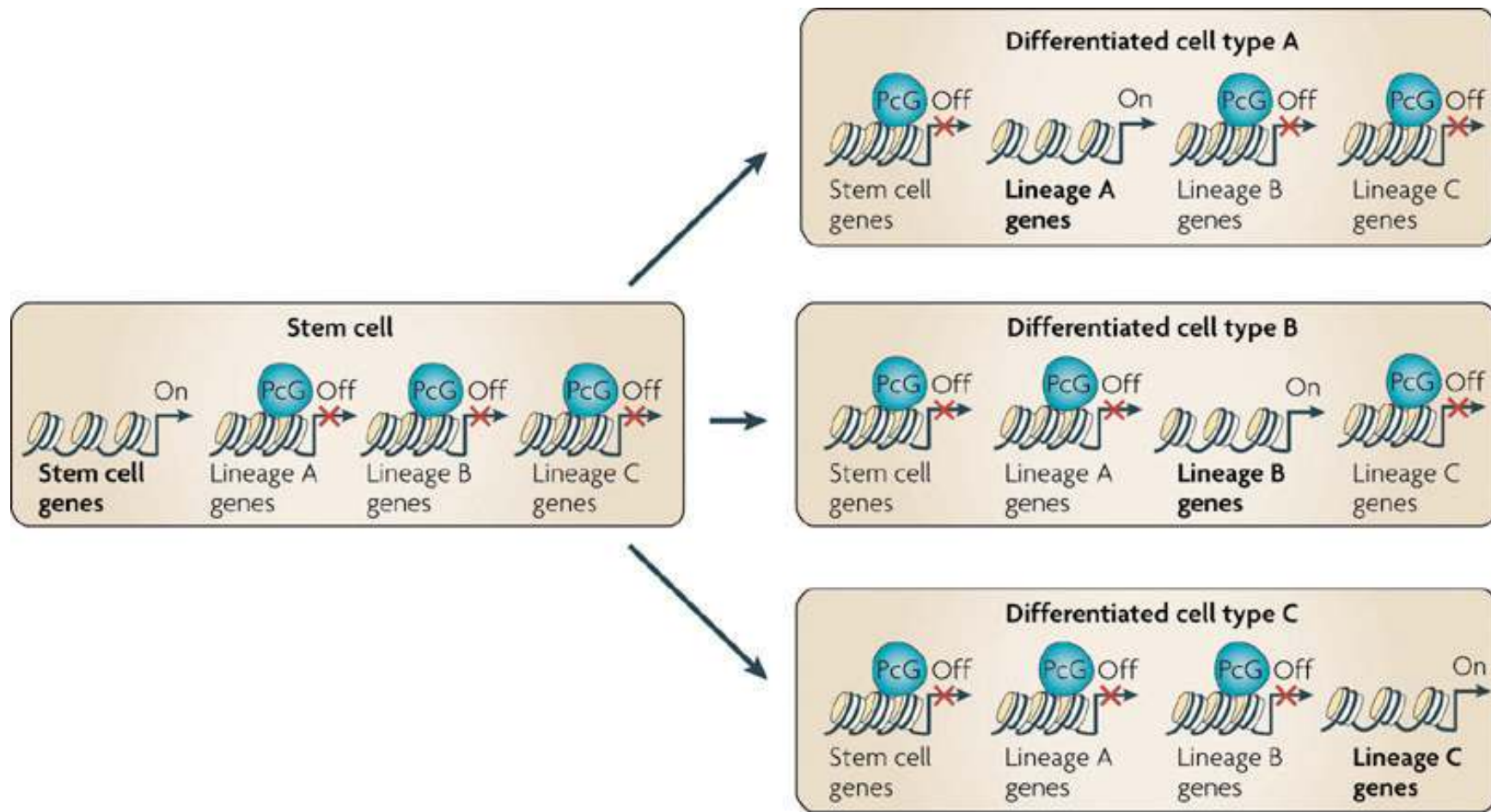
*Polycomb group genes evitano aberrazioni dei programmi trascrizionali
e proteggono l'identità cellulare*

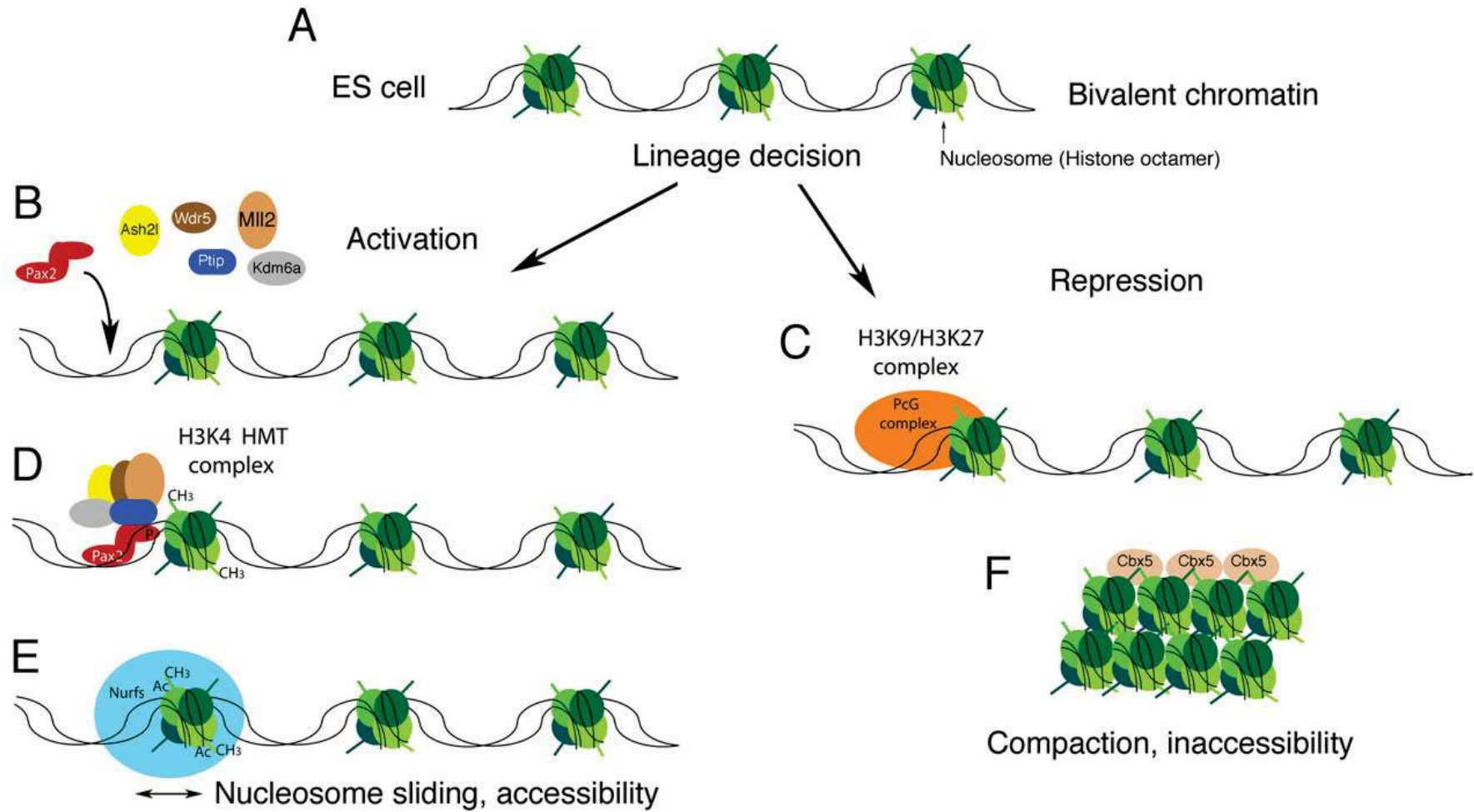


PcG bodies

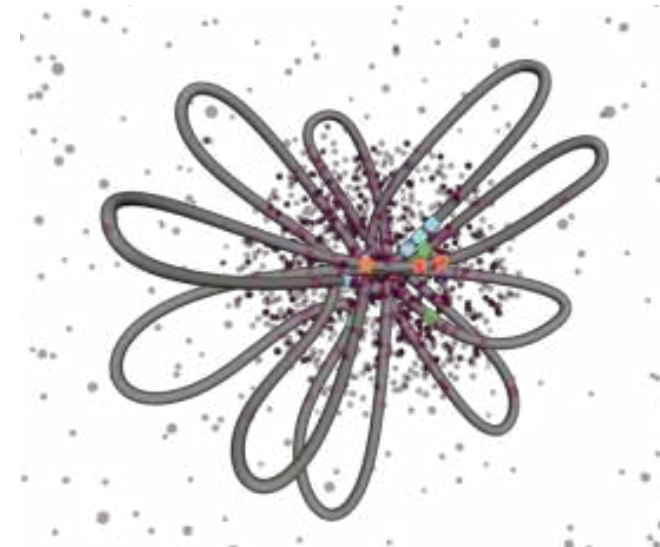
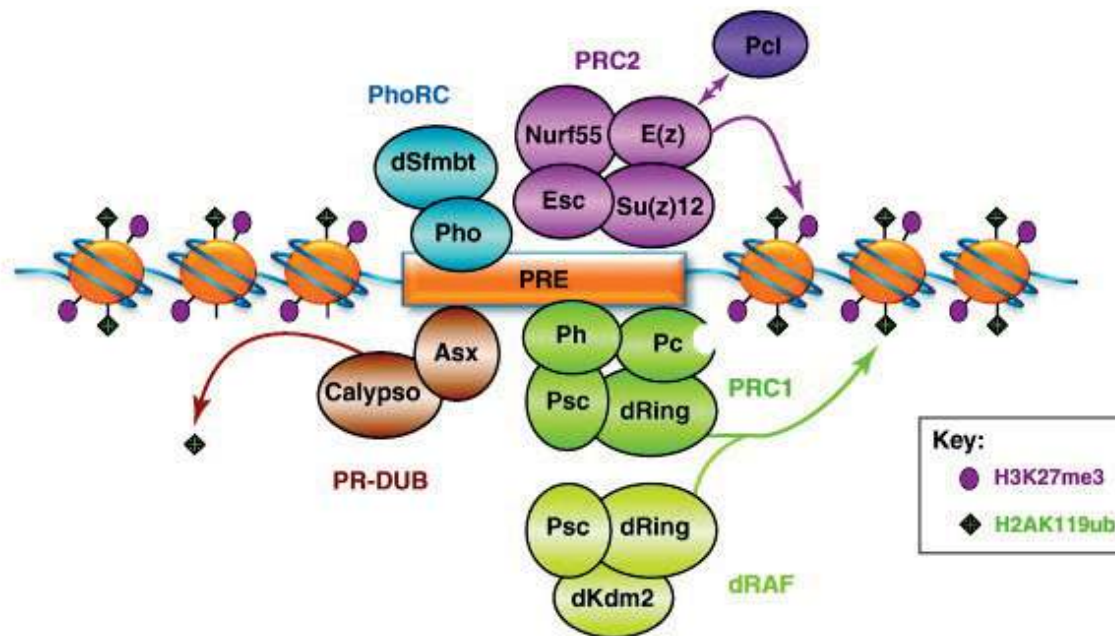


*Il rilascio delle proteine Polycomb dai geni specifici della linea cellulare
è necessario per un corretto differenziamento*



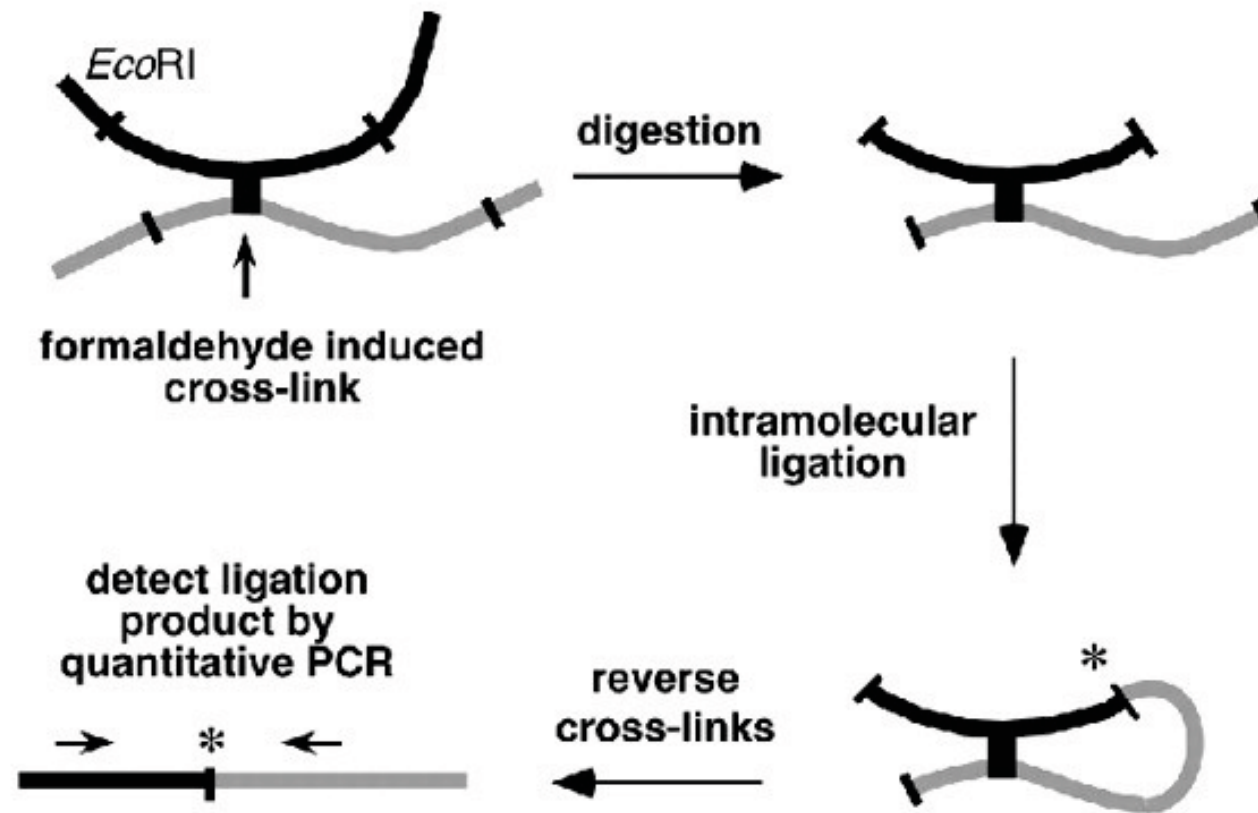


Le proteine Polycomb mediano la formazione di strutture tridimensionali a loop

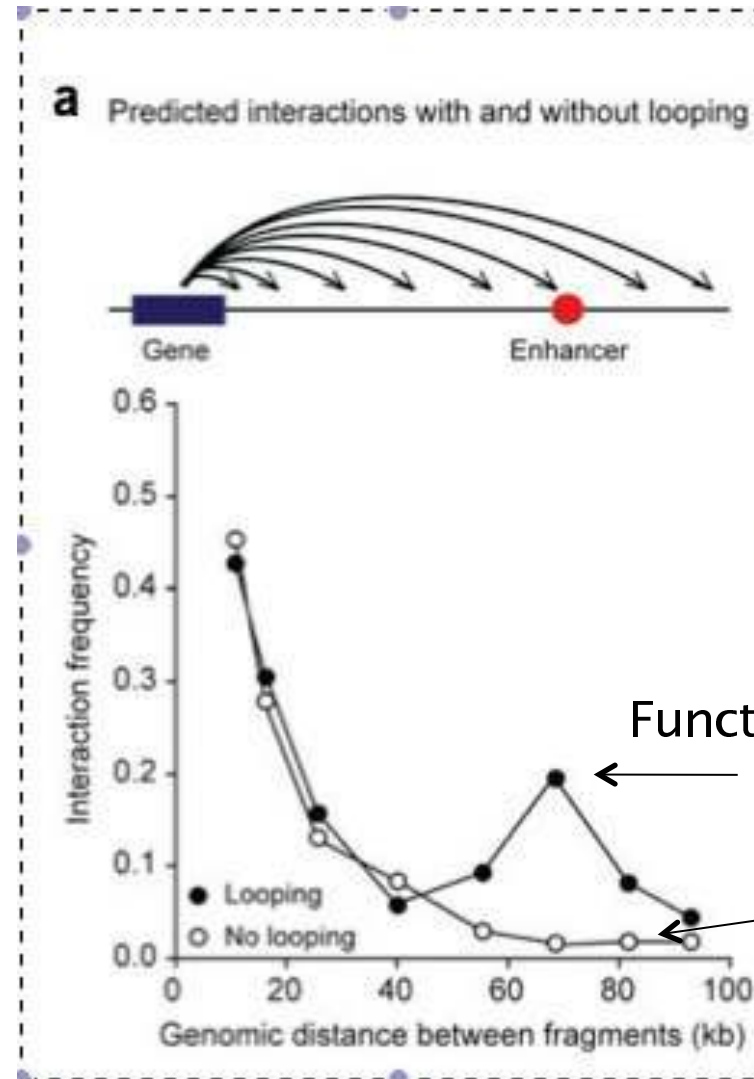


Lanzuolo C. et al., 2007, Nat Cell Biol.

Chromosome Conformation Capture (3C)



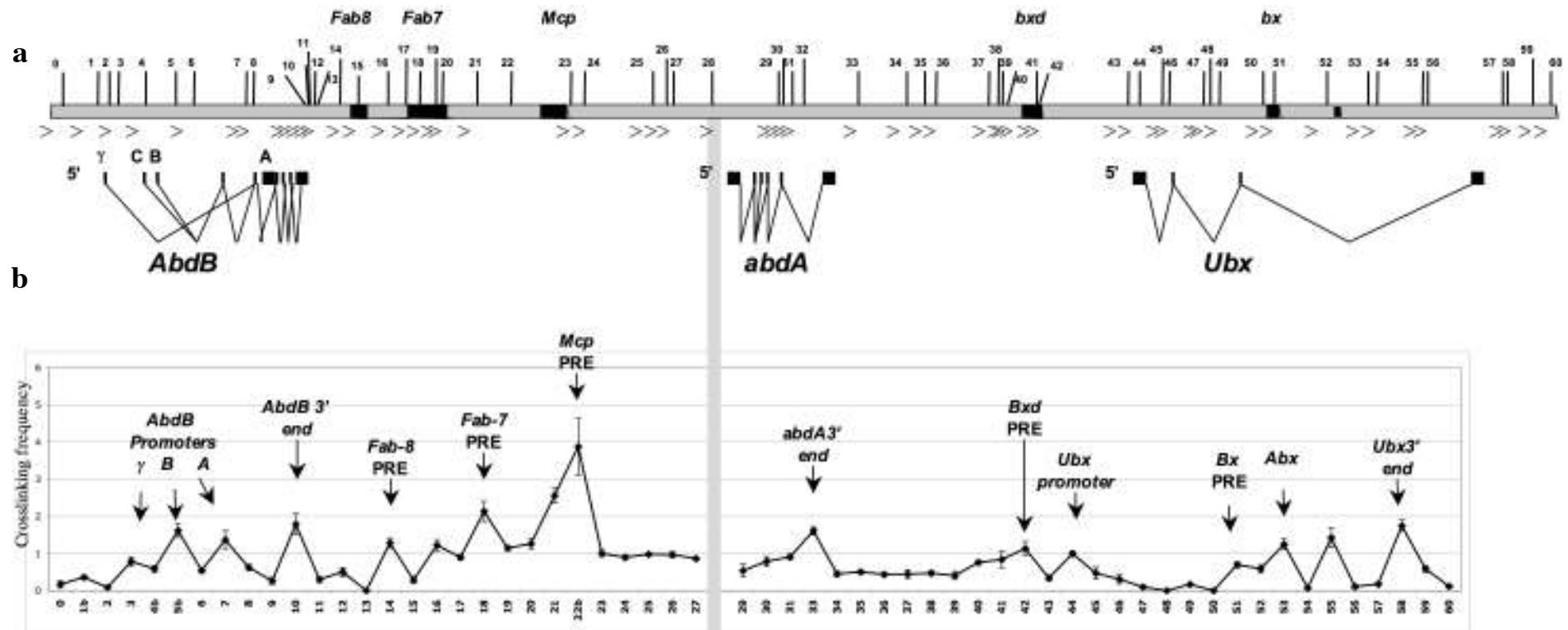
Dekker, J. et al., Science 2001



Functional interaction

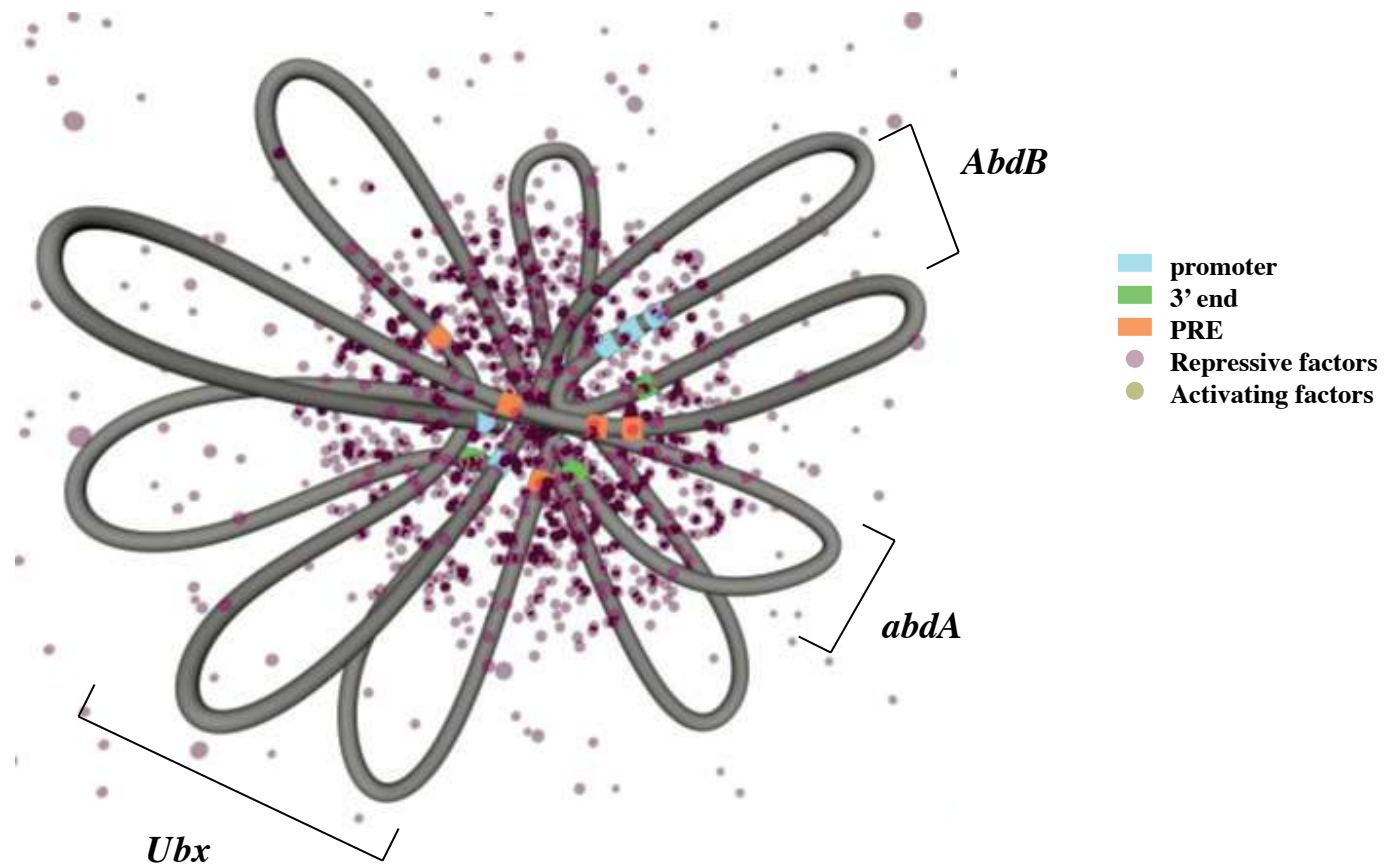
Random interaction

Nel Bithorax Complex le sequenze target di Polycomb interagiscono tra loro...

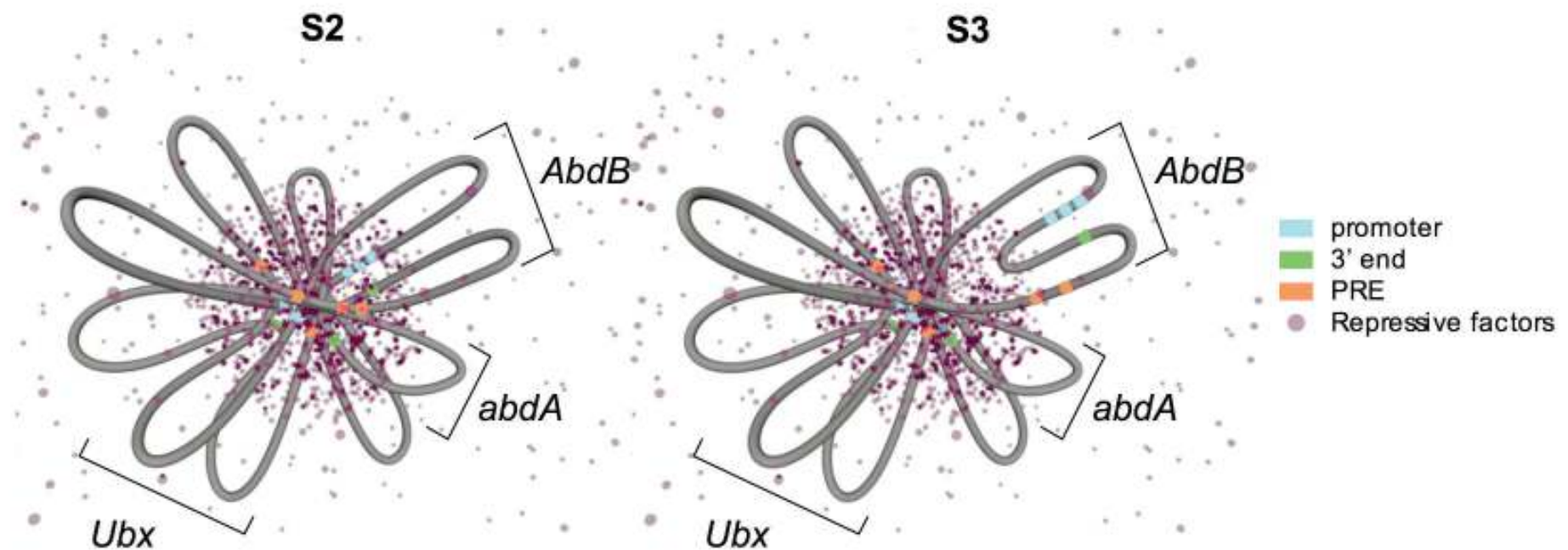


	<i>AbdB</i>	<i>abdA</i>	<i>Ubx</i>
S2	-	-	-

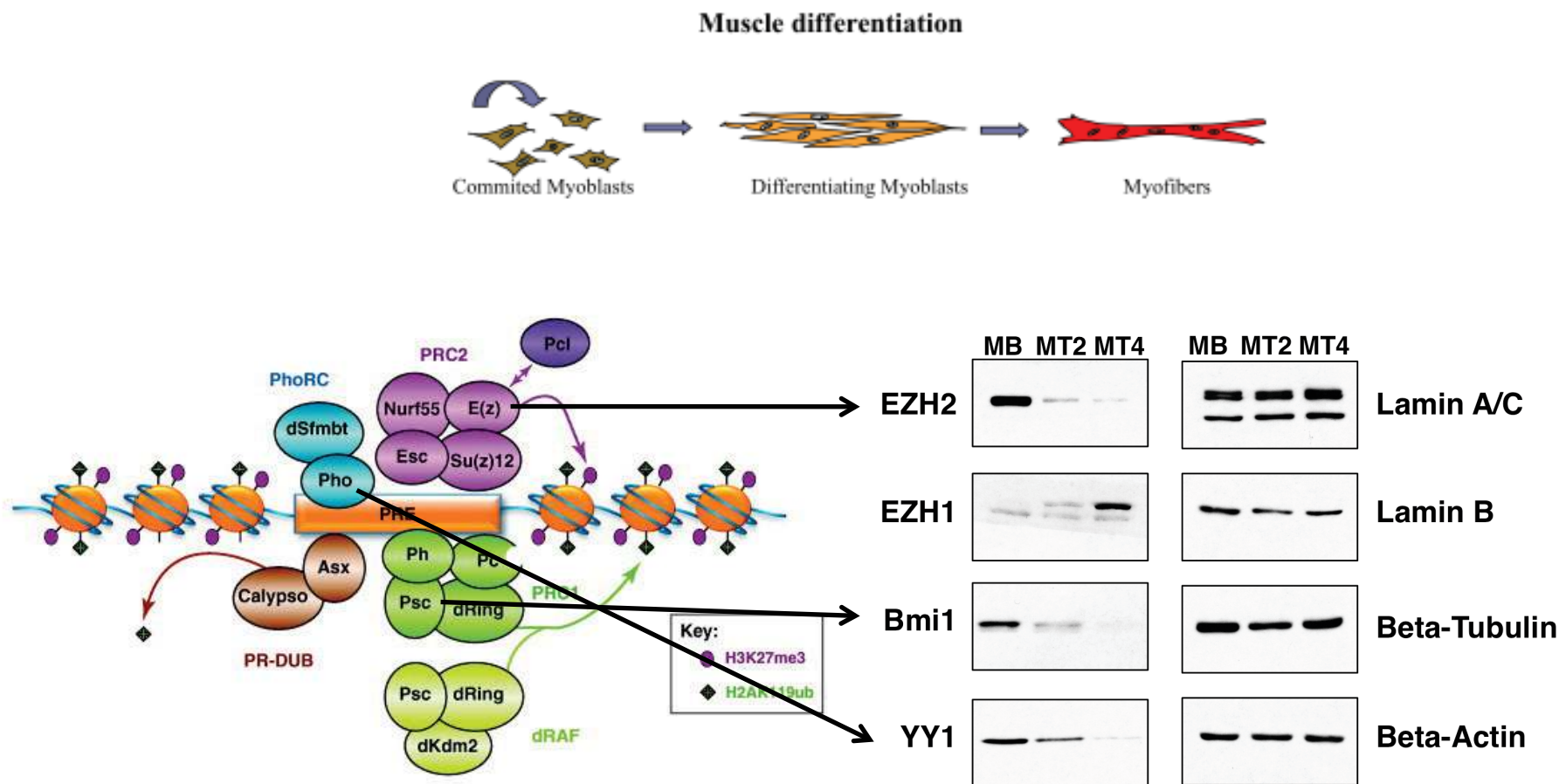
... formando una struttura a “rosetta”



Strutture tridimensionali diverse corrispondono a specifici stati trascrizionali



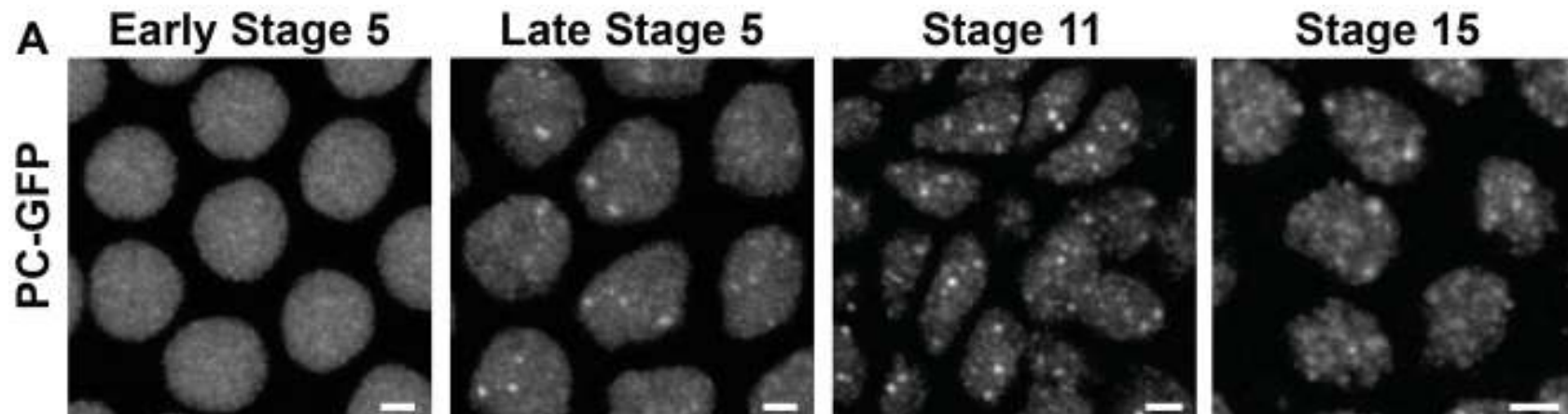
La miogenesi è caratterizzata da una specifica dinamica delle proteine Polycomb



Progressive Polycomb Assembly on H3K27me3 Compartments Generates Polycomb Bodies with Developmentally Regulated Motion

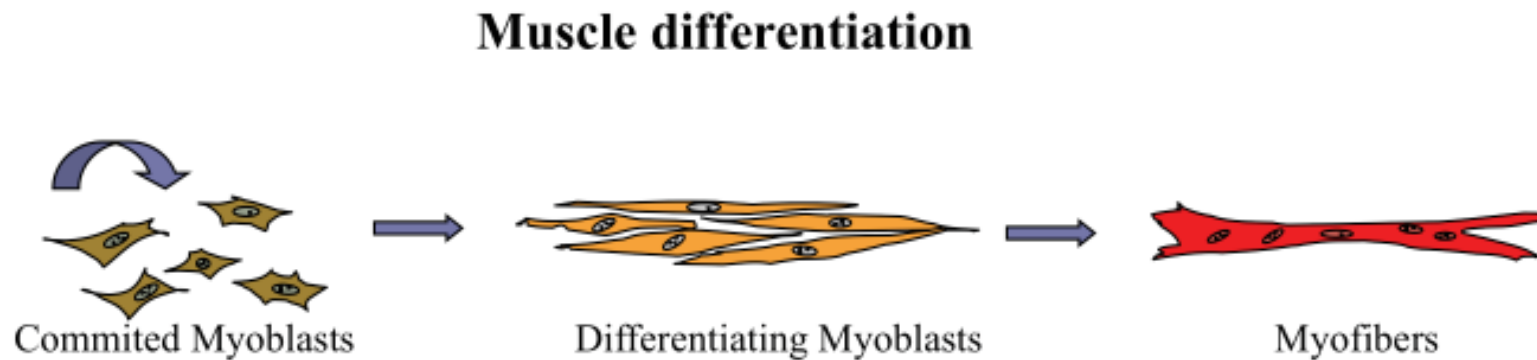
Thierry Cheutin, Giacomo Cavalli*

Institut de Génétique Humaine, CNRS UPR 1142, Montpellier, France

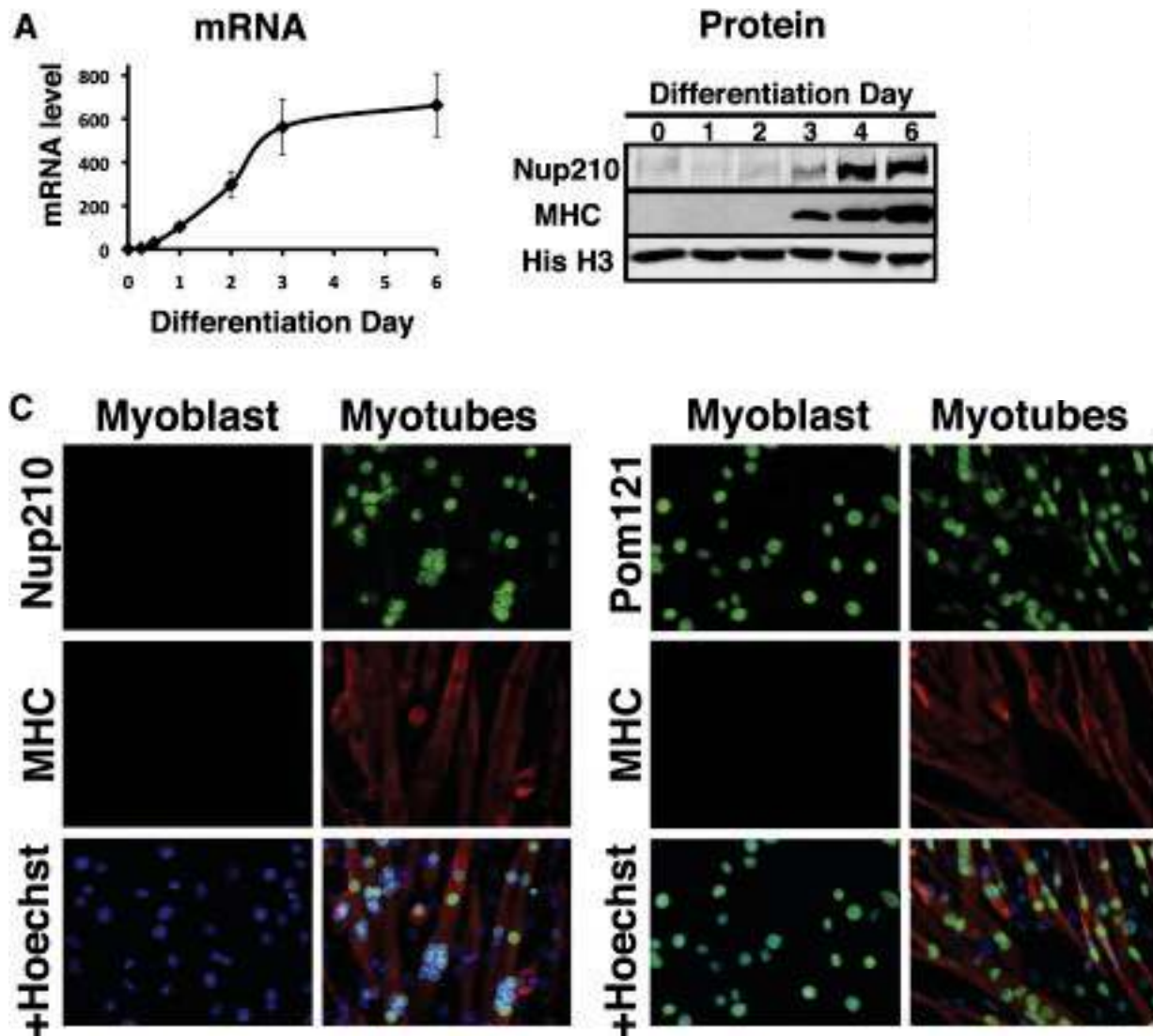


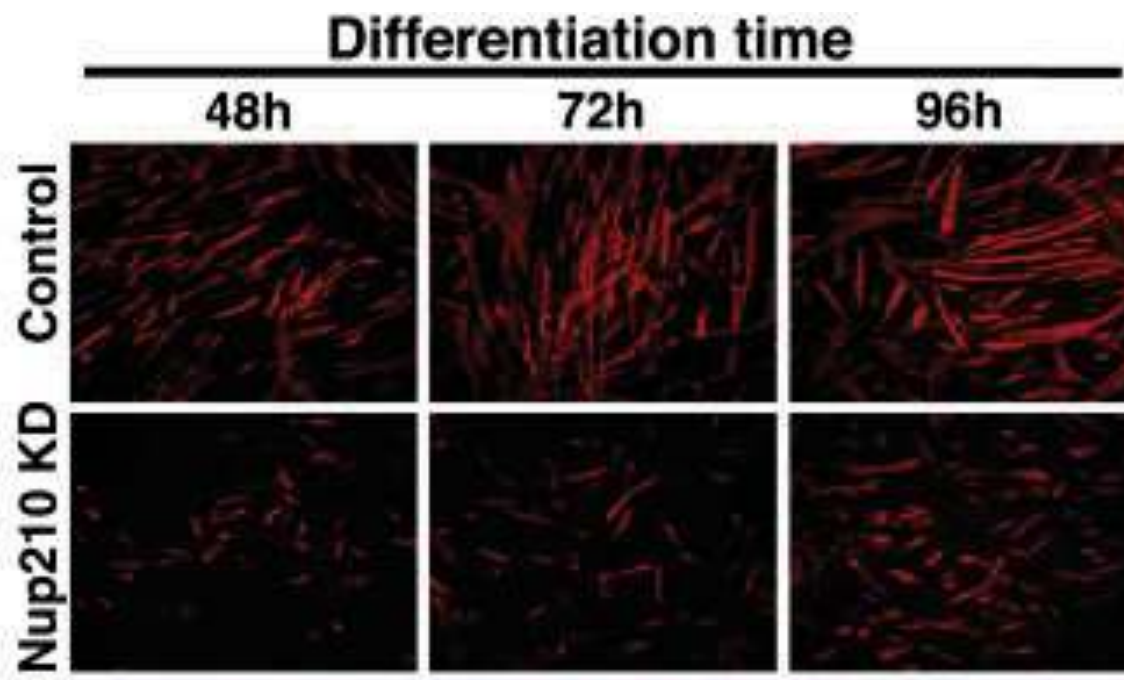
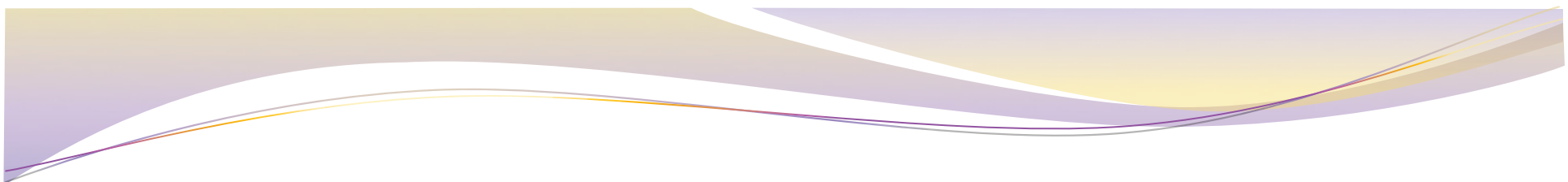
Problem solving

Quali proteine contribuiscono ad un corretto differenziamento muscolare?

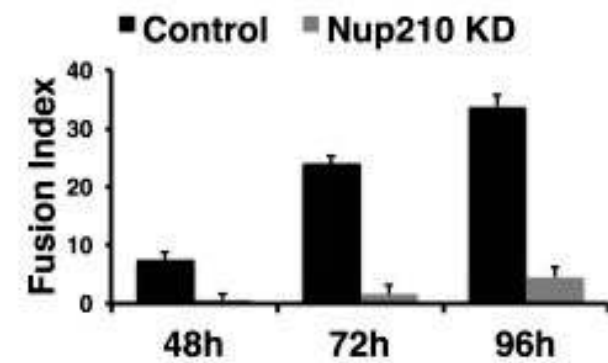


Problem solving

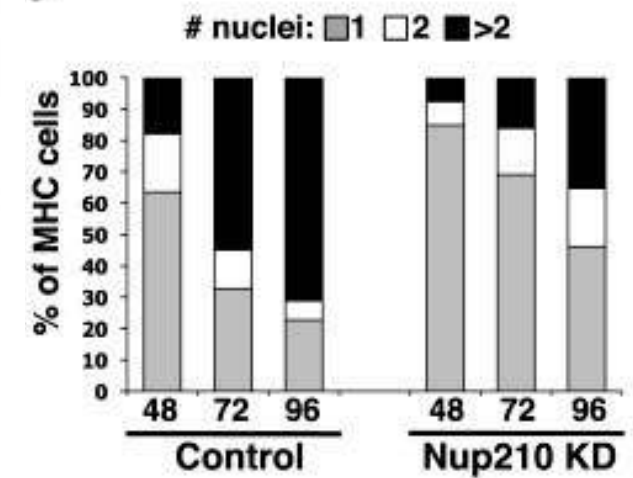


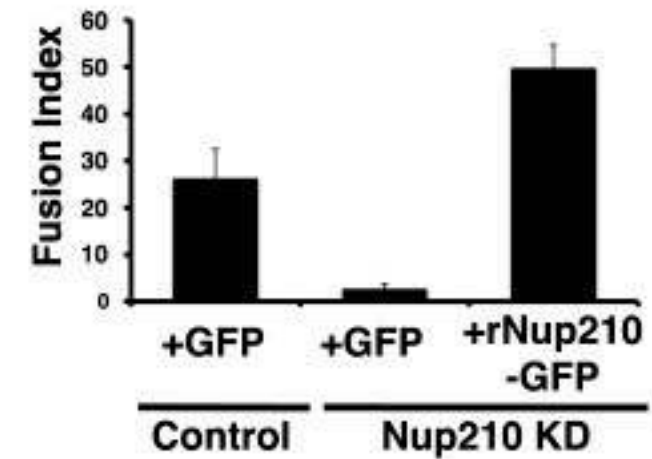
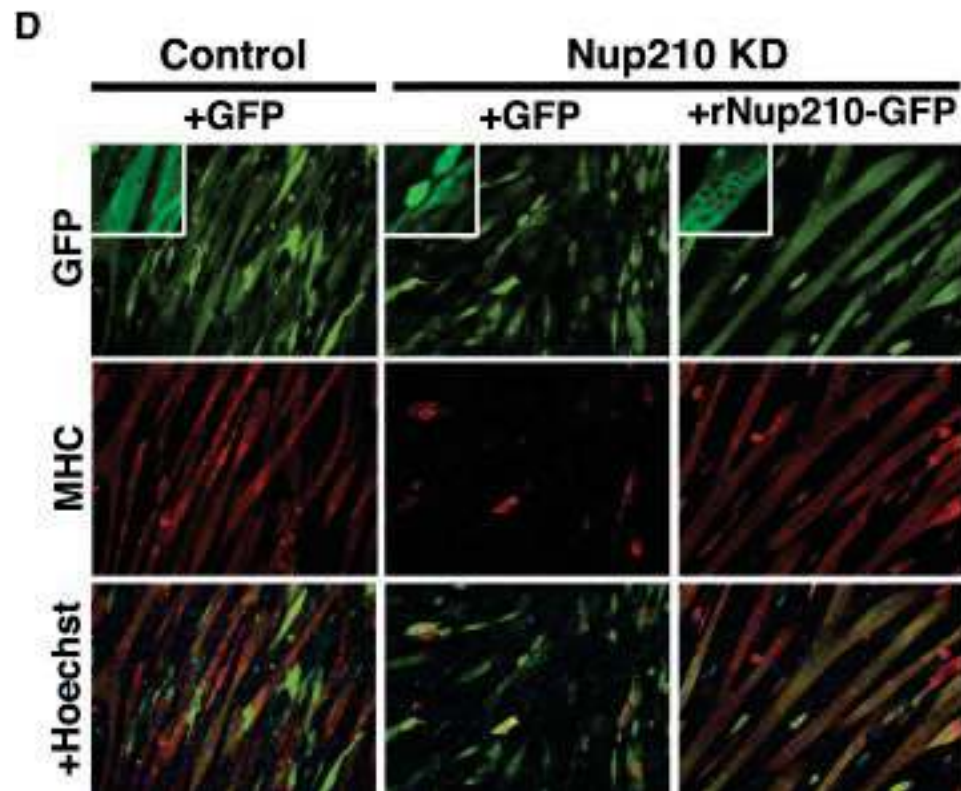


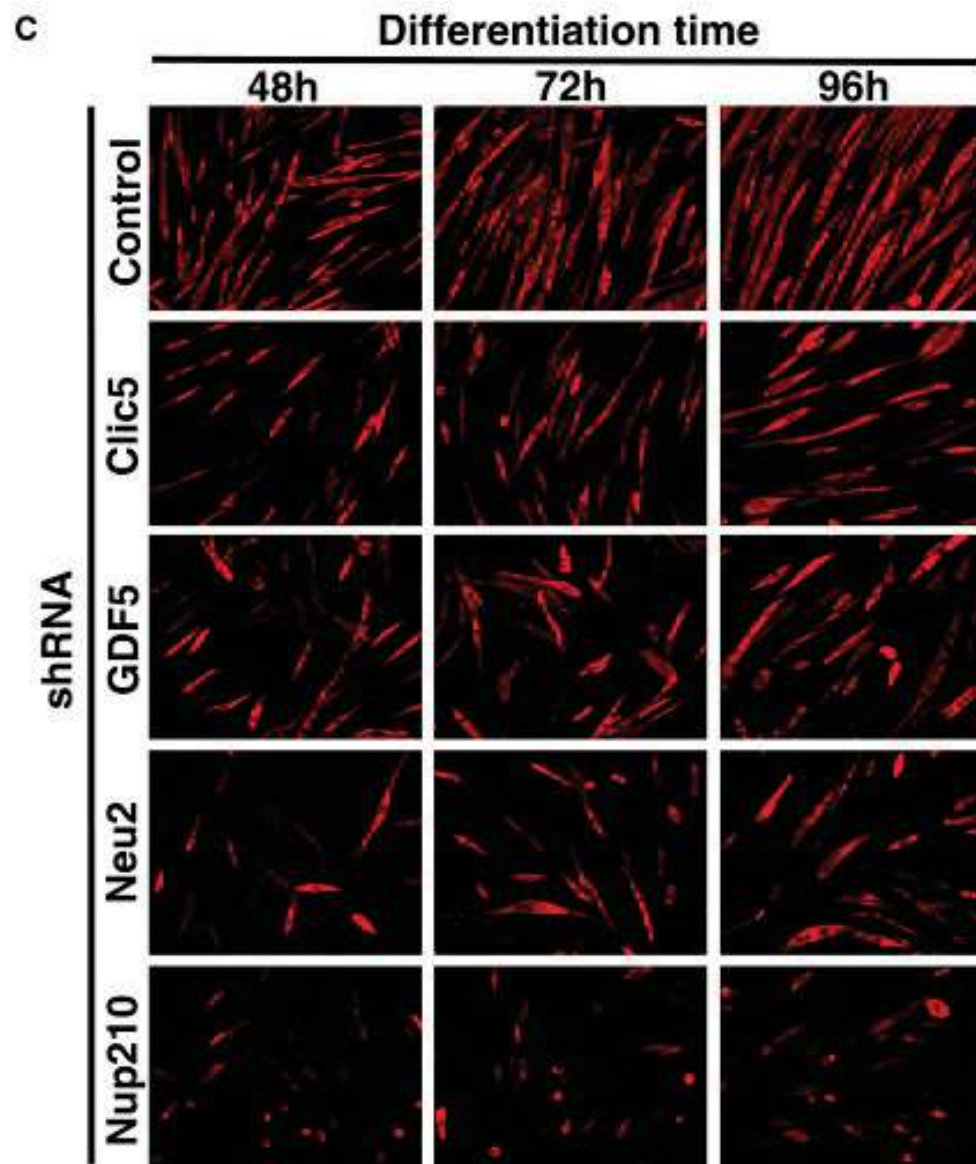
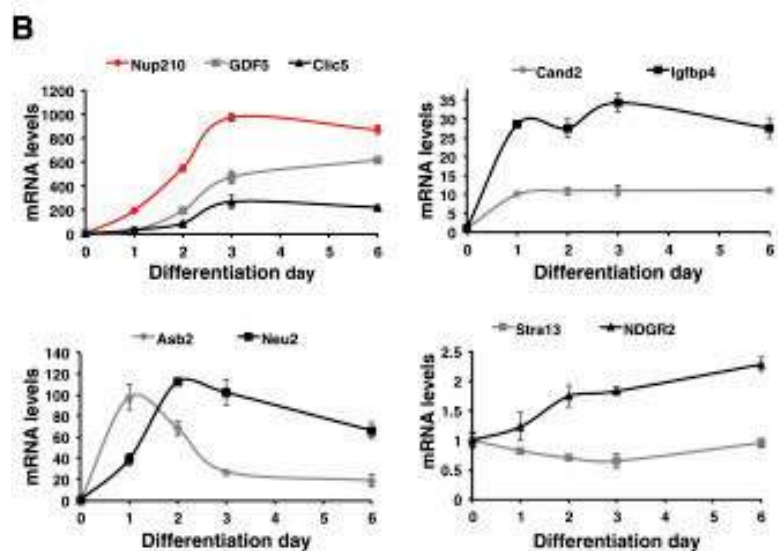
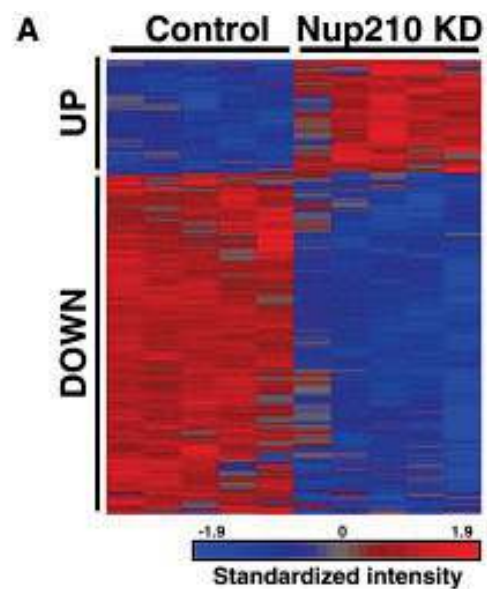
B

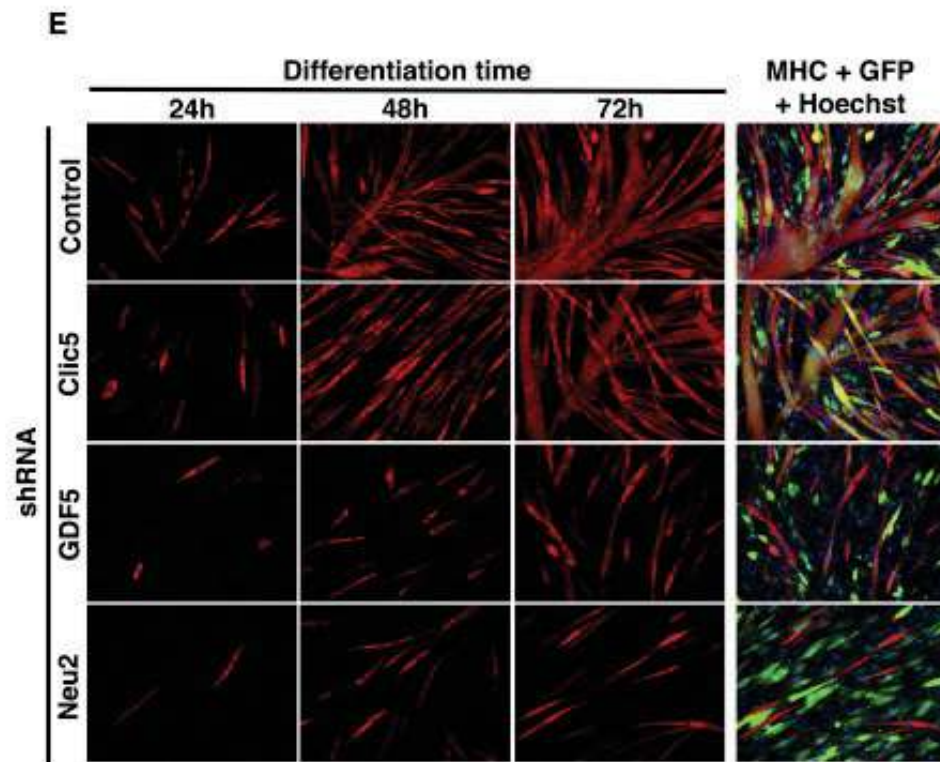
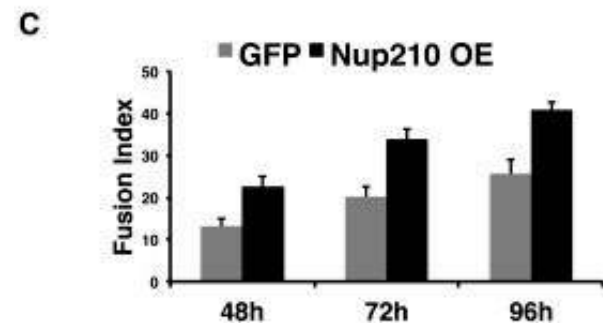
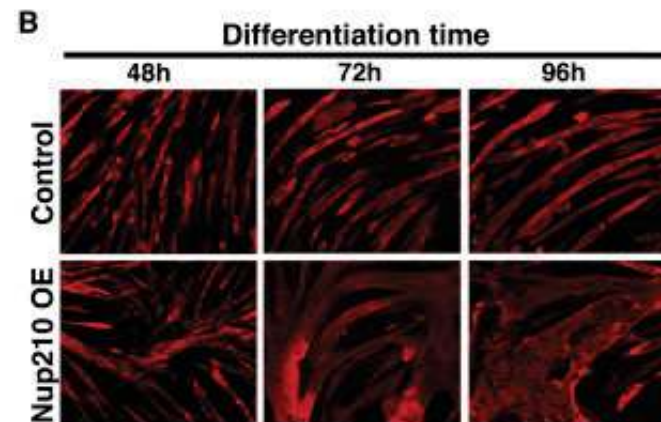
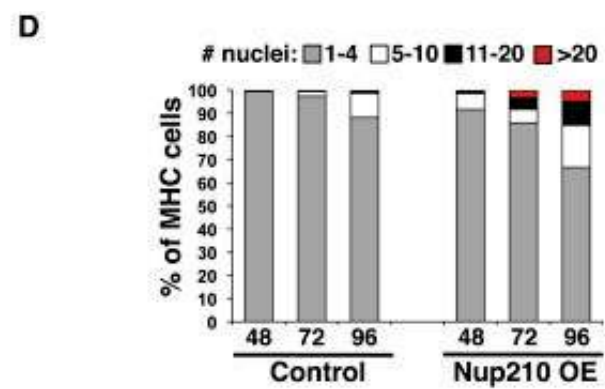
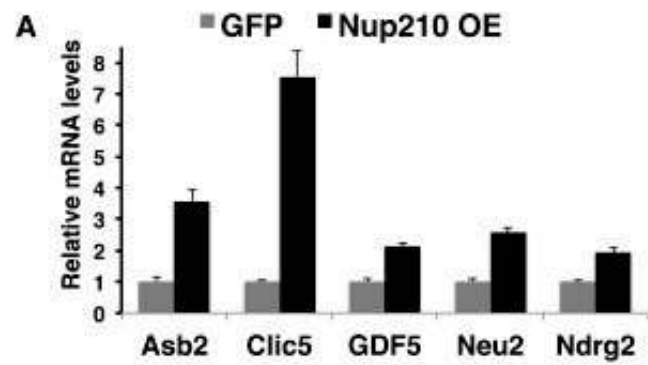


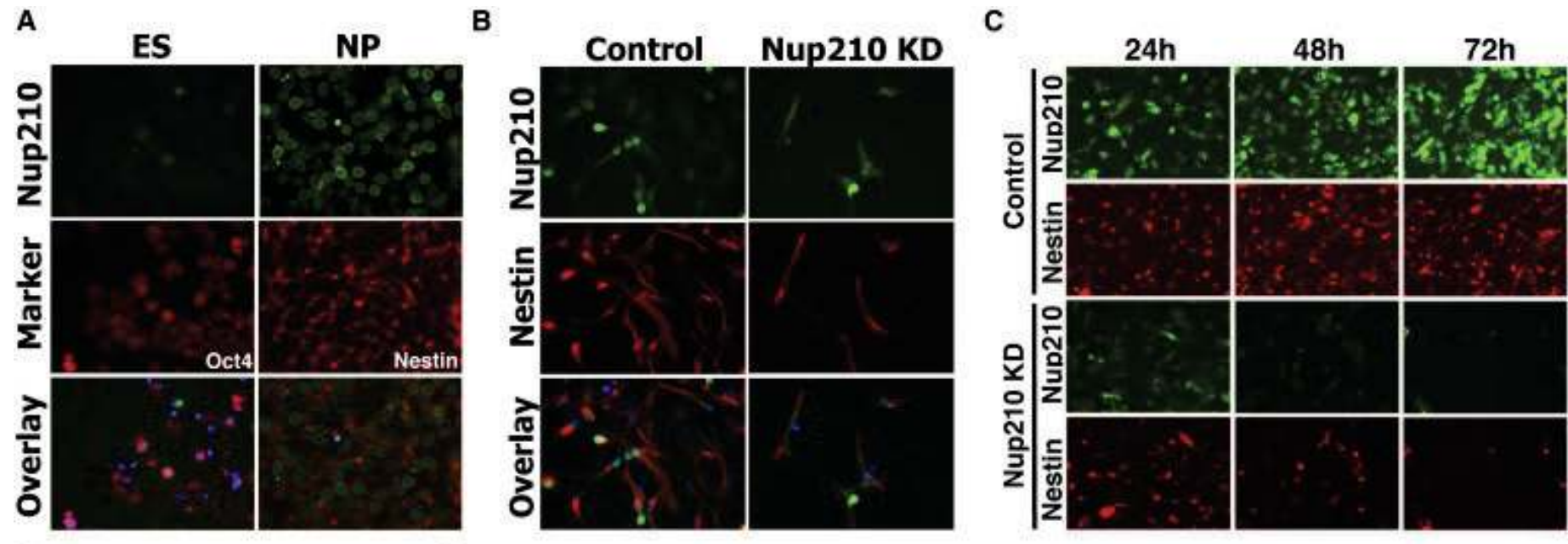
C











A Change in Nuclear Pore Complex Composition Regulates Cell Differentiation

Maximiliano A. D'Angelo,^{1,2,3,*} J. Sebastian Gomez-Cavazos,^{1,2} Arianna Mei,¹ Daniel H. Lackner,¹ and Martin W. Hetzer^{1,*}

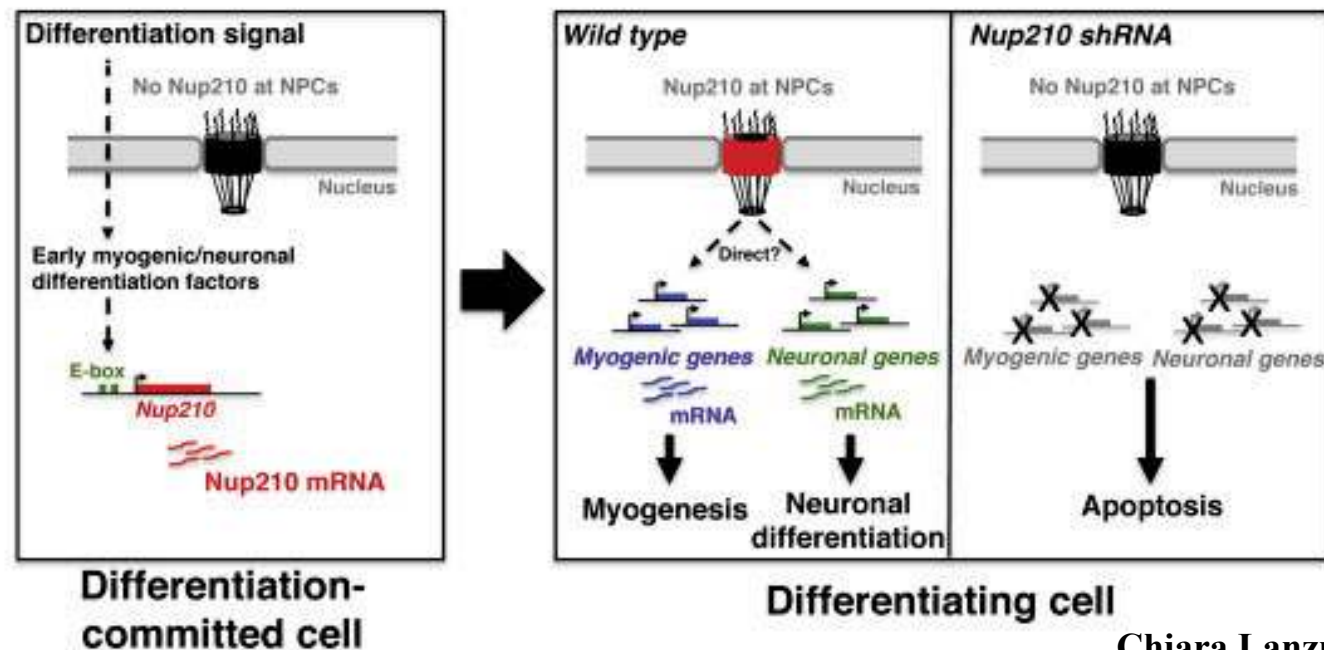
¹Salk Institute for Biological Studies, Molecular and Cell Biology Laboratory, 10010 N. Torrey Pines Road, La Jolla, CA 92037, USA

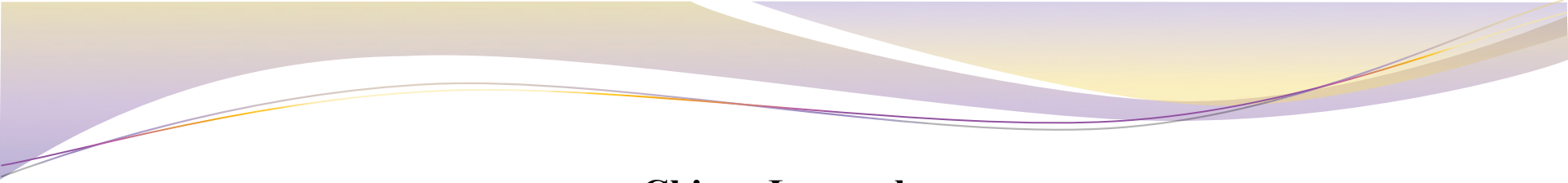
²These authors contributed equally to this work

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