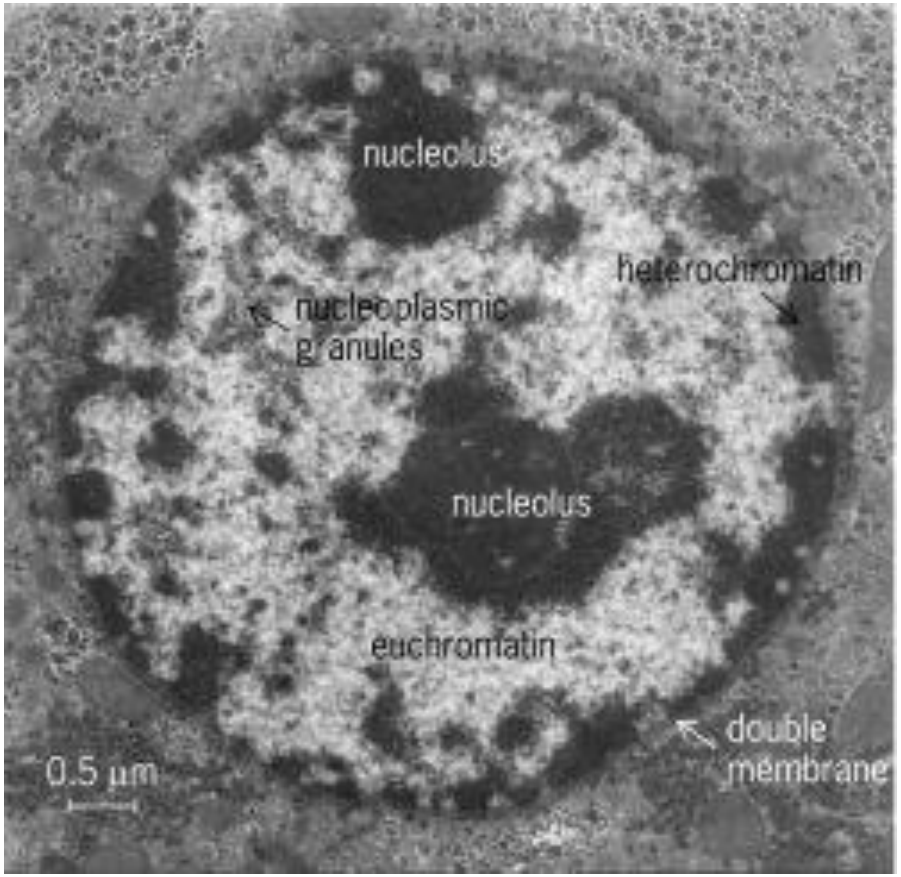
Ch 1 – L 4.1

Chromosomes and Nuclear organization



A rat liver cell nucleus at Transmission E.M.

TextBook 2 for Chaper 1

Cell

Leading Edge
Review

Lamina-Associated Domains: Links with Chromosome Architecture, Heterochromatin, and Gene Repression

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http://dx.doi.org/10.1016/j.cell.2017.04.022

In metazoan cell nuclei, hundreds of large chromatin domains are in close contact with the nuclear lamina. Such lamina-associated domains (LADs) are thought to help organize chromosomes inside the nucleus and have been associated with gene repression. Here, we discuss the properties of LADs, the molecular mechanisms that determine their association with the nuclear lamina, their dynamic links with other nuclear compartments, and their proposed roles in gene regulation.

Cell 169, May 18, 2017 – pagg 780-791

Why a review on LADs as a TextBook for Nuclear organization ?

We used an older review until last year (Geyer et al 2011, next slide)
but I found this definitely more interesting.
First, since it reviews also more recent results;
Second, since it goes through almost all aspects of nuclear organization in a quite clear and complete way,

LADs are, as a matter of facts, the most studied and interesting intranuclear structure regulating genome activity

Available online at www.sciencedirect.com

Former Textbook

Current Opinion in Cell Biology

Nuclear organization: taking a position on gene expression

Pamela K Geyer, Michael W Vitalini and Lori L Wallrath

Eukaryotic genomes are divided into chromosomes that occupy defined regions or territories within the nucleus. These chromosome territories (CTs) are arranged based on the transcriptional activity and chromatin landscape of domains. In general, transcriptionally silent domains reside at the nuclear periphery, whereas active domains locate within the interior. Changes in nuclear position are observed for stress-induced and developmentally regulated tissue-specific genes. Upon activation, these genes move away from a CT to inter-chromosomal space containing nuclear bodies enriched in gene expression machinery. Gene activation is not always accompanied by movement, as positioning is dictated by many determinants, including gene structure and the local genomic environment. Collectively, tissue-specific nuclear organization results from a culmination of inputs that result in proper transcriptional regulation.

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Current Opinion in Cell Biology 2011, **23**:354–359

chemical cross-linking and massive parallel sequencing to define genome-wide relationships [3–5]. Results from these studies suggest that the genome is arranged as interdigitated CTs rather than randomly inter-twined chromosomes [6]. Emerging from these investigations is a picture of the nucleus as an ordered organelle; the consequences of this organization are just being realized.

Nuclear organization during differentiation

Studies have linked nuclear organization to cellular differentiation. Cultured pluripotent mouse embryonic stem (ES) cells possess dispersed chromatin with limited compaction. Upon differentiation, they show changes in chromatin structure that include large-scale compaction of genomic domains [7]. Consistent with these findings, embryonic development proceeds from a single cell embryo possessing a 'featureless' nucleus with dispersed chromatin, to differentiated cells possessing nuclei with peripherally located compact chromatin domains [8]. Interestingly, an extended and dispersed chromatin meshwork was identified in the eight-cell epiblast, reminiscent of nuclear structures defined in cultured ES cells. In contrast to the 'open' chromatin structure in the epiblast nuclei,

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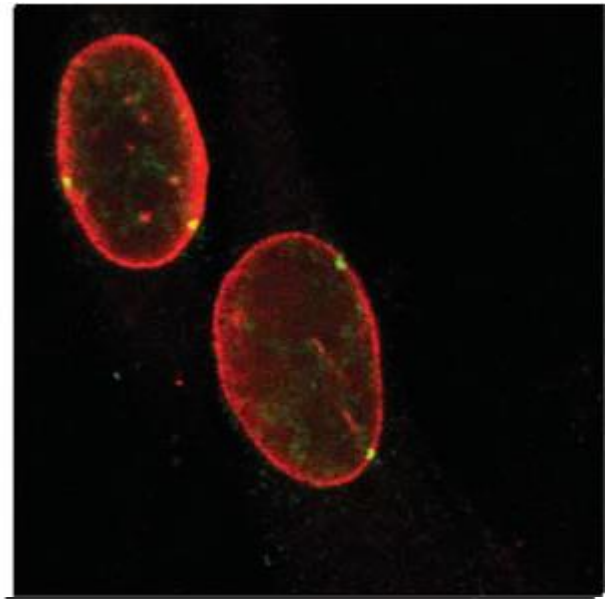
Gene-poor regions and **silenced genes** are frequently found at the **nuclear periphery** (same as heterochromatin)

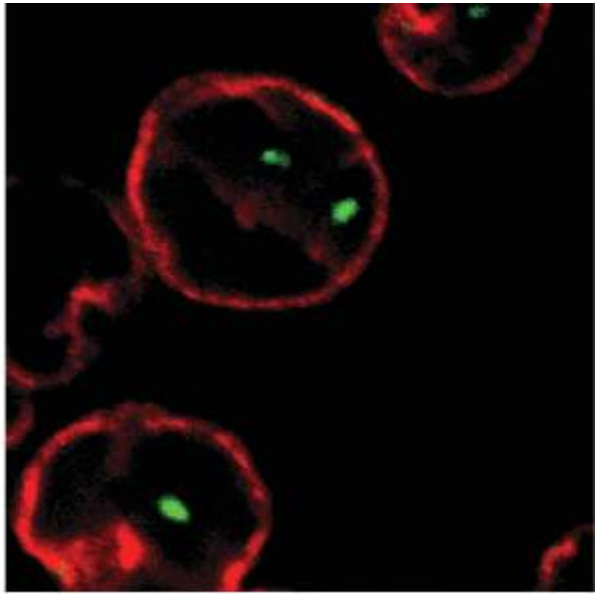
How do we know this ?

3D DNA immunoFISH of the **Igh** loci

What is this ? Go to NCBI-Gene database



fibroblast



Pro-B cell

Immuno-FISH

From: Reddy et al., 2008 (Research paper 1)

Several new concepts:

Chromosomal territories

Chromatin landscapes

Transcriptionally silent domains

Transcriptionally active domains

Changes in nuclear position (induced genes)

Input → tissue specific nuclear organization → proper transcriptional regulation

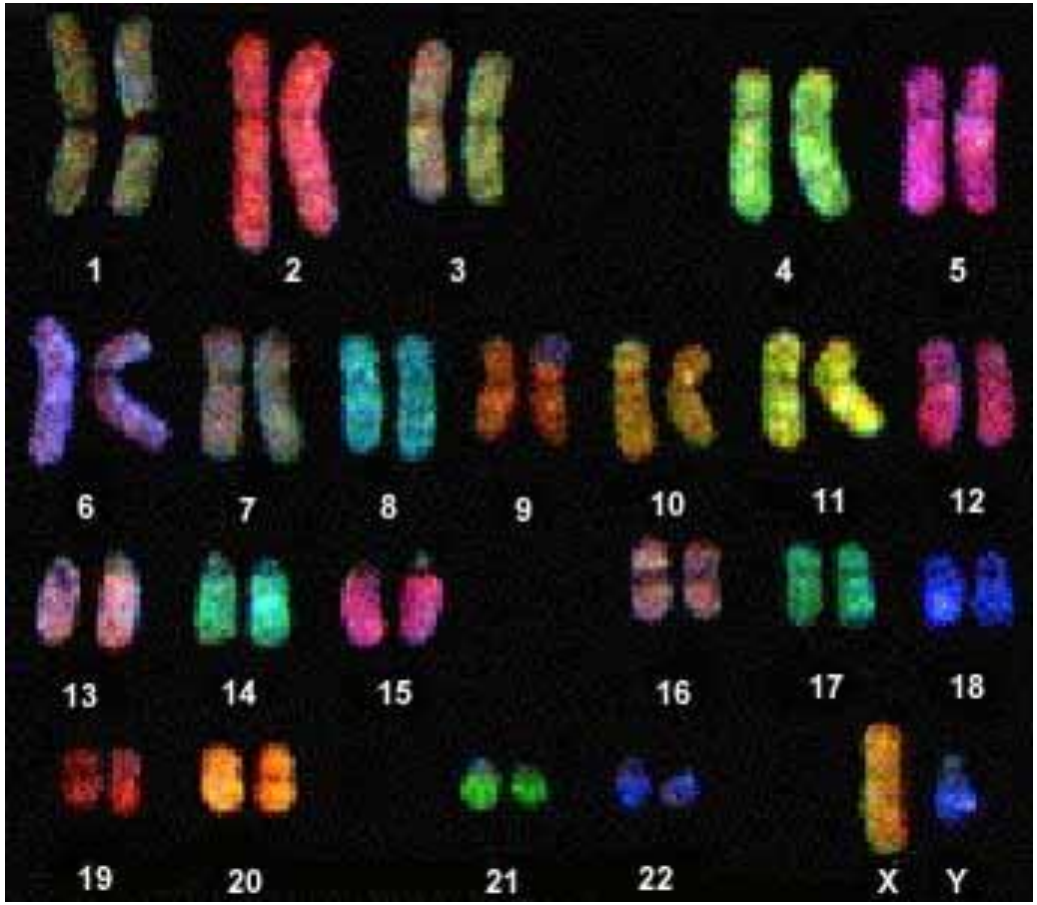
Chromosomal territories (CT)

can we «see» chromosomes in cell nuclei ?

Individual chromosomes can be «painted» and maintain separate territories in interphase nuclei

Chromosome painting techniques can visualize individual chromosomes both at the metaphase and interphase

Individual «chromosome painting» is a **FISH technique**

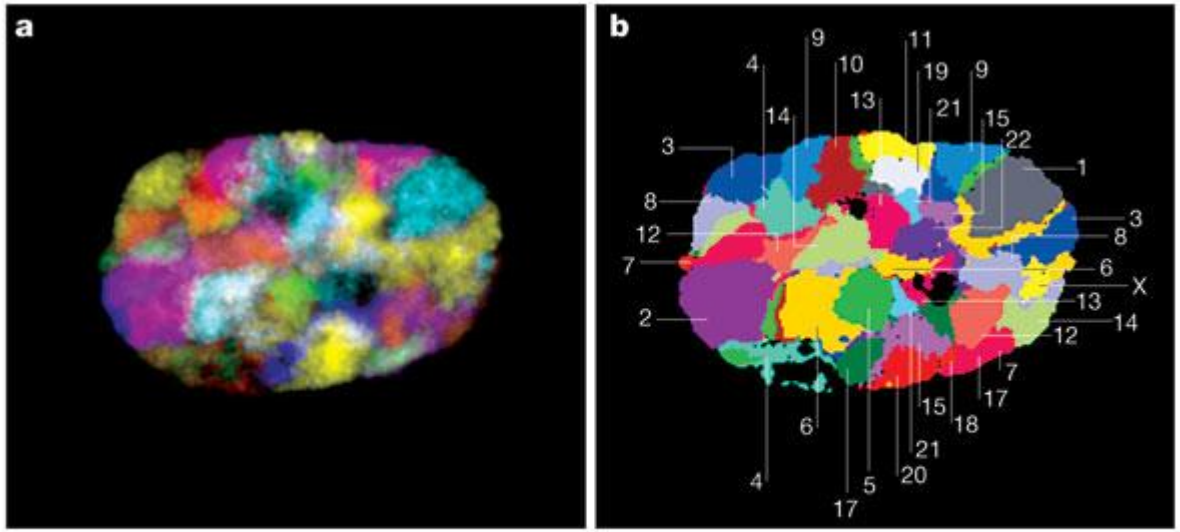


Metaphase human chromosomes

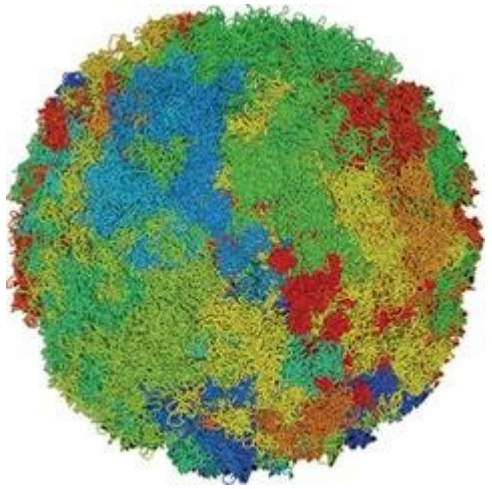
Results from these studies suggest that the genome is arranged as interdigitated CTs rather than randomly inter-twined chromosomes [6]. Emerging from these investigations is a picture of the nucleus as an ordered organelle; the consequences of this organization are just being realized.

Interdigitated, inter-twined or inter-twingled CTs ?

CT = chromosomal territory



Mapping CTs in cell nucleus



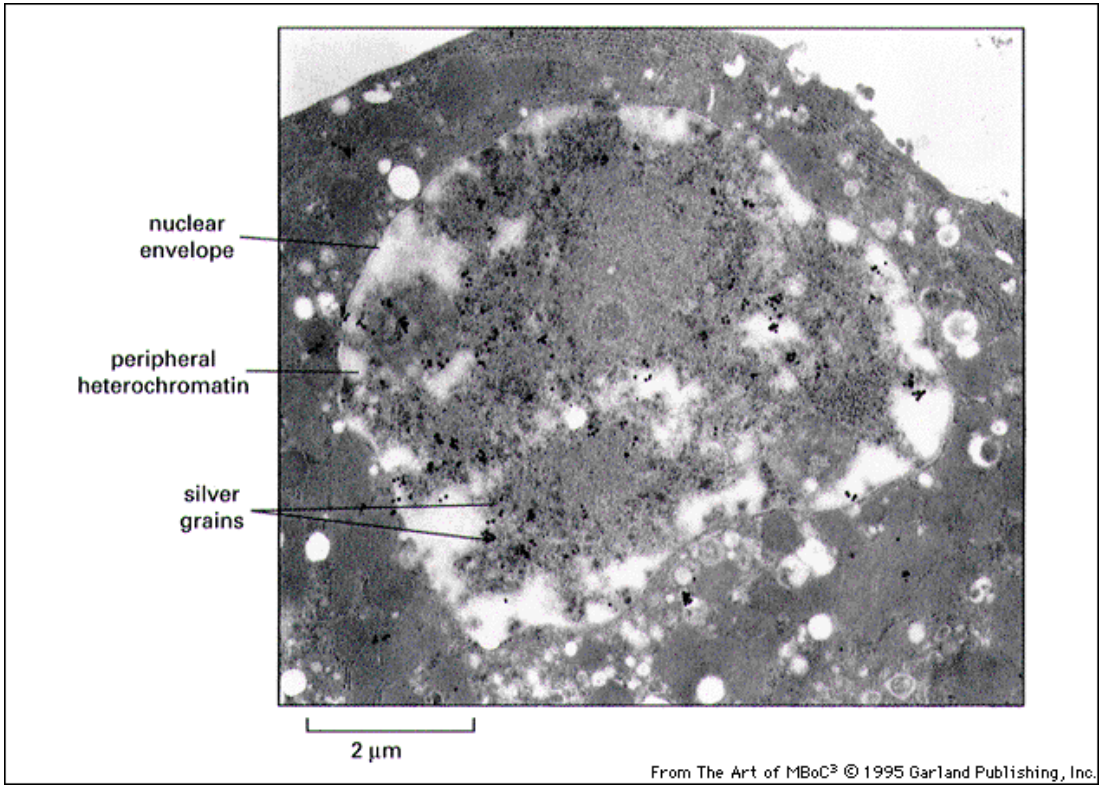
One interesting question: if heterochromatin and CT are established during differentiation...

Does heterochromatin i.e. nuclear organization,

differ

from one cell type to another?

This is quite old concept, indeed….



Macroscopic

http://www.google.it/search?q=nucleus+electron+microscopy&hl=it&client=firefox-a&hs=rE0&rls=org.mozilla:it:official&prmd=imvns&source=lnms&tbm=isch&ei=IJ1dT-SSF9HoOYWWlfYM&sa=X&oi=mode_link&ct=mode&cd=2&ved=0CBQQ_AUoAQ&biw=1330&bih=647

Do macroscopic differences reflect different (macro)-molecular organization ?

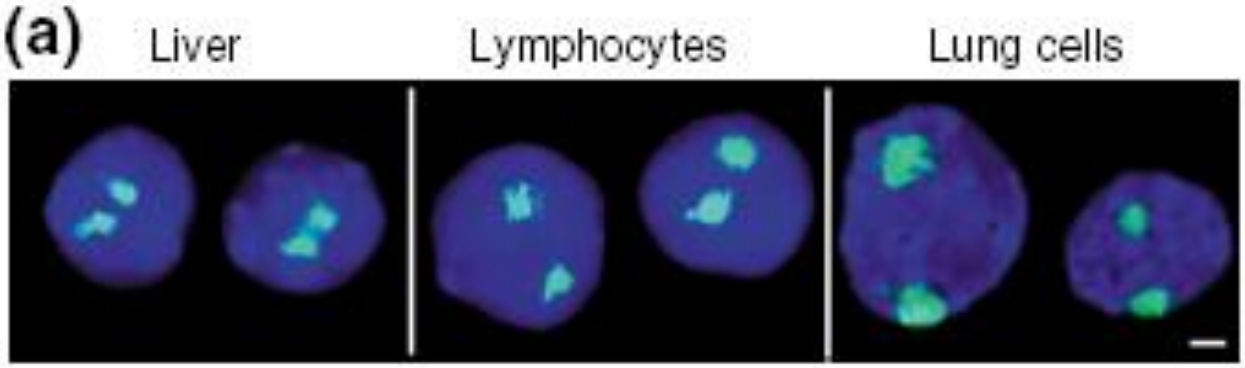
Let's see how Parada et al. , using two-dimensional and three-dimensional **fluorescence *in situ* hybridization (FISH)** have carried out a systematic analysis of the spatial positioning of a subset of mouse chromosomes in several tissues.

Chromosomes exhibit tissue-specific organization

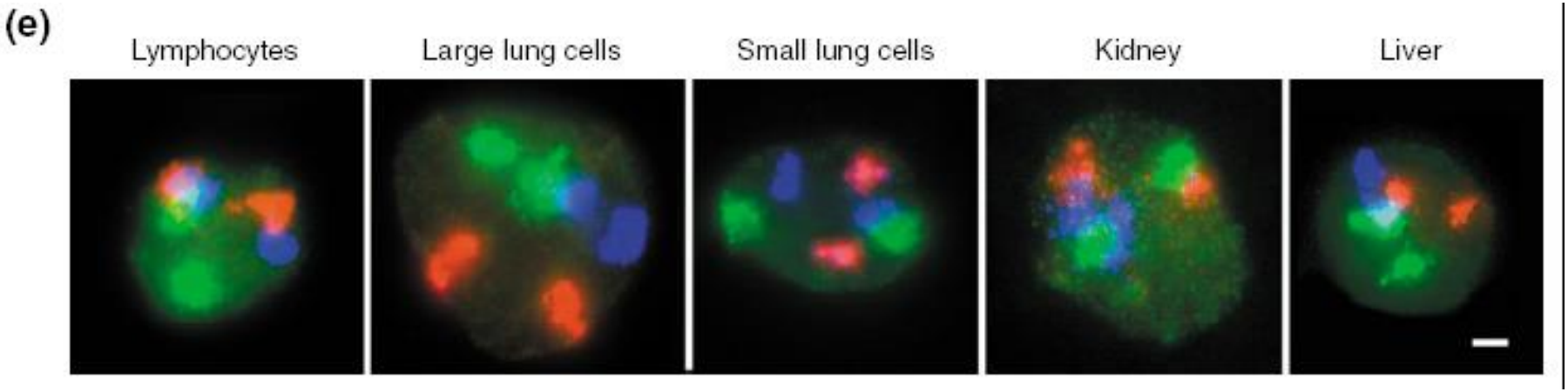
Chromosomes are distributed tissue-specifically with respect to their position relative to the center of the nucleus and also relative to each other.

Subsets of chromosomes form distinct types of spatial clusters in different tissues

2D and 3D FISH



Chromosome 5 painting



Tissue-specific **relative positioning** of chromosomes 12, 14 and 15

From Parada et al., 2004, Genome Biol. 5:R44.

Reference (not assigned paper)

Open Access

Research

Tissue-specific spatial organization of genomes

Luis A Parada*, Philip G McQueen† and Tom Misteli*

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Correspondence: Tom Misteli. E-mail: mistelit@mail.nih.gov

Published: 21 June 2004

Genome ***Biology*** 2004, **5**:R44

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2004/5/7/R44

Received: 21 April 2004
Revised: 24 May 2004
Accepted: 25 May 2004

Take-home messages:

- Interphase chromosomes occupy discrete “territories” within the nucleus
- Position of interphase chromosomes is cell-specific
- Relative positioning is also cell type-specific

Question

If chromosome territories and the relative position differ from one type of cell to the other,

does nuclear organization change during development and cell differentiation ?

Nuclear organization parallels cellular differentiation

Nuclear organization during differentiation

Studies have linked nuclear organization to cellular differentiation. Cultured pluripotent mouse embryonic stem (ES) cells possess dispersed chromatin with limited compaction. Upon differentiation, they show changes in chromatin structure that include large-scale compaction of genomic domains [7]. Consistent with these findings, embryonic development proceeds from a single cell embryo possessing a 'featureless' nucleus with dispersed chromatin, to differentiated cells possessing nuclei with peripherally located compact chromatin domains [8]. Interestingly, an extended and dispersed chromatin meshwork was identified in the eight-cell epiblast, reminiscent of nuclear structures defined in cultured ES cells. In contrast to the 'open' chromatin structure in the epiblast nuclei, lineage-restricted nuclei that give rise to extraembryonic tissues contained a distinctive 'closed' chromatin structure. These investigations indicate that global changes in gene expression correlate with chromatin reorganization, which plays a role in lineage restriction during development.

Geyer 2011

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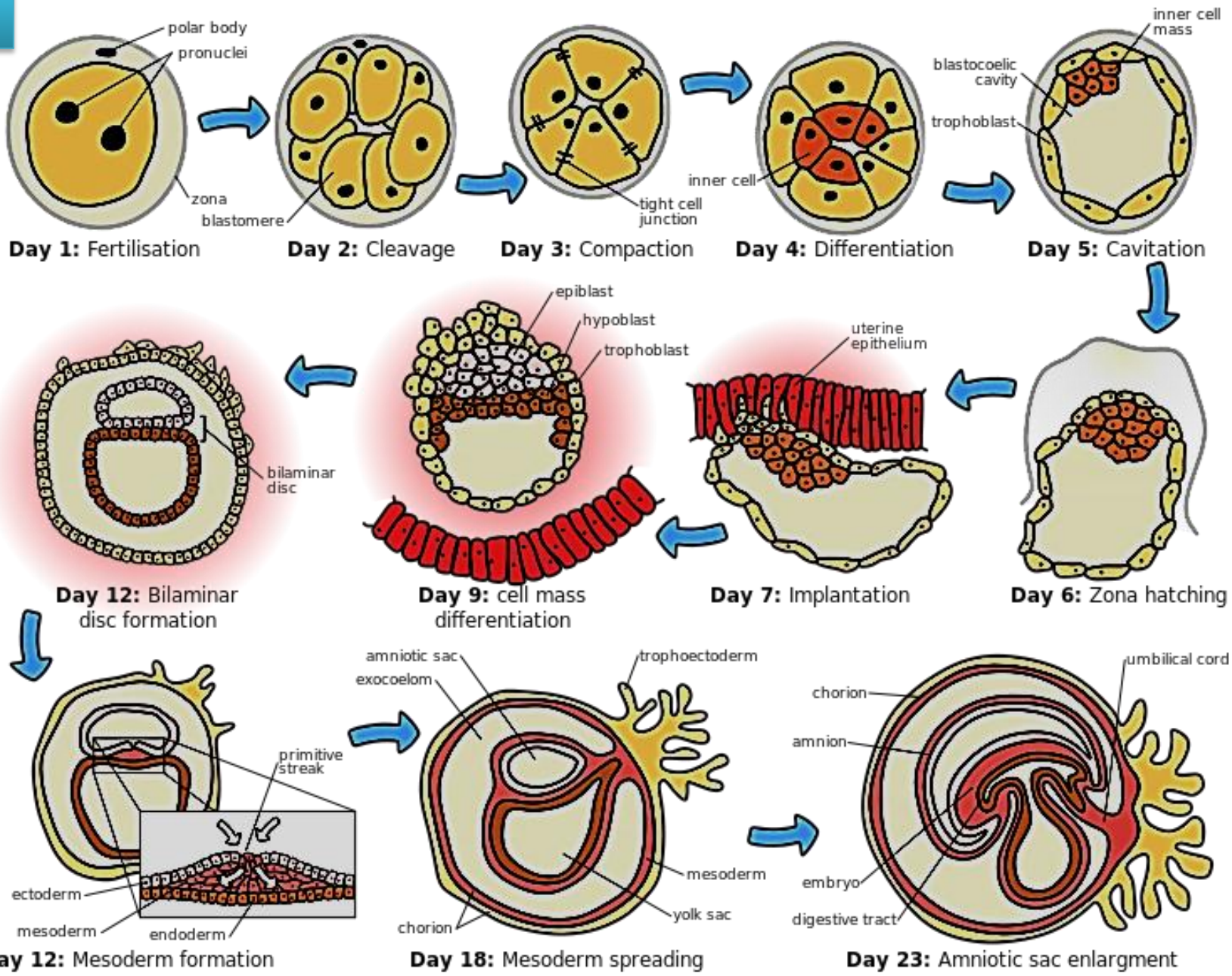
Geyer et al., 2011

wikipedia


polar body
pronuclei
zona
blastomere
tight cell junction
inner cell
blastocoelic cavity
trophoblast
inner cell mass
Day 1: Fertilisation
Day 2: Cleavage
Day 3: Compaction
Day 4: Differentiation
Day 5: Cavitation
Day 6: Zona hatching
uterine epithelium
Day 7: Implantation
epiblast
hypoblast
trophoblast
Day 9: cell mass differentiation
bilaminar disc
Day 12: Bilaminar disc formation
primitive streak
ectoderm
mesoderm
endoderm
Day 12: Mesoderm formation
amniotic sac
exocoelom
trophoectoderm
mesoderm
yolk sac
chorion
Day 18: Mesoderm spreading
chorion
amnion
umbilical cord
embryo
digestive tract
Day 23: Amniotic sac enlargment

http://www.genecards.org/cgi-bin/carddisp.pl?gene=NPM1

ES cells

neuronal progenitor cells

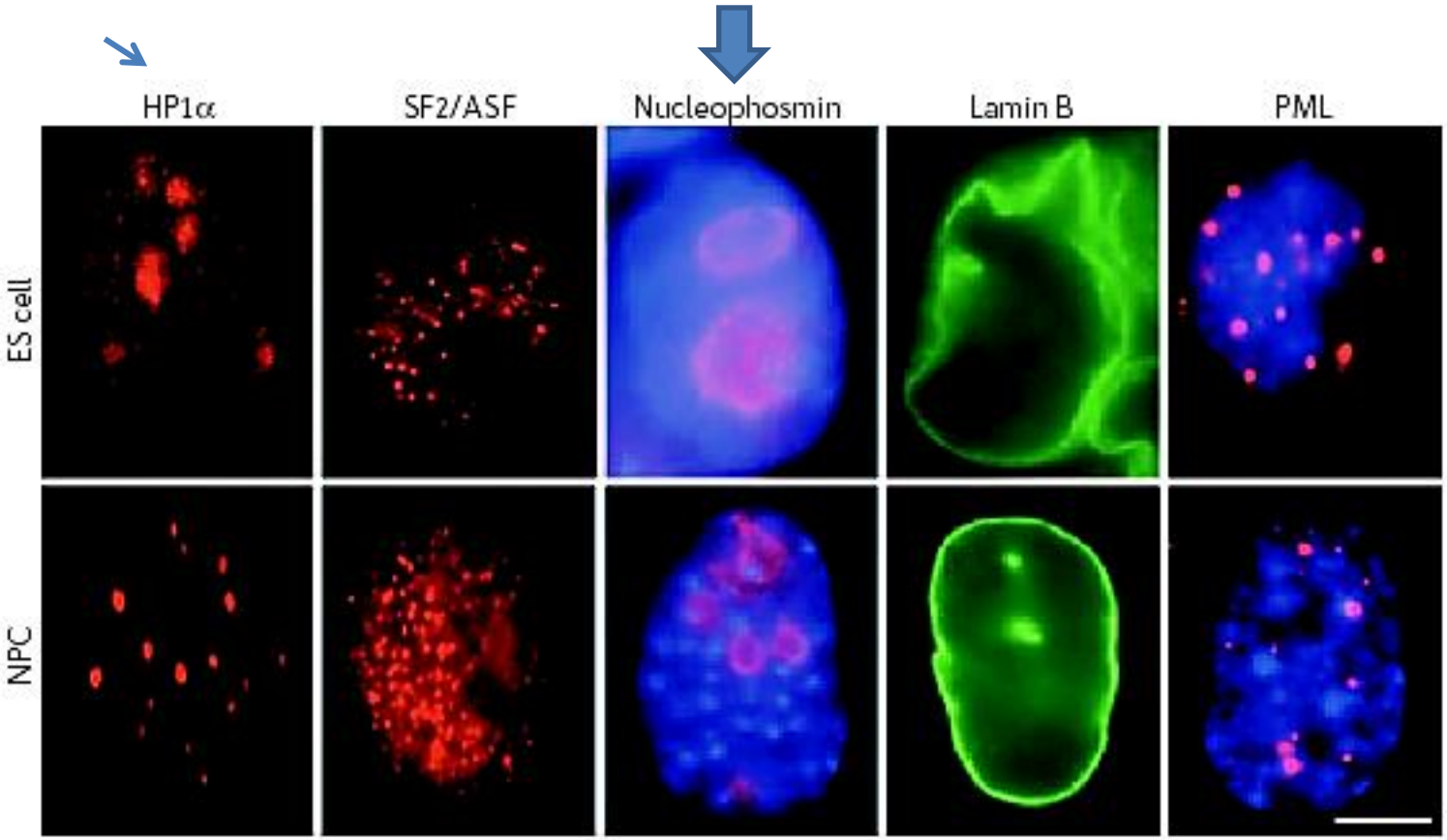


Figure 1 | **Nuclear architecture in ES cells and differentiating ES-derived cells.** Nuclear domains in an undifferentiated embryonic stem (ES) cell (top) and a differentiating ES-derived neuronal progenitor cell (NPC, bottom). From left to right: heterochromatin, as detected with an anti-HP1α antibody, is confined to fewer and larger foci in ES cells compared with NPCs; nuclear speckles, as detected with an anti-SF2/ASF antibody, appear as small, dispersed foci in ES cells and become more conspicuous in NPCs; nucleoli, as identified with an anti-nucleophosmin antibody, appear larger in ES cells compared with NPCs; the ill-defined nuclear lamina in ES cells, stained with an anti-lamin B antibody, becomes round and distinct in NPCs; promyelocytic leukaemia (PML) bodies labelled with an anti-PML antibody show similar patterns in ES cells and NPCs. DAPI, blue. Scale bar, 5 μm.

(from Meshorer & Misteli, 2006)

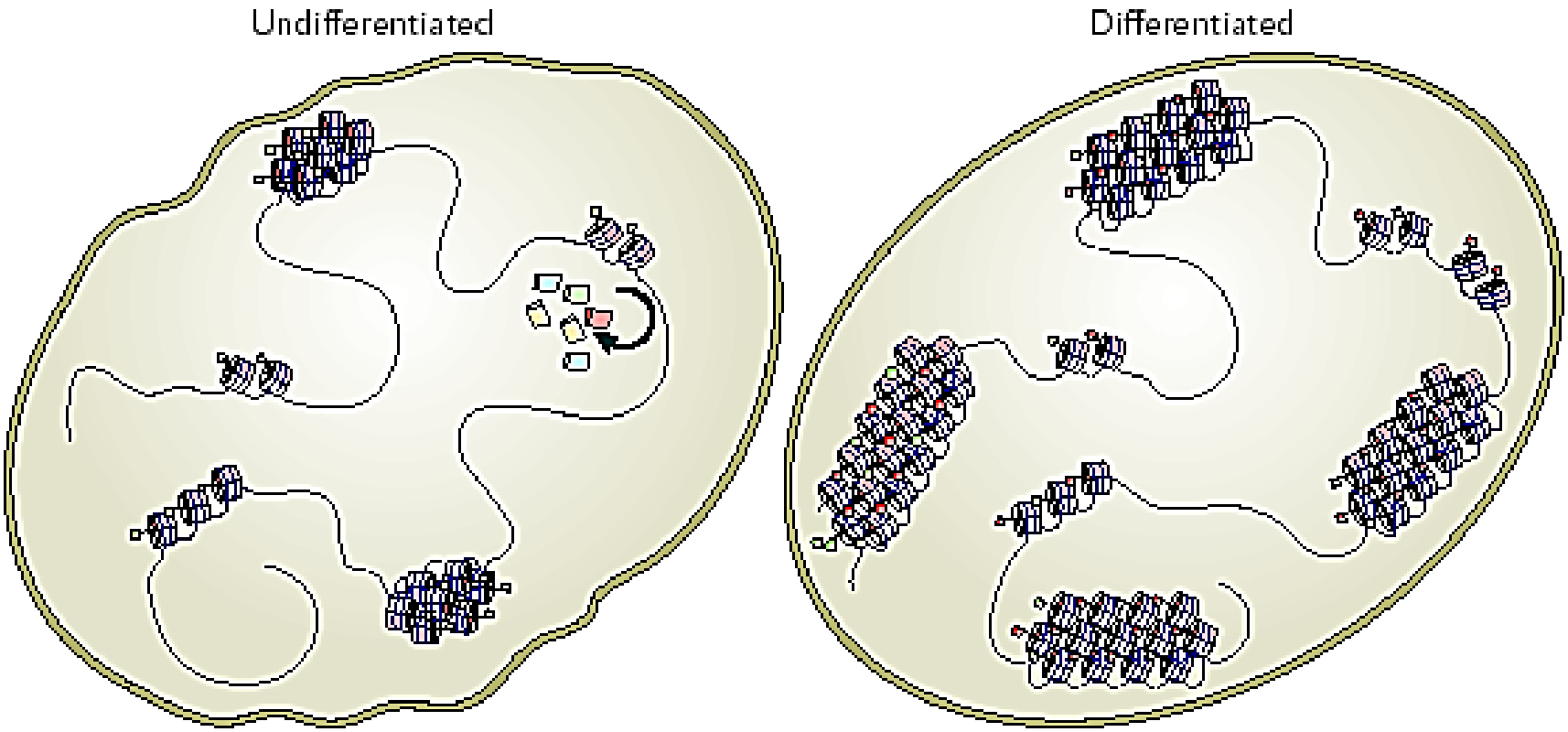


Figure 2 | **Chromatin during ES-cell differentiation.** In pluripotent embryonic stem (ES) cells (left), chromatin is globally decondensed, enriched in active histone marks (green circular tags), and contains a fraction of loosely bound architectural chromatin proteins. As cells differentiate (right), regions of condensed heterochromatin form, silencing histone marks (red circular tags) accumulate, and structural chromatin proteins become more stably associated with chromatin.

(from Meshorer & Misteli, 2006)

These investigations indicate that global changes in gene expression correlate with chromatin reorganization, which plays a role in lineage restriction during development.

Geyer et al., 2011

We can conclude that the organization of nuclei reflects the overall functional states of the different parts of genome

or that

the different functional states of different parts of the genome will determine the organization of cell nuclei

This seems to me the frequent question.....

Which Came First the Chicken or the Egg?

Take the Chicken Guard Poll

Vote Egg

Vote Chicken

Lesson 4 Part 2 at 10:00