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The influencers' era: how the environment shapes chromatin in 3D

Lorenz Pudelko[1,2,*] and Daphne S Cabianca[1,*]

Environment–epigenome interactions are emerging as contributors to disease risk and health outcomes. In fact, organisms outside of the laboratory are constantly exposed to environmental changes that can influence chromatin regulation at multiple levels, potentially impacting on genome function. In this review, we will summarize recent findings on how major external cues impact on 3D chromatin organization in different experimental systems. We will describe environment-induced 3D genome alterations ranging from chromatin accessibility to the spatial distribution of the genome and discuss their role in regulating gene expression.

Addresses
[1] Institute of Functional Epigenetics, Helmholtz Zentrum München, Neuherberg, Germany
[2] Faculty of Medicine, Ludwig-Maximilians Universität München, Munich, Germany

Corresponding author: Cabianca, Daphne S (daphne.cabianca@helmholtz-munich.de)
* Twitter account: @daph_cabi, @lorenz_pudelko

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Introduction

Increasing evidence suggests that the onset of diseases with an environmental contribution, such as, for example, obesity and type-2 diabetes, cannot be explained by genetics alone and involves epigenetic mechanisms [1].

To fit within the limited space of the nucleus, the genome is compacted and organized at multiple levels in a manner that allows for a precise spatiotemporal regulation of gene expression not only during development but also to respond to environmental changes.

Here, we will discuss how the 3D genome is regulated by environmental signals and how this may contribute to a functional transcriptional output. We will focus on five external stimuli: nutrient availability, temperature shifts, pathogen encounters, hypoxia, and osmotic stress (Figure 1). In particular, we will discuss the effects on chromatin compaction and accessibility, promoter–enhancer interactions, topologically associating domains (TADs), A–B genome compartmentalization, and the spatial distribution of chromatin, leaving aside work characterizing changes in histone posttranslational modifications and DNA methylation, which were reviewed elsewhere [2–4].

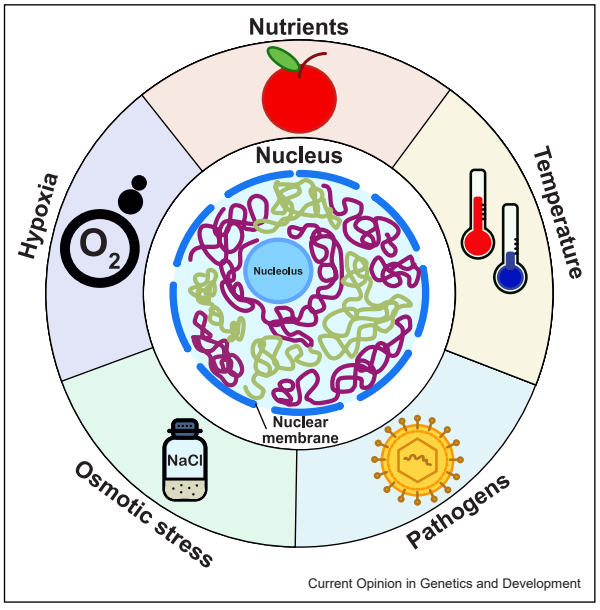
Environmental factors regulating chromatin organization

Nutrient availability

Changes in the quality and quantity of nutrients consumed occur in virtually all species and affect organismal and intracellular metabolism. Chromatin-modifying enzymes use metabolites (e.g. acetyl-CoA and S-adenosylmethionine) as substrates for their enzymatic reactions and are susceptible to metabolites' concentration. Thus, it is perhaps not surprising that dietary alterations affect chromatin modifications [2]. In recent years, a role for nutrients in modulating chromatin organization beyond the modification of DNA and histones started to emerge, as discussed below.

Chromatin compaction typically refers to the physical folding of DNA. At the simplest level, the DNA wraps around histones to form the nucleosome. Next, arrays of nucleosomes are condensed to different degrees and reach increasingly compacted states, with the maximum level observed in metaphase chromosomes. Closed chromatin loci can be decompacted by pioneer transcription factors (TFs) [5]. As shown by live microscopy, the pioneer TF B- lymphocyte-induced maturation protein-1 (BLMP-1) is required to decompact, before its transcriptional activation, the locus containing *lin-4*, a miRNA essential for the temporal control of post-embryonic development in *C. elegans* [6] (Figure 3). In the absence of food, *C. elegans* larvae arrest development and reduce the expression of BLMP-1, allowing for chromatin opening at a critical target for developmental progression to be coupled to the presence of food [6]. Both in worms and in mice, BLMP-1/Blimp-1 interacts with chromatin remodelers and histone modifiers [7,8],

Figure 1



Environmental factors influencing 3D chromatin architecture discussed in this review. Here, we will describe how genome architecture is regulated in response to lack and overabundance of nutrients, cold and heat stress, pathogen encounters, hypoxia, and hyper- and hypo-osmotic stress.

providing a mechanistic basis for chromatin decompaction.

In the primordial germ cells of early worm larvae, live imaging of histone H2B revealed that lack of nutrients triggers an AMP-activated protein kinase (AMPK)-dependent global chromatin compaction (Figure 3) [9]. AMPK is activated when the cellular adenosine triphosphate/adenosine monophosphate (ATP/AMP) ratio is low, which occurs when nutrients are scarce. Intriguingly, direct ATP depletion leads to a global chromatin condensation in mammalian cells, as shown by quantitative microscopy approaches [10,11]. Briefly, when ATP is low, the free pool of multivalent cations, such as polyamines and Mg^{2+} that normally interact with ATP [12], increases [13–15] and promotes the shielding of the negatively charged sugar-phosphate backbone of DNA, ultimately compacting chromatin [13,16,17]. Thus, it is possible that a reduction in ATP contributes to the observed starvation-induced global chromatin compaction in worms.

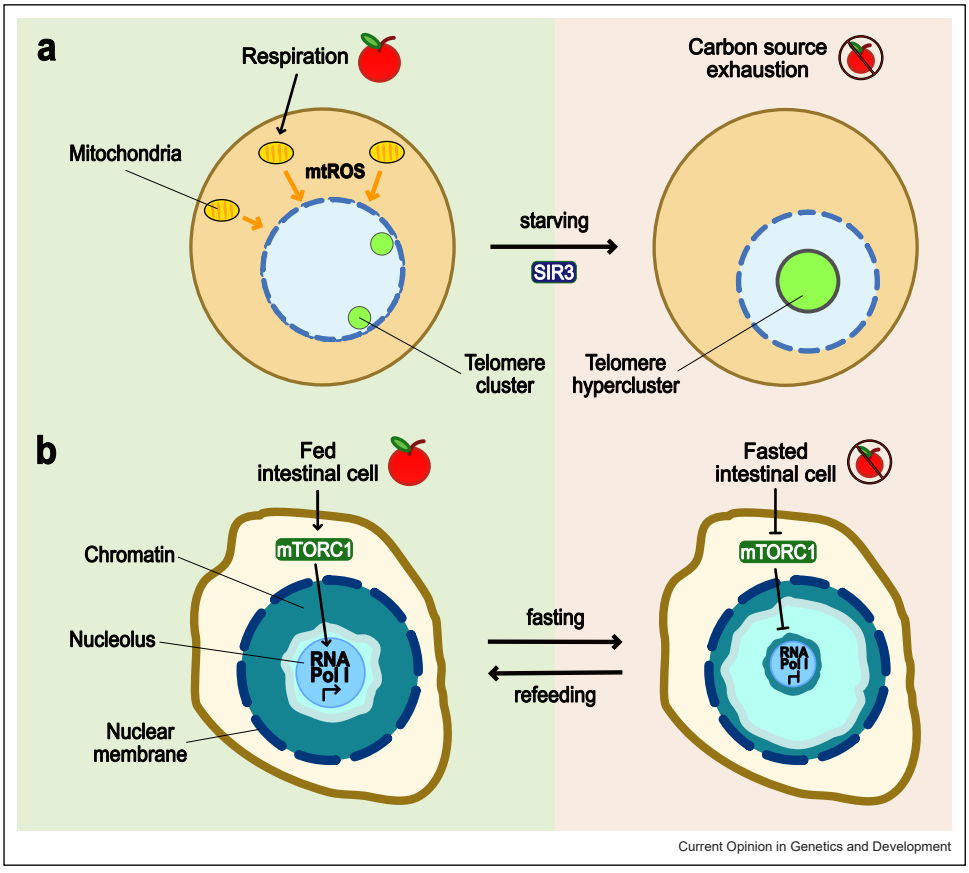
Chromatin folding constitutes an additional layer of genome regulation. Interactions between enhancers and promoters occurring through the formation of loops [18], contribute to regulating transcription. Interestingly, the activation of preformed enhancer–promoter interactions regulating metabolic genes in the liver of mice occurs in a diet-dependent fashion, likely involving signal-activated TFs, such as HNF4α under a high-lipid diet [19]. Additionally, a carbohydrate-rich diet increases the frequency of interactions at specific enhancer–promoter pairs, or induces new ones, contributing to regulating gene expression [19] (Figure 3).

Chromosome conformation capture technologies revealed that most eukaryotic genomes fold into TADs, which are genomic segments characterized by a high local, intrasegment contact frequency [20]. No obvious changes in TADs were observed in the liver under a high-fat or high-carbohydrate diet [19,21], indicating that these topological structures are stable under different nutritional states. The same was true also for A and B compartments, corresponding to transcriptionally active and inactive genomic regions, respectively [22], which remained unaffected in the liver upon dietary alterations [19,21].

The spatial distribution of chromatin within the nucleus enables a functional compartmentalization of the genome that segregates transcriptionally active and inactive regions in 3D [23]. Remarkably, carbon source exhaustion during the stationary phase alters the typical clustering of telomeres at the nuclear periphery in *S. cerevisiae*, leading to the formation of a telomere hypercluster located at the nuclear interior. This process requires the repressive factor Silent Information Regulator 3 (SIR3) but is silencing-independent [24] (Figure 2a, Figure 3). More recently, it was shown by live imaging of DNA and histones that fasting induces a tissue-specific reorganization of the whole genome in *C. elegans* [25]. In particular, the chromatin of intestinal cells, but not that of muscle or hypoderm, becomes enriched at the nuclear and nucleolar periphery in the absence of nutrients, a phenomenon that is fully reversed by refeeding. This 3D genome reorganization is independent of AMPK and is regulated by another nutrient-sensing pathway: the mechanistic target of rapamycin (mTOR). Despite regulating all three RNA polymerases, mTOR shapes the 3D genome in response to nutrients exclusively through regulation of RNA Pol I (Figure 2b). In fact, only the inhibition of RNA Pol I transcription, but not that of RNA Pol II or III, is sufficient to induce a fasting-like chromatin architecture in fed animals and impede the restoration of a fed-like genome architecture upon refeeding of fasted animals [25] (Figure 2b). Interestingly, the two studies conducted on nutrient-deprived *C. elegans* larvae [9,25] highlight how the same environmental stimulus can impact on chromatin organization differently in the various cell types of a multicellular organism, possibly through the modulation of distinct signaling pathways.

Both large-scale 3D genome reorganizations in 'starved' yeast and worms accompany the formation of long-lived states [26,27] and the 3D chromatin reconfiguration may support longevity in yeast [24]. Additionally, the

Figure 2



Effects of nutrient deprivation on the spatial distribution of chromatin in *S. cerevisiae* and *C. elegans*. **(a)** Carbon source exhaustion during the stationary phase alters the typical perinuclear clustering of telomeres in *S. cerevisiae*, leading to the formation of a telomere hypercluster located at the nuclear interior [24]. Hormetic reactive oxygen species derived from mitochondria (mtROS) during the exponential phase prime the cells to form hyperclusters upon starvation in a SIR3-dependent manner [24]. **(b)** Fasting induces a tissue-specific reorganization of the whole genome in *C. elegans*. Chromatin of intestinal cells becomes enriched at the nuclear and nucleolar periphery upon fasting in a mTOR- and RNA Pol I-dependent manner. The fasting-induced chromatin reorganization is fully reversed by refeeding [25].

manipulation of nutrient-regulated factors that influence chromatin accessibility and looping affects transcriptional programs [28,29]. Yet, to which degree nutrient-stress-dependent changes in genome architecture represent a consequence of transcription or have an 'upstream' function in regulating the transcriptional output themselves, requires further investigation.

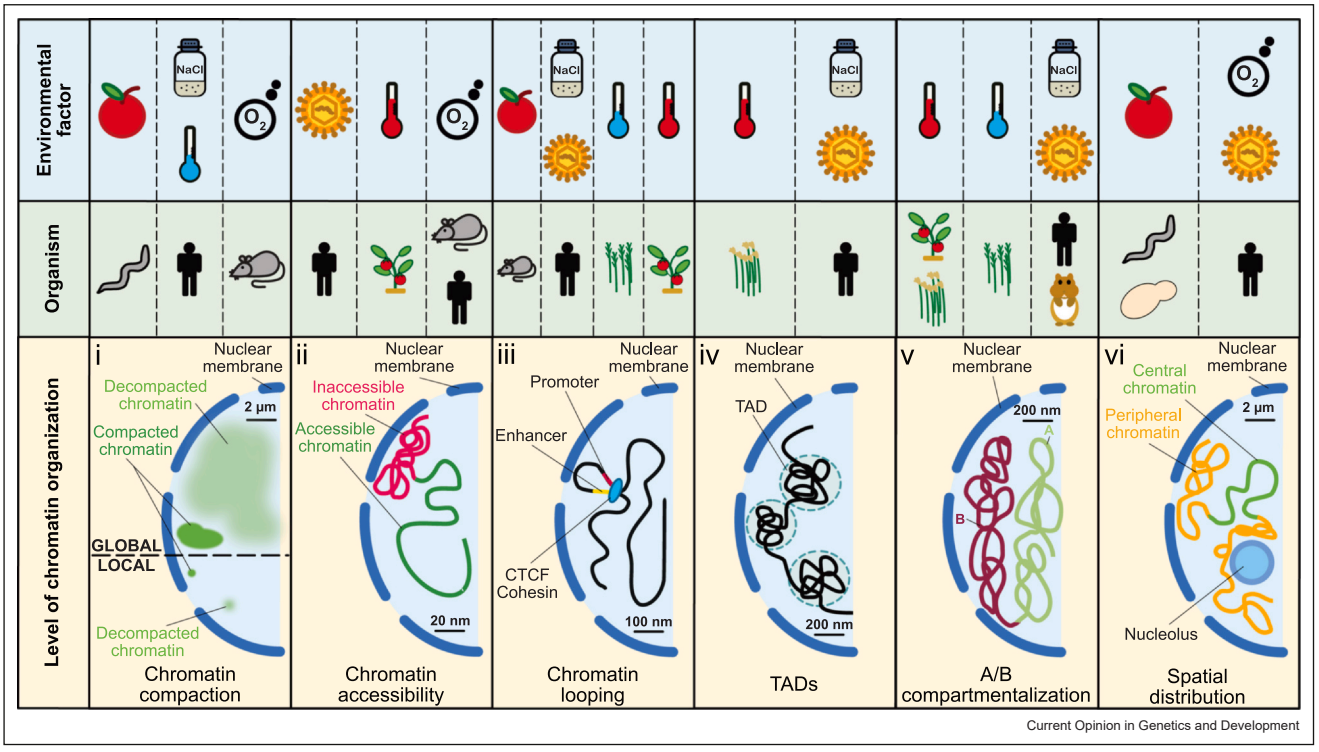
Temperature

Each organism has an optimal growth temperature. Yet, individuals are regularly exposed to temperatures above or below this optimum. To cope with this, sophisticated transcriptional stress responses have evolved, such as the highly conserved heat shock response (HSR), reviewed elsewhere [30].

Only few studies on the effects of cold shock on genome organization were conducted, revealing increased short-range and reduced long-range interactions and A–B compartment switches in plants [31] and the induction of a reversible global compaction of chromatin in human cardiomyocytes, detected with 3D-structured illumination microscopy [32] (Figure 3). Notably, the cold-induced global chromatin compaction does not arise from, and does not lead to, a general inhibition of RNA Pol II transcription [32]. Instead, a major driver for the reorganization might be Ca^{2+} signaling. Intracellular Ca^{2+} increases upon cold exposure [33] and can contribute to chromatin compaction in the interphase by charge shielding [34], analogously to what we discussed for other divalent cations, such as Mg^{2+}.

The role of heat shock (HS) in regulating chromosome structure dates back to the 1960s, when puffs on polytene chromosomes of heat-shocked *Drosophila* larvae were discovered.

Figure 3



Levels of chromatin organization affected by the different environmental factors. **i)** Chromatin compaction is affected by many of the environmental stimuli discussed here, either locally, such as for nutrient availability in *C. elegans* [6] or globally, by nutrient availability in *C. elegans* germ cells [9], cold stress in human cardiomyocytes [32], ischemic conditions in mouse cardiomyocytes [13], and by hyperosmotic [64,65] and hypo-osmotic stress [64] in various human cell types. **ii)** Chromatin accessibility was reported to be affected by heat stress in tomato [35], by various pathogens, such as EBV in human B cells [39] and HIV-1 in human T cells [40], and by hypoxia in various human cell types [57,59] and mouse cardiomyocytes [58]. **iii)** Chromatin looping is influenced by dietary changes in mice [19], heat stress in tomato [35], cold stress in *Brachypodium distachyon* [31], various pathogen encounters, such as EBV [41,42,46], SARS-CoV-2 [43], HTLV-1 [44], IAV [49], and bacterial exposure [45] in different human cell types, and also by hyperosmotic stress in a human breast cancer cell line [67]. **iv)** HS regulates TADs in rice [36]. EBV [41] and Ad5 infection [50] changes TAD boundaries in human cells and hyperosmotic stress decreases insulation and TAD number in human cells [67]. **v)** A and B compartments are altered by HS in tomato [35] and rice [36], by cold in *Brachypodium distachyon* [31], and by several pathogen encounters, such as Ad5 [50], EBV [41], and IAV [49] again in various human cell types and SARS-CoV-2 [48] in hamsters. Additionally, A and B compartments are altered by hyperosmotic stress in a human breast cancer cell line [67]. **vi)** The large-scale spatial distribution of chromatin is reorganized in the absence of nutrients in *S. cerevisiae* [24] and *C. elegans* intestine [25]. Immune-responsive and hypoxia-responsive genes change their spatial location in human neutrophils upon microbial exposure [45] and in human breast cancer cells upon hypoxia [62], respectively. Furthermore, SEs contribute to the spatial repositioning of HIV-1 RIGs toward the outer nuclear shell during T-cell activation in man [54].

Typically, chromatin accessibility correlates with compaction and reflects the degree to which nuclear factors can interact with the chromatinized DNA. It is usually modulated locally, at regulatory sequences (enhancers and promoters) to regulate gene expression, and is influenced by nucleosome occupancy and by TF binding. Recently, dynamic changes in chromatin accessibility, measured with the assay for transposase-accessible chromatin combined to sequencing (ATAC-seq), were characterized in tomatoes exposed to HS (Figure 3). In particular, regions opening up at different time points during stress are enriched for different TF-binding sites [35]. Furthermore, heat-shocked tomatoes form transient enhancer–promoter contacts that are mediated by heat shock factor 1A (HSF1A), a master TF driving HS-responsive gene expression [35].

In plants, HS can influence compartmentalization and TADs (Figure 3). For example, the A compartment is strengthened, either by positively affecting A–A interactions and reciprocally reducing B–B interactions in tomato [35], or by inducing B–A conversions in rice [36], where TAD size increases upon HS [36]. In contrast to plants, TADs and compartment structures remain unchanged upon HS in human K562 cells, despite a dramatic transcriptional response [37]. This suggests that the chromatin topology necessary for a robust HSR is largely pre-established in unstressed mammalian cells. Thus, while TFs drive the transcriptional response to heat across species, the effect on the 3D genome beyond local chromatin loosening, seems to be species-specific. Notably, because plants lack a clear CCCTC-binding factor (CTCF) homolog [38], how TADs

are defined and rearranged, is likely to vary compared with vertebrates, potentially explaining the different outcomes upon HS.

Pathogens

Virtually all species are affected by pathogens, taxonomically diverse organisms that cause disease in their host.

Recent ATAC-seq experiments showed that chromatin accessibility of the host is altered by viral infection (Figure 3), for example, by Epstein–Barr virus (EBV) [39] and human immunodeficiency virus 1 (HIV-1), where chromatin opens downstream of the integrated HIV-1 genome when this is transcriptionally activated [40].

Different types of pathogens were reported to trigger chromatin looping changes, for example, EBV [41,42], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [43], human T-lymphotropic virus type 1 (HTLV-1) [44], and bacterial infection [45] (Figure 3). Upon bacterial exposure, the cohesin complex is rapidly loaded on the neutrophils' genome and de novo chromatin loops are formed, linking a subset of pro-inflammatory genes to both preexisting and newly formed transcriptional enhancers [45]. The HTLV-1 provirus forms chromatin loops in *cis* with the flanking host sequences of infected CD4+ T lymphocytes, at least partially through CTCF binding [44]. Upon EBV infection, viral TFs such as EBV nuclear antigen 3A (EBNA3A) [41] and EBNA2 [42] alter the chromatin looping landscape of the host. In particular, resting B lymphocytes (RBLs) are converted into lymphoblastoid cell lines (LCLs) through the assembly of EBV super-enhancers (ESEs) [46], which interact to target genes through EBNA3A and shape the host 3D genome to control genes that promote LCL growth and survival [41].

Olfactory receptor (OR) gene clusters from different chromosomes converge to specific foci in the nuclei of olfactory sensory neurons (OSNs), facilitating stable and singular OR transcription [47]. SARS-CoV-2 infection triggers a reduction in long-range *cis*- and *trans*-genomic contacts of OR gene clusters in OSN, thus disrupting OR nuclear architecture [48]. Interestingly, these changes in chromatin architecture precede the downregulation of OR gene expression, providing a possible 3D genome-based explanation for COVID-19-induced anosmia [48]. Alterations in chromatin compartmentalization are not unique to SARS-CoV-2. More B–A than A–B compartment switches have been detected in EBV-infected LCLs compared with RBLs, suggesting a general increase in transcriptional activation [41]. Similar trends were observed in human monocyte-derived macrophages after influenza-A virus (IAV) infection, where read-through transcription into heterochromatin caused the switching of many genomic regions from B to A compartment [49]. In particular, the IAV protein NS1 inhibits transcriptional termination at highly transcribed genes, causing RNA Pol II transcription to extend to regions normally repressed and located even hundreds of kbs away. The passage of RNA Pol II displaces cohesin, promoting loss of chromatin looping [49]. Infection of hepatocytes with adenovirus type 5 (Ad5) triggers B–A compartment switching and TAD reorganization [50]. However, in the same study, hepatocytes infected with hepatitis-B virus show no alteration in compartmentalization and TADs [50], revealing virus-specific effects on chromatin architecture. Interestingly, 21% of TAD boundaries are gained and 8% are lost in EBV-induced LCLs compared with RBLs, with changes at these boundary sequences correlating with a gain or reduction in CTCF binding, respectively [41]. Thus, it appears that while TADs in mammals are largely unaffected by environmental cues, specific viral infections constitute an exception [41,50]. It is tempting to speculate that this may stem from a loss of cell identity, for example, in LCLs compared with RBLs [41], or from the ability of the viral DNA to directly interact with, and possibly perturb, TAD borders, as seen for Ad5 [50].

Upon microbial infection and before releasing chromatin within extracellular traps that contribute to killing bacteria [51], neutrophils lose the spatial separation between eu- and heterochromatin [52]. While large-scale A and B compartments remain unaffected, genomic regions enriched in neutrophil defense response genes increase their euchromatic character, consistent with the transcriptional activation of at least some of them, and reposition away from the transcriptionally repressive nuclear periphery [45].

Pathogen infections profoundly influence chromatin organization, leading to perturbations at almost every level (Figure 3), thus complicating the task of determining which layer(s) drive the alterations in gene expression and cell function.

Not only pathogen infection can alter the spatial distribution of genes (Figure 3), but also the spatial organization of chromatin can influence the infection process by determining the integration sites of the viral genome. Notably, recurrent HIV-1 integration genes (RIGs) are positioned at the nuclear periphery yet are enriched in active histone marks and excluded from heterochromatic lamina-associated domains (LADs) [53]. Intriguingly, RIGs are proximal to super-enhancer elements (SEs) [54], which contribute to the spatial repositioning of RIGs toward the outer nuclear shell during T-cell activation [54]. This occurs through the interaction of nuclear pore proteins with SEs [55] and with the HIV-1

provirus [53], thus contributing to the integration of the viral DNA within sequences at the nuclear periphery, in proximity of SEs.

Hypoxia

Deprivation of an adequate oxygen supply, a condition known as hypoxia, represents a critical abiotic stress that is induced in ischemic tissues or at high altitudes, for example. Central to the transcriptional response to low oxygen are hypoxia-inducible factors (HIFs), TFs that translocate to the nucleus and bind to hypoxia response elements (reviewed in [56]).

Recently, several studies have shown that chromatin accessibility changes in response to hypoxia, as measured by ATAC-seq [57–59] (Figure 3). A time-course experiment in human umbilical vein endothelial cells (HUVECs) exposed to low oxygen revealed that the regions where chromatin accessibility is altered change over time, with different TF motifs being enriched [57]. Remarkably, accessibility alterations precede gene expression changes [57]. Consistently, when HL-1 cardiomyocytes [58] or HeLa cells [59] are exposed to low oxygen, the differentially open regions overlap with hypoxia-responsive genes in a manner that is reversible upon reoxygenation [58,59], suggesting that chromatin accessibility at target genes is a highly dynamic means of regulating their expression in response to hypoxia, through the master TF HIF [59].

A derivative of chromosome conformation capture, termed Capture-C, was used to detect multiview interactions between distal HIF-binding sites and the promoters of its target genes [60]. Intriguingly, HIF acts on chromatin interactions that are already established in mammary epithelial MCF-7 cells under normoxic conditions and remain unaltered during hypoxia [60]. Likewise, hypoxia does not alter compartmentalization and TADs in HUVECs [61]. On the contrary, low-oxygen exposure alters the spatial positioning of hypoxia-responsive genes, albeit without a clear correlation with gene activity [62].

Lack of oxygen reduces mitochondrial ATP production, potentially causing a loss-of-ATP-dependent general chromatin compaction, as explained earlier in the review. Whether hypoxia alone induces a large-scale chromatin compaction is currently unknown. However, a combination of oxygen and nutrient deprivation, which mimics ischemic conditions, induces a global chromatin compaction in cardiomyocytes, measured by DNAse I sensitivity and microscopy [13]. This suggests that ATP levels might indeed play a major role in hypoxia-mediated chromatin changes, a topic that requires further investigation.

Osmotic stress

The balance between hydration and solute concentration is tightly controlled within organisms [63], as exposure to an increased or decreased solute concentration induces a hyper- or hypo-osmotic stress, respectively.

Hyper-osmotic stress, for example, caused by high concentration of sucrose or NaCl, induces a general chromatin compaction in mammalian cells, readily detected by microscopy [64,65]. On the contrary, hypo-osmotic conditions cause chromatin to decondense [64] (Figure 3). Intriguingly, the nucleus shrinks and swells under hyper- and hypo-osmotic conditions, respectively [66]. This alters the nuclear concentration of macromolecules and cations, which we speculate may contribute to regulating global chromatin compaction. Intriguingly, hyper-osmotic conditions induce dehydration, which deforms the shape of the nucleus [66], distorting the nuclear lamina. Whether this has any consequences for LAD organization is currently unexplored.

In agreement with an augmented chromatin compaction, hyper-osmotic stress in mammalian T47D cells increases the frequency of long-range interactions and the number of genomic sequences defined as B compartment, while short-range interactions, TAD insulation, and number decrease [67] (Figure 3).

Concluding remarks

Individual environmental stimuli induce distinct, often species- or cell-type-specific responses. Yet, common features in the chromatin architecture response to different external cues begin to emerge (Figure 3). For example, chromatin compaction can be regulated globally by changes in the concentration of free cations, which can be induced by different stresses. A/B compartment switches tend to be associated with transcriptional changes [35,36,49,67], while changes in TADs are uncommon, particularly in mammals, suggesting that they are rather stable structures. Chromatin accessibility at gene regulatory regions is altered by several stimuli and correlates with TF binding [39,42,59]. At least in some cases, increased accessibility precedes gene activation, suggesting that local chromatin decompaction promotes environment-responsive gene expression [57]. Changes in chromatin interactions induced by environmental cues are often mediated by TFs that are implicated in the transcriptional response to the stimulus itself [6,35,41,42,59], complicating the task of determining to which degree the topological changes have a function *per se*. Notably, the involvement of TFs in regulating chromatin architecture reveals parallels to what is known for developmental genes,

where dedicated TFs shape the chromatin architecture landscape and regulate the transcriptional output [68]. Thus, TF-mediated changes in chromatin accessibility and contacts induced by the environment are likely to follow principles similar to those occurring at developmentally regulated loci during differentiation [69].

The disruption of OR chromatin interactions in OSNs by SARS-CoV-2 is non-cell-autonomous, as it does not require a direct viral encounter but can be mimicked by exposing the olfactory epithelium to a SARS-CoV-2-inactivated serum from infected animals [48]. This shows that not only the direct exposure to external agents but also the environment in which a cell lives critically contributes to 3D genome regulation.

Cells *in vivo* integrate inputs from organismal-external cues, neighboring cells, and distant tissues. Thus, they are exposed to a very complex environment that may contribute to shaping 3D genome architecture in unique ways, compared with cells in culture. Indeed, unusual spatial genome configurations have been discovered *in vivo*, for example, in rod photoreceptors of nocturnal rodents, which possess an 'inverted' chromatin architecture [70], and in intestinal cells of *C. elegans*, where two 'chromatin rings' are induced by fasting [25].

We propose that *in vitro* studies will be instrumental to dissect the regulation of genome architecture at the molecular level, while *in vivo* experiments will be fundamental to uncover novel chromatin configurations in normal and environmentally perturbed conditions. By combining complementary experimental systems and technical approaches, future research in the field of chromatin architecture holds great potential for deciphering how lifestyles influence health and disease through epigenetics.

CRediT authorship contribution statement

Conceptualization: **LP and DSC**. Writing – original draft: **LP**. Writing – review & editing: **LP and DSC**. Figures: **LP**. Supervision: **DSC**. Funding acquisition: **DSC**.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

Lorenz Pudelko and Daphne S. Cabianca, authors of the mini-review entitled "The influencers' era: how the environment shapes chromatin in 3D", declare that they have no conflict of interest.

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- • of special interest
- •• of outstanding interest

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