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The Physics of Cancer: The Role of Epigenetics and Chromosome Conformation in Cancer Progression

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Abstract. Cancer progression is generally described in terms of accumulated genetic alterations and ensuing changes in cell properties. However, intermediary modifications are involved in the establishment of cancer cell phenotypes, at different levels of nuclear organization: DNA damages and their structural consequences, epigenetic modifications and their impact on chromatin architecture, changes in chromosome 3D organization. We review some of these alterations with a focus on their physical aspects. The challenge is to understand the multiscale interplay between generic physical mechanisms and specific biological factors in cancer cells. We argue that such an interdisciplinary perspective offers a novel viewpoint on cancer progression, early diagnosis and possibly therapeutic targets.

INTRODUCTION

Physics of cancer may refer to the use of a physical framework to describe quantitatively the biological processes involved in cancer progression, or the development of physical materials and techniques for reconstructive medicine (e.g. implants), tumor imaging (e.g. nanoparticles) or cancer cell characterization (e.g. atomic force microscopy), as presented in these proceedings. We here propose an alternative meaning, namely the understanding of physical constraints and mechanisms at work in biological functions and their misregulation, or even failure, in cancer.

Cancer progression is currently associated with cell modifications due to genetic alterations induced by radioactivity or genotoxic agents, together with some random or inherited variations. However, understanding the mechanisms involved in cancer progression cannot be reduced to a list of specific mutations, translocations and copy number alterations. Additional determinants are nowadays invoked to explain the development of the disease [1, 2]. In particular, not only genetic, but also epigenetic modifications [3–5] and changes in 3D genome organization [6, 7] or nuclear architecture [8] could participate to the cancerous symptoms.

Actually mutational patterns vary even among tumors of the same cancer type [9, 10]: distinct series of genomic alterations could affect in the same way a signaling or functional pathway, and lead to the same cancer phenotype. This suggests that the explanation lies more at the level of phenotypic changes than at the genetic level, and further supports a physiological view supplemented with the account of physical aspects.

A novel direction is thus to investigate the possible physical determinants of cancer, at various scales, from the genomic scale to the cell or tissue scale. We here mean the physical mechanisms and physical features that are both affected by cancer-related biological anomalies (such as mutations and chromosomic alterations, abnormal epigenetic patterns, activation of cancer-related pathways, cytological changes) and affecting the functioning of the cell (e.g. transcriptional regulation, intracellular transport, cell adhesion or motility). We will consider in this physical perspective some genome-based processes and their alterations in cancer cells.

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An important feature of the eukaryotic genome is its multiscale organization, from the level of DNA molecule to that of nucleosomes (basic units formed of 146 base pairs of DNA wrapped around a core of eight histone proteins), to nucleosome arrays forming the chromatin fiber, up to the level of chromosomes. Both DNA and the chromatin fiber can be described mesoscopically as flexible filaments, endowed with elasticity properties and experiencing mechanical stresses [11]. This structural and spatial organization of the genome is associated with physical constraints, and plays an important and often underrated role in the regulation of gene expression. Here, we will review and discuss cancer-related changes in this multiscale organization, affecting either DNA structure, epigenetic patterns, chromosome conformation or nuclear architecture.

DNA DAMAGES

Physical damages of the DNA molecule, typically double-strand breaks due for instance to an intense and localized energy deposit during irradiation [12], are involved in cancer progression. Such breaks trigger several biological events, leading to the recruitment of repair machineries [13]. Importantly, they have also underrated physical consequences, in particular in terms of chromatin decondensation [14].

A simple mechanistic approach is to consider the topological effect of DNA breaks on chromatin conformation. DNA can be described as a semi-flexible ribbon characterized by its linking number (the number of turns one strand makes around the other). This number is a topological invariant, conserved in a DNA stretch with fixed ends (or a closed DNA loop). Any difference with respect to its value in relaxed DNA, what is termed DNA supercoiling, is associated with topological constraints. DNA supercoiling can be due either to its wrapping around nucleosomes of variable shape [15] or to the spatial conformation of the chromatin fiber [16]. Supercoiling and associated topological constraints are higher in compact chromatin states. A DNA break allows the relaxation of these constraints, which causes a decondensation of the chromatin fiber.

This effect can be observed *in vivo* by fluorescent tagging of the H2AX histone variants that are replacing plain H2A in the signaling response to radiation-induced damages [17, 18]. However, in dense heterochromatin, a double-strand break may not be enough to trigger decondensation due to stacking interactions between nucleosomes [19]. An additional consequence of chromatin compaction is a more complicated repair due to steric hindrance [7, 20].

Overall, understanding the effects of DNA breaks requires a mechanical and geometrical analysis, on top of the identification of biological factors recruited following these damages. DNA damages have been observed to lead to different biological outcomes: they are either cytotoxic and then induce ageing, or mutagenic and then induce cancer [13]. It will be interesting to investigate how physical determinants participate in these two different fates. Another open direction is to investigate whether the intrinsic nonlinear dynamics of the DNA molecule and its internal degrees of freedom [21], sustained by thermal energy and driven by some initial perturbation, can promote a transient energy localization and in this way, participate to an irreversible break in the covalent phosphate back-bone [22].

CANCER EPIGENETICS

Epigenetics nowadays refers to the molecular determinants of gene regulation that are heritable through cell division but do not involve the genetic sequence. They rely on epigenetic marks, mainly DNA methylation and histone posttranslational modifications (typically methylation, acetylation and phosphorylation of specific residues) [3, 23]. Epigenetic marks are set up in an active and reversible way by specific enzymes. Experimental techniques now allow a genome-wide access to epigenetic marks, whose profiles (along the genome) are freely available in genome browsers. Epigenetic marks play a key role in the control of gene activity and nuclear organization, hence any alteration is likely to be associated with diseases. In particular, abnormal epigenetic patterns have been found in numerous types of cancers [24]. Epigenetics is at the core of cell differentiation, during which cells sharing the same genome have different fates. Epigenetic marks reflect the print of life history (i.e. diet of the mother during pregnancy) and external factors (pollutants, diet). As such, they act as a mediator of the impact of environment on the cells. Cancer epigenetics thus offers a new view on cancer risk and cancerogenous factors [1, 3–5].

At the DNA level, DNA methylation corresponds to the transfer of a methyl group onto some cytosines, achieved by specific enzymes (methyltransferases). This epigenetic modification of DNA is reversible, the removal of methyl groups being achieved by another class of enzymes (demethylases). The dominant feature is a massive hypomethylation, balanced with a local and targeted hypermethylation. In more details, hypomethylation of repetitive sequences, who are normally heavily methylated, may lead to genomic instability [25]. Another

acknowledged link between loss of methylation and cancer comes from imprinted genes, that is, genes whose expression is depending on their parental origin. In these genes, the memory of the parental origin of the alleles is specified by the presence or the absence of DNA methylation onto a specific region of the locus sequence (the Imprinting Control Region, ICR). The direct consequence of ICR differential methylation is the expression of only one allele. Spurious loss of ICR methylation in cancer cells may thus lead to the biallelic expression hence overexpression of imprinted genes [25]. In contrast, promoters located in the so-called CpG islands (CpG-rich regions that are normally devoid of methylation) become methylated in cancer cells, whereas they have a low methylation level in normal cells [26]. In turn, this hypermethylation of promoter regions leads to the transcriptional silencing of the associated genes. This is dramatically associated with cancer when these silenced genes are tumor-suppressor or DNA-repair genes. Changes in DNA methylation patterns during cancer progression are possibly due to over-expression or under-expression of the corresponding enzymes [27]. An open issue is then to understand why and how certain genomic sequences are targeted for methylation or demethylation.

At the chromatin level, important dysregulations of both the epigenetic machinery and the histone modifications have been discovered in cancer cells [25, 28, 29]. Histone deacetylation has been shown to be a common hallmark of cancer cells [30, 31]. Histone modification patterns have been proposed as a tool for cancer prognosis [32].

DNA methylation also offers novel signatures of cancer prognosis. Interestingly, DNA methylation pattern is already modified in pre-cancer cells [33, 34], providing a path to cancer prediction at an early pre-cancerous stage, far before other means of diagnosis. A more ambitious direction recently opens: epigenetic therapy. Indeed, the reversible nature of epigenetic modifications are reversible makes possible to envision therapeutic actions [3, 35, 36]. For instance, a folate-free diet to reduce SAM synthesis (the methyl-group donor in DNA methylation), resulting in DNA hypomethylation with a beneficial effect against tumorigenesis [31]. Also the administration of demethylating agents has been considered to compensate for DNA hypermethylation of promoters [37].

The action of epigenetic marks is currently understood in terms of chemical recognition and recruitment of specific factors or co-factors. However, a physical reading of epigenetic marks has been proposed [19, 38, 39]. At the DNA level, epigenetics may regulate genomic processes via a tuning of the mechanical properties of the genomic DNA. Cytosine methylation is associated with a higher probability of hydrogen-bond breaking, a decrease of the twist and width of the minor groove and a local sequence-dependent change in the flexibility and twist rate of DNA [23]. Also, methyl-DNA binding activities directly or indirectly (via the recruitment of complexes) affect the structure of chromatin, ultimately controlling its local transcriptional state [40]. Histone modifications strongly influence the chromatin fiber structure [19, 39] and its properties *in vivo* [41], up to the chromosome level [42]. Epigenetics thus affects gene expression (hence the cell state) not only via a direct control of the recruited transcription factors and machinery, but also via changes in 3D genome architecture. Accordingly, understanding the causal links between epigenetic alterations and various types of cancers require to also consider the higher levels of nucleus organization.

3D GENOME ORGANIZATION IN CANCER CELLS

The standard view on chromosome organization [43–45] has been recently renewed by technical advances in experimental *in vivo* methods. In particular, chromosome conformational capture and various imaging techniques [6] have led to dramatic advances in our knowledge of the supranucleosomal level of organization [46, 47]. Moreover, algorithms have been developed for reconstructing three-dimensional (3D) genome structure from the measure of pairwise contacts between genomic loci provided by chromosome conformational capture experiments [48]. The visualization of all genome annotations in their 3D spatial context is now at reach [49].

A first direction in cancer research is thus to investigate the location of cancer risk loci (determined in genome-wide association studies) within the reference 3D genome structure obtained in conformational capture studies of normal cells. It allows understanding which long-range interactions these loci could develop and in turn, the mechanisms underlying their at-risk status. For instance, risk loci for multiple epithelial cancers, including colon, breast, and prostate cancers, are plausible enhancers forming a long-range chromatin loop with the *MYC* proto-oncogene in a tissue-specific way [50]. Somatic copy-number alterations have been investigated in their 3D context, which appears to act as a (positive or negative) selective force in the evolution of cancer cells [51]. Also, spatial proximity is likely to mediate genomic rearrangements and translocations in lymphomas and sarcomas cells [52].

A second direction is to investigate the numerous changes observed in the chromosome architecture [7] and nuclear organization [8] of cancer cells. Investigating changes in chromatin and nuclear structure can not only reveal biomarkers but also gives insights on the mechanisms of cancer progression, e.g. how alterations are partly driven

by epigenetic marks and their physical consequences. Here also, a physical view appears to provide new paths of investigation and understanding.

Chromosome conformational capture techniques, based on a chemical crosslinking of spatially close genomic loci followed by their sequencing, are difficult to use in cancer cells. Indeed multiple chromosomic rearrangements make difficult to align the crosslinked fragments and to properly locate contacting loci in the cancerous chromosomes. To date only a few studies have been performed. Nevertheless, significant changes in genomic contacts have been obtained by a method of this class in bladder cancer and lymphomas [53], revealing altered chromatin architecture [54]. Genome-wide analyses evidenced changes in telomere clustering with less contacts in MCF7 breast cancer cells while an increased contact frequency is observed within the small chromosomes, from chr16 to chr22 [55]. Other studies have evidenced a displacement of specific genes with respect to their original location within a chromosome territory. Chromosome arrangements have been observed to undergo alterations in a cell-specific way in breast cancer [56]. However, the relative interphase positioning of chromosomes may not be affected, as observed in mouse lymphoma cells [57]. Also a change in the 3D organization of telomeres has been observed, with the formation of telomeres aggregates mediating genomic instability [58].

3D genome organization heavily relies on architectural proteins. Consequently, mutations or transcriptional misregulation of these proteins in cancer produce global alterations in chromatin structure [7]. For instance, the protein SATB1 promotes the formation of loops and its expression correlates with a bad prognosis. In contrast, it is the loss of the protein HP1 which correlates with bad prognosis. Both loss and over-expression of the protein CTCF have severe effects [6], as can be expected from numerous observations showing that CTCF is an important mediator between nuclear organization and gene expression [59].

As mentioned above, epigenetics and genome architecture are closely coupled, and the coupling centrally involves physical properties. For instance, it has been shown, using polymer modeling of the chromatin fiber, that epigenetic histone modifications significantly affect the compaction and flexibility properties of the fiber [41]. An open research direction is thus to investigate how cancer-related epigenetic changes directly reflect in the physical properties and 3D organization of the chromatin fiber, and the consequences on gene regulation.

At higher organization level, nuclear bodies are important functional features of nuclear organization [60]. A link between cancer and modifications of nuclear bodies, via the regulation of the tumor-suppressor gene p53, has been recently evidenced [61]. A new type of nuclear bodies, involved in the trafficking of some messengers RNA, has also been observed in some cancers [62]. Investigating the features of nuclear bodies in cancer cells is thus a promising direction. Part of the authors have developed in this aim a new technique named the HRS-seq. The principle of the experiment relies on a high-salt treatment (High-Salt Recovery) of transcriptionally active nuclei, followed by the sequencing of the DNA trapped in the resulting insoluble ribonucleoproteic complexes [63]. The HRS-seq method makes possible the identification of genomic sequences lying inside specific nuclear compartments, including those associated with nuclear bodies, in normal and cancer cells.

Overall, changes of 3D genomic structure in cancer cells span several scales and levels of organization, from the DNA itself to the nuclear architecture. Our perspective thus underlines the need of a multiscale approach.

MULTISCALE APPROACH OF CANCER PROGRESSION

Our multiscale approach to bridge the above-described features shares a central idea of mesoscopic physics: the use of effective parameters to capture at a given scale the contributions of the underlying scales. However, the scheme does not stop here in complex systems, in particular in biological systems. Indeed, the collective modes and emergent structures could trigger the appearance of new degrees of freedom at smaller scales, as in complex solids [64]. In biological systems, they can even modify the very activity of the biological actors at these smaller scales. In practice, the scheme for multiscale integration in biology amounts to identify at each level collective modes and effective parameters, and to jointly achieve the description of elementary processes within their global context [65]. However, only the self-consistent closure of these bottom-up and top-down analyses can account for the regulation at work in biological systems, and explain the misregulations associated with pathologies.

This multiscale approach can be applied not only to genome-based processes inside the cell nucleus, but also to the entire set of relevant levels, from DNA structure to tissue properties. The challenge is to bridge, using the above multiscale scheme, processes observed in the nucleus of cancer cells with changes in cell morphology and properties (e.g. cell mechanical response) and features of both healthy and tumor tissues.

The guideline provided by physical constraints and mechanobiology is specially relevant for this multiscale approach. The examples presented in the previous sections are only a limited illustration of the potential of a

physical perspective on cancer-related alterations. Many other facts and processes could have been described. For instance, chromosomic abnormalities in cancer may result from a problem in chromosome segregation, when physical tensions applied by microtubules within the mitotic spindle are defective [66]. Also physical determinants of the altered shape of cancer cell nuclei, currently used as a diagnosis tool [8], are still to be explored. For this question, the open multiscale challenge will be to physically relate the chromosomal rearrangements and chromatin decondensation during cancer progression to the altered size and shape of cancer cell nuclei [67–69], then to the abnormal mechanical response of cancer cells (see Lyapunova et al., this issue). Another possible multiscale investigation concerns the force transmission between the cytoskeleton and the nucleus, across the nuclear membrane. It is involved in intracellular nuclear movement and positioning, with a central role of a class of proteins, the lamins [70]. The possibility of direct transmission from the cytoskeleton to chromatin, through lamina-associated domains (lamina is the nuclear membrane coated with lamins) has been suggested, but remains to be quantitatively assessed. Such a nucleo-cytoskeletal coupling appears to be essential in cancer metastasis.

CONCLUSION

Understanding cancer progression requires to integrate numerous observations of different natures and at different scales. We here focused on the multiscale interplay between physical mechanisms and biological factors, and its observed alterations in cancer cells. Our approach is to investigate the physical consequences of specific biological events, and how these physical features could modify subsequent biological processes. It offers a guideline to articulate cancer-related genetic, epigenetic and nuclear modifications, that can be extended at the cell or tissue level. This interdisciplinary perspective opens novel research directions for early diagnosis, identification of cancer susceptibility and factors at-risk, and possibly new therapeutical targets.

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The study reported in this article was conducted according to accepted ethical guidelines involving research in humans and/or animals and was approved by an appropriate institution or national research organization. The study is compliant with the ethical standards as currently outlined in the Declaration of Helsinki. All individual participants discussed in this study, or for whom any identifying information or image has been presented, have freely given their informed written consent for such information and/or image to be included in the published article.

REFERENCES

1. H. Easwaran, H. C. Tsai, and S. B. Baylin, Molecular Cell **54**, 716–727 (2014).
2. D. Hanahan and R. A. Weinberg, Cell **100**, 57–70 (2000).
3. M. A. Dawson and T. Kouzaridès, Cell **150**, 12–27 (2012).
4. P. A. Jones and S. B. Baylin, Cell **128**, 683–692 (2007).
5. P. W. Laird, Human Molecular Genetics, **14**, R65–R76 (2005).
6. D. Babu and M. J. Fullwood, Nucleus **6**, 382–393 (2015).
7. T. Misteli, Cold Spring Harbor Perspectives Biol. **2**, a000794 (2010).
8. D. Zink, A. H. Fischer, and J. A. Nickerson, Nat. Rev. Cancer **4**, 677–687 (2004).
9. M. Gerstung and N. Beerenwinkel, Math. Population Studies **17**, 115–135 (2010).
10. Q. Zhang and R. H. Austin, Annual Rev. Condens. Matter Phys. **3**, 363–382 (2012).
11. A. Lesne and J. M. Victor, Eur. Phys. J. E **19**, 279–290 (2006).
12. M. Falk, E. Lukasova, and S. Kozubek, Mutation Res. Rev. Mutation Res. **704**, 88–100 (2010).
13. J. H. J. Hoeijmakers, New Eng. J. Med. **361**, 1475–1485 (2009).
14. C. Lavelle and N. Foray, Int. J. Biochem. Cell Biology **49**, 84–97 (2014).
15. J. Mozziconacci, L. Lavelle, M. Barbi, A. Lesne, and J. M. Victor, FEBS Lett. **580**, 368–372 (2006).
16. M. Barbi, J. Mozziconacci, and J. M. Victor, Phys. Rev. E **71**, 031910 (2005).

17. N. Chavaudra, J. Bourhis, and N. Foray, Radiotherapy Oncology **73**, 373–382 (2014).
18. L. J. Kuo and L. X. Yang, In Vivo **22**, 305–309 (2008).
19. A. Lesne, N. Foray, G. Cathala, T. Forné, H. Wong, and J. M. Victor, J. Phys. Condens Matter **27**, 064115 (2015).
20. P. J. Johnston and P. E. Bryant, Int. J. Radiation Biology **66**, 531–536 (1994).
21. M. Barbi, S. Cocco, M. Peyrard. and S. Ruffo, J. Biological Phys. **24**, 97114 (1999).
22. O. B. Naimark, Phys. Mesomech. **10**, 33–45 (2007).
23. R. Cortini, M. Barbi, B. Caré, C. Lavelle, A. Lesne, J. Mozziconacci, and J. M. Victor, Rev. Modern Phys. **88**, 025002 (2016).
24. C. B. Santos-Reboucas and M. M. G. Pimentel, Eur. J. Human Genetics **15**, 10–17 (2007).
25. M. Esteller, Nat. Rev. Genetics **8**, 286–298 (2007).
26. M. R. Hassler and G. Egger, Biochimie **94**, 2219–2230 (2012).
27. M. Pedersen and K. Helin, Trends Cell Biology **20**, 662–671 (2010).
28. P. Chi, C. D. Allis and G. G. Wang, Nat. Rev. Cancer **10**, 457–469 (2010).
29. Z. Wang, H. Yao, S. Lin, X. Zhu, Z. Shen, G. Lu, W. S. Poon, D. Xie, M. C. Lin. and H. F. Kung, Cancer Lett. **331**, 1–10 (2013).
30. M. F. Fraga, E. Ballestar, A. Villar-Garea, M. Boix-Chornet, J. Espada, G. Schotta, T. Bonaldi, C. Haydon, S. Ropero, K. Petrye, and N. G. Iyer, Nat. Genetics **37**, 391–400 (2005).
31. L. T. Smith, G. A. Otterson, and C. Plass, Trends Genetics **23**, 449–456 (2007).
32. D. B. Seligson, S. Horvath, M. A. McBrian, V. Mah, H. Yu, S. Tze, Q. Wang, D. Chia, L. Goodlick, and S. K. Kurdistani, Am. J. Pathology **174**, 1619–1628 (2009).
33. A. Feinberg and B. Tycko, Nat. Rev. Cancer **4**, 143–153 (2004).
34. W. Timp and A. Feinberg, Nat. Rev. Cancer **13**, 497–510 (2013)
35. R. M. Campbell and P. J. Tummino, J. Clinical Investigation **124**, 64–69 (2014).
36. K. Shinjo and Y. Kondo, Adv. Drug Delivery Rev. **95**, 56–64 (2015).
37. P. M. Das and R. Singal, J. Clinical Oncology **22**, 4632–4642 (2004).
38. B. R. Caré, P. Carrivain, T. Forné, J. M. Victor, and A. Lesne, Communications Theor. Phys. **62**, 607–616 (2014).
39. A. Lesne, C. Bécavin, and J. M. Victor, Phys. Biology **9**, 013001 (2012).
40. E. Ballestar and M. Esteller, Carcinogenesis **23**, 1103–1109 (2002).
41. V. Ea, T. Sexton, T. Gostan, L. Herviou, M.O. Baudement, Y. Zhang, S. Berlivet, M. N. LeLay-Taha, G. Cathala, A. Lesne, J. M. Victor, Y. Fan, G. Cavalli, and T. Forné, BMC Genomics **16**, 607 (2015).
42. N. Kleckner, D. Zickler, G. H. Jones, J. Dekker, R. Padmore, J. Henle, and J. Hutchinson, Proc. Nat. Acad. Sci. USA **101**, 12592–1259 (2004).
43. T. Cremer and C. Cremer, Nat. Rev. Genetics **2**, 292–301 (2001).
44. P. C. Park and U. De Boni, Life Sci. **64**, 1703–1718 (1999).
45. D. L. Spector, Annual Rev. Biochemistry **72**, 573–608 (2003).
46. M. R. Branco and A. Pombo, Trends Cell Biology **17**, 127–134 (2007).
47. V. Ea, M. O. Baudement, A. Lesne, and T. Forné, Genes **6**, 734–750 (2015b).
48. J. B. Morlot, J. Mozziconacci, and A. Lesne, Eur. Phys. J. Nonlinear Biomed. Phys. **4**, 2 (2016).
49. A. Lesne, J. Riposo, P. Roger, A. Cournac, and J. Mozziconacci, Nat. Methods **11**, 1141–1143 (2014).
50. N. Ahmadiyeh, M. M. Pomerantz, C. Grisanzio, P. Herman, L. Jia, V. Almendro, H. H. He, M. Brown, X. S. Liu, M. Davis, J. L. Caswell, C. A. Beckwith, A. Hills, L. MacConnail, G. A. Coetzee, M. M. Regan, and M. L. Freedman, Proc. Nat. Acad. Sci. USA **107**, 9742–9746 (2010).
51. G. Fudenberg, G. Getz, M. Meyerson, and L. A. Mirny, Nat. Biotechnology **29**, 1109–1113 (2011).
52. J. M. Engreitz, V. Agarwala, and L. A. Mirny, PloS One **7**, e44196 (2012).
53. K. S. Sandhu, G. Li, H. M. Poh, Y. L. K. Quek, Y. Y. Sia, S. Q. Peh, F. H. Mulawadi, J. Lim, M. Sikic, F. Mengi, A. Thalamuthu, W. K. Sung, X. Ruan, M. J. Fulwood, E. Liu, P. Csermely, and Y. Ruan, Cell Rep. **2**, 1207–1219 (2012).
54. M. J. Zeitz, F. Ay, J. D. Heidmann, P. L. Lerner, W. S. Noble, B. N. Steelman, and A. R. Hoffman, PLoS One **8**, e73974 (2013).
55. A. R. Barutcu, B. R. Lajoie, R. P. McCord, C. E. Tye, D. Hong, T. L. Messier, G. Browne, A. J. van Wijnen, J. B. Lian, J. L. Stein, and J. Dekker, Genome Biology **16**, 1–14 (2015).
56. N. V. Marella, S. Bhattacharya, L. Mukherjee, J. Xu, and R. Berezney, J. Cellular Physiology **221**, 130–138 (2009).

57. L. A. Parada, P. G. McQueen, P. J. Munson, and T. Misteli, Current Biology **12**, 1692–1697 (2002).
58. T. Klonisch, L. Wark, S. Hombach-Klonisch, and S. Mai, Annals Anatomy-Anatomischer Anzeiger **192**, 292–301 (2010).
59. R. Ohlsson, V. Lobanenkov, and E. Klenova, Bioessays **32**, 37–50 (2010).
60. Y. S. Mao, B. Zhang, and D. L. Spector, Trends Genetics **27**, 295–306 (2011).
61. D. Guan and H. Y. Kao, Cell Bioscience **5**, 60 (2015).
62. H. Zhou, J. Zhang, Y. Gu, X. Gan, Y. Gan, W. Zheng, B. W. Kim, X. Xu, X. Lu, Q. Dong, and S. Zheng, Oncotarget **7**, 4724–4734 (2015).
63. M. O. Baudement, HRS-seq: a new high-throughput method to analyze genomic sequences associated with nuclear bodies, Ph.D. thesis, University of Montpellier, 2015.
64. O. B. Naimark, Phys. Mesomech. **13**, 306–317 (2010).
65. A. Lesne, Acta Biotheoretica **61**, 3–19 (2013).
66. Z. Bertalan, Z. Budrikis, C. A. La Porta, and S. Zapperi, PloS One **10**, e0141305 (2015).
67. G. Bussolati, F. Maletta, S. Asioli, L. Annaratone, A. Sapino, and C. Marchiò, To be or not to be in a good shape: Diagnostic and clinical value of nuclear shape irregularities in thyroid and Breast cancer, in *Cancer Biology and the Nuclear Envelope*, edited by E. C. Schirmer and J. I. de las Heras (Springer, New York, 2014), pp. 101–121.
68. V. Nandakumar, L. Kelbauskas, K. F. Hernandez, K. M. Lintecum, P. Senechal, K. J. Bussey, P. Davies, R. H. Johnson, and D. R. Meldrum, PloS One **7**, e29230 (2012).
69. M. Webster, K. L. Witkin, and O. Cohen-Fix, J. Cell Science **122**, 1477–1486 (2009).
70. P. Isermann and J. Lammerding, Current Biology **23**, R1113–R1121 (2013).