Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Deep Insight Section

Three-dimensional organization of the mammalian nucleus in normal and tumor cells

Sabine Mai

Manitoba Institute of Cell Biology, CancerCare Manitoba, The University of Manitoba, 675 McDermot Avenue, Winnipeg MB R3E 0V9, Canada

Published in Atlas Database: November 2005

Online updated version: http://AtlasGeneticsOncology.org/Deep/3DOrganizNuclID20053.html
DOI: 10.4267/2042/38310

Nuclear organization and genome stability

The three-dimensional organization of the genome and nucleus play pivotal roles in tumor development. As Theodor Boveri (1862-1915) postulated a century ago, aberrant chromosome numbers are associated with aberrant cell division and linked to tumor formation (Boveri, 1902; Boveri, 1914). Studying cell division in Ascaris and in sea urchin eggs under normal conditions and following double fertilization, he observed normal as well as aberrant cell divisions. From the latter with aberrant chromosome constitutions he inferred similar changes could occur in cancer cells (Boveri, 1914). A concept of chromosome and centrosome cycles emerged from his work and Boveri's seminal observations are as valid today as they were a century ago. They are often considered the basis for the first genetic model of cancer development (Moritz and Sauer, 1996; Wunderlich, 2002). Today's researchers in the field of nuclear structure and genome organization are still gathering many details of this organizational puzzle, which is important for determining normal or aberrant nuclear organization and cellular fate.

Imaging of nuclear structures

Advances in imaging, and specifically in fluorescent imaging, have contributed to our understanding of the three-dimensional organization of the nucleus. The transition from two-dimensional (2D) to three-dimensional (3D) imaging has allowed us to better understand how the nucleus is spatially organized. In addition to 3D approaches, live cell imaging has added a new dimension to our ability of developing clear concepts about the dynamics of nuclear organization (Liu and Chang, 2003; Garini et al., 2005). Live cell imaging with 3D resolution is often called four-dimensional (4D) imaging, where the fourth dimension of time is added to the imaging in the x,y, and z planes, that constitute a 3D image. Such 4D studies involve light microscopy and fluorescent imaging approaches, and use fluorescent proteins or fluorescent labeled nucleic acids (Haraguchi et al., 1999; Stephens and Allen, 2003; Gatlin et al., 2003; Solovei et al., 2002; Molenaar et al., 2003; Bystricky et al., 2004, 2005).

The images shown below indicate how 2D and 3D images differ with respect to the spatial information given. The same object, a lymphocyte nucleus (blue) with telomeres (red), is shown in 2D (Fig. 1, top) and in 3D (Fig. 1, bottom). Using illustrations such as the one shown in Fig. 2, one can imagine how 3D information is collected. However, 3D movies as published online (Louis et al., 2005) best reflect the spatial order of objects in the nucleus. Since the depth and spatial relationships are lost when imaging a 3D object in one focal plane, i.e. in two dimensions (Fig. 1, top), 3D imaging methods that account for the overall structure of the object are an obvious and necessary choice for any spatially relevant study. 3D imaging whether through confocal or deconvolution approaches give a representation of the true spatial organization of the nucleus (Fig. 1, bottom) and will ultimately allow us to link structure and function. Finally, the dynamic nature of the nucleus becomes evident through time lapse and live cell studies (i.e. Molenaar et al., 2003).

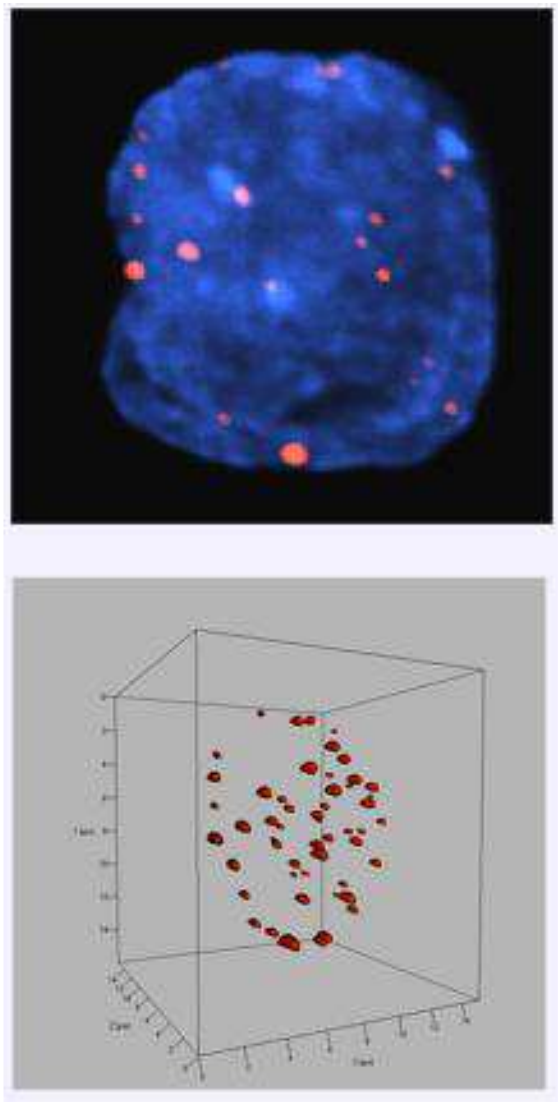

Figure 1. Two-dimensional (2D) and three-dimensional image of a mouse lymphocyte nucleus and its telomeres.
Top: 2D image. The nucleus (blue) is stained with 4',6-diamidino-2-phenylindole (DAPI). The telomeres (red) are labeled with a Cy3-conjugated peptide-nucleic acid (PNA) probe (DAKO). 2D and 3D images were acquired using a Zeiss Axioplan 2 with cooled AxioCam HR CCD, AxioVision, a PlanApo 63x1.4 oil immersion objective and DAPI and Cy3 filters. The pixel distance in the lateral plane was Dx = Dy = 106 nm; the axial sampling was Dz = 200 nm.
Bottom: Three-dimensional (3D image) of the mouse lymphocyte nucleus and its telomeres shown in 2D image (Top). The blue counterstain has been 'removed' (i.e. the blue color channel is switched off) to only visualize the telomeres (red).

The normal mammalian nucleus

Chromosomal organization

While some laboratories reported that chromosomes are organized randomly in the interphase nucleus (Cerda et al., 1999; Holley et al., 2002; Cornforth et al., 2002), most research groups find a consistent distribution of chromosomes within the mammalian nucleus and observe that the normal mammalian nucleus has a cell-type–specific shape and structure in which chromosomes are observed in probable non-random territories (Cremer et al., 2001; Parada et al., 2004; Misteli, 2002; Essers et al., 2005). As recently shown for all chromosomes in primary human cells, the order of chromosomes is consistent from cell to cell within the identical primary cell population (Bolzer et al., 2005). In this recent study, the authors examined the organization of all chromosomes in primary human fibroblasts, amniotic fluid cells, and in prometaphase rosettes. Small chromosomes were found in the centre of these nuclei irrespective of their gene density, and larger chromosomes were observed in closer proximity to the nuclear periphery or rosette rim. The cells analyzed by this group and in the above study exhibit flat-ellipsoid nuclei, and their organization may differ from the one in spherical lymphocytes. This conclusion is supported by others who report that the positions of chromosome territories are cell-type-dependent (Parada et al., 2002; Parada and Misteli, 2002; Parada et al., 2004). It appears that different patterns of nuclear chromosome territories are not only dependent on nuclear shape and space, but also on gene-rich and gene-poor chromatin domains (Bolzer et al., 2005) and on the differentiation status of the cell: Nuclei of embryonic stem cells appear to have their very specific 3D chromosomal organization that differs from the position the same chromosomes have in differentiated cells (Wiblin et al., 2005).
It was also shown that the 3D nuclear order of chromosomes within the same cell type is inherited during mitosis: daughter cells will show an organizational pattern that resembles their parental cell (Cremer et al., 2001; Gerlich et al., 2003; Essers et al., 2005). Moreover, the chromosomal order within the 3D nuclear space is evolutionarily conserved (Tanabe et al., 2002) strongly suggesting that the structural organization of the nucleus that is relevant to its stability and overall function has been established during evolution.

Chromosome movement or static order in the interphase nucleus?

Are chromosomes at the same position all the time? This is an area of intense research and no consensus has been reached. This is often due to the use of different cell lines, imaging and analysis conditions used. In addition, cell cycle and developmental stages of nuclei examined may have affected the results. The chromosome movements that were reported are of three types; 1) repositioning of sub-chromosomal regions within stable chromosome territories, 2) selective movement of single territories, and 3) small scale refolding events within sub-chromosomal regions (Zink and Cremer, 1998). Positional changes of chromosomes during the cell cycle have been observed by several groups (Walter et al., 2003; Vourc'h et al., 1993; Ferguson and Ward, 1992; Bridger et al., 2000; Chubb

et al., 2002; Essers et al., 2005). Moreover, work by Bridger and co-workers (2000) suggests that the nuclear architecture changes when cells become quiescent and senescent. Using chromosomes 19 and 18 as examples, the authors show that chromosomes are localized differently in proliferating, quiescent and senescent cells. When quiescent cells are activated to re-enter into the cycle, the nuclear positions of chromosomes change. Similarly, the architecture of chromosome territories changes during hematopoiesis in chicken (Stadler et al., 2004). In contrast to the above, static positions of chromosomes have been described by others (Abney et al., 1997; Gerlich et al., 2003).

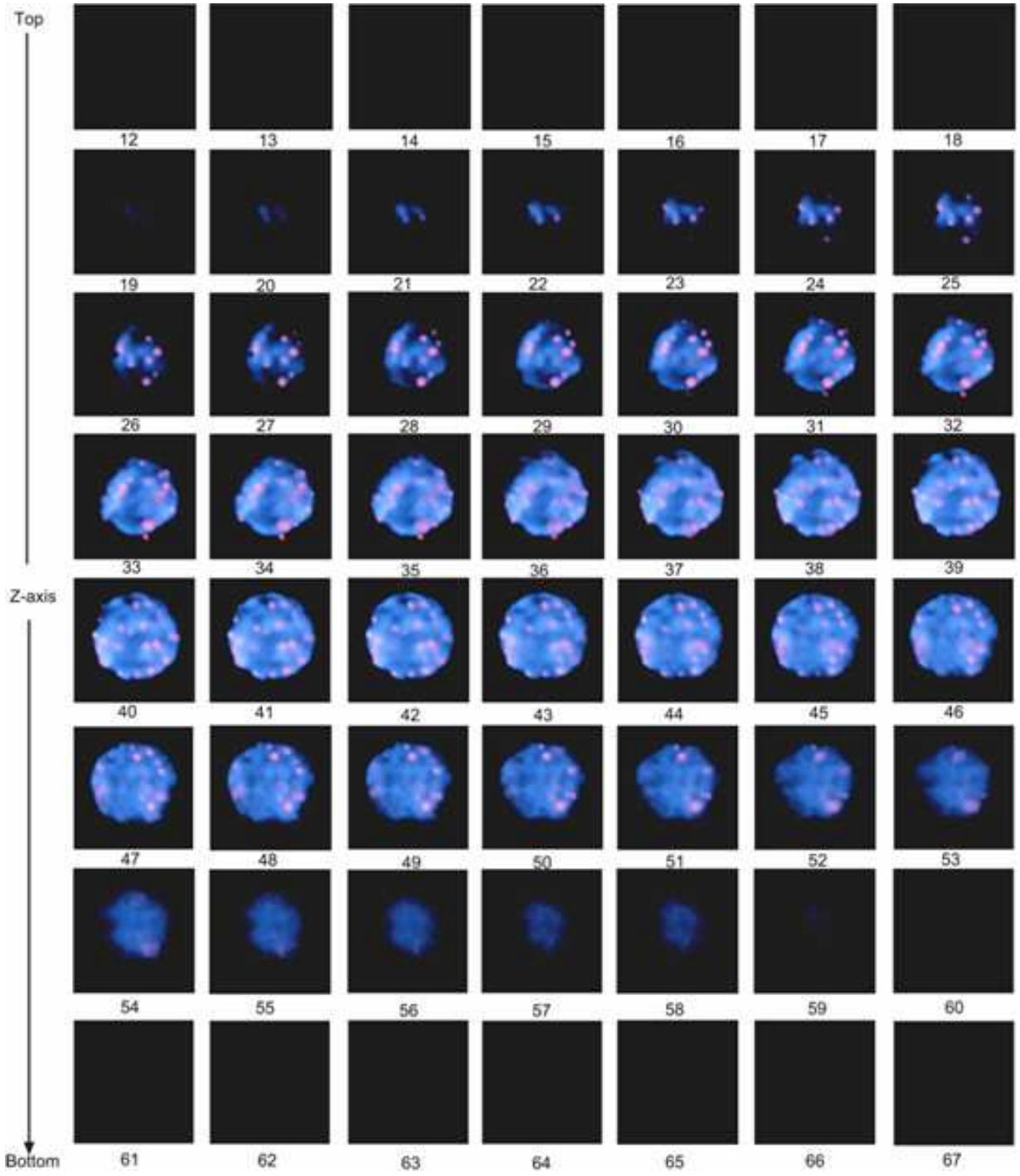

Figure 2. Three-dimensional (3D) organization of telomeres (red) in a mouse lymphocyte nucleus (blue). Shown are individual z stacks acquired as optical sections are collected by a fluorescent microscope. Sections 12-67 are shown. Note the telomere distribution in different z stacks.

Telomeric organization in normal cells

As shown by live cell imaging, telomere positions in the 3D nucleus are not static. Telomeres can move in the interphase nucleus (Molenaar et al., 2003). The distances they move vary (ibid). Telomeres are organized in a very typical way within the 3D space of the nucleus. Normal lymphocytes of mouse or human origin show a cell cycle-dependent organization of telomeres in their interphase nuclei. In an unperturbed nucleus and under optimal growth conditions, telomeres are widely distributed throughout the nucleus in normal G0/G1 cells (Weierich et al., 2003; Chuang et al., 2004). S-phase cells display a similar pattern of telomere organization and, in addition, show replicative structures of telomeres (Chuang et al., 2004). In G2, telomeres assemble into a telomeric disk, first observed by us (Chuang et al., 2004). Human keratinocyte cell lines with flatter nuclei perform less reorganization of telomeres but also exhibit a dynamic cell-cycle-specific organization (Ermler et al., 2004). Thus, telomeres reorganize in the 3D space of the nucleus during a normal cell cycle (Fig. 3). At no time during a normal cell cycle do telomeres of normal cells come into such close association that they form clusters or aggregates (Chuang et al., 2004). In fact, telomeres of normal cells do not overlap (Chuang et al., 2004).

Telomeric organization in tumor cells

Telomeres of tumor cell nuclei show an altered 3D nuclear organization. In contrast to normal cells, telomeres of tumor cells form aggregates. One or more telomeric aggregate can be observed per interphase nucleus, and these telomere clusters can be of various sizes (Chuang et al., 2004). Some telomeric aggregates represent telomeric fusions and thus generate dicentric chromosomes. This spatial alteration in the 3D organization of telomeres is causal to the initiation of breakage-bridge-fusion cycles and directly results in genomic instability (Louis et al., 2005). Further studies will elucidate the molecular mechanisms of telomeric aggregate formation.

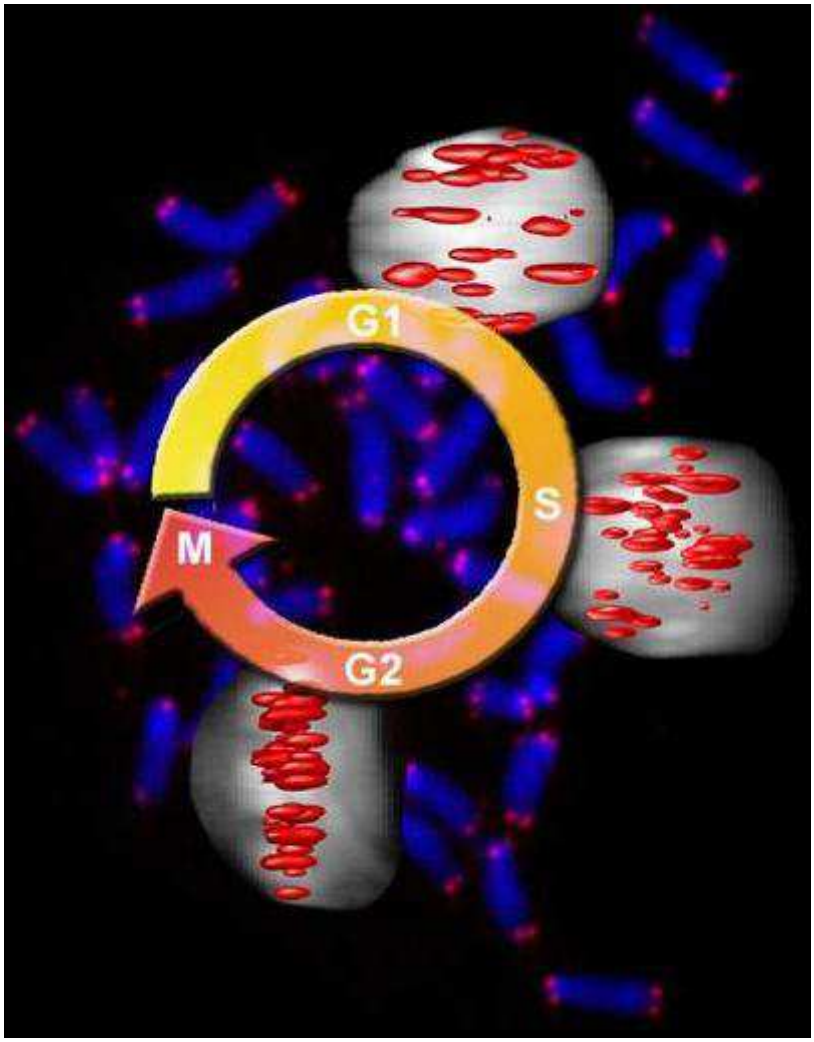

Figure 3. Overview of the telomeric positions during the cell cycle of normal lymphocytes. The examples shown here are from primary mouse lymphocytes. For details, see Chuang et al., 2004.

Measurement of nuclear structures

Chromosomes

In order to speak of chromosomal positions, one needs to be able to measure them. Tools to achieve this have been developed (Walter et al., 2003; Solovei et al., 2002). For specific questions related to chromosomal positions and overlaps, additional programs are also in use (Louis et al., 2005). What is required for future investigations are additional analytical tools and comparative evaluations of existing tools.

Telomeres

To measure the 3D organization of telomeres, we have developed TeloViewTM (Chuang et al., 2004; Vermolen et al., 2005). Briefly, the program measures telomere positions that can vary during the cell cycle. The nuclear area that contains the telomeres is best characterized as an oblate spheroid. In this spheroid, the two main axes, a and b, are of equal length, while the third axis, c, is shorter. It is this axis that varies during the cell cycle. The 3D organization during the cell cycle is thus reflected by the a/c ratio, and it is 1.4+0.1, 1.5+0.2, and 14+2 respectively for normal lymphocytes in G0/G1, S and G2 (Vermolen et al., 2005). In addition, the program quantitates the 3D fluorescent intensity of each telomere that is found in the nucleus. The relative fluorescent intensity measured is proportional to the telomere size (Poon et al., 1999).

The tumor cell nucleus and nuclear remodeling

During tumorigenesis, the nucleus is remodeled (Pienta et al., 1989). We have studied oncogenic remodeling of the mammalian nucleus, using the impact of c-Myc deregulation as example (Louis et al., 2005). Induction of c-Myc leads to the formation of telomeric aggregates that are commonly found in tumor cells and not present in normal cells. Some of the c-Myc-induced telomeric aggregates represent end-to-end chromosomal fusions. Dicentric chromosomes that are generated during c-Myc induction are chromosomal end-to-end fusions that initiate breakage-bridge-fusion (BBF) cycles in the subsequent anaphases. Propagation of such BBF cycles leads to ongoing chromosomal rearrangements and typically generates unbalanced chromosomal translocations and terminal deletions. New BBF cycles will continue until no more telomere free ends are available for fusions (Louis et al., 2005). Thus remodeling of the 3D telomeric organization induces genomic instability that is a hallmark of tumors (Mitelman et al., 2005; Hanahan and Weinberg, 2000; Vogelstein and Kinzler, 2004; Gollin et al., 2005; Weaver and Cleveland, 2005).

Nuclear remodeling as a result of c-Myc deregulation does not stop at the telomeric ends. During the process of c-Myc-mediated nuclear remodeling, chromosomes also alter their normal positions (Louis et al., 2005). When studying mouse chromosomes 5 and 13, 7 and 10, 7 and 17, 15 and 11 in PreB lymphocytes, we found that all of them change their positions as a result of c-Myc deregulation. The generated overlap between the above mentioned chromosome pairs is commonly associated with their involvement in translocations, as our spectral karyotyping (SKY) data suggest. The analysis of chromosomal overlaps, that were measured in interphase nuclei following chromosome painting, and the occurrence of recurrent translocations, found in metaphases after SKY, matched for mouse chromosomes 5 and 13, 7 and 17, 7 and 10 in Myc-activated PreB cells (Louis et al., 2005). However, this relationship did not hold true for chromosomes 11 and 15 (reviewed in Mai and Garini, 2005). Thus, the close vicinity of chromosomes represents most of the time a favorable condition for chromosomal translocations. It is evident that additional factors are required to facilitate the occurrence of translocations. These may include double strand breakage, sequence homologies, and recombination. Future studies will be needed to elucidate these processes further.

Data by others support the notion that close spatial proximity of chromosomes or specific chromosomal neighborhoods contributes to translocation frequencies. For example, mouse chromosomes 12 and 15 that are frequently involved in translocations in mouse plasmacytoma are found in closer vicinity to each other in mouse B cells than in mouse hepatocytes (Parada et al., 2004). In human chronic myeloid leukemia, chromosomes 9 and 22 are found in close proximity and this fact has been linked to the predisposition for translocations between the two chromosomes (Neves et al., 1999). A comprehensive study that examined 11,010 human constitutional translocations concluded that the frequency of constitutional translocations depended on three main factors, and these included the chromosome positions, chromosome sizes and specific DNA sequences (Bickmore and Teague, 2002).

Other events also contribute to nuclear remodeling. Examples include activated HaRas that leads to chromatin coarsening and loss of heterochromatin aggregates and correlates with metastatic potential (Fischer et al., 1998; Zink et al., 2004), viral infections (Igakura et al., 1998; De Noronha et al., 2001), and DNA damaging agents (Abdel-Halim et al., 2004; Bickmore and Teague, 2002; Gazave et al., 2005).

Thus, the impact of a single remodeling-promoting event can be with long lasting consequences to the cell. The generation of an aberrant cell that is able to multiply, evade growth control and apoptosis and form a tumor is one outcome. Telomeric reorganization may also contribute to mental retardation since subtelomeric rearrangements are a frequent cause for these diseases (Kok et al., 2005; Hwang et al., 2005). On the other hand, additional pathways affect nuclear organization. For example, an altered nuclear matrix organization

contributes to tumor development as shown for HMGY (I) (Takaha et al., 2002; Leman et al., 2003). Structural changes in the nuclear envelope contribute to the Hutchinson-Gilford progeria syndrome as demonstrated for mutations in Lmna that encodes lamins A and C that are structural components of the nuclear envelope (Pollex and Hegele, 2004).

We conclude that nuclear organization of the genome, cellular function, genome stability and disease are tightly linked. Irrespective of the type of genetic and/or structural changes present in tumors or in other genetic diseases, the 3D nuclear organization is different from that found in normal cells. It is therefore feasible, in the future, to benefit from the exact knowledge about the 3D structure of the nucleus for diagnosis, monitoring of disease, and therapeutic intervention.

Acknowledgement

I would like to thank Drs. Michael Mowat and Francis Wiener for critical reading. I express my sincere thanks to all my lab members and colleagues who were involved in studies reviewed here. My work was funded through CancerCare Manitoba Foundation, the Canadian Institutes of Health Research, the National Cancer Institute of Canada and the Canada Foundation for Innovation.

References

Abdel-Halim HI, Imam SA, Badr FM, Natarajan AT, Mullenders LH, Boei JJ. Ionizing radiation-induced instant pairing of heterochromatin of homologous chromosomes in human cells. Cytogenetic and genome research. 2004 ; 104 (1-4) : 193-199.

Abney JR, Cutler B, Fillbach ML, Axelrod D, Scalettar BA. Chromatin dynamics in interphase nuclei and its implications for nuclear structure. The Journal of cell biology. 1997 ; 137 (7) : 1459-1468.

Bickmore WA, Teague P. Influences of chromosome size, gene density and nuclear position on the frequency of constitutional translocations in the human population. Chromosome research . 2002 ; 10 (8) : 707-715.

Bystricky K, Heun P, Gehlen L, Langowski J, Gasser SM. Long-range compaction and flexibility of interphase chromatin in budding yeast analyzed by high-resolution imaging techniques. PNAS. 2004 ; 101 (47) : 16495-16500.

Bystricky K, Laroche T, van Houwe G, Blaszczyk M, Gasser SM. Chromosome looping in yeast: telomere pairing and coordinated movement reflect anchoring efficiency and territorial organization. The Journal of cell biology. 2005 ; 168 (3) : 375-387.

Bolzer A, Kreth G, Solovei I, Koehler D, Saracoglu K, Fauth C, Müller S, Eils R, Cremer C, Speicher MR, Cremer T. Three-dimensional maps of all chromosomes in human male fibroblast nuclei and prometaphase rosettes. PLoS biology. 2005 ; 3 (5) : page e157.

Boveri T. Ueber mehrpolige Mitosen als Mittel zur Analyse des Zellkerns. Verh Phys Med Gesellschaft Würzburg. 1902 ; 35 : 67-90.

Boveri T. Zur Frage der Entstehung maligner Tumoren. Fischer, Jena. 1914.

Bridger JM, Boyle S, Kill IR, Bickmore WA. Re-modelling of nuclear architecture in quiescent and senescent human fibroblasts. Current biology : CB. 2000 ; 10 (3) : 149-152.

Chuang TC, Moshir S, Garini Y, Chuang AY, Young IT, Vermolen B, van den Doel R, Mougey V, Perrin M, Braun M, Kerr PD, Fest T, Boukamp P, Mai S. The three-dimensional organization of telomeres in the nucleus of mammalian cells. BMC biology. 2004 ; 2 : page 12.

Chubb JR, Boyle S, Perry P, Bickmore WA. Chromatin motion is constrained by association with nuclear compartments in human cells. Current biology : CB. 2002 ; 12 (6) : 439-445.

Cerda MC, Berríos S, Fernández-Donoso R, Garagna S, Redi C. Organisation of complex nuclear domains in somatic mouse cells. Biology of the cell. 1999 ; 91 (1) : 55-65.

Cremer M, von Hase J, Volm T, Brero A, Kreth G, Walter J, Fischer C, Solovei I, Cremer C, Cremer T. Non-random radial higher-order chromatin arrangements in nuclei of diploid human cells. Chromosome research . 2001 ; 9 (7) : 541-567.

Cornforth MN, Greulich-Bode KM, Loucas BD, Arsuaga J, Vázquez M, Sachs RK, Brückner M, Molls M, Hahnfeldt P, Hlatky L, Brenner DJ. Chromosomes are predominantly located randomly with respect to each other in interphase human cells. The Journal of cell biology. 2002 ; 159 (2) : 237-244.

Ermler S, Krunic D, Knoch TA, Moshir S, Mai S, Greulich-Bode KM, Boukamp P. Cell cycle-dependent 3D distribution of telomeres and telomere repeat-binding factor 2 (TRF2) in HaCaT and HaCaT-myc cells. European journal of cell biology. 2004 ; 83 (11-12) : 681-690.

Essers J, van Cappellen WA, Theil AF, van Drunen E, Jaspers NG, Hoeijmakers JH, Wyman C, Vermeulen W, Kanaar R. Dynamics of relative chromosome position during the cell cycle. Molecular biology of the cell. 2005 ; 16 (2) : 769-775.

Ferguson M, Ward DC. Cell cycle dependent chromosomal movement in pre-mitotic human T-lymphocyte nuclei. Chromosoma. 1992 ; 101 (9) : 557-565.

Fischer AH, Chadee DN, Wright JA, Gansler TS, Davie JR. Ras-associated nuclear structural change appears functionally significant and independent of the mitotic signaling pathway. Journal of cellular biochemistry. 1998 ; 70 (1) : 130-140.

Garini Y, Vermolen BJ, Young IT. From micro to nano: recent advances in high-resolution microscopy. Current opinion in biotechnology. 2005 ; 16 (1) : 3-12.

Gatlin J, Melkus MW, Padgett A, Petroll WM, Cavanagh HD, Garcia JV, Jester JV. In vivo fluorescent labeling of corneal wound healing fibroblasts. Experimental eye research. 2003 ; 76 (3) : 361-371.

Gazave E, Gautier P, Gilchrist S, Bickmore WA. Does radial nuclear organisation influence DNA damage? Chromosome research . 2005 ; 13 (4) : 377-388.

Gerlich D, Beaudouin J, Kalbfuss B, Daigle N, Eils R, Ellenberg J. Global chromosome positions are transmitted through mitosis in mammalian cells. Cell. 2003 ; 112 (6) : 751-764.

Gollin SM. Mechanisms leading to chromosomal instability. Seminars in cancer biology. 2005 ; 15 (1) : 33-42.

Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000 ; 100 (1) : 57-70.

Haraguchi T, Ding DQ, Yamamoto A, Kaneda T, Koujin T, Hiraoka Y. Multiple-color fluorescence imaging of chromosomes and microtubules in living cells. Cell structure and function. 1999 ; 24 (5) : 291-298.

Holley WR, Mian IS, Park SJ, Rydberg B, Chatterjee A. A model for interphase chromosomes and evaluation of radiation-induced aberrations. Radiation research. 2002 ; 158 (5) : 568-580.

Hwang KS, Pearson MA, Stankiewicz P, Lennon PA, Cooper ML, Wu J, Ou Z, Cai WW, Patel A, Cheung SW. Cryptic unbalanced translocation t(17;18)(p13.2;q22.3) identified by subtelomeric FISH and defined by array-based comparative genomic hybridization in a patient with mental retardation and dysmorphic features. American journal of medical genetics. Part A. 2005 ; 137 (1) : 88-93.

Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M, Bangham CR. Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. Science (New York, N.Y.). 2003 ; 299 (5613) : 1713-1716.

Kok K, Dijkhuizen T, Swart YE, Zorgdrager H, van der Vlies P, Fehrmann R, te Meerman GJ, Gerssen-Schoorl KB, van Essen T, Sikkema-Raddatz B, Buys CH. Application of a comprehensive subtelomere array in clinical diagnosis of mental retardation. European journal of medical genetics. 2005 ; 48 (3) : 250-262.

Leman ES, Madigan MC, Brünagel G, Takaha N, Coffey DS, Getzenberg RH. Nuclear matrix localization of high mobility group protein I(Y) in a transgenic mouse model for prostate cancer. Journal of cellular biochemistry. 2003 ; 88 (3) : 599-608.

Liu YC, Chiang AS. High-resolution confocal imaging and three-dimensional rendering. Methods (San Diego, Calif.). 2003 ; 30 (1) : 86-93.

Louis SF, Vermolen BJ, Garini Y, Young IT, Guffei A, Lichtensztejn Z, Kuttler F, Chuang TC, Moshir S, Mougey V, Chuang AY, Kerr PD, Fest T, Boukamp P, Mai S. c-Myc induces chromosomal rearrangements through telomere and chromosome remodeling in the interphase nucleus. PNAS. 2005 ; 102 (27) : 9613-9618.

Mai S, Garini Y. Oncogenic remodeling of the three-dimensional organization of the interphase nucleus: c-Myc induces telomeric aggregates whose formation precedes chromosomal rearrangements. Cell cycle (Georgetown, Tex.). 2005 ; 4 (10) : 1327-1331.

Misteli T. Spatial positioning; a new dimension in genome function. Cell. 2004 ; 119 (2) : 153-156.

Mitelman F, Johansson B, Mertens F. Mitelman Database of Chromosome Aberrations in Cancer. http://cgap.nci.nih.gov/Chromosomes/Mitelman. 2005.

Molenaar C, Wiesmeijer K, Verwoerd NP, Khazen S, Eils R, Tanke HJ, Dirks RW. Visualizing telomere dynamics in living mammalian cells using PNA probes. The EMBO journal. 2003 ; 22 (24) : 6631-6641.

Moritz KB, Sauer HW. Boveri's contributions to developmental biology--a challenge for today. The International journal of developmental biology. 1996 ; 40 (1) : 27-47.

Neves H, Ramos C, da Silva MG, Parreira A, Parreira L. The nuclear topography of ABL, BCR, PML, and RARalpha genes: evidence for gene proximity in specific phases of the cell cycle and stages of hematopoietic differentiation. Blood. 1999 ; 93 (4) : 1197-1207.

de Noronha CM, Sherman MP, Lin HW, Cavrois MV, Moir RD, Goldman RD, Greene WC. Dynamic disruptions in nuclear envelope architecture and integrity induced by HIV-1 Vpr. Science (New York, N.Y.). 2001 ; 294 (5544) : 1105-1108.

Parada LA, McQueen PG, Munson PJ, Misteli T. Conservation of relative chromosome positioning in normal and cancer cells. Current biology : CB. 2002 ; 12 (19) : 1692-1697.

Parada L, Misteli T. Chromosome positioning in the interphase nucleus. Trends in cell biology. 2002 ; 12 (9) : 425-432.

Parada LA, McQueen PG, Misteli T. Tissue-specific spatial organization of genomes. Genome biology. 2004 ; 5 (7) : page R44.

Pienta KJ, Partin AW, Coffey DS. Cancer as a disease of DNA organization and dynamic cell structure. Cancer research. 1989 ; 49 (10) : 2525-2532.

Pollex RL, Hegele RA. Hutchinson-Gilford progeria syndrome. Clinical genetics. 2004 ; 66 (5) : 375-381.

Poon SS, Martens UM, Ward RK, Lansdorp PM. Telomere length measurements using digital fluorescence microscopy. Cytometry. 1999 ; 36 (4) : 267-278.

Stadler S, Schnapp V, Mayer R, Stein S, Cremer C, Bonifer C, Cremer T, Dietzel S. The architecture of chicken chromosome territories changes during differentiation. BMC cell biology. 2004 ; 5 (1) : page 44.

Stephens DJ, Allan VJ. Light microscopy techniques for live cell imaging. Science (New York, N.Y.). 2003 ; 300 (5616) : 82-86.

Solovei I, Cavallo A, Schermelleh L, Jaunin F, Scasselati C, Cmarko D, Cremer C, Fakan S, Cremer T. Spatial preservation of nuclear chromatin architecture during three-dimensional fluorescence in situ hybridization (3D-FISH). Experimental cell research. 2002 ; 276 (1) : 10-23.

Tanabe H, Müller S, Neusser M, von Hase J, Calcagno E, Cremer M, Solovei I, Cremer C, Cremer T. Evolutionary conservation of chromosome territory arrangements in cell nuclei from higher primates. PNAS. 2002 ; 99 (7) : 4424-4429.

Takaha N, Hawkins AL, Griffin CA, Isaacs WB, Coffey DS. High mobility group protein I(Y): a candidate architectural protein for chromosomal rearrangements in prostate cancer cells. Cancer research. 2002 ; 62 (3) : 647-651.

Vermolen BJ, Garini Y, Mai S, Mougey V, Fest T, Chuang TC, Chuang AY, Wark L, Young IT. Characterizing the three-dimensional organization of telomeres. Cytometry. Part A : the journal of the International Society for Analytical Cytology. 2005 ; 67 (2) : 144-150.

Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nature medicine. 2004 ; 10 (8) : 789-799.

Vourc'h C, Taruscio D, Boyle AL, Ward DC. Cell cycle-dependent distribution of telomeres, centromeres, and chromosome-specific subsatellite domains in the interphase nucleus of mouse lymphocytes. Experimental cell research. 1993 ; 205 (1) : 142-151.

Walter J, Schermelleh L, Cremer M, Tashiro S, Cremer T. Chromosome order in HeLa cells changes during mitosis and early G1, but is stably maintained during subsequent interphase stages. The Journal of cell biology. 2003 ; 160 (5) : 685-697.

Weaver BA, Cleveland DW. Decoding the links between mitosis, cancer, and chemotherapy: The mitotic checkpoint, adaptation, and cell death. Cancer cell. 2005 ; 8 (1) : 7-12.

Weierich C, Brero A, Stein S, von Hase J, Cremer C, Cremer T, Solovei I. Three-dimensional arrangements of centromeres and telomeres in nuclei of human and murine lymphocytes. Chromosome research . 2003 ; 11 (5) : 485-502.

Wiblin AE, Cui W, Clark AJ, Bickmore WA. Distinctive nuclear organisation of centromeres and regions involved in pluripotency in human embryonic stem cells. Journal of cell science. 2005 ; 118 (Pt 17) : 3861-3868.

Wunderlich V. JMM---past and present. Chromosomes and cancer: Theodor Boveri's predictions 100 years later. Journal of molecular medicine (Berlin, Germany). 2002 ; 80 (9) : 545-548.

Zink D, Cremer T. Cell nucleus: chromosome dynamics in nuclei of living cells. Current biology : CB. 1998 ; 8 (9) : R321-R324.

Zink D, Fischer AH, Nickerson JA. Nuclear structure in cancer cells. Nature reviews. Cancer. 2004 ; 4 (9) : 677-687.

This article should be referenced as such:

Mai S. Three-dimensional organization of the mammalian nucleus in normal and tumor cells. Atlas Genet Cytogenet Oncol Haematol.2006;10(2):134-141.