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Initiation of Telomere-Mediated Chromosomal Rearrangements in Cancer

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ABSTRACT

Telomeres are the ends of chromosomes and protect them from degradation and fusion. As such, their stability is required for normal cellular function. Telomere dysfunction is found often at the origin of cellular transformation and contributes to the onset of genomic instability, a hallmark of cancer cells. In this article, I discuss current data and concepts on telomere-mediated chromosomal rearrangements in cancer. J. Cell. Biochem. 109: 1095–1102, 2010. © 2010 Wiley-Liss, Inc.

KEY WORDS: TELOMERE; GENOMIC INSTABILITY; CANCER

The 2009 Nobel Prize in Physiology or Medicine was awarded to three researchers in the field of telomere research, Elizabeth H Blackburn, Carol W Greider, and Jack W Szostak, for the discovery of "how chromosomes are protected by telomeres and the enzyme telomerase." Research leading to this understanding is best described by the three Nobel laureates themselves [Blackburn et al., 2006]. Early work that initiated this field of study was carried out by Müller [1938] and McClintock [1941, 1942] and was summarized in our previous Prospect article [Mai and Garini, 2006].

When telomeres become dysfunctional cells can respond in three ways; they can become senescent, enter crisis or begin breakage-bridge-fusion (BFB) cycles that initiate ongoing genomic instability [Deng et al., 2008; Misri et al., 2008; Lansdorp, 2009]. Many cancer cells display chromosomal aberrations that are the direct result of telomere dysfunction. Examples include osteosarcoma [Selvarajah et al., 2006], prostate cancer [Vukovic et al., 2003, 2007], breast cancer [Meeker et al., 2004], and colon cancer [Stewénius et al., 2005; for reviews, see DePinho and Polyak, 2004; Lansdorp, 2009; Murnane and Sabatier, 2004].

NUCLEAR ARCHITECTURE—ORDER AND FUNCTION

THE THREE-DIMENSIONAL (3D) VIEW: NUCLEAR ARCHITECTURE AND CHROMOSOMES—AN ORDER THAT ASSURES FUNCTION

Recent data have convincingly proven that there is a link between nuclear order and function [Solovei et al., 2009]. These data have wide implications on our understanding of nuclear order and function and conclude a long period of research and observations into nuclear organization. Since these data enlighten our understanding of nuclear architecture, some important aspects leading to these recent findings will be reviewed below.

Hansemann (1858–1920) first observed and noted that nuclear architecture plays a significant role in the normal function of a cell. He described aberrant mitoses that were present in cancer tissues only and concluded that their presence was associated with malignancy. His observation was further experimentally examined and conceptually developed by Boveri (1862–1915) [Boveri, 1914, 1929] [for comment, see Bignold et al., 2009; for reviews, see Hardy and Zacharias, 2005; Ried, 2009]. Boveri concluded that an additional chromosome was deleterious not only to the process of normal cell division cycles but also incompatible with normal development [Boveri, 1914, 1929]. These findings led Boveri to postulate that aberrant nuclear organization is found at the onset of tumor initiation [ibid.].

Since that time, data generated by many research groups support the importance of nuclear architecture in nuclear function. The finding of evolutional conservation of chromosome positions [Tanabe et al., 2002], the positioning of specific chromosomes, that is, the localization of inactive X versus the active X chromosomes [Dyer et al., 1989; Dietzel et al., 1999; Heard and Bickmore, 2007], and altered chromosomal positions in different cell types [Parada et al., 2004] indicated that there is a conserved functional organization and compartmentalization of the chromosomes.

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Alteration in the positioning of chromosomes 12 and 16 was associated with differentiation of adipocytes [Kuroda et al., 2004]. Recent data by Marella et al. [2009] demonstrated changes in spatial positioning of chromosomes 18 and 19 that depended on the stage of differentiation in human epidermal keratinocytes. Overall, a 3D chromosomal territory code is hypothesized that facilitates the regulation of gene expression [Marella et al., 2009].

The most direct link between organization and function of the nucleus was described in the retinal rod cell nuclei of diurnal and nocturnal animals [Solovei et al., 2009]. The authors were able to link the chromosomal organization of these nuclei to optimal adaptation to nocturnal versus diurnal vision [ibid.]. The study of rod cell nuclei of diurnal and nocturnal/crepuscular animals allowed the authors to conclude that chromosomal organization determines the direction that light travels through the rod cell nuclei. The inverted nuclear architecture in nocturnal and crepuscular animals generates a core part with a high refractive index, which is advantageous for the passage of light straight through the rod nuclei. In contrast, the conventional chromosomal organization found in rod cells of diurnal animals is unable to permit the passage of the light in a focused and straight manner, thus preventing these animals from having a clear night vision.

In conclusion, the nucleus provides the structural landscape for our cells enabling their proper function. Similarly, telomeres assume a regulated order in nuclei of normal cells, and their aberrant organization is linked to the initiation and dynamic propagation of genomic instability, a hallmark of cancer cells.

THE 3D VIEW: NUCLEAR ORGANIZATION OF TELOMERES—NORMAL VERSUS ABERRANT ORGANIZATION IN GENOMIC (IN)STABILITY AND TUMOR DEVELOPMENT

Telomere dysfunction at the chromosomal level is commonly assessed using metaphase chromosomes. The analysis of chromosomes illustrates consequences of telomere dysfunction, including the lack of telomeric signals at chromosomal ends, the formation of dicentric chromosomes due to critically shortened telomeres or to telomere uncapping, or interstitial telomere signals that are the result of previous BFB cycles.

What is the origin of these chromosomal changes and how does this impact on genomic instability and cellular transformation? We set out to investigate these questions by the use of 3D imaging and quantitative 3D analysis of interphase nuclei. These data were independently validated using molecular cytogenetic approaches for metaphase chromosomes, including quantitative fluorescent in situ hybridization (Q-FISH) of telomeres and spectral karyotyping (SKY).

NUCLEAR ORGANIZATION OF TELOMERES IN NORMAL, IMMORTALIZED, AND TUMOR CELLS

In order to understand the 3D localization of telomeres in nuclei of normal, immortalized and tumor cells, we examined nuclei of cells from the same cell lineage. This avoided the comparison of cells of different origins and permitted the detailed analysis of alterations that accompany the transformation process.

We first examined the localization of telomeres within the nuclear space of normal lymphocytes and followed their 3D positions throughout the cell cycle [Chuang et al., 2004]. We observed that telomeres are organized throughout the nuclear space in primary mouse lymphocytes in G0/G1 and S phase, while they localize into a telomeric disk in late G2 [ibid.]. Furthermore, we noted telomeric aggregates (TAs) in tumor cells. TAs are clusters of telomeres, that at the Abbe resolution of 200 nm, cannot be resolved further. Further quantitative 3D telomere analysis required the development of a quantitative 3D measurement tool, TeloView^{TM} [Vermolen et al., 2005] that we have used since to examine nuclear positions of telomeres in various cell types and species [Louis et al., 2005; Gonzalez-Suarez et al., 2009; Knecht et al., 2009a,b].

Recent data by De Vos et al. [2009] have confirmed our data on nuclear telomere organization as demonstrated in Chuang et al. [2004] and showed for the first time, using controlled light exposure microscopy (CLEM), that microterritories can harbor several telomeric ends. The latter can be further resolved by using high-resolution microscopy methods [Garini et al., 2005] including 3D-SIM [Gustafsson, 2000; Schermelleh et al., 2008]. Such a territorial telomeric neighborhood organization may facilitate recombination events that continuously take place in normal cells [Linardopoulou et al., 2005; Rudd et al., 2007; for review, see Mefford and Trask, 2002]. The regular 3D nuclear organization of telomeres will, if disturbed, lead to aberrant recombination events and/or the formation of TAs, features of tumor cells that we first described in earlier work [Chuang et al., 2004; Mai and Garini, 2005, 2006] and have since also described in Hodgkin's lymphoma and glioblastoma (GBM) [Gadji et al., 2009; Knecht et al., 2009a,b].

MECHANISMS AND CONSEQUENCES OF ALTERED TELOMERIC NUCLEAR ORGANIZATION

c-Myc and 3D nuclear organization of telomeres and chromosomes—role in initiation of tumor development. Our previous work demonstrated that the conditionally deregulated expression of the c-Myc oncogene led to the generation of cycles of TAs over a period of 144 h that was clearly past the initial c-Myc deregulation [Louis et al., 2005]. The time of c-Myc deregulation was proportional to the number of TA cycles observed. c-Myc induced TA cycles, but the oncoprotein was no longer required for the downstream effects of subsequent cycles of TA formation. The data were consistent with ongoing cycles of genomic instability mediated by TA formation and the subsequent initiation of telomere-driven BFB cycles (Fig. 1). Upon examination of metaphase chromosomes at all time points related to the TA cycles, we were able to definitively conclude that c-Myc induced cycles of TA formation that led to BFB cycles [ibid.]. Thus, as a result of c-Myc deregulation, TA formation preceded chromosomal end-to-end fusions, change in nuclear telomeric proximity and the onset of dynamic chromosomal instability. TAs representing fusions were confirmed when internuclear bridges and dicentric chromosomes formed as the cells progressesed through cell division. c-Myc-induced TA formation does not require critical shortening of telomeric ends and is independent of telomerase [Louis et al., 2005] and appears to involve telomere uncapping. TAs can form when telomeres become critically

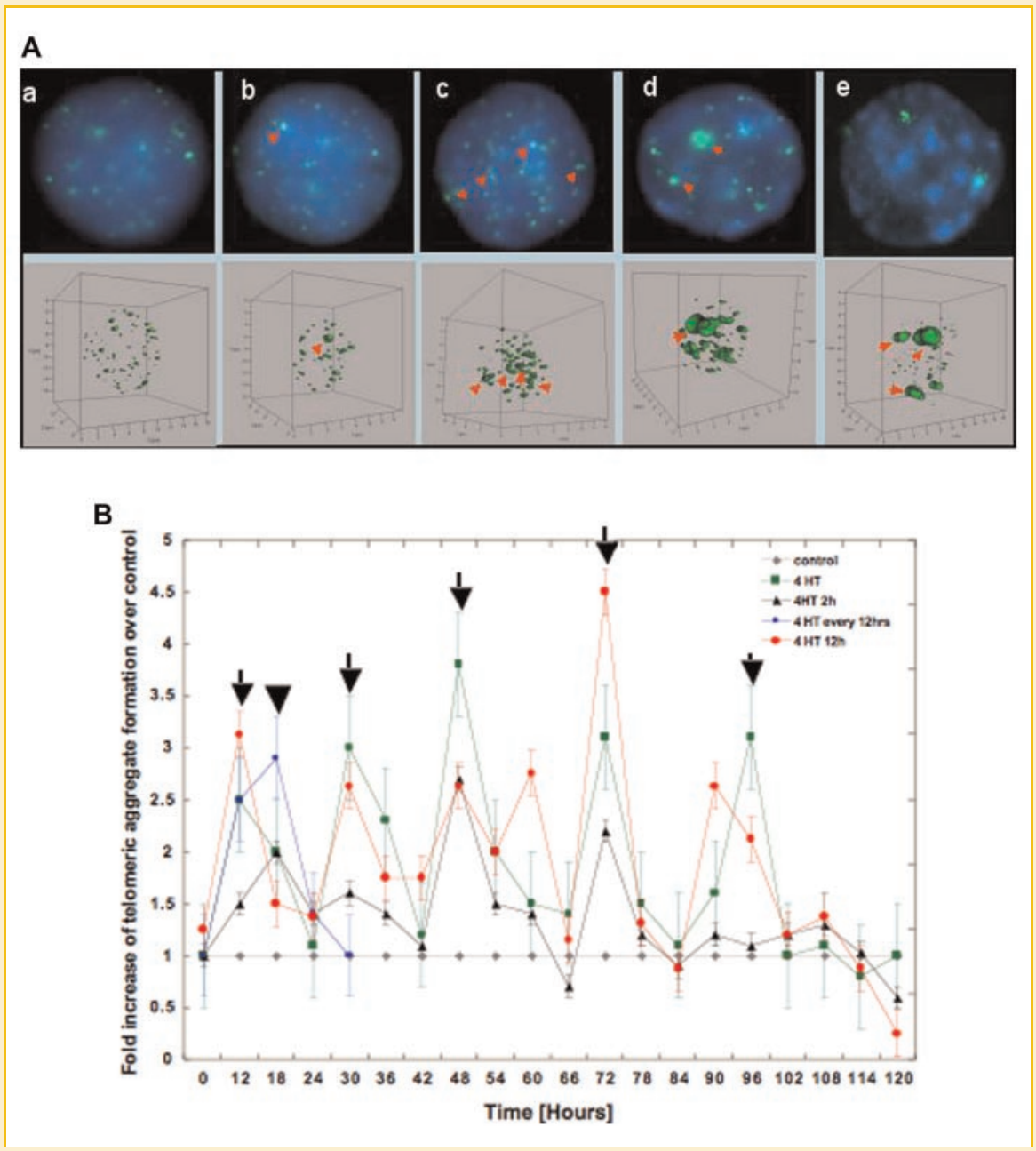

Fig. 1. c-Myc-induced telomeric aggregates appear in cycles. c-Myc-induced telomeric aggregates appear in cycles. A: Conditional c-Myc deregulation causes TA formation. Aa: Negative control: non-Myc deregulated PreB nucleus with non-overlapping 3D telomeric nuclear positions. bb–bd: TAs of various sizes and numbers are present after conditional c-Myc expression at any given time point of TA formation. Telomeres are shown in green; TAs by red arrows. Ae: Positive control: plasmacytoma cell line, MOPC460D, with constitutive c-Myc deregulation due to T12;15, shows TAs. Similar results were obtained with primary plasmacytoma cells (data not shown). B: c-Myc induces cycles of TAs. Fold increase in TAs over control levels during a period of 120 h. During this period, c-Myc had been up-regulated for different lengths of time (see figure). Black, 4HT given for 2 h and removed; red, 4HT administered for 12 h and removed; green, 4HT added once and not removed; blue, 4HT added at 0, 12, and 24 h; gray, control cells. The highest levels of TA formation and a single TA peak observed after consecutive activations of MycER are shown by arrows and an arrowhead, respectively. Error bars represent a 95% confidence interval of binomial distributions. This figure is reproduced with permission from Louis et al. [2005].

short [Knecht et al., 2009a,b], but this is not the case when c-Myc is conditionally deregulated.

Transient chromosome movements were also noted during c-Myc-induced TA formation [Louis et al., 2005]. Mouse chromosomes pairs 5 and 13, 7 and 10, and 7 and 17 changed their nuclear position and nuclear proximity relative to each other over the time period of 96 h that followed conditional c-Myc deregulation. Concomitantly, SKY analysis showed that chromosomes 7, 10, and 13 were involved in rearrangements at significant frequencies. Other rearrangements were also observed but did

not reach statistical significance [ibid.]. SKY thus confirmed that chromosomal movements and newly generated overlaps between the affected chromosomes were linked to chromosomal rearrangements.

Interestingly, in the context of telomere remodeling into TAs, *myc box II* mutant Δ106 was unable to induce TA formation indicating that *myc box II* is required for TA formation [Caporali et al., 2007]. *Myc box II* is a conserved element within the N-terminus of c-Myc and is needed for all known functions of c-Myc [Stone et al., 1987]. However, not all c-Myc target genes need this element for activation. Recent data showed that *myc box II* is required to rescue the proliferation defect of *myc*-null fibroblasts [Cowling and Cole, 2008].

The above data link TA formation to the induction of tumorigenesis as only full length (wild-type) c-Myc but not *myc box II* mutant Myc is able to induce tumor formation in SCID mice [Fest et al., 2005]. These data suggest that an oncogene, such as c-Myc, is able to remodel nuclear telomere organization that leads to dynamic instability followed by tumor initiation.

Whether other oncogenes are capable of nuclear remodeling remains to be investigated. Data on Ha-*ras* indicate that this oncogene induces chromosomal rearrangements that involve telomeric sequences in BALB/3T3 cells [Peitl et al., 2002]. Since telomere-free ends, interstitial telomeric signals and chromosome fusions are observed in this system, it is tempting to speculate that Ha-*ras* may, similar to c-Myc, alter the nuclear organization of telomeres.

Epstein–Barr Virus and 3D nuclear organization of telomeres and chromosomes—role in the onset of genomic instability. Our recent data demonstrated that Epstein–Barr virus (EBV) is able to mediate the formation of TAs [Lacoste et al., 2009]. Ex vivo EBV-infected human B cells, but not mitogen-induced controls, acquired telomere- and DNA-damage-dependent genomic instability within the first week after viral infection. The instability induced was initially polyclonal. Later, specific clones were selected in vitro. EBV induced aberrations were consistent with telomere dysfunction. These included the formation of dicentric chromosomes, unbalanced translocations and fragments, sister chromatid fusions and interstitial telomeric signals. Partial uncapping of telomeres was found to be a direct consequence of the viral infection. In addition, within a week after EBV infection of primary human B cells, DNA breaks were seen at the chromosomal level in metaphase chromosomes as well as by Mre11 and γH2AX-staining of interphase nuclei [ibid.]. The latter is consistent with previously published data [Kamranvar et al., 2007; Gruhne et al., 2009a,b].

Thus EBV induces sufficient damage to enable multiple genetic changes in the target B cell. The types of changes caused by EBV infection are similar to those observed in c-Myc transformed cells (DNA-damage and telomere dysfunction). After EBV infection, the chromosomes and loci hit are random resulting in a polyclonal group of unstable cells (Fig. 2). Some of these cells will have the genetic changes that allow them to become transformed. This study demonstrates that; (1) the EBV-infected target cells accumulate multiple genetic hits, (2) the acquired hits differ from cell to cell, (3) the generation of multiclonal changes is "immediate" (within a week postinfection), and (4) the selection for specific clones occurs in parallel (Fig. 2).

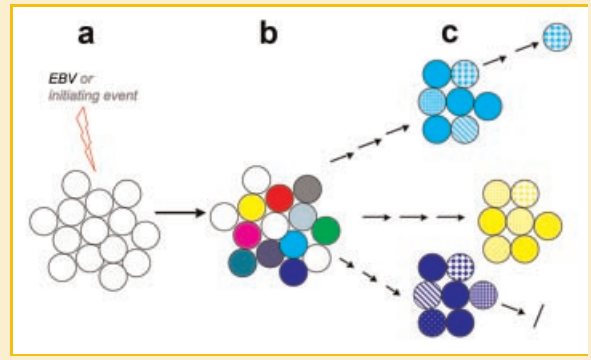

Fig. 2. Scheme depicting the development of early genetic lesions after EBV infection of normal human B cells. a: Normal B cells. b: B cells after EBV infection. They display different genetic lesions symbolized here by the use of different colors. Although the type of lesions (telomere dysfunction and DNA damage) is similar, the loci hit are random. c: After clonal selection and further changes, some clones will continue to grow and others will stop proliferating and/or die. It is feasible that other genotoxic agents induce similar pathways of instability.

These data raise the question whether the cell population that is at the initiation of the tumorigenic process is in fact polyclonal and has previously escaped detection because we have studied tumors that already passed these initial stages of cellular changes. I hypothesize that at least some tumors follow this path and postulate that telomere dysfunction (alone or in combination with more extensive DNA damage) serves the purpose of creating a large pool of cells with multiple genetic hits. Each of these cells is capable of undergoing its own microevolution that is modulated based on selective pressures. Thus, in this context, the occurrence of random genomic changes is a reflection of multi-hit cellular remodeling, and the occurrence of non-random instability a result of selection of the suitable changes that allow these cells to ultimately thrive and create the tumor tissue.

TELOMERE-DRIVEN TRANSITION OF H TO RS CELL IN HODGKIN'S LYMPHOMA

Hodgkin lymphoma is characterized by the presence of mononuclear H and the bi- to multinucleated Reed–Sternberg (RS) cells, the latter representing the diagnostic cells for this disease [Küppers, 2009]. The 3D analysis of telomere dysfunction in Hodgkin's lymphoma recently permitted us to understand the origin and fate of the RS cells [Knecht et al., 2009a,b]. We were able to show that telomere dysfunction (critical telomere shortening and TA formation) is involved in the transition of the H cell to the RS cell [Knecht et al., 2009a]. The latter is generated by aberrant cell divisions of the H cell (Fig. 3a,b) that displays high levels of DNA damage. This was manifested by the presence of Mre11 and γH2AX foci, centrosome and spindle aberrations as well as telomere uncapping. Studies are under way to elucidate the structural organization of chromosomes specifically in the RS cells.

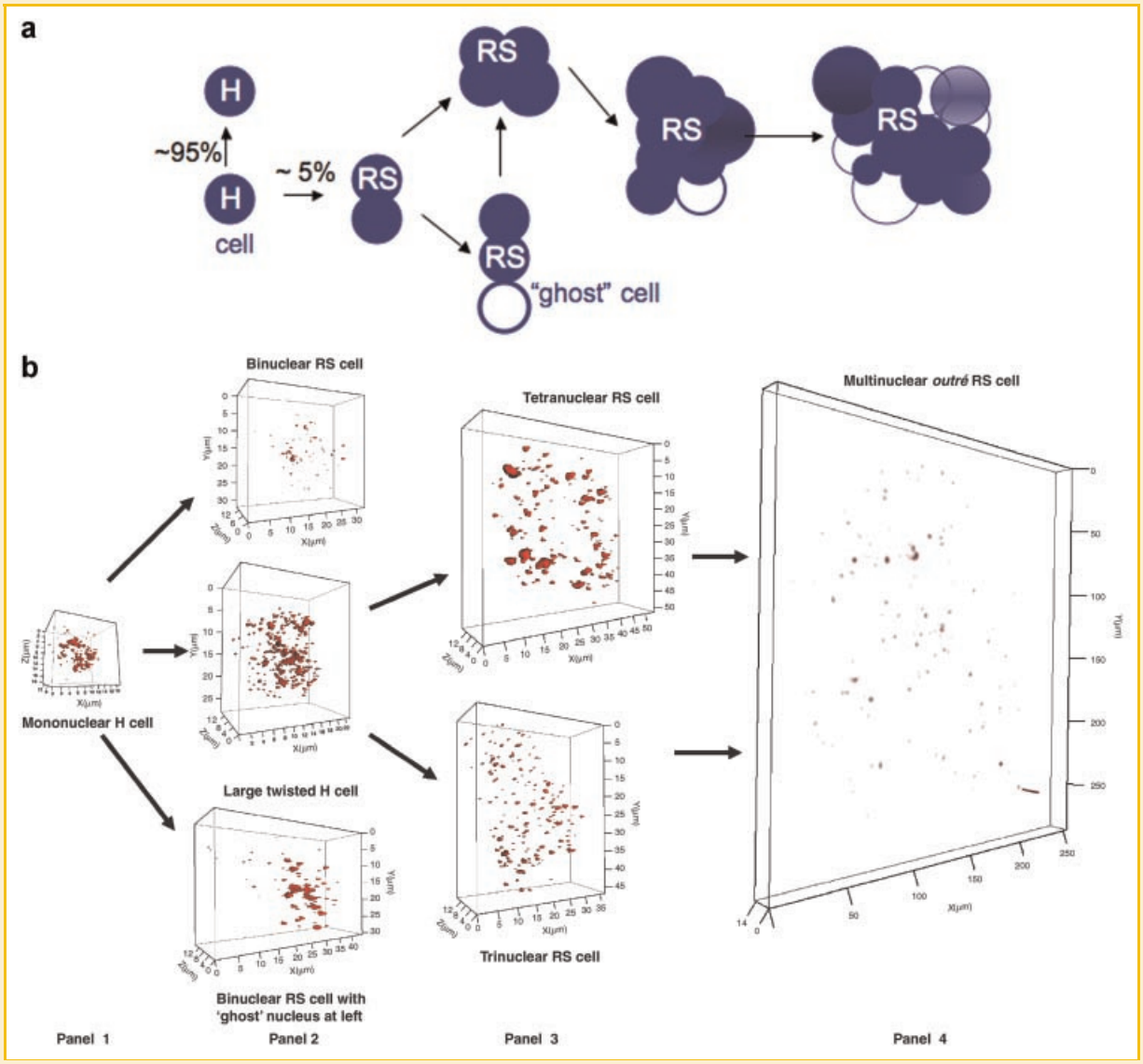

Fig. 3. a: Telomere-driven generation of the Reed–Sternberg (RS) cell. Scheme illustrating that the RS cell is generated from mono-nucleated Hodgkin (H) cell through synchronous/asynchronous nuclear divisions in the absence of cell division. b: Telomere-dysfunction associated generation of the RS cell. This figure is reproduced with permission from Knecht et al. [2009a].

TELOMERE CHANGES MAY PREDICT OVERALL SURVIVAL AND TIME TO PROGRESSION IN GLIOBLASTOMA (GBM)

GBM is a brain tumor with an average time to progression of 12 months [Louis et al., 2002]. No curative treatments have thus far been discovered. In an attempt to understand the nuclear architecture and its role in GBM, we performed a double-blinded pilot study on tumors from GBM patients that were treatment-naive. We were able to identify three patient groups with distinct nuclear telomeric architecture [Gadji et al., 2009]. The 3D telomeric profile that was characteristic of each group correlated with short-term, intermediate and long-term survival and time to progression in our patient cohort [ibid.]. Thus the significant differences in 3D telomeric signatures identified three GBM patient subgroups that could not be previously categorized. These findings now open new avenues in molecular genetic profiling and therapy design for GBM.

FUTURE RESEARCH INTO THE TELOMERIC ORDER WITHIN THE NUCLEUS

As we learn more about the nuclear architecture of telomeres in normal and diseased cells, we will be able to assess with greater detail stages of tumor initiation and progression. New high-resolution imaging technologies will aid in this undertaking as they will enable us to better resolve these structures [Gustafsson, 2000; Garini et al., 2005; Schermelleh et al., 2008]. The nature of TAs will become more apparent as illustrated in Figure 4 using 3D-SIM high-resolution

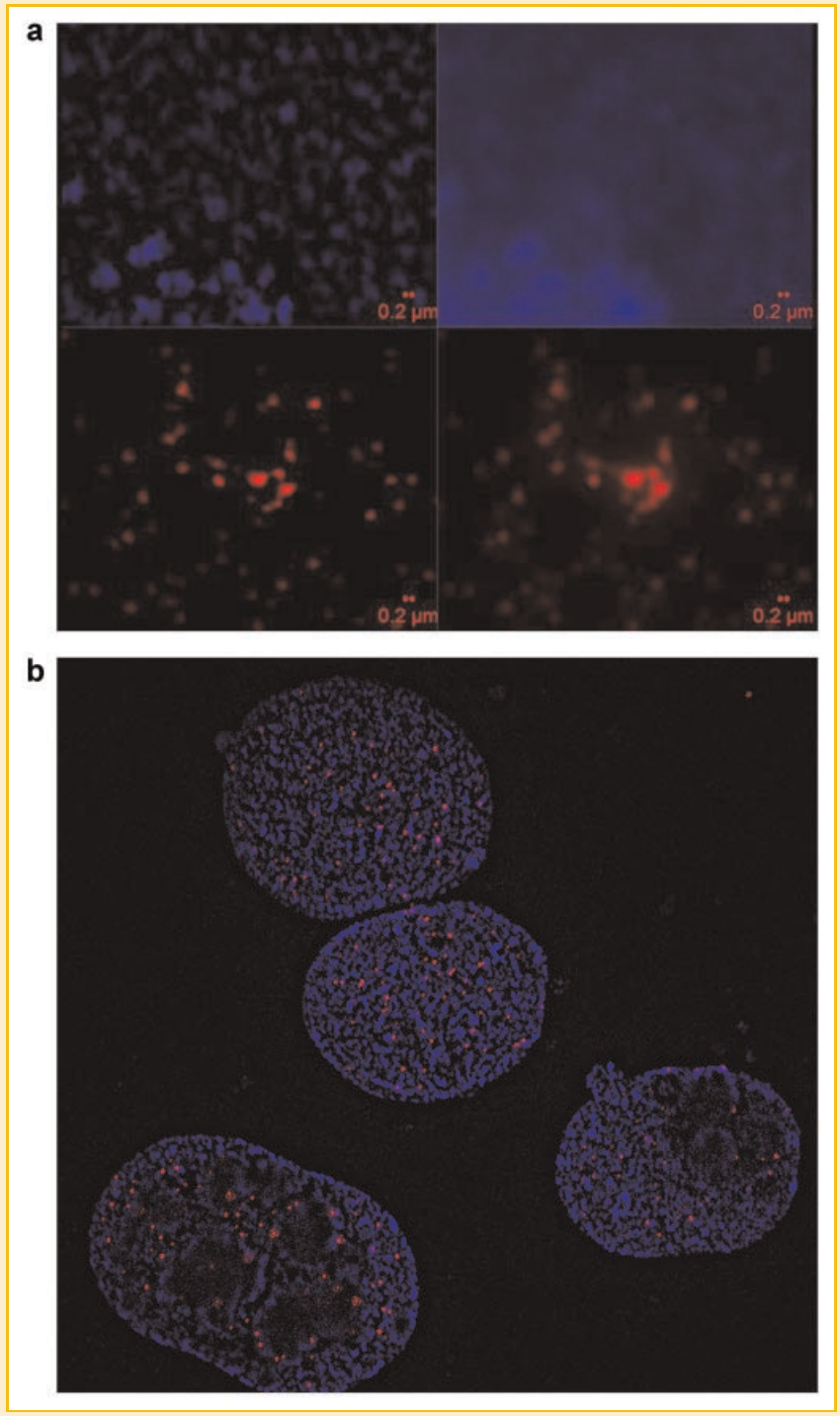

Fig. 4. High-resolution image analysis of telomeric aggregates. a: Comparison of wide field (right panels) and 3D-SIM imaging of nuclear DAPI stain (blue, top) and telomeric aggregates (red, bottom). The 3D-SIM images allow detailed analysis of nuclear architecture. b: Image of Hodgkin lymphoma nuclei after 3D-SIM (x,y: 40 nm, z: 125 nm).

imaging [Schermelleh et al., 2008]. Figure 4 shows the gain in resolution that 3D-SIM offers when compared to wide-field microscopy (Fig. 4a) and the gain in resolution of nuclear architecture in Hodgkin's lymphoma (Fig. 4b). Not only do we achieve a better resolution of TAs (Fig. 4a, bottom panel), but also can we discern regularity versus irregularity of nuclear chromatin organization as revealed by 3D-SIM images (Fig. 4a, top panels, and b).

In parallel, new clinical 3D scanning applications will also become more prominent. It will be important to identify aberrant cells within large numbers of normal cells to aid in identifying

patients at risk or who require different treatment options. Automated 3D scanning of telomeres is also expected to aid in predicting treatment response. It is even feasible to design new treatment opportunities based on the unique 3D telomeric profiles one detects. A first glimpse of this possibility is given in our recent study on GBM [Gadji et al., 2009].

To better understand normal and aberrant nuclear processes, live cell imaging will continue to improve our current knowledge. For example, recent studies have examined telomere motion in live cells [Hediger et al., 2002; Molenaar et al., 2003; Wang et al., 2008; Bronstein et al., 2009] and have shown that telomeres in mammalian cells are mobile [Molenaar et al., 2003; Wang et al., 2008; Bronstein et al., 2009] and move at size-dependent speeds [Molenaar et al., 2003; Wang et al., 2008]. As well, the shelterin capping protein TRF2 performs restricted movements in the nucleus, termed transient anomalous diffusion [Bronstein et al., 2009].

CONCLUSIONS

Conventional 3D imaging has allowed us to understand the onset of genomic nuclear remodeling and genomic instability in mouse and human cancer cells. High-resolution 3D imaging promises even deeper insights into the architecture of telomeres in nuclei of cells and will enable us to fine-map the contribution of spatial alterations to the dynamic process of genome rearrangements. Combined with live cell imaging, dynamic changes and processes in cells will become more transparent, and this new knowledge will permit the identification of normal, developmental, differentiation and senescence-associated telomeric profiles as well as aberrant stages of cell function. In the field of cancer research, 3D imaging and quantitative analysis have allowed us to understand and automate the analysis of cells with specific architectural features. Changes specific to the stages of the disease can now for the first time be defined using the signatures of unique 3D telomeric organization.

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