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26

The Functioning of "Aged" Heterochromatin

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1. Introduction

1.1 Heterochromatin – Substratum of aging

The aging process is programmed in the genome of each organism and is manifested late in life. Any change in normal homeostasis, particularly any further loss of the cell function with aging, occurs in the functional units of the chromatin domains.

Modification of the chromatin structure and function by hetero- or deheterochromatinization occurs throughout life and plays a pivotal role in the irreversible process in aging by affecting gene expression, replication, recombination, mutation, repair, and programming (Gilson and Magdinier, 2009; Elcock and Bridger, 2010). Among chromatin modifications, methylation and acetilation of lysine residues in histones H3 and H4 are critical to the regulation of chromatin structure and gene expression. Compacted heterochromatin regions are generally hypoacetylated and methylated in a discrete combination of lysine methylated marks such as H3K9me2 and 3 (its recognition by specific structural proteins such as HP1 is required for heterochromatin assembly and spreading) and H4K20me1 (Trojer and Reinberg, 2007; Vaquero, 2009). Hypermethylation may cause heterochromatinization and thus would result in gene silencing (Mazin, 1994, 2009). It was found that HP1 is associated with transcripts of more than one hundred euchromatic genes. All these proteins are in fact involved both in RNA transcript processing and in heterochromatin formation. Loss of HP1 proteins causes chromosome segregation defects and lethality in some organisms; a reduction in levels of HP1 family members is associated with cancer progression in humans (Dialynas et al., 2008). This suggests that, in general, similar epigenetic mechanisms have a significant role on both RNA and heterochromatin metabolisms (Piacentini et al., 2009).

Current evidence suggests that SirT1-7 (NAD-dependent deacetylase activity proteins), now called "sirtuins," have been emerging as a critical epigenetic regulator for aging (Imai, 2009). The first event, arrival of and SirT1 at chromatin, results in deacetylation of H4K 16 and H3K9Ac, and direct recruitment of the linker histone H1, in the formation of heterochromatin, a key factor in the formation of the 30 nm fiber **(**Vaquero, 2004; Michishita *et al*., 2005). The fact that such histones modifications are reversible (Dialynas *et al*., 2008; Kouzarides, 2007) offers the potential for therapy (Dialynas *et al*., 2008). The first level of chromatin organization, the 10 nm fiber, corresponds to a nucleosome array. This fiber is accessible to the transcriptional machinery and is associated with transcriptionally active regions, which are also known as active chromatin or euchromatin (Trojer and Reinberg, 2007).

Heterochromatin is divided into two main forms according to their distinct structural functional dynamics: constitutive heterochromatin (CH) and facultative heterochromatin (FH). CH refers to the regions that are always maintained as heterochromatin; these span large portions of the chromosome and have a structural role. CH regions contain few genes and are located primarily in pericentromeric regions and telomeres. FH refers to those regions that can be formed as heterochromatin in a certain situation but can revert to euchromatin once required. FH can span from a few kilobases to a whole chromosome and generally includes regions with a high density of genes. SirT1 contains both forms of heterochromatin (Prokofieva-Belgobskaya, 1986; Vaquero, 2004, 2009). Heterochromatin composed of distinct life-important functional domains, includes: 1. constitutive heterochromatin, almost entirely composed of non-coding sequences (satellite DNA) that are mostly localized at or are adjacent to the centromeric and telomeric regions; 2. NOR-satellite stalk heterochromatin reflecting the activity of synthetic processes (Ag-positive - coding chromatin and Ag-negative – non-coding chromatin) and 3. facultative heterochromatin (heterochromatinization - condensed euchromatic regions) that mainly consist of "closed" transcribe genes.

According to this view, we discuss of the levels of: 1) total heterochromatin; 2) constitutive (structural) heterochromatin; 3) nucleolus organizer regions (NORs) heterochromatin and 4) facultative heterochromatin in lymphocytes cultured from individuals at the age of 80 and over.

2. Facultative heterochromatin (condensation of eu- and heterochromatin regions)

We have used differential scanning microcalorimetry to produce a calorimetric curve in cultured human lymphocytes over the temperature range 38–130°C. It was determined that the clearly expressed shoulder of the heat absorption curve in the temperature interval from 40°C to 50°C with Tm(I)=45+1°C corresponds to melting of membranes and some cytoplasm proteins, maxima at Tm(II)=55+1°C correspond to melting (denaturation) of non-histone nuclei proteins, maxima at Tm(IV)70+1°C corresponds to the ribonucleoprotein complex, and maxima at Tm(III)=63+1°C and Tm(V)=83+1°C correspond to cytoplasm proteins. Other clearly expressed peaks at Tm(VI)=96+1°C and Tm(VII)=104+1°C correspond to the chromatin denaturation (Monaselidz et al.,2006,2008). The heating process produced clear and reproducible endothermic heat absorption peaks. We found that an endothermic peak at T_m=104±1°C corresponds to melting of 30 nm-thick fibers, which represents the most condensed state of chromatin in interphase nuclei (heterochromatin), and that an endothermic peak at 96±1°C corresponds to melting of 11 nm-thick filaments.

The chromatin heat absorption peaks VI and VII changed significantly with age. In particular, in the shifted endotherms VI and VII, the temperatures increased by 2°C and 3°C accordingly in old age (80-86 years). Additional condensation of the eu- and heterochromatin was demonstrated by an increase in T_m by 2°C and 3°C in comparison with the meddle age (25-40 years) (Fig.1). These prominent changes in chromatin stability indicated transformation of eu- and heterochromatin in condensed chromatin (heterochromatinization).

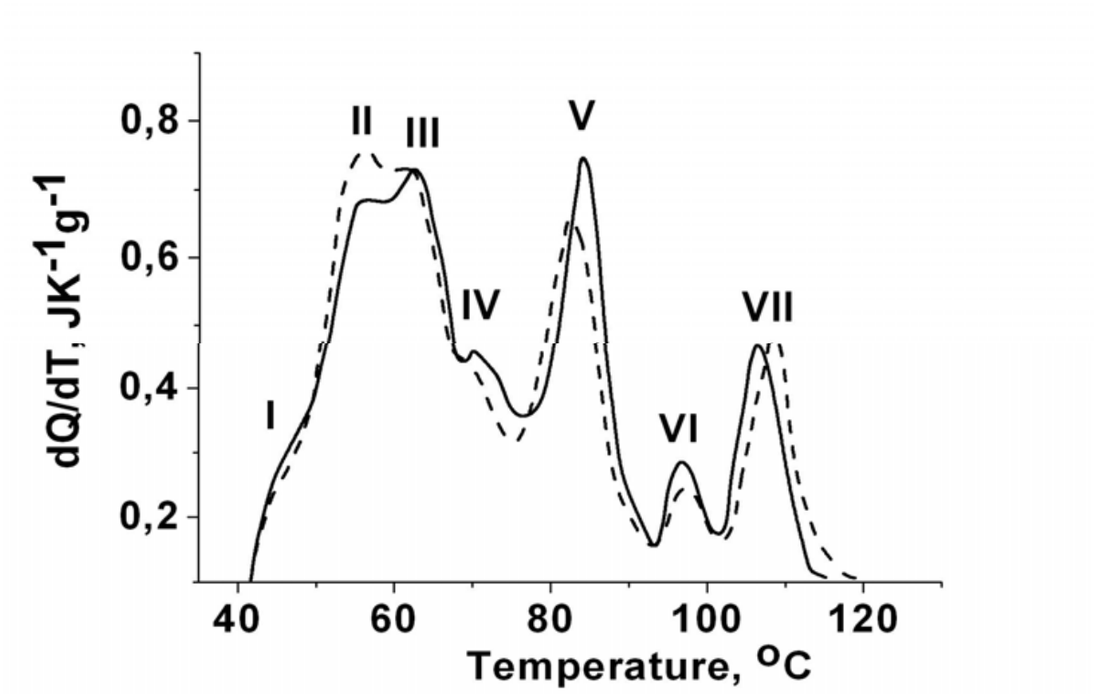

Fig. 1. The excess of heat capacity (ΔC_p=dQ/dT) as function of temperature for lymphocytes cultures from young donors (------) and old donors (— —) (48 –hour cell culture), dry biomass (------) - 8.5 mg and 87 µg DNA, dry biomass (— —) 8.8mg and 90 µg DNA

One of the potential epigenetic mechanisms is heterochromatinization of chromatin within the region of the genome containing a gene sequence, which inhibits any further molecular interactions with that underlying gene sequence and effectively inactivates that gene (Ellen *et al.,* 2009). The chromatin peak behavior described above shows progressive heterochromatinization of lymphocyte chromosomes from old individuals and confirms previously reported data (Lezhava, 1984, 2001, 2006; Vaquero, 2004).

These significant changes in chromatin stability in old age indicate that the aging process involves transformation of the eu- and heterochromatin into condensed forms and that further compaction or progressive heterochromatinization occurs during aging.

3. Constitutive heterochromatin (pericentromeric and telomeric heterochromatin)

Centromeric and telomeric heterochromatin differs from each other by structure and sensitivity to exogenous factors. Centromeric heterochromatin showed increased H3-K27 trimethilation in the absence of SUV39h1 and Suv39h2HMTases. Such modification was not detectable at telomeric heterochromatin. Despite the differences between the two heterochromatin domains and the distinction of functions, they have much in common (Blasco, 2004; Lam *et al*., 2006).

3.1 Pericentromeric heterochromatin

The heterochromatin regions of human chromosomes near the centromere vary and the degree of variability is related to the amount and molecular organization of DNA, which contains only a fraction of satellite DNA. The amount and function of heterochromatin regions have a close relationship with the organization and functioning of the entire genome.

Satellite DNA (tandemly repeated noncoding DNA sequences) stretch over almost all native centromeres and surrounding pericentromeric heterochromatin. Satellite DNA was considered to be an inert by-product of genome dynamics in heterochromatic regions. However, recent studies have shown that the evolution of satellite DNA involved an interplay of stochastic events and selective pressure. This points to the functional significance of satellite sequences, which in (peri) centromeres may play some fundamental roles. First, specific interactions between satellite sequences and DNA-binding proteins are proposed to complement sequence-independent epigenetic processes. Second, transcripts of satellite DNA sequences initialize heterochromatin formation through an RNAi mechanism. In addition, satellite DNAs in (peri)centromeric regions affect chromosomal dynamics and genome plasticity (Mehta *et al*., 2007; Plohl *et al*., 2008). Satellite DNA is localized in human (peri) centromeres heterochromatin chromosomes 1,9, 16 and Y.

The data on comparative of (peri) centromeric heterochromatin (C-segment) were provided for all three chromosome pairs (1, 9 and 16) indicating that the variants of large C-segments (d and e) were registered more often in old individuals than in the cells of the younger ones: for chromosome 1 – X^2_4 =21.9, ($p<0.001$); for chromosome 9 – X^2_4 =10,6 ($p<0.001$); for chromosome 16 – X^2_4 =18.7, ($p<0.001$). The increased size of the C-segments were also found in the Y- chromosomes of the family : the father and the grandfather (59 and 88 years, respectively), compared with the 30 year old son (Lezhava, 2006).

Thus, the (peri) centromeric heterochromatin on three chromosome pairs (1, 9 and 16) and the C-segments of the Y chromosome increase in size in old age, pointing to the heterochromatinization of these heterochromatin regions of chromosomes.

In some cases, without pretreatment metaphases from old individuals, blocks of centromeric heterochromatin were common on homologous chromosomes 1qh C-band locations were similar to those seen after an alkaline or thermal pretreatment or staining with buffered Giemsa.

In a percentage without pretreatment of metaphases, the heterochromatin-positive 1qh chromosomes displayed some packing impairment. Sizes and distribution of centromeric heterochromatin on the 1qh homologous varied in some metaphases of 6 from 24 individuals aged 81 to 114 years and was absents in control group ranging in age from 13 to 34 years.

Of interest was a sample from a 114-year-old man whose 1qh showed dark-stained heterochromatin sites sized 1.5-fold greater than counterpart sites in other individuals samples. However, intrahomologous variability was often related to sizes and the absents of heterochromatin blocks in one of the homologous chromosome 1 (Fig.2).

The control of cellular senescence by specific human chromosomes was examined in interspecies cell hybrids between diploid human fibroblasts and an immortal, Syrian hamster cell line. Most such hybrids exhibited a limited life span comparable to that of the human fibroblasts, indicating that cellular senescence is dominant in these hybrids. Karyotypic analyses of the hybrid clones that did not senesce revealed that all these clones had lost both copies of human chromosome 1, whereas all other human chromosomes were observed in at least some of the immortal hybrids. The application of selective pressure for retention of human chromosome 1 to the cell hybrids resulted in an increased percentage of hybrids that senesced. Further, the introduction of a single copy of human chromosome 1 to the hamster cells by microcell fusion caused typical signs of cellular senescence. These findings indicate that human chromosome 1 may participate in the control of cellular senescence and further support a genetic basis for cellular senescence (Sugawara et al., 1990).

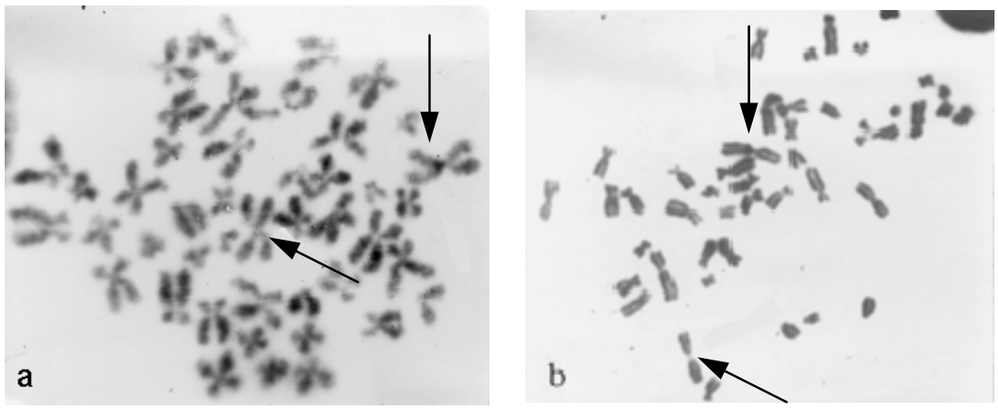

Fig. 2. Distribution of C-bands on one of the homologous of the 1qh chromosomes without preparation pretreatment and unbuffered Unna blue staining. Metaphases: from 114-year-old man (a) and from 83-year-old man (b). Arrows indicate: homologous chromosomes 1 with and without bands

3.2 Telomeric heterochromatin

Telomeres are specialized DNA–protein structures that form loops at the ends of chromosomes (Boukamp et al., 2005). In human cells they contain short DNA repeat sequences $(TTAGGG)_n$ added to the ends of chromosomes by telomerase. Telomere heterochromatin in most human somatic cells loses 50–200 bp per cell division (lansdorp, 2000; Geserick and Blasco, 2006). Telomeres serve multiple functions, including the protection of chromosome ends and prevention of chromosome fusions. They are essential for maintaining individuality and genome stability (Lo *et al*., 2002; Murnane, 2006). A major mechanism of cellular senescence involves telomere shortening (Horikawa and Barrett, 2003; Opresko et al., 2005), which is directly associated with many DNA damage–response proteins that induce a response similar to that observed with DNA breaks (Bradshow et al., 2005; Wright and Shay, 2005).

Terminal telomere structures consist of tandemly repeated DNA sequences, which vary in length from 5 to 15 kb in humans. Several proteins are attached to this telomeric DNA, including PARP-1, Ku70/80, DNA-PKcs, Mre11, XRCC4, ATM, NBS and BLM, some of which are also involved in different DNA damage response (repair) pathways. Mutations in the genes coding for these proteins cause a number of rare genetic syndromes characterized by chromosome and/or genetic instability and cancer predisposition (Callen and Surralles, 2004; Hande, 2004; Bradshow et al., 2005).

Based on the presented data, we concluded that telomeric chromatin undergoes progressive heterochromatinization (condensation) with aging that determines: (a) inactivation of the gene coding for the catalytic subunit of telomerase, hTERT; and (b) switching off the genes for Ku80, Mre11, NBS, BLM, etc causing chromosome disorders related to chromosome syndromes. Telomere shortening is another consequence of age-related.

Heterochromatinization that is reportedly due to unrepaired single-strand breaks of DNA in telomere regions resulting in unequal interchromatid and interchromosome exchanges and inactivation of the telomerase-coding gene-determining telomere length (Golubev,2001; Gonzalo et al., 2006).

Our experimental data showed that the number of cell with end-to-and telomere associations and the total frequency of aberrant telomeres were considerably increased at the old age in comparison with those at middle age (lezhava,2006).

The higher frequency of chromosome end-to-and telomere associations in extreme old age may be due to the loss of heterochromatin telomere regions (Fig.3). Mouse embryonic fibroblast cells lacking Suv39h1 and Suv39h2 exhibit reduced levels of H3K9me and HP1 (deheterochromatinization).These alterations in chromatin correlate with telomere elongation (Garcia-Cao et al., 2004).

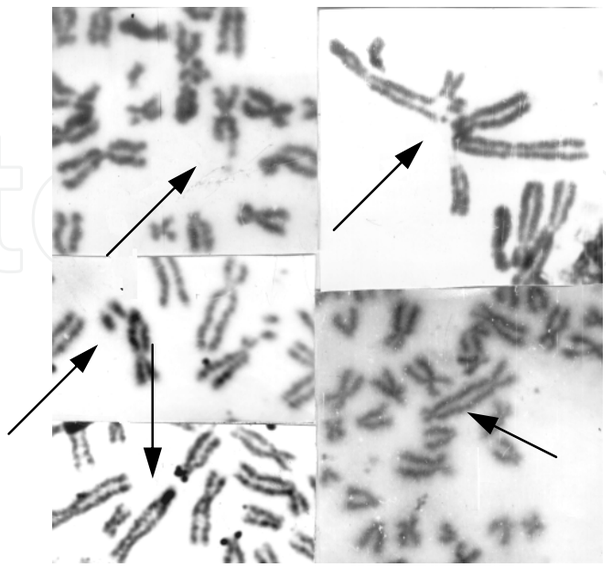

Fig. 3. Telomeres aberrations and end-to-end associations of chromosomes from elderly are shown by arrows.

According to previous publications (Prokofieva-Belgovskaya, 1986; Hawley and Arbe, l993) sister chromosome exchanges (SCEs) do not occur or are less frequent in heterochromatin or heterochromatinized regions. The evaluation of SCE in individuals aged 80 years and more has revealed that single-cell SCE counts appear to be lower than in middle age (lezhava, 2006), that is, exchanges between sister chromatids mostly take place in euchromatic regions.

In old age, $CoCl_2$ alone and in combination with the tetrapeptide bioregulator Livagen enhanced the distribution of SCE; that is, pericentromeric heterochromatin appeared to be more sensitive to the $CoCl_2$ effect alone (15.4 ± 1.8% SCE), whereas SCE was mostly observed in telomere heterochromatin when $CoCl_2$ in combination with livagen was used (12 ± 1.2% SCE) (control, 2.8 ± 0.5% SCE, respectively).Because exchanges occur in euchromatic uncondensated regions, the obvious effect of $CoCl_2$ alone and in combination with Livagen could be attributed to its decondensing deheterochromatinization effect on pericentromeric and telomeric heterochromatin, which would elevate the possibility of SCE ((lezhava and Jokhadze, 2007). At the same time, the deheterochromatinization of telomeric heterochromatin contributes to activation of DNA repair. That is, the intensity of unscheduled DNA synthesis increases (lezhava and Jokhadze, 2004) and creates a basis for activation of inactivated genes during aging and development of diseases.

4. Nucleolus Organizer Regions (NOR) heterochromatin

The heterochromatic regions of secondary constrictions (NORs) in human D (13, 14, 15) and G (21, 22) group acrocentric chromosomes contain genes coding for 18S and 28 ribosomal RNA. It has been established that genetically active NORs can appear with nucleolar form of DNA-dependent RNA-polymerase and selectively stain with silver (Ag-stained). It has also been found that association between Ag-stained satellite stalks of acrocentric chromosomes in metaphase cells (Fig.4) are determined primarily by their function as nucleolar organizers.

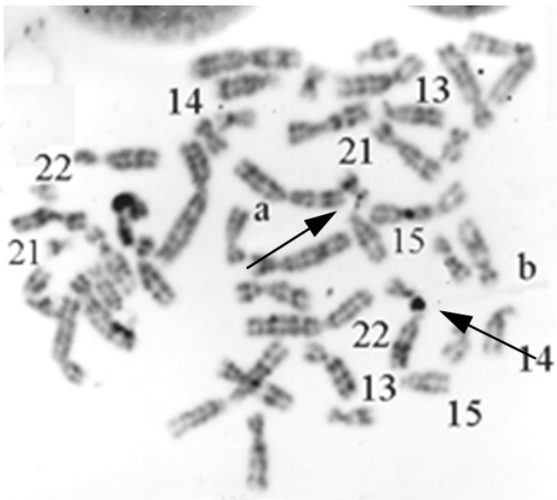

Fig. 4. Metaphases with variable sizes of Ag-positive nucleolar organizer regions. Arrows indicate a - "open" satellite stalks association; b - "closed" satellite stalks association.

The acrocentric association phenomenon may induce acrocentric nondisjunction during the meiosis or early zygote division, and chromosome rearrangements. Chromosomes can associate when two chromatid satellites are available, and so they are defined as associated, when their satellites make up a pair. Therefore, prematurely condensed silver-stained acrocentrics have similar rates of interphase and metaphase association. It was shown (Lezhava,1984; Verma and Rodriguez, 1985) that the likelihood of acrocentric chromosome associations is related to an extent of satellite stalk heterochromatinization.

Heterochromatinization of stalks – NORs has been studied by association frequencies in lymphocytes. In humans of a very old age (80–93 years), the estimated number of Ag-positive nucleolus organizer regions (NORs) for all chromosomes per cell, both associated and nonassociated, was significantly lower (6.10 in individuals 80–93 years old) in comparison with that in young individuals (7.05; $p < 0.01$). The frequency of acrocentric chromatid association in individuals aged 80 years and over was significantly decreased in comparison with those in a control group.

Increase of associations frequency was parallel to the growth of Ag segment size. At the same time, chromosomes containing NORs of grade 2 frequently formed associations among the middle-aged individuals, rather than in the older group.

Moreover, the transcriptional activity of ribosomal cistrons, which determine activity of a nucleolar form of DNA-dependent RNA polymerase - were from 668–721 imp/min in old individuals. They were significantly decreased in comparison with the control: from 1020 to 1120 imp/min.

The above considerations imply that a decreased number of chromosomes with Ag-positive NORs, a lower frequency of association of acrocentric chromatids, and a decrease in endogenic RNA-polymerase activity of ribosomal cistrons, result in alterations in the length of chromosomal satellite stalks that is caused by heterochromatinization in the process of aging (Lezhava and Dvalishvili,1992).

4.1 Cis- and trans-types of chromatid association

Most of acrocentric chromosome associations (85 percent) are formed by single chromatid satellite stalks (Lezhava et al., 1972; Verma et al., 1983). The exposure of lymphocyte cultures to 5-bromodeoxyuridine (BrDU) during two replication cycles revealed two-acrocentric associations that were either at a cis-position (differentially stained acrocentric chromatids with a dark-to-dark or light-to-light association) or a trans-position (chromatids with a dark-to-light or light-to-dark association) (Chemitiganti et al., 1984).

Frequencies of the cis- and trans-orientation of acrocentric chromatid association have been studied in old individuals. Lymphocyte cultures were prepared with a conventional methodology. The study examined 173 metaphases from 9 individuals aged 80 to 89 years and 124 metaphases from 6 individuals aged 20 to 48 years. For differential staining of sister chromatids BrDU (7.7 μg/ml) was added to the cultures immediately on their initiation. The lymphocytes were incubated in darkness for 96 h at 37°C. Giemsa stain was employed after DNA thymine was substituted by BrDU. In DNA thymine was totally substituted in one of second-mitosis sister chromatids which stained light and was denoted chromatid 1; only half of DNA thymine was substituted in the other chromatid which stained dark and was defined as chromatid 2 (Fig. 5). According to association criteria of cis-1 position was the

term adopted for the light-to-light association, cis-2 position for the dark-to-dark association, and trans-position for the light-to-dark association (Fig. 5).

Statistical analysis of association frequencies proceeded from the assumption that the cis-1 and cis-2 associations have similar chances to occur, and the chances make half of the probability of the trans-oriented association, that is

$$P_{\text{cis-1}}(DD) = P_{\text{cis-2}}(DD) = 1/2\ P_{\text{trans}}(DD) \quad (1)$$

$$P_{\text{cis-1}}(GG) = P_{\text{cis-2}}(GG) = 1/2\ P_{\text{trans}}(GG) \quad (2)$$

$$P_{\text{cis-1}}(DG) = P_{\text{cis-2}}(DG) = 1/2\ P_{\text{trans}}(DG) \quad (3)$$

These equalities represent the hypothesis that chromatids-1 and chromatids-2 participated in the association with the same probability.

The data of the middle-aged group fitted the hypotheses (2) and (3). The statistics

$$X^2(GG) = \frac{\left(V_{cis-1}(GG) - V(GG)/4\right)^2}{(1/4)V(GG)} + \frac{\left(V_{cis-2}(GG)\right) - V(GG)/4\right)^2}{(1/4)V(GG)} + \frac{(V_{trans}GG) - V\left(GG/2\right)^2}{(1/2)V(GG)}$$

should be almost $X^2(2)$-distributed if (3) is true; they yielded the value of 0.69. Similar statistics X^2(DG) for testing (3) gave the value of 1.54. Equalities (1) proved less supportive: the verifying statistics X^2(DD) gave 5.14 while the presumptive value was 0.08.

A different pattern was seen in the old individuals group. While the data fitted equalities (2), (1) and (3) had to be rejected since the statistics were X^2(DD) = 5.76 and X^2(DG) = 18.

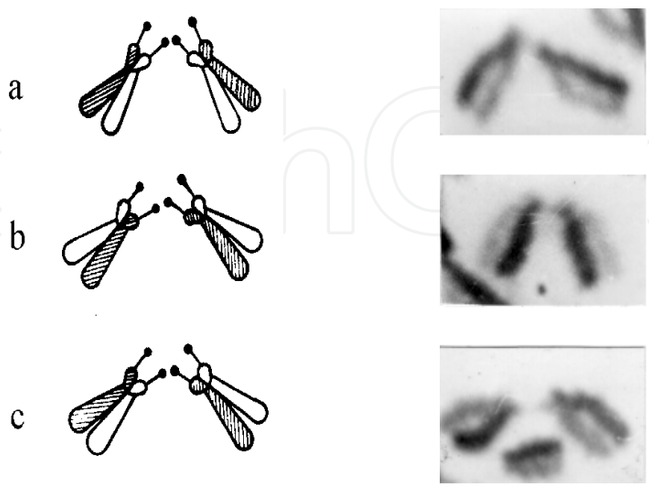

Fig. 5. Associations of acrocentric chromatid satellite stalks. a - cis-1 position (light -to-light chromatid association); b - cis -2 position (dark-to dark association); c - trans-position (dark-to-light association).

An important consideration is deviation of the data from the hypotheses (1)-(3). The deviation suggested that chromatids 1 and 2 of D chromosomes had different associative activities, unlike G-chromosome chromatids. Indeed, if D-chromosome chromatid 2 were more active than chromatid 1, probabilities should be

$$P_{\text{cis-1}}(DD) < 1/2\ P_{\text{trans}}(DD) < P_{\text{cis-2}}(DD) \quad (4)$$

$$P_{\text{cis-1}}(DG) < 1/2\ P_{\text{trans}}(DG) < P_{\text{cis-2}}(DG) \quad (5)$$

and these agreed well with the actual findings.

In conclusion, sister chromatids of acrocentric chromosomes show a functional heterogeneity in very old individuals (Lezhava, 1987, 2006).

5. Correlation between mutation, repair and hetheterochromatinization of chromosomes in aging

Progressive heterochromatinization of chromosome regions observed during aging correlates with the greater frequency of chromosome aberrations and the reduced intensity of reparative events. Chromosome alterations have been studied in 70 individuals aged 80–114 years (30 women and 40 men). In these samples, the percentages of aberrant metaphase and chromosomal aberrations were 4.08±0.41% in women and 5.15±0.45% in men; these values are significantly higher than the published control levels (aged 25–40 years)of 1.8±0.42% and 2.15±0.35%, respectively (Lezhava, 2001, 2006).

The incidence of cell with chromosome aberrations in 80- to 90-year-old individuals was 4.75±0.71% for 25 women and 3.06±0.54% for 31 men; these means were also above those of 20-to 48-year-old individuals. The incidence of aberrant cells in men aged 91 to 114 years (5.62±1.45%) was higher than that in women aged 91 to 108 years and control individuals (Fig. 6, 7).

Our studies have also demonstrated a marked decline in the unscheduled DNA synthesis (repair) rates in 80-90 year- old individuals in response to UV irradiation at a dose of 10–15 J/mm² compared with the middle-aged individuals ($P < 0.03$, $P < 0.01$ respectively). These data suggest that human lymphocytes from older people have a significantly reduced capacity for unscheduled DNA synthesis–excision repair (Lezhava, 1984, 2001).

Progressive heterochromatinization of chromosome regions observed during senescence correlates with the lowered intensity of reparative events and the increases frequency of chromosome aberrations. To explain the prevalence of the accumulation of damage in heterochromatin and in the heterochromatinization regions, it has been assumed that the repair of lesions capable of causing aberrations is possible only in those areas of DNA that are actively involved in transcription and that are within physically accessible of reparative enzymes, i.e. in euchromatin areas (Yeilding, 1971). Assuming that heterochromatinized regions are inaccessible to reparative enzymes and therefore number of cells with chromosome aberrations profoundly affects the functioning of the genome in old age (Fig.8).

Our results indicate that decreases in the repair processes and increases in the frequency of chromosomal aberrations in aging are secondary to the progressive heterochromatinization and that chromosome heterochromatinization is a key factor in aging.

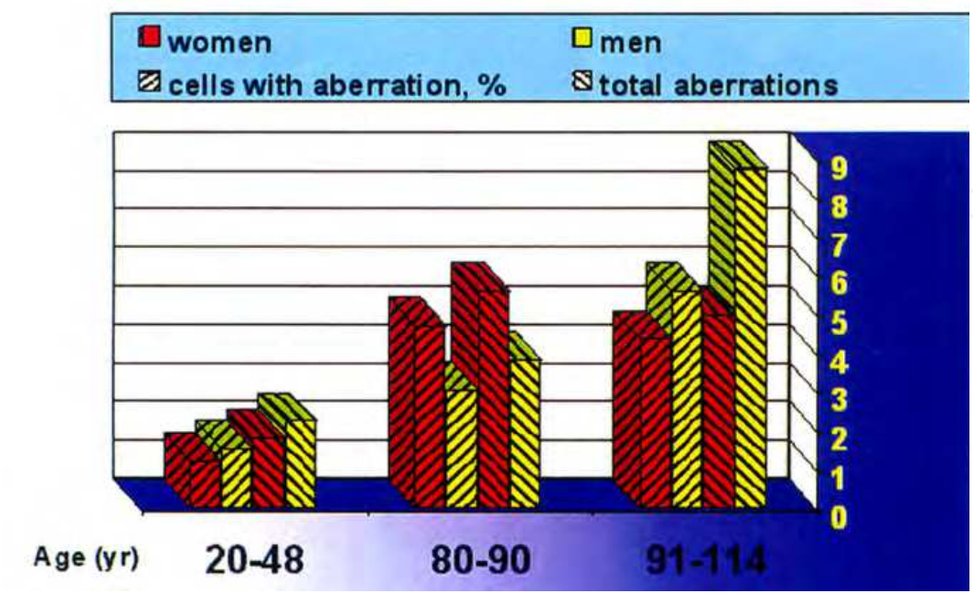

Fig. 6. Spontaneously structural chromosome aberration at 80 years and over

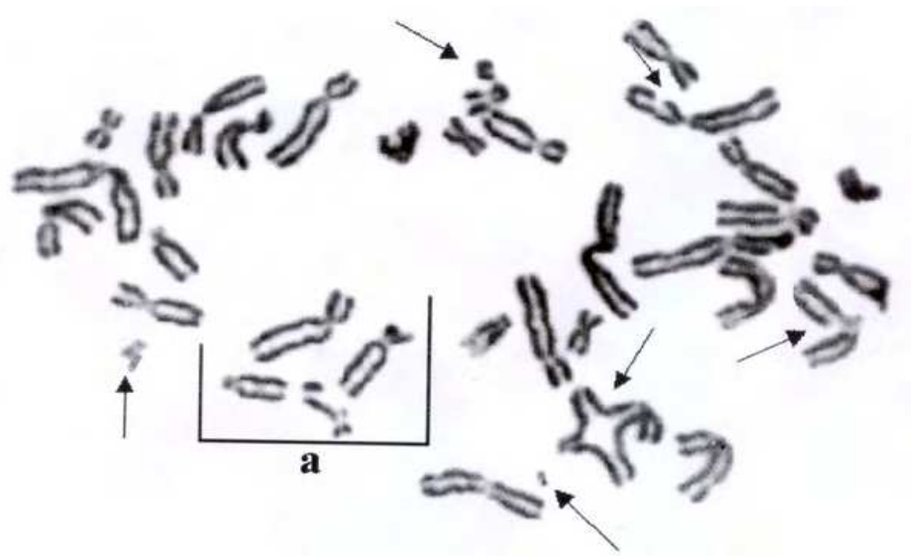

Fig. 7. 114-year-old man's metaphase with aberrant chromosomes. a – association of telomeric regions

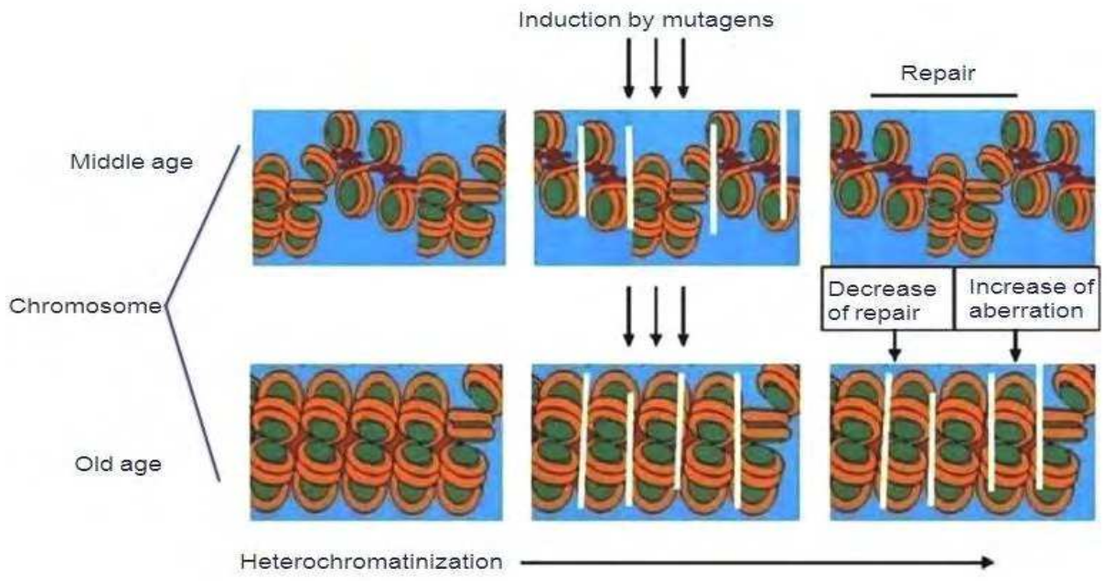

Fig. 8. Heterochromatinized regions inaccessible to reparative enzymes and therefore the number of cells with chromosome aberrations profoundly affects the functioning of the genome in old age.

6. Heterochromatin and pathology

Heterochromatinization progresses with aging and can deactivate many previously functioning active genes. It blocks certain stages of normal metabolic processes of the cell, which inhibits many specific enzymes and leads to aging pathologies. The action of genetic systems reveals general rules in the behavior of such systems, such as the connection between the structural and functional interrelationships between the "directing" and "directed" structures. In the respect, it should be noted that heterochromatinized regions in chromosomes can reverse. Many physical and chemical agents, hormones and peptide bioregulators (Epitalon - Ala-Glu-Asp-Gly; Livagen - Lys-Glu-Asp-Ala; Vilon - Lys-Glu) (Khavinson *et al.,* 2003; Lezhava and Bablishvili, 2003; Lezhava *et al.*, 2004, 2008) cause deheterochromatinization (decondensation) releasing the inactive (once being active)genes that seems to favour purposive treatment of diseases of aging.

We have demonstrated also that Co^{2+} ions alone and in combination with the bioregulator Livagen can reverse the deheterochromatinization of precentromeric and telomeric heterochromatin (Fig.9), to normalize the telomere length in cells from old individuals (Lezhava and Jokhadze, 2007; Lezhava *et al.*,2008). Blood cholesterol levels in an animal model (rabbit) for atherosclerosis was reduced (41% on the average) by pretreatment with combination of livagen and $CoCl_2$ - normalization of telomere length (unpublished data of research – STCU 4307- grants in 2007-2009) (Lezhava *et al.,* 2007-2009).

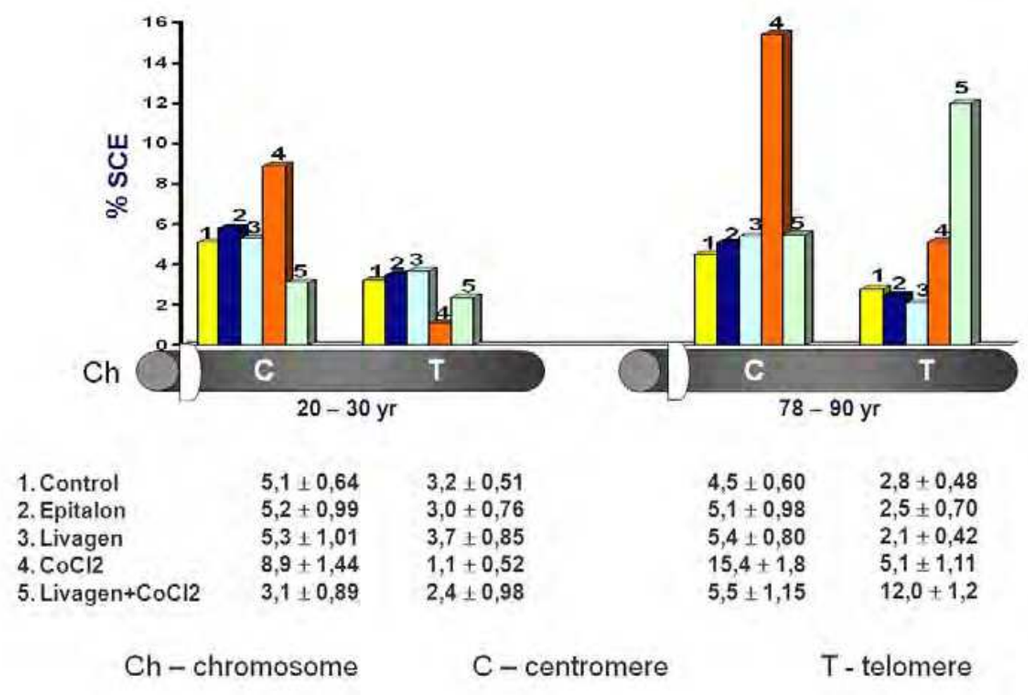

Fig. 9. The effect of Co^{2+} ions separate and with peptide bioregulators Epitalon (Ala-Glu-Asp-Gly) and Livagen (Lys -Glu-Asp-Ala) distribution of SCE among centromer and telomer heterochromatin regions.

7. Conclusion

In the present investigation, we assessed the modification of total, constitutive (pericentromeric, telomeric and nucleolus organizer region (NOR) heterochromatin) and facultative heterochromatin in cultured lymphocytes exposed to the influence of heavy metal and bioregulators from individuals aged 80 years and over.

The results showed that: (1) progressive heterochromatinization of total, constitutive (pericentromeric, telomeric and NOR heterochromatin) and facultative heterochromatin occurred with aging; (2) a decrease in repair processes and an increase in frequency of chromosome aberrations with aging is secondary to the progressive heterochromatinization of chromosomes; (3) peptide bioregulators induce deheterochromatinization of chromosomes in old age and (4) Co^{2+} ions alone and in combination with the tetrapeptide bioregulator, Livagen (Lys-Glu-Asp-Ala), have different chromosomal target regions; that is, deheterochromatinization of pericentromeric (Co^{2+} ions) and telomeric (Co^{2+} ions in combination with livagen) heterochromatin regions in lymphocytes of olderaged individuals.

The proposed genetic mechanism responsible for constitutive (pericentromeric, telomeric and nucleolus organizer region (NOR) heterochromatin) and facultative heterochromatin remodeling (hetero- and deheterochromatinization) of senile pathogenesis highlights the importance of external and internal factors in the development of diseases and may lead to the development of therapeutic treat.

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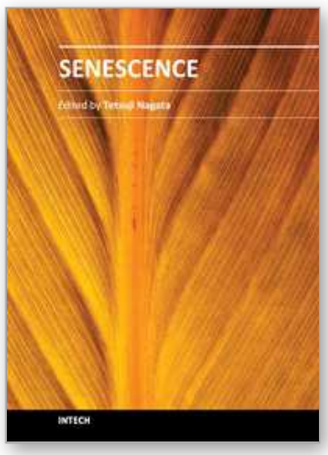

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The book "Senescence" is aimed to describe all the phenomena related to aging and senescence of all forms of life on Earth, i.e. plants, animals and the human beings. The book contains 36 carefully reviewed chapters written by different authors, aiming to describe the aging and senescent changes of living creatures, i.e. plants and animals.

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