Cancer Cells Possess Different Isotopic Enrichment

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Running Title:

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Abstract

Although the dynamics of telomeres during the life expectancy of normal cells have been extensively studied, there are still some unresolved issues regarding this research field. For example, the conditions required for telomere shortening leading to malignant transformation are not fully understood. In this work, we mass analyzed DNA of normal and cancer cells for comparing telomere isotopic compositions of white blood cells and cancer cells. We have found that the 1327 Da and 1672 Da characteristic telomere mass to charge cause differential mass distributions of about 1 Da for determining isotopic variations among normal cells relative to cancer cells. These isotopic differences are consistent with a prior theory that replacing primordial isotopes of ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{24}Mg, ^{31}P and/or ^{32}S by nonprimordial, uncommon isotopes of ^{2}D, ^{13}C, ^{15}N, ^{17}O, ^{25}Mg and/or ^{33}S leads to altered enzymatic dynamics for modulating DNA and telomere codons towards transforming normal cells to cancer cells. The prior theory and current data are consistent also with a recently observed non-uniform methylation in DNA of cancer cells relative to more uniform methylation in DNA of normal cells.

Introduction

The functions of the DNA replication, RNA transcriptions and protein translations are altered intrinsically due to possible mutations, including the abnormal replacement of nucleotides. In normal cells, mutations are avoided by DNA repair mechanisms and due to the functions of telomeres with appropriate lengths. When telomeres are shortened, they can no longer fulfill their protective function and therefore mutations accumulate [1]. If some of these mutations are cancerous and telomerase (the enzyme that prevents telomere shortening) is upregulated, a tumor might develop [1]. Currently, it is unknown what leads to the accumulation of mutations in the DNA and the assumption is that this is a random process.

In general, random mutations that lead to a constant activity of certain oncogenes products or the downregulation of other tumor suppressor gene products are the main causes of cancer. Cancer cells divide constantly in an unregulated way and develop a tumor mass. At an advanced lethal stage tumors develop metastasis to other organs, usually to the liver, brain and lungs.

A prior theory has proposed another explanation for the formation of mutations. According to this theory isotopes in enzymes can manifest different chemical and

enzymatic properties due to many body interactions, magnetism and nano, molecular and atomic sizes [2, 3]. Thus, isotopic replacements in proteins and associated nucleic acids may lead to altered properties of the biomolecules, accounting for diseases such as cancer caused by nonrandom mutations. On this basis, we propose that isotopic replacements of possible (common, primordial) ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{24}Mg, ^{31}P, ^{32}S, ^{43}Ca and/or others for (uncommon, nonprimordial) ^{2}D, ^{13}C, ^{15}N, ^{17}O, ^{25}Mg, ^{33}S, ^{43}Ca and/or others may be a basis for alterations of telomere lengths, leading to malignant transformations of normal cells. Since isotopes (atoms of the same elements) have the same number of protons but different number of neutrons, it has been thought that isotopes have the same chemical properties for a given element. But based on the prior theory [2,3], the interior part of enzymes was proposed to distinguish between isotopes by nuclear magnetic moments (NMM); as non-zero NMM(s) were proposed to transiently alter enzymes structures and dynamics affecting their activities. In this work, it is demonstrated by mass spectrometry that isotopic replacements are different in cancer cells versus normal white blood cells.

On this basis, our work provides further confirmation of recent theory [2,3] and the observed selective sensitivity of cancer cells to the nonprimordial isotopes: ^{25}Mg, ^{43}Ca and ^{67}Zn versus normal cells sensitivity. This may explain also the lack of sensitivity to the nonprimordial isotopes of ^{24}Mg, ^{40}Ca, and ^{64}Zn of cancer and normal cells [4]. Additionally, this work may explain recent twin experiments of NASA [5] where telomeres of prolonged, space orbiting twin brother were elongated relatively to earth bound twin brother. According to their theory [2,3] cosmic rays may transmute ^{1}H, ^{12}C, ^{14}N, ^{16}O, ^{24}Mg, ^{32}S, and/or ^{42}Ca to possibly ^{2}D, ^{13}C, ^{15}N, ^{17}O, ^{25}Mg, and/or ^{43}Ca, thus affecting telomerase activity and elongation of the telomeres of the twin brother in orbit relative to the brother on the surface of earth. The data reported here and prior theory [2,3] also are consistent with observation regarding higher extent of nonrandom methylation of DNA in cancer cells [6] versus that of normal cells and [7].

Results

The results of the mass spectroscopy analysis are shown in the following Figures I and II. The observed masses correspond to fragmented pieces of the DNA of the cancer

cells, normal B lymphocytes and total white blood cells. By analyzing the masses that are identical from the cancer (DNA-K562) to the other white (DNA-wbc) and normal B lymphocytes (DNA-skw) blood cells some fragments are assigned to the telomere codon of the DNAs. The telomere fragments were assigned to masses 1327 Da and 1672 Da on basis of prior mass analysis of as in reference [8]. However, other fragment may also represent telomere codons T_2AG_3. These include fragments of various masses and charges ranging from -1 to -6. Cancer cells in general show smaller full width half maxima (FWHM) values manifesting fewer molecular fragments and isotopic differences. Smaller masses tend to be nucleotides and nucleosides of the DNA and some are of the telomeres. Medium mass pieces are larger segments of telomere domains and there are some heavier masses of telomeres themselves.

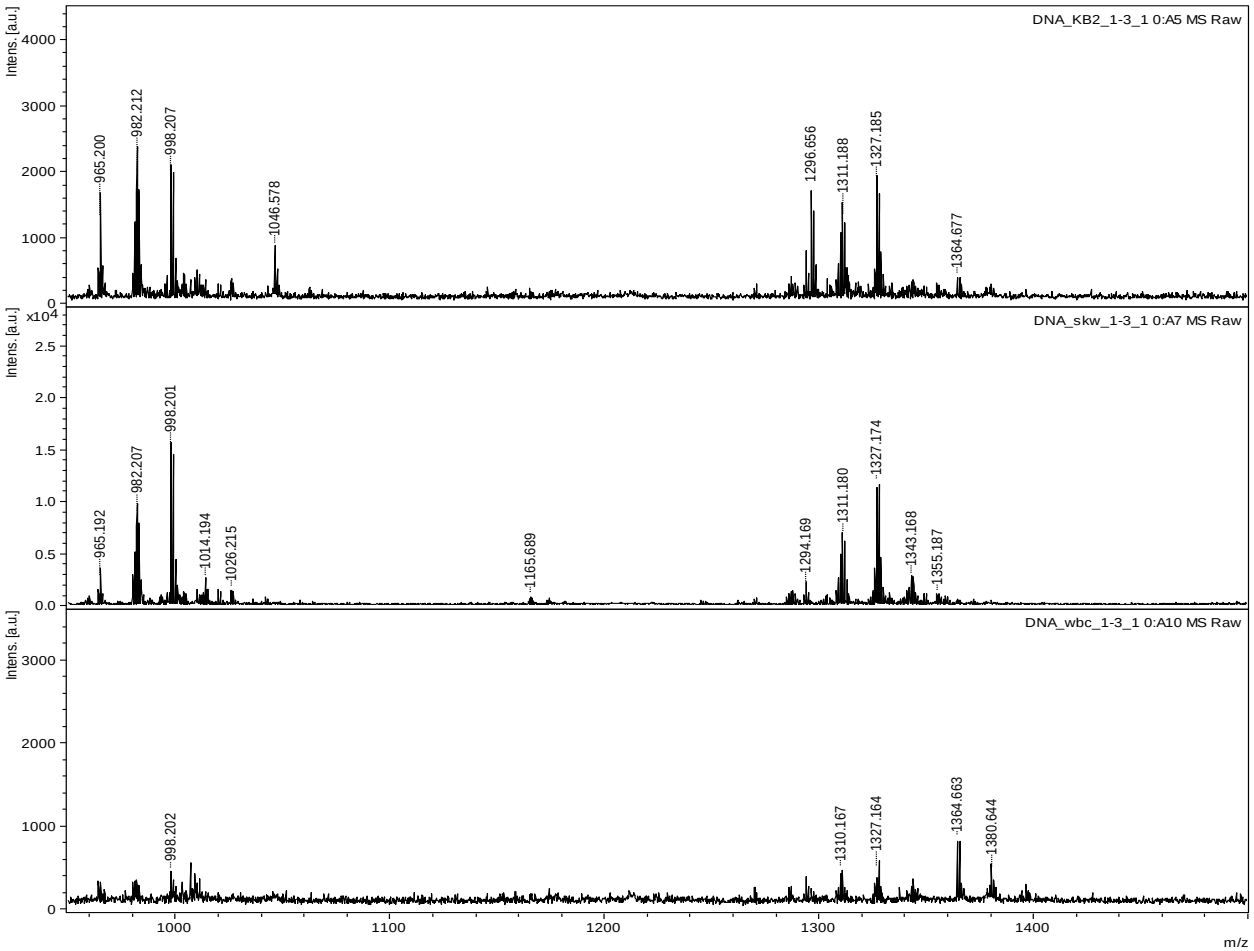

Figure I. – Mass Spectra from 975 Da to 1500 Da: The DNA K562 is mass spectrum of the cancer cells; the DNA SKW is the mass spectrum of the lymphocytes cells; and the DNA WBC is the mass spectrum of the white blood cells.

Figure I and II show mass spectra of DNA from three different cells: cancer cells, white blood cells and lymphocytes. The different peaks correspond to various fragments of the DNA having different possible masses and charges (mass to charge). According to reference [8] the masses at 1327-1328 Da, 1672 and 1673 Da correspond to telomere fragments. Although many other fragments are observed, the signals at 1327 Da and 1672 Da enable to compare telomeres from the cancer cells, WBC and lymphocytes. The difference signals express different relative intensities of the DNA fragments. The different signals also express different FWHM values in the DNA of the cancer cells, WBC and lymphocytes. In general, cancer cells possess smaller FWHM relative to those of the WBC and lymphocytes. The smaller FWHMs values reflect the signal involving fewer molecular fragments and fewer isotopic differences. The 1327 Da and 1672 Da telomere signals with nearby peaks correlate with de-functionalization (heavier) and functionalization (less massive peaks) of these 1327 Da and 1672 Da telomeric peaks, respectively, by possible isotopes of CH_3.

In particular, the 1327 Da (mass/charge) corresponds to the telomere codon $[G_3(T_2\ AG_3)_3]^{5-}$ as reported in reference [8] See Figure II. For this $[G_3(T_2\ AG_3)_3]^{5-}$ codon the relative intensity is greater in the cancer cell DNA at 1327 Da, but the relative intensity is greater at 1328 Da for the WBC and lymphocytes. The difference of mass of 1 Da between the signals correlates with isotopic differences of elements (H, C, N, and O) in the telomeres, See Table I. At 1327 Da the cancer cells seem to be enriched in primordial isotopes and at 1328 Da the lymphocytes and WBC appear to be enriched in the nonprimordial isotopes. The FWHM of 1327 Da is smaller relative to FWHM at 1328 Da of WBC and lymphocytes telomeres. The 1327 Da and 1328 Da mass/charge have nearby signals at 1313 Da to 1309 Da for mass differences ranging from 14 Da to 16 Da. The mass differences (Δm) of WBC are narrower with range of (1327 - 1312) = 15 Da to (1328 - 1310) = 18 Da. The Δm of the cancer and lymphocytes are larger ranging from (1327 – 1313) = 14 Da to (1328 – 1309) = 19 Da. These mass differences may involve the 1327 to 1328 Da defunctionalization by loss of CH_3, NH_2 and/or OH groups to masses 1309 to 1313 Da. It is also observed that less massive signals at 1303 – 1309 Da for mass differences of 1327 – 1304 = 23 Da to 1328-1303 = 25 Da, which may involve loss of $^{24}Mg^{2+}$ or $^{25}Mg^{2+}$ from the telomere pieces. The Mg^{2+} is known to bind DNA and are

associated with many enzymes associated with replication of nucleic acids [4]. In addition to the less massive signals about 1317 Da to 1328 Da, more massive signals are observed. Heavier signals at 1333 to 1334 Da involve Δ m of 5-7 Da which are possible for mass to charge range of 10 - 14 Da demonstrating possible methylation /demethylation. Heavier signals in range 1341-1345 Da involve Δm ranging from (1341-1328) = 13Da to (1345 – 1327 Da) 18 Da or Δm = 13-18 Da explaining range of possible methylations, aminations and hydroxylations, See Table II. Heavier signals in range 1349 to 1350 Da involve Δm of (1349 -1328) = 21 to (1350 – 1327 =) 23 Da that may explain possible hydroxylation or Na^{+} and/or Mg^{2+} ions.

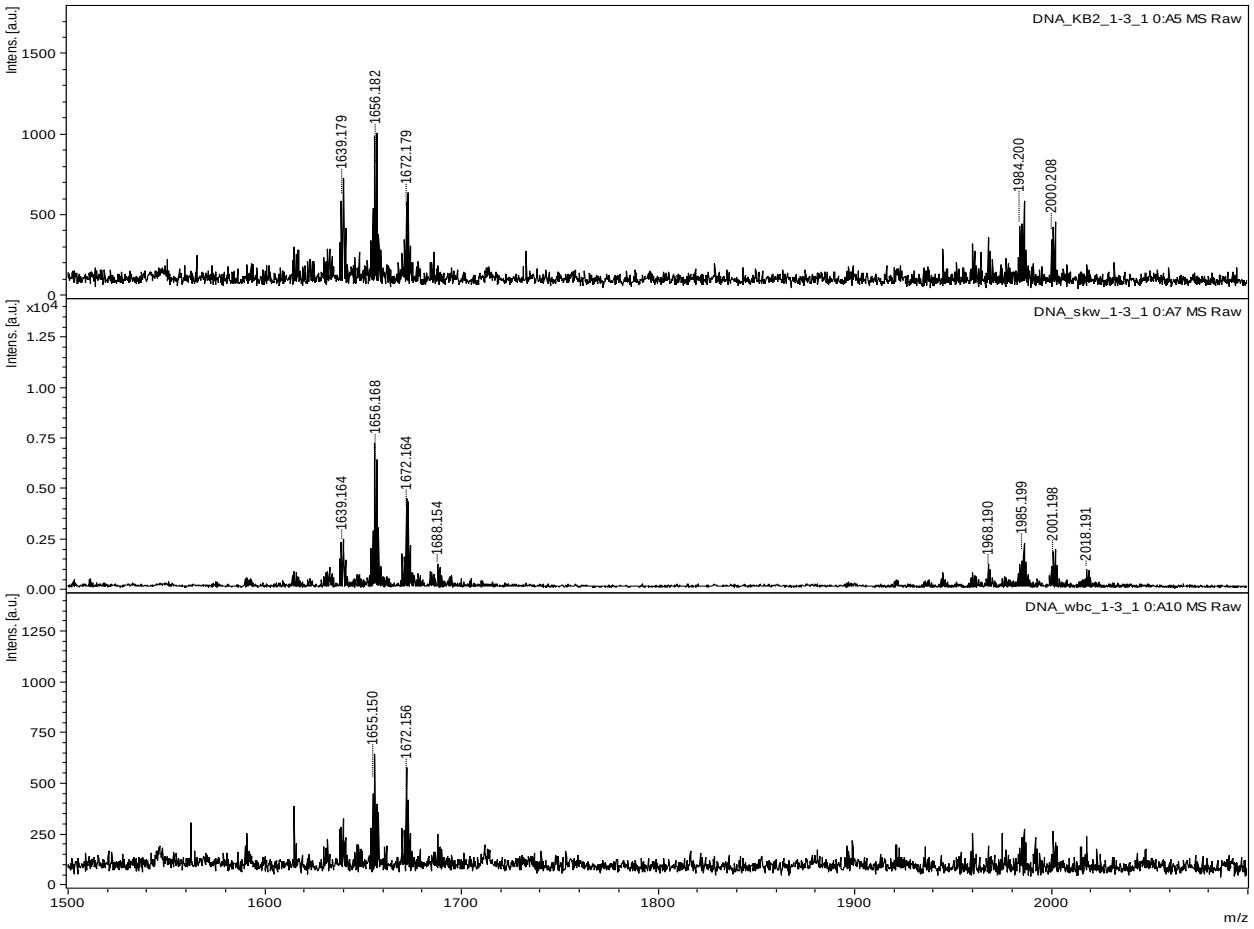

Figure II – Mass Spectra from 1500 Da to 2100 Da: The DNA K562 is mass spectrum for the cancer cells; the DNA SKW is the mass spectrum for the lymphocytes cells; and the DNA WBC is the mass spectrum for the white blood cells.

The 1670-1674 Da (mass to charge) corresponds to the telomere codon $[G_3(T_2AG_3)_3]^{4-}$, See Figure II. For this $[G_3(T_2AG_3)_3]^{4-}$ codon the relative intensity is greater for the cancer cell at 1674 Da, but at 1672 Da the relative intensity is greater for the WBC and lymphocytes. See Table III. The difference in mass of 1Da between the samples correlates with isotopic differences of elements (H, C, N, and O) in the telomeres. The FWHM of the 1673 Da signal of cancer telomeres is smaller than the FWHM of the 1672 Da of the WBC and lymphocyte telomeres. The 1672 to 1673 Da mass to charges have nearby signals of lesser mass to charges at 1655 to 1657 Da for mass differences ranging (1672-1657) =15 Da to (1673-1655) = 18 Da demonstrating possible amination or hydroxylation. At 1657 Da the cancer is enriched in nonprimordial isotopes and WBC and lymphocytes are enriched in the primordial isotopes. In addition to the less massive signal about the 1672-1673 Da, more massive signal at 1688 – 1689 Da is observed. The lymphocytes and WBC are enriched at 1688 Da and cancer is enriched at 1689 Da. Heavier signal at 1688 and 1689 Da involves Δm (1688 – 1673) =15 Da to (1689 -1672) =17 Da (15 to 17 Da) reflecting possible amination (15 to 16 Da) and/or hydroxylation (16-17 Da). The FWHM at 1672-1673 Da is bigger or smaller than the FWHM at 1688 – 1689Da.

Discussion

In this study, we describe for the first time the differences in mass distribution isotopes in telomeres from cancer versus normal cells. The observed difference is about 1327 to 1328 Da mass to charge. This difference may stem from different isotopic compositions and distributions in the telomeric codons in cancer cells relative to the normal cells. Telomeres of cancer cells are enriched in the primordial isotopes (^{12}C at 1327 Da) possibly due to the more dynamical chemical transformations of the clustered, non-primordial isotopic (^{13}C) in the cancer DNA for 1328 Da mass to charge. Since the clustered, nonprimordial (^{13}C) isotopes in the 1328 Da masses in cancer telomeres are more rapidly defunctionalize and degrade to smaller mass pieces of 1309 to 1313 Da, ^{13}C is depleted from cancer telomeres. The observed enrichment of the nonprimordial isotopes at 1311 Da in the cancer cells versus the enrichment of primordial isotopes in the white blood cells at 1311 Da is consistent with this view. The greater variation of the

FWHM in the cancer telomere at 1309-1313 Da is consistent with these clustered, nonprimordial isotopes which induced variation in the stability of 1328 Da leading to defunctionalization of fragments with masses of 1309-1313 Da. Normal cells having primordial ^{12}C isotopes with more random methylation lack the ^{13}C --- ^{13}C in the DNA internal interactions resulting in accelerated defunctionalization. The large -5 charge induces $^{12}CH_3$ defunctionalization in the normal cell telomeres. The defunctionalization of the 1328 Da masses in the cancer telomere is more induced (relative to the defunctionalization of the 1672 and 1673 Da masses) due to larger -5 charge of this codon $\{[G_3(T_2\ AG_3)_3]^{5-}\}$ of the 1328 Da mass. Larger negative charging may be explained by the present of more $^{13}CH_3$ in the telomeres as the $^{13}CH_3$ has a positive nuclear magnetic moment (NMM) and therefore tends to stabilize greater negative charge fragments. Based on the theory explained in ref 2, 3 [2, 3] the larger negative charge (and indirectly the clustered $^{13}CH_3$ in the cancer cells) induces higher rate of rapid defunctionalization of the ^{13}C containing telomeres relative to the $^{12}CH_3$ containing telomeres.

The larger negative charge may induce a higher loss of $^{13}CH_3$ from the original 1328 Da telomeric pieces to form masses of smaller range from 1309 to 1313 Da. The negative charge probably increases demethylation due to the larger negative charge which increases the probability of rehybridizations of $^{13}CH_3$ during defunctionalization. The presence of other nonprimordial isotopes with the $^{13}CH_3$ in the telomere may increase defunctionalization of CH_3. The opposite is observed in the normal white blood cells as they are less able to defunctionalize since they contain less nonprimodial ^{13}C isotopes with random distributions in 1328 Da pieces. Thereby (after defunctionalizations) they have more residual nonprimordials at 1328 Da but less nonprimordials at the defunctionalized products with smaller masses of 1309-1313 Da.

The observed difference in mass distributions in the 1672-1673 Da mass to charge may stem from different isotopic compositions of the telomeric codon in the cancer cells relative to the normal cells. The cancer telomeres seem to be enriched in the primordial isotopes (of ^{12}C at 1327 Da) possibly due to the more dynamical chemical transformations of the nonprimordial isotopic (^{13}C) telomeres having 1328 Da mass to charge; however, the nonprimordial (^{13}C) containing 1673 Da defunctionalize less rapidly to smaller mass pieces of 1655 - 1657 Da and the smaller pieces have heavier enrichments at 1656 Da. The normal cells manifest more random, less nonprimordial (^{13}C) isotopes in their DNA

and are less enriched in nonprimordial ^{13}C isotopes at 1673 Da; therefore, the telomeres of normal cells have higher peak at 1672 Da of enriched primordials and normal telomeres that do defunctionalize have mass distributions of less massive primordial pieces at 1655 Da. The observed enrichment of the nonprimordial ^{13}C isotopes at 1656 Da in the cancer cells versus the enrichment of primordial ^{12}C isotopes in the white blood cells at 1655 Da is consistent with this view. The greater variation of the FWHM in cancer telomere at 1672 - 1673 Da is consistent with this clustered, nonprimordial ^{13}C isotopic essence of the cancer telomeres and the induced variation in stability of 1673 Da to defunctionalize fragments of masses 1655-1657 Da. This defunctionalization of the ^{13}C clustered nonprimordial 1673 Da is less induced relative to the ^{13}C clustered nonprimordial 1327 Da telomeric piece due the smaller charge of -4 {on codon $[G_3(T_2AG_3)_3]^{4-}$} of 1672-1673 Da pieces relative to the larger charge of larger -5 of 1327 – 1328 Da pieces. The larger negative charge at 1327 to 1328 Da may cause more functionalization and defunctionalizations of $^{13}CH_3$ in the telomeres of mass to charge 1327 to 1328 Da relative to their defunctionalization of the (-4) decreased charge 1672 to 1673 Da fragments. The $^{13}CH_3$ has a positive nuclear magnetic moment and therefore tends to stabilize greater negative charged fragments; as a result, the larger negative charges tend to form better complexes in telomeres with more CH_3. The resulting smaller negative charge of 1672 – 1673 Da inhibits a loss of $^{13}CH_3$ from the original 1673 Da fragments thus there will be less number of smaller mass of 1655 – 1657 Da. The smaller negative charge in cancer telomeres is probably decreases demethylation due to the smaller negative charge decreasing probability of rehybridizations of $^{13}CH_3$ during the defunctionalization. The opposite is observed in the normal white blood cells as they are more able to defunctionalize their random primordial ^{12}C isotopes in the 1672 Da fragments as there is less ^{13}C to stabilize the negative charge (as in the cancer telomeres). Thereby the normal cells have more residual ^{12}C primordials at 1672 Da and more ^{12}C primordials at the defunctionalized products with smaller masses of 1655 to 1657 Da.

This observed enrichment and clustering of $^{13}CH_3$ in cancer cell DNA are consistent with higher methylation rate of DNA in cancer cells [6] and more nonrandom clustering of methyl groups in DNA of cancer cells relative to normal cells [7]. The $^{13}CH_3$ may provide an explanation for the higher clustered methylation in the DNA in cancer cells as the $^{13}CH_3$ may be considered a stronger nucleophile than the $^{12}CH_3$ [2, 3]. The positive NMM of

$^{13}CH_3$ relative to the null (0) NMM of the $^{12}CH_3$ causes valence (?) electrons in the ^{13}C nucleophile to be pulled more strongly to nuclei to form higher rehybridizations and nucleophilicity of the $^{13}CH_3$ and as a consequence a higher stability of the resulting R-$^{13}CH_3$ methylated group relative to $^{12}CH_3$ nucleophile and methylated groups. The observed greater clustered $^{13}CH_3$ distribution in the DNA of cancer cells and the observed higher stability of negative charge accumulation inducing greater fragmentation of the $^{13}CH_3$ enriched telomeres is consistent with stronger and differing possible interactions of $^{13}CH_3$ enriched telomeres in cancer cells with ^{25}Mg (- NMM) relative to ^{24}Mg (null (0) NMM) for - NMM. These interactions result in adversely interaction and alteration of the binding and replication of DNA in cancer cells relative to normal cells (having less clustered $^{13}CH_3$ and less negative charge). The observations of this work are further consistent with study of isotopes in twins in space and earth. The authors of this study have found that the elongation of DNA of orbiting twin astronauts relative to earth bound twin as the orbiting astronaut may experience neutrons in cosmic rays that enrich methyl groups with ^{13}C and increase the nucleophilic attack of the DNA by $^{13}CH_3$ thus elongating their telomeres. The $^{13}CH_3$ in the orbiting twin's telomeres may alter the unraveling of the telomere during reproductions as the $^{13}CH_3$ is a stronger base than $^{12}CH_3$ so the $^{13}CH_3$ containing telomere may not frazzle their ends as much for increasing stability. The functionalization by $^{13}CH_3$ may induce more addition to the telomere rather than their decomposition and frazzling.

Materials and Method

Cell growth

The experimental system consisted of three different cell types: total white blood cells, K562 (chronic myeloid leukemia) and SKW6.4 (B lymphocyte cell line). Total white blood cells were isolated by lysis of the red blood erythrocyte by using the Red Blood Cells lysis solution (Biological Industries, Israel) according to the provided manual. Briefly, cells were mixed with the lysis solution, agitated for 10 minutes and centrifuged for 2 minutes at 3125 RPM. The supernatant was then discarded. The lysis step was repeated twice and the pellet was used for DNA isolation. K562 cells were cultured in the presence of RPMI-1640 growth medium containing 10% FCS supplemented with 2mM L-Glutamine, 100units/ml penicillin and 100μg/ml streptomycin (Biological Industries Beit Haemek, Israel). Cells

were grown in a 95% humidity incubator with 5% CO_2. SKW6.4 cells were cultured in the presence of RPMI-1640, 10% FCS, 2mM L-Glutamine and 10mM HEPES, 100units/ml penicillin and 100µg/ml streptomycin (Biological Industries Beit Haemek, Israel). Cells were grown in a 95% humidity incubator with 5% CO_2.

DNA isolation

Cells were harvested and DNA was isolated by using the QIAamp DNA Mini Kit (Qiagen, MD, USA) according to the manufacturer's instructions. Basically, samples were first lysed using proteinase K. The lysate in buffering conditions was loaded onto the mini spin column. During centrifugation, DNA was selectively bound to the column membrane. The remaining contaminants and enzyme inhibitors were removed in two wash steps and the NA was then eluted in TE buffer.

MALDI

DNA samples of K562, SKW, and WBC were analyzed. 20 µL of water were added to each sample tube to dissolve the dried samples. Sample water solution was mixed with THAP (2′,4′,6′-Trihydroxyacetophenone monohydrate) matrix (saturated in 25 mM ammonium citrate in ACN/Water 50/50) at 1:3 (v/v) sample to matrix ratio. The mass measurements were performed on a Bruker Rapiflex MALDI TOF/TOF mass spectrometer (Bruker Daltonics, U.S.A.) in positive linear mode and with a 355 nm Bruker scanning smartbeam™ 3D laser.

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Supplementary Materials

Table I – Individual Peak Mass/Charge, Intensity and FWHM about 1327 and 1328 Da

White Blood Cells	Cancer Cells	Red Blood Cells
1308.170 0.015 0.154	1308.184 0.035 0.068	1308.170 0.029 0.162
1309.169 0.019 0.169	1309.191 0.059 0.051	1309.170 0.055 0.163
1310.163 0.029 0.162	1310.169 0.104 0.066	1310.159 0.100 0.163
1311.174 0.030 0.157	1311.194 0.148 0.068	1311.180 0.144 0.162
1312.161 0.021 0.159	1312.189 0.118 0.068	1312.177 0.127 0.163
1313.162 0.015 0.168	1312.646 0.052 0.053	1312.632 0.012 0.360
1325.183 0.013 0.168	1313.193 0.051 0.061	1313.180 0.053 0.164
1326.157 0.022 0.166	1313.653 0.041 0.055	1314.178 0.024 0.164
1327.177 0.028 0.160	1314.198 0.033 0.036	1323.174 0.014 0.185
1328.162 0.036 0.154	1323.194 0.029 0.028	1324.161 0.019 0.164
1329.162 0.018 0.165	1326.186 0.051 0.092	1325.159 0.033 0.163
1337.644 0.016 0.162	1327.187 0.186 0.057	1326.166 0.080 0.161
	1328.188 0.160 0.073	1327.175 0.217 0.164
	1329.181 0.076 0.047	1328.169 0.226 0.165
	1330.191 0.043 0.054	1329.170 0.091 0.164
		1330.168 0.036 0.165

Table II – Individual Peak Mass/Charge, Intensity and FWHM about 1344 Da and 1365 Da

White Blood Cells	Cancer Cells	Red Blood Cells
1345.171 0.015 0.208	1343.175 0.032 0.076	1343.168 0.063 0.164
1346.146 0.017 0.166	1344.179 0.035 0.114	1344.162 0.059 0.164
1364.663 0.052 0.165	1364.680 0.037 0.087	1345.161 0.031 0.159
1365.664 0.041 0.168	1365.680 0.038 0.065	1364.681 0.014 0.170
1366.656 0.023 0.177	1366.684 0.029 0.031	1365.656 0.012 0.166
1367.643 0.017 0.181		1366.146 0.011 0.173
		1370.137 0.011 0.178

Table III – Individual Peak Mass/Charge, Intensity and FWHM about 1670 to 1674 Da

White Blood Cells	Cancer Cells	Red Blood Cells
1670.147 0.019 0.187	1671.196 0.033 0.086	1670.164 0.044 0.181
1671.146 0.019 0.176	1672.179 0.055 0.077	1671.163 0.042 0.181
1672.155 0.032 0.181	1673.171 0.061 0.057	1672.162 0.101 0.183
1673.151 0.027 0.179	1674.175 0.030 0.091	1673.161 0.092 0.183
1674.142 0.017 0.173		1674.159 0.048 0.183
1675.157 0.012 0.184		1675.148 0.021 0.187