Telomere Attrition and Decreased Fetuin-A Levels Indicate Accelerated Biological Aging and Are Implicated in the Pathogenesis of Colorectal Cancer

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Abstract

Purpose: Increasing chronological age is a risk factor for many types of cancer including colorectal. An understanding of the biology of aging and factors which regulate it may provide insight into cancer pathogenesis. The role of telomere biology in both the cancer and aging process could prove useful in this regard.

Experimental Design: Using quantitative PCR, we determined telomere length in the peripheral blood leukocytes of 64 colorectal cancer (CRC) patients and 1,348 controls. We also measured telomere length in 32 colorectal tumor samples and matched normal tissue. We aimed to assess whether telomere lengths were reflected in circulating mediators of inflammation and redox control factors, including fetuin-A, a circulating modulator of calcium homeostasis.

Results: CRC patients had shorter telomeres [adjusted mean ratio of relative telomere repeat copy number to single-copy gene number (RelT/S) = 0.61] compared with chronologically older controls (mean age = 75, adjusted mean RelT/S = 0.70; ANCOVA, P = 0.004). Telomere length in tumor tissue [median = 0.43, interquartile range (IQR) = 0.40] was significantly shorter than adjacent normal tissue (median = 0.65, IQR = 0.28; P = 0.004). Patients with low fetuin-A levels were shown to have significantly shorter telomeres (P = 0.041). Patients with rectal tumors had significantly higher levels of fetuin-A than those with colonic tumors (P = 0.045).

Conclusions: We have observed that patients with CRC display clear evidence of telomere attrition compared with controls. This is congruent with accelerated biological aging in the pathogenesis of CRC. An imbalance in redox control mechanisms and calcium homeostasis may be a contributing factor to telomere dynamics in our patients. Furthermore, fetuin-A levels can be used to distinguish between colon and rectal cancers. Clin Cancer Res; 17(17); 5573–81. ©2011 AACR.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United Kingdom and is responsible for approximately 16,000 deaths every year. This is despite 5-year survival rates having doubled over the last 30 years. Increasing chronological age is a risk factor for many types of cancer including colorectal, with 80% of CRC cases occurring in patients over the age of 60 (1). Consequently, an understanding of the biology of aging may provide insight into cancer pathogenesis (2). Biological aging comprises aging at the cellular and organ level and is affected by genetic, metabolic, and environmental factors. Fully delineating the key molecular mechanisms underpinning both the biological aging and cancer processes could improve the understanding of the disease process and lead to the discovery of novel biomarkers or targets for therapeutic intervention, further improving survival rates.

A key manifestation of aging at the cellular level is telomere attrition. Telomeres are nucleoprotein structures located at the ends of all eukaryotic chromosomes and are composed of a repetitive guanine-rich DNA sequence (TTAGGG)n (3). They possess a number of critical functions including maintenance of genomic integrity by protecting chromosomes from fusion events, repair of DNA damage, and maintenance of cellular stability (2). Telomere attrition is associated with increasing chronological
age and furthermore may act as a biomarker of replicative aging or mitotic clock (4). Once this progressive loss of telomeric DNA content reaches a critical level, cells are stimulated to either apoptose or enter replicative senescence (5).

Telomeres not only potentially serve as biomarkers of senescence and biological aging but also form part of a damage sensing and signaling system, facilitating DNA repair or apoptosis (6). Potential determinants of telomere length are varied. Telomere length is highly heritable, therefore, a proportion is genetically determined (7). Alteration in the expression of telomerase can significantly affect telomere dynamics. In mice, knockout of the telomerase-coding sequence resulted in progressive loss of telomeric DNA and progeria (8). Reintroduction of telomerase reversed both these effects (9). A major influence on telomere length and hence, telomere function is the control of redox state and potential damage induced by reactive oxygen species (10, 11). Correlation of telomere length with genes controlling redox state in a narrow age range cohort provides further evidence for a plausible mechanistic link between redox control and telomere biology (12). Pertinent in this respect is the observation that fetuin-A, a mediator of redox homeostasis in the circulation, displays a dependent relationship with peripherally known markers of systemic inflammation, and fetuin-A (this group will be referred to as the CRC PBL group). The second group utilized CRC tissue (tumor and normal) collected during diagnostic workup and used to measure PBL telomere lengths in addition to potential correlates of telomere length including redox control factors, markers of systemic inflammation, and fetuin-A (this group will be referred to as the CRC PBL group). The second group utilized CRC tissue (tumor and normal) collected under the auspices of the local biobank (NHS Greater Glasgow & Clyde). Patients were approached preoperatively by biobank staff and full informed consent given for the collection and use of excess tissue for research purposes. All samples were snap frozen in liquid nitrogen and stored at −80°C until use. All tissue samples were validated by a consultant pathologist and deemed representative of the pathologic specimen. A total of 62 paired samples were obtained from the biobank; however, DNA was available for analysis from 32 (this group will be referred to as the CRC tissue group). Where possible, biochemical, hematologic, and pathologic data were extracted from a prospectively maintained database. The Peterson Index (PI) was used as an additional measure to identify patients with pathologically more aggressive disease and hence poorer outcome. Pathologically determined vascular invasion, margin involvement, or serosal breach was allocated a score of 1, with tumor perforation scoring 2. A cumulative score of 0 to 1 indicates a low-risk PI and 2 to 5 a high-risk PI. A high-risk PI suggests aggressive disease and has been shown to correlate with a poorer outcome from CRC in lymph node negative patients (23). Table 1 presents details of the patient clinical and pathologic variables for both groups. Full ethical approval from the local NHS ethics committee was gained prior to the commencement of any sample collection.

The control population was composed of subjects from the West of Scotland Twenty-07 Cohort. Subjects used to form this cohort comprised 1,348 individuals aged either
57 (n = 847) or 76 (n = 501). This is a community-based cohort study designed to longitudinally investigate the social processes that produce or maintain inequalities in health and has been described in detail previously (24). The 2 age groups were specifically chosen to show that both the chronologically older group and an age-adjusted combined group had longer telomeres than CRC patients.

**DNA extraction**

DNA was extracted from both blood and tissue using the Maxwell Automated Purification System according to the manufacturer’s instructions (Promega). Briefly, whole blood samples were spun down into cellular and plasma components. The red cells and buffy coat were thoroughly mixed and 300 μL aliquoted into the predispensed reagent cartridges. Tissue samples were thawed and 50 mg added to the reagent cartridge. The DNA concentration and purity were quantified using the Nanodrop Spectrophotometer (ThermoFisher Scientific). All DNA samples were validated on 0.5% agarose gel.

**Telomere length determination**

Telomere lengths were determined from DNA samples, from the PBLs of both the control and CRC population, and from the colorectal normal and cancerous tissue by quantitative PCR (25). Telomere length determination was conducted blindly using a Roche Light Cycler LC480. Briefly, telomere length analyses were conducted in triplicate for each sample, using a single-copy gene amplicon primer set (acidic ribosomal phosphoprotein, 36B4) and a telomere-specific amplicon primer set (26). This method determines the ratio of telomere repeat copy number to single-copy gene number (T/S) ratio in experimental samples relative to a control sample DNA. This normalized T/S ratio was used as the estimate of relative telomere length (RelT/S). The coefficient of variation (CV) for the telomere assay was 17%.

**Measurement of plasma fetuin-A**

Fetuin-A concentrations were measured from the plasma of blood samples of CRC PBL patients using a commercial Human Fetuin-A ELISA kit (BioVendor R&D). Fetuin-A was not measured in either the CRC tissue group or the control population. Samples were measured in triplicate. Absorbance of each sample was read by a microplate reader at dual wavelengths 405 and 650 nm, and sample concentrations were then calculated using the standard curve. All methodologies were carried out according to the manufacturer’s instructions.

**Measurement of markers of systemic inflammation**

For the CRC PBL patients only, all routinely available indices of inflammation (CRP, albumin, white cell, neutrophil, and lymphocyte count) were measured using routine methods in the Departments of Haematology and Biochemistry, Glasgow Royal Infirmary. Plasma concentrations of interleukin (IL) 6, IL-10, and vascular endothelial growth factor (VEGF) were measured using commercially available ELISA kits. The neutrophil to lymphocyte ratio (NLR) and modified Glasgow Prognostic Score (mGPS) were calculated for each patient thereby

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^aIncludes patients with inoperable disease and patients who underwent synchronous resection of their primary cancer and liver metastasis.

^bSynchronous resection of liver metastasis.

This compares with 58% of the control population who had "ever" smoked.
analyses were conducted using SPSS version 15 (SPSS Inc.). Clinical Cancer Research; 17(17) September 1, 2011

Results

Telomere length and CRC

Analysis of telomere lengths in PBLs of CRC patients and healthy controls. Sixty-four patients were available for analysis in the CRC PBL patient group (mean age = 68 ± 10.8). These were compared with 1,348 West of Scotland control subjects (no diagnosed cancer), aged approximately 57 (n = 847; male 46%, female 54%) and 76 (n = 501; male 42%, female 58%) years old (mean age = 64 ± 9.24). As expected, there was a significant negative association between chronological age and telomere length in the healthy controls (Pearson \( r = -0.215 \), \( P < 0.001 \)). Likewise, a significant negative relationship was observed between chronological age and PBL telomere length in the CRC group (Pearson \( r = -0.257 \), \( P = 0.04 \)), indicating that as patient age increased, telomere length decreased. This age-related telomere attrition shows the association between chronological and biological aging.

Patients had consistently shorter telomeres than the control population (\( P < 0.001 \); Fig. 1), indicating that the CRC patients were of increased biological age. Because the median age of the control population was greater than that of the CRC group, analyses were conducted correcting for both age and gender. After correction of telomere length for age and gender, CRC patients still had consistently shorter telomeres (adjusted mean ± SE RelT/S = 0.66 ± 0.02) compared with those in the control group (adjusted mean ± SE RelT/S = 0.75 ± 0.005, \( P < 0.001 \)), indicating that CRC patients were of increased biological age. To further validate that the cancer patients were more biologically aged, we compared them to a subgroup of the control population, those individuals aged 76 years. Analysis of covariance revealed that despite being on average chronologically younger, the cancer group had significantly shorter telomeres (adjusted mean ± SE RelT/S = 0.61 ± 0.03) than the control population (adjusted mean ± SE RelT/S = 0.70 ± 0.01) and hence were more biologically aged (\( P = 0.004 \)). The median duration of diagnosis in the CRC PBL group (defined as the date of positive tissue diagnosis until date of sample collection) was 42 (6–185) days. Analysis did not reveal any association between duration of diagnosis and telomere length.

Comparison of telomere lengths in colorectal tumor tissue and normal adjacent tissue. The RelT/S ratio of 32 matched colorectal tumor tissue and adjacent normal mucosa samples was compared to determine whether a difference in biological age was apparent between tissue types. Telomere length in the tumor tissue (median = 0.43, IQR = 0.40) was found to be significantly shorter than in the adjacent normal tissue (median = 0.65, IQR = 0.28; \( P = 0.004 \), Fig. 2).

Clinical and laboratory correlates of telomere length in CRC patients

Association between PBL telomere length and patient clinicopathologic characteristics. No associations were observed between PBL telomere length and the various clinicopathologic parameters when analyzed using the continuous variable. Consequently, patients were categorized into those with short telomeres (RelT/S < 0.55, short-end quartile) and those with long telomeres (RelT/S ≥ 0.55). Short telomere length was significantly positively associated with high-risk pathologic features indicated by a high-risk PI (\( \chi^2, P < 0.035 \)). However, no significant relationship was identified between tumor site, Dukes stage, and any other clinicopathologic characteristic measured. No significant relationship was observed between telomere length and CRP, proinflammatory cytokines, or mGPS. However, there was a significant relationship between patients with short telomere length and an elevated NLR (Mann-Whitney, \( P = 0.047 \); Table 2). There was no significant association between telomere length and antioxidant status, as determined by the measurement of antioxidant vitamins and micronutrients.

Plasma levels of fetuin-A are associated with chronological and biological age in CRC. Fetuin-A concentration of plasma samples was measured to assess whether levels were
associated with chronological and biological aging within the CRC PBL group. A significant relationship was observed between fetuin-A concentration and the chronological age of subjects (Pearson \( r = -0.32, P = 0.011 \); Table 2). Increasing chronological age was associated with decreasing fetuin-A concentration. For analysis of the relationship between fetuin-A concentration and telomere length, patients were categorized into 2 groups around the median plasma level giving a low fetuin-A level group (fetuin-A < log median = 1.47/median = 29.6) and a high fetuin-A level group (fetuin-A > log median = 1.47/median = 29.6). Patients with low fetuin-A levels were shown to have significantly shorter telomeres (median RelT/S = 0.6) than those patients with high fetuin-A levels (median RelT/S = 0.72; Pearson \( r = 0.3, P = 0.019 \); Mann-Whitney, \( P = 0.041 \); Table 2). This relationship was maintained when the analysis was adjusted for age. Patients with low fetuin-A levels had significantly shorter telomeres (adjusted mean RelT/S = 0.59) in comparison to those patients with high fetuin-A levels (adjusted mean RelT/S = 0.68, \( P = 0.047 \)). No difference in fetuin-A levels or telomere length was observed between males and females.

**Associations between fetuin-A plasma levels and patient clinicopathologic parameters.** No association was apparent between fetuin-A concentration and tumor characteristics, such as T stage, lymph node involvement, or Dukes stage, within the CRC PBL group. However, increasing concentrations of fetuin-A were significantly associated with increasing levels of albumin (Pearson \( r = 0.28, P = 0.03 \)) and calcium (Pearson \( r = 0.30, P = 0.022 \)) but decreasing levels of IL-6 (Pearson \( r = -0.483, P = 0.005 \); Table 2). A trend also existed between fetuin-A concentration and IL-10 (Pearson \( r = -0.21, P = 0.061 \); Table 2), whereby increasing concentrations of fetuin-A in patients was associated with decreasing levels of IL-10.

**Tumor site is distinguishable by fetuin-A and white cell count.** Patients in the CRC PBL group with rectal tumors (\( n = 22 \)) were associated with higher circulating concentrations of fetuin-A (log median = 1.52/median = 33.5), whereas those with colonic tumors (\( n = 42 \)) were associated with lower concentrations (log median = 1.45/median = 28.7; \( P = 0.045 \); Fig. 3A). Further comparison of the clinicopathologic differences between colonic and rectal tumors showed that colonic tumors were significantly associated with an increased white cell count (median = 7.9) compared with rectal tumors (median = 6.8; \( P = 0.011 \); Fig. 3B).

**Association between tumor tissue telomere length and patient clinicopathologic characteristics.** A significant relationship existed between tumor tissue telomere length and albumin concentration (Pearson \( r = 0.36, P = 0.009; n = 32 \)). As CRC tissue telomere length increased, albumin concentration also increased. No relationship was observed between the telomere length from either the cancer or normal tissue and any of the other clinicopathologic parameters.

**Discussion**

Our study shows that patients with CRC display clear evidence of accelerated biological aging in the form of telomere attrition when compared with healthy control subjects. The relationship between telomere length and cancer risk is proving to be a difficult one to fully delineate. Our demonstration of telomere attrition in PBls of CRC patients is similar to that reported by Pooley and colleagues (29) in both retro- and prospectively recruited patients. These data contradict 2 studies of both male and female CRC patients where no relationship between CRC and telomere length was identified (30, 31). However,
patients with the shortest telomeres have pathologically
in patients in the shortest telomere group when compared
both cancer risk and mortality from cancer were increased
followed up over a period of 10 years. They reported that
study to investigate cancer risk in 787 healthy participants
entities, including gastric (20), bladder (19), ovarian (21),
Moreover, our findings are in keeping with those of
Maxwell et al.
Fetuin-A 27.16 (14.71
Fetuin-A
0.28 (IQR
VEGF 84.75 (7.28-952.96) pg/mL NS
IL-10 11.2 (5.68-34.82) pg/mL NS
IL-6 6.5 (1.75-39.8) pg/mL NS
CRP 7.5 (0.40-95.0) mg/L NS
Systemic inflammation
CRP 7.5 (0.40-95.0) mg/L NS
IL-6 6.5 (1.75-39.8) pg/mL NS
IL-10 11.2 (5.68-34.82) pg/mL NS
VEGF 84.75 (7.28-952.96) pg/mL NS
NLR 0.32 (0.04-0.94) 0.047
mGPS, n (%) 0 42 (65.6) NS
1 13 (20.3) NS
2 9 (14.1) NS
Redox control Retinol 1.80 (0.7-3.70) μmol/L NS
α-Tocopherol 26.5 (12.0-40.0) μmol/L NS
Lutein 88.0 (21.0-607.0) μg/L NS
Lycopene 83.0 (10.0-373.0) μg/L NS
α-Carotene 15.5 (10.0-151.0) μg/L NS
β-Carotene 65.5 (10.0-862.0) μg/L NS
Fetuin-A 27.16 (14.71-67.27) ng/mL 0.041
Ageα r = −0.32 0.011
Albuminβ r = 0.28 0.03
Calciumβ r = 0.30 0.022
IL-10β r = −0.21 0.061
IL-6β r = −0.483 0.005
Abbreviation: NS, not significant.
αSignificant difference in NLR between short [RelT/S < 0.55, 
NLR = 0.39 (IQR = 0.90)] and long [RelT/S > 0.55, NLR = 
0.28 (IQR = 0.71)] telomere group (Mann–Whitney).
βPatients with low fetuin-A (fetuin-A <log median = 1.47/ 
median = 29.6) had significantly shorter telomeres (median 
T/S = 0.6 vs. 0.72, Mann–Whitney).
αRelationship with plasma log Fetuin-A concentration 
displayed as Pearson correlation.
more prevalent studies investigating a number of other cancer entities, including gastric (20), bladder (19), ovarian (21), and lung (22) cancer, are in concordance with our observations. Moreover, our findings are in keeping with those of Willeit and colleagues (32), who employed a longitudinal study to investigate cancer risk in 787 healthy participants followed up over a period of 10 years. They reported that both cancer risk and mortality from cancer were increased in patients in the shortest telomere group when compared with the longest (32). Our analysis suggests that the patients with the shortest telomeres have pathologically significant decline in telomere length and low plasma levels of the anti-inflammatory factor fetuin-A, which is a potent inhibitor of senescent cell senescence and a marker of systemic inflammation. These findings are consistent with previous reports showing that short telomeres are associated with higher cancer risk, i.e., increased cancer incidence and mortality, in several studies, including those on lung, gastrointestinal, and other cancers (11, 33, 37).
Various investigators, using a number of experimental modalities, have identified damage induced by reactive oxygen species and oxidative stress as a key determinant of telomere erosion rates (11, 33). The relationship between redox state and telomere dynamics is likely to be a complex one involving interaction between a wide array of genetic and environmental factors. We investigated the potential role of disordered redox state by determining levels of antioxidant vitamins, micronutrients, and fetuin-A. While we did not observe a significant relationship between telomere length and antioxidant levels, patients with lower fetuin-A levels had shorter telomeres. These findings are consistent with those in chronic kidney disease patients where there is an established link between low fetuin-A levels and short telomere length (13). This relationship shows that biological aging is associated with reduced redox capacity within the blood of CRC patients. IL-6, a proinflammatory cytokine, alters the gene expression and synthesis of fetuin-A by hepatocytes, similar to its action on albumin (34). Our study showed that decreasing fetuin-A levels correlates with decreasing albumin concentration and increasing IL-6 and IL-10 levels, supporting the hypothesis of inflammation-dependent downregulation of fetuin-A expression. These observations concur with those described in patients with renal failure on dialysis (35) and also with results from a rodent model of lethal systemic inflammation where fetuin-A exerted a protective role (36). However, the relationship between fetuin-A is not a straightforward one given the finding of elevated levels in patients with previous myocardial infarction and obesity (37).
In patients with glioblastoma, the most commonly occurring brain tumor low serum fetuin-A levels predicted poor survival (38). Moreover, Rho and colleagues (39) report differential expression of fetuin-A between lung adenocarcinoma and adjacent normal tissue with both total protein and mRNA abundance reduced in cancer samples. These findings, in conjunction with our own observations, lead to the intriguing possibility of utilizing fetuin-A as a prognostic/predictive marker for tumors from a histologically varied origin. Work is required to determine whether it is by virtue of its role in calcium homeostasis and hence redox state that fetuin-A contributes to the determination of telomere length.
Cellular senescence is a permanent state of growth arrest and hence a potent mechanism of tumor suppression. The triggers of senescence in vivo include critical telomere attrition, activation of oncopgenes, oxidative stress, genotoxic stress, and some therapeutic interventions (e.g., irradiation and chemotherapy). Recent evidence indicates that senescent cells secrete a multitude of signaling factors, termed the "senescence-associated secretory phenotype" (SASP; ref. 40). These signals are mostly proinflammatory...
and include factors such as IL-1α and IL-1β, IL-6, and IL-8. The SASP provides an intuitive explanation of our observed association between short telomere length and systemic inflammation, indicated in our patients by a raised NLR. Interestingly, patients with ulcerative colitis, an inflammatory condition of the colon, who exhibit an increased risk of CRC display evidence of telomere attrition in leukocytes (41). Even minute quantities of proinflammatory cytokines released by populations of senescent cells in biologically aged individuals could stimulate a more chronic systemic inflammation by virtue of positive feedback loops. At the peritumoral level, these factors could also act in a paracrine fashion to create an environment where tumor cells can flourish by stimulating hyperproliferation, dedifferentiation, immune evasion, migration, and invasion (42).

In concordance with previous studies, we have confirmed that telomere length in CRC tissue is significantly shorter than normal adjacent colorectal mucosa (43). One might expect that given telomerase activity in neoplastic cells, including those of a colorectal origin, telomere length would be elongated in representative neoplastic tissue. However, our data suggest the opposite, meaning telomerase must maintain telomeric DNA content at a level consistent with a high rate of cell proliferation. This avoids the initiation of senescence or apoptosis which would otherwise mean exit from the cell cycle and prohibit the rapid proliferation of neoplastic cells. These cells can therefore continue to divide but do so with requisite maintenance of telomere length. The adenoma-carcinoma sequence of colorectal neoplastic initiation still holds in the face of these observations. This is further reinforced by work showing that telomere length in epithelial cells at the earliest morphologically definable stage of carcinoma (high-grade dysplasia with minimal invasive growth) was shorter than surrounding adenoma (44).

Rampazzo and colleagues (45) have also shown that colorectal tumor telomere length is shorter than adjacent mucosa. Furthermore, they have identified right-sided tumors as having shorter telomere length than left-sided and rectal cancers, which may result from an alteration in mismatch repair pathways (45). The molecular and clinical characteristics of right and left colon cancers are well established (46). Our observation that fetuin-A levels vary with the anatomic site of the primary tumor is pertinent. The preoperative management of colonic and rectal cancers in the context of chemoradiotherapy differs, hence, further molecular differentiation of colon and rectal cancers could lead to the discovery of new therapeutic targets thereby improving the outcome of rectal cancer. Obviously, further work in a larger patient group is required to substantiate these preliminary findings.

We have observed that patients with CRC have significantly shorter telomeres than control subjects, congruent with accelerated biological aging in the pathogenesis of CRC. These observations are in keeping with the hypothesis of telomere attrition predisposing to disease. Furthermore, patients with shorter telomeres display evidence of systemic inflammation and pathologically more advanced disease. An imbalance in redox control mechanisms and calcium homeostasis may be a contributing factor to telomere dynamics in our group of patients. We believe further work is merited to fully delineate the factors determining telomere length and whether the risk profile of CRC could be altered by manipulating these factors.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Grant Support**

P.G. Shiel, F. Maxwell, and L.M. McGlynn were supported by an unrestricted award from the NHGSCC Endowments Fund.

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Received December 13, 2010; revised June 18, 2011; accepted July 6, 2011; published OnlineFirst July 13, 2011.
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