Available online at www.sciencedirect.com

ScienceDirect

www.nrjournal.com

Original Research

A positive association between umbilical cord RBC folate and fetal TL at birth supports a potential for fetal reprogramming

Adetola F. Louis-Jacques[a,*], *Hamisu M. Salihu*[b], *Lindsey M. King*[c], *Arnut Paothong*[c], *Rachel G. Sinkey*[a], *Anupam Pradhan*[d], *Bridget M. Riggs*[e], *Erin M. Siegel*[e], *Jason L. Salemi*[b], *Valerie E. Whiteman*[a]

[a] *Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of South Florida Morsani College of Medicine, Tampa, FL 33606*
[b] *Department of Family and Community Medicine, Baylor College of Medicine, Houston, TX 77098*
[c] *Department of Epidemiology Biostatistics, College of Public Health, University of South Florida, Tampa, FL 33612*
[d] *Department of Global Health, College of Public Health, University of South Florida, Tampa, FL 33612*
[e] *Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612*

ARTICLE INFO

Article history:
Received 24 September 2015
Revised 11 January 2016
Accepted 28 January 2016

Keywords:
Telomere
Folic acid
Folate
DNA
Newborn
Fetus

ABSTRACT

Telomere length (TL) has been studied extensively in adults; however, limited information exists regarding maternal influences on TL in utero. The objective of this study was to investigate the relationship between fetal red blood cell (RBC) folate levels, a surrogate measure for maternal folate levels, and TL. We hypothesized that umbilical cord RBC folate concentrations would positively correlate with fetal TL. Data for this analysis were collected as part of a prospective cohort study that recruited pregnant women upon admission into labor and delivery. Cord blood was collected for 96 maternal-fetal dyads, and DNA analysis was performed using quantitative polymerase chain reaction. The telomere to single copy gene ratio method was used to determine TL, and RBC folate levels were measured. Statistical analysis was conducted by incorporating a bootstrapping approach into generalized linear modeling–based analyses. Consistent significant positive correlations were observed between RBC folate and TL (telomere to single copy gene ratio) with 9880 of the 10000 (98.8%) iterations performed having a *P* value less than .05. Our study shows a positive association between umbilical cord RBC folate and fetal TL at birth. These findings may provide a pathway of understanding and preventing adult-onset disease and mortality through intrauterine reprogramming.

Abbreviations: Ct, cycle threshold; GLM, generalized linear modeling; NTD, neural tube defect; qPCR, quantitative polymerase chain reaction; RBC, red blood cell; STL, shortened telomere length; T/S, telomere to single copy gene; TL, telomere length; USF, University of South Florida.

* *Corresponding author at:* Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of South Florida Morsani College of Medicine, 2 Tampa General Circle, Tampa, FL 33606.

E-mail addresses: alouisjacques@health.usf.edu, adetolalouisjacques@gmail.com (A.F. Louis-Jacques), Hamisu.Salihu@bcm.edu (H.M. Salihu), lking1@health.usf.edu (L.M. King), arnut_tu@hotmail.com (A. Paothong), rsinkey@health.usf.edu (R.G. Sinkey), apradhan.usf.health@gmail.com (A. Pradhan), Bridget.riggs@moffitt.org (B.M. Riggs), Erin.siegel@moffitt.org (E.M. Siegel), jason.salemi@bcm.edu (J.L. Salemi), vwhitema@health.usf.edu (V.E. Whiteman).

http://dx.doi.org/10.1016/j.nutres.2016.01.009
0271-5317/

1. Introduction

Folate is an essential micronutrient with a central role in cell growth and metabolism [1,2]. Folic acid is methylated into 5-methyltetrahydrofolate and 5,10 methylenetetrahydrofolate in routine nucleic acid biosynthesis and repair (Fig. 1). Folate deficiency results in incorporation of uracil into DNA, a decrease in DNA methylation, and hyperhomocysteinemia [2,3]. Uracil within the DNA results in genetic instability [4]. Prior research associates variations in DNA methylation and hyperhomocysteinemia with cancer, cardiovascular disease, and immunologic and neurologic diseases [2,5,6].

Inadequate preconceptional and periconceptional folate intake leads to an increase in neural tube defects (NTDs), fetal growth restriction, and maternal anemia [3]. A 1998 Food and Drug Administration mandate requiring folate grain fortification led to an increase in red blood cell (RBC) folate concentrations of childbearing age women and a concomitant decrease in the prevalence of NTDs [7]. Yet, 22% of women of childbearing age in the United States, particularly those of Hispanic ethnicity, have low RBC folate levels [7].

Folate has been explored as a determinant of telomere length (TL). Telomeres are repeats of small nucleotide sequences of TTAGGG. They function as a cap at the end of chromosomes [2,8]. Telomeres prevent DNA degradation and impede rearrangement of chromosomes [8]. Factors such as age [9], sex [10], unhealthy diet and lifestyle [11,12], obesity [13], and psychological stress [12] influence TL. Shortened TL (STL) has been implicated in chronic diseases, multiple malignancies, cardiovascular disease, and autoimmune and neurodegenerative disorders [11,14].

In the last decade, studies have examined fetal correlates of TL using umbilical cord blood or placental tissue. Fetal growth restriction is associated with telomere attrition in the placenta [15,16]. Neonatal TL is inversely correlated with maternal history of hypertension in prior pregnancies [17], psychosocial stress [18], and smoking [19]. Elucidating factors that influence fetal/neonatal TL is important because STL in early life may be an underlying mechanism of fetal programming and subsequent development of chronic diseases in adulthood [17].

We sought to investigate the relationship between maternal folate levels and fetal TL length. We used umbilical cord RBC folate concentrations as a correlate for maternal folate levels secondary to a unidirectional transplacental maternal to fetal transport of folate [20-22]. We hypothesized that folate concentrations would be positively associated with fetal TL.

2. Methods and materials

2.1. Study population

As part of a prospective cohort study conducted by the University of South Florida (USF) Morsani College of Medicine, pregnant women were recruited from July 2011 to September 2012 upon their admission to the labor and delivery unit at Tampa General Hospital in Tampa, Florida. To be eligible for the study, women must have been (1) 18 to 44 years of age, (2) of singleton gestation with no indication of congenital malformations, and (3) capable of speaking English or Spanish.

We did not perform a power analysis for this hypothesis. This was a nested study in an ongoing parent study, and we used all

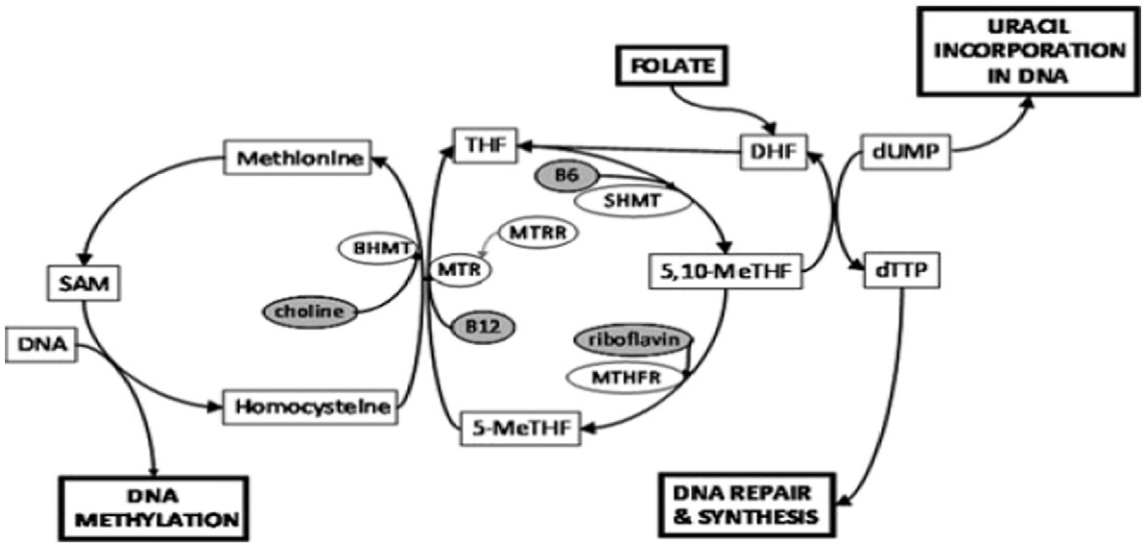

Fig. 1 – Folate metabolism. Folate, along with choline, methionine, cobalamin, pyridoxine, and riboflavin, is involved in several essential metabolic processes within the cell, in particular DNA synthesis, repair, and methylation. Folate is also essential as a methyl donor in the maintenance of dUMP/dTTP ratios within the cell. When the ratio of dUMP/dTTP is increased, there is an increased incorporation of uracil into the DNA. Image modified from Ref. 78. Abbreviations: 5-MeTHF, 5-methyltetrahydrofolate; 5,10-MeTHF, 5,10-methylenetetrahydrofolate; B6, pyridoxine; B12, cobalamin; BHMT, betaine homocysteine methyltransferase; DHF, dihydrofolate; dUMP, deoxyuridine monophosphate; dTTP, deoxythymidine triphosphate; MTHFR, methylenetetrahydrofolate reductase; MTR, methionine synthase; MTRR, methionine synthase reductase; SAM, S-adenosyl methionine; SHMT, serine hydroxymethyltransferase; THF, tetrahydrofolate. This figure was reproduced with permission from Moores et al [2].