Colonocyte telomere shortening is greater with dietary red meat than white meat and is attenuated by resistant starch

Nathan J. O’Callaghan, Shusuke Toden, Anthony R. Bird, David L. Topping, Michael Fenech and Michael A. Conlon
Overview

• Background
  • Telomeres
  • CRC risk
  • Fibre + Protein

• Animal study
  • Design
  • Results

• Conclusion
Nutrition, health and DNA

Nutrition

Health & Well Being

Genome Health
What are telomeres?

- protection, replication, and stabilisation of the chromosome ends
- all vertebrates appear to have the same simple sequence repeat
- (TTAGGG)n repeat
Diseases associated shortened telomeres:

• Cancers (all)
• Vascular: CVD, stroke
• Diabetes
• AD

Age and telomere length

Njajou O T et al. PNAS 2007;104:12135-12139
Telomeres and the Telosome

Telomere length is modified by life-style factors

Telomere attrition accelerated by:

- Smoking
- Obesity and low physical activity
- Psychological stress
- Diet (inc. malnutrition)
Diet impacts on telomere length

Shorter telomeres are associated with:
- low fruit & veg intake
- Increased alcohol intake
- Increased processed meat intake

Telomere length is positively associated with:
- plasma folate
- Multi-vitamin use
- Vitamin E
- Fish intake
- Dietary fibre (cereals)
- Vitamin D
**Vitamin D as an example**


\[ n = 2160, \text{Pearson's correlation coefficient} = 0.07, \ P = 0.0010 \]

age-adjusted leukocyte telomere length

\[ n = 2160, \text{Pearson's correlation coefficient} = 0.09, \ P < 0.0001 \]
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Diet and Colorectal Cancer risk

• Most common internal malignancy in Australia

• Diet is an important factor in the aetiology of important non-infectious diseases, including colorectal cancer (CRC).
Epidemiology evidence - meat

• Based on recent human epidemiological studies red meat and processed meat intake is associated with colorectal cancer risk

• 500,000 people, followed over 4.8 years (EPIC)
  Positive association between colorectal cancer incidents and red and processed meat (but not poultry) (Norat et al. 2005)

• 150,000 mature adults, followed over 20 years
  Prolonged high intakes of red or processed meat were associated with elevated risks of colorectal cancer (Chao et al. 2005)

• 60,000 Swedish women, followed over 13.9 years
  Positive association between red meat consumption and development of colon cancer (Larsson et al. 2005)
Epidemiological evidence - fibre

• Epidemiological studies show that fibre is inversely associated with colorectal cancer risk
  Bingham et al. Lancet 2003

• Main fibre components identified:
  • NSP (non-starch polysaccharides)
  • RS (resistant starch)

• RS may have a greater role against colorectal cancer than NSP
  Cassidy et al. B J Cancer 1994

• Potential Protective Mechanisms of RS
  • Short chain fatty acids (SCFA)
  • Increasing faecal bulking
  • Reducing faecal pH (changing microbial environment)
RS mitigates colonic DNA damage

RS reduces protein-induced colonic DNA damage in a dose-dependent manner.

RS restored reduction of the mucus layer thickness induced by a high-protein diet.

10% RS in the diet was able to attenuate the colonic DNA damage.

Toden et al, 2007 Carcinogenesis
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Study Objectives

• Associative evidence on dietary factors that may affect telomere length,
  • specific impact that increased red meat intake and increased RS has on telomere length in colorectal mucosa is unknown.

• AIM
  • to determine whether telomeres are influenced by dietary red and white meat and whether these effects are modulated by RS within the colon.
Dietary Groups

4- week trial

12 dietary groups
  • 15, 25 & 35 % Red Meat
  • 15, 25 & 35 % White Meat
  • With or Without Dietary RS

• Male Sprague-Dawley rats
  • N=8 per group

• Colonocytes collected
  • DNA isolated
  • Telomere length measure by qPCR
Telomere length shortening with increasing dietary red meat

O'Callaghan et al, Clinical Nutrition, Acc Sep 2011

P=0.08, P-trend=0.03
Telomere length shortening with increasing dietary meat

O’Callaghan et al, Clinical Nutrition, Acc Sep 2011

Without HAMS

Red

White

Telomere Length (kb/genome)
Telomere length shortening with increasing dietary meat is attenuated by RS

O’Callaghan et al, Clinical Nutrition, Acc Sep 2011

P=0.08
Telomere length was related to other indices of colonic health

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMET</td>
<td></td>
</tr>
<tr>
<td>Single strand breaks</td>
<td>-0.36 *</td>
</tr>
<tr>
<td>Double strand breaks</td>
<td>-0.37 **</td>
</tr>
<tr>
<td>Colonic Malondialdehyde</td>
<td>-0.28 *</td>
</tr>
<tr>
<td>Caecal SCFA Pools</td>
<td></td>
</tr>
<tr>
<td>Acetate</td>
<td>0.31 *</td>
</tr>
<tr>
<td>Propionate</td>
<td>0.28 *</td>
</tr>
<tr>
<td>Butyrate</td>
<td>-0.04</td>
</tr>
<tr>
<td>Total caecal SCFA</td>
<td>0.31 *</td>
</tr>
<tr>
<td>Caecal phenol</td>
<td>-0.51</td>
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<tr>
<td>Caecal p-cresol</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

*indicates P<0.05; **indicates P<0.01; n=96; SCFA = short chain fatty acid
Conclusions

• increased dietary red leads to greater telomere shortening in rat colonocytes.

• inclusion of RS in the diet attenuated telomere shortening
  • induced by feeding high levels of red meat.

• This study provides greater evidence for dietary components significantly influences genomic stability within the colon.
  • Can dietary intervention alter CRC risk?
Acknowledgements

- Food Futures Flagship
  - Shusuke Toden
  - Tony Bird
  - David Topping
  - Michael Conlon

- Michael Fenech
Diets

Table I. Composition of experimental diets (g/kg diet)

<table>
<thead>
<tr>
<th>Dietary treatment</th>
<th>0% HAMS</th>
<th>20% HAMS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Red meat</td>
<td>White meat</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>Red meat</td>
<td>150</td>
<td>250</td>
</tr>
<tr>
<td>White meat</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>580</td>
<td>500</td>
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<tr>
<td>HAMS</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Sucrose</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Sunflower oil</td>
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<td>30</td>
</tr>
<tr>
<td>Tallow</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>L-cystine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Choline bitartrate</td>
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<td>2.5</td>
</tr>
<tr>
<td>Vitamins (AIN-93)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Minerals (AIN-93)</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Total protein and fat of white meat groups were matched with corresponding red meat groups. Diets based on AIN-93 formulation.