Concurrent Session 3: Immune Function, Cancer, Type 2 Diabetes

The effect of folic acid supplementation on DNA biomarkers of colorectal cancer risk (uracil misincorporation, global and gene-specific DNA hypomethylation): a randomised intervention study
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Background – Alterations in folate status are associated with colorectal carcinogenesis. Folate’s role has been postulated to be either via prevention of changes in DNA methylation or uracil misincorporation.

Objective – To investigate the effect of folic acid supplementation on colonicocyte folate status and DNA biomarkers.

Design – Twenty individuals harbouring colonic adenomas were randomised to receive folic acid (600 µg daily) or placebo for 6 months post polypectomy. Systemic and colonicocyte folate status was determined at baseline and following the intervention. Modified Comet assays were used to determine uracil misincorporation and global DNA hypomethylation at the site adjacent to the polyp and a site distal to the polyp.

Outcomes – Supplementation resulted in increased colonicocyte folate, which approached significance, at the site adjacent to the polyp (P = 0.06) but not distal to the polyp (P = 0.36); correspondingly there was a reduction in uracil misincorporation at the site adjacent to the polyp (P = 0.02) and the distal site showed no such trend (P = 0.39). There were no significant changes in global DNA hypomethylation at either site post-intervention.

Conclusions – Folic acid supplementation resulted in increased colonicocyte folate and decreased uracil misincorporation at the site of the adenoma but not distal to the adenoma. This supports the hypothesis that localised areas of folate deficiency may exist in human colonic mucosa which respond to folic acid supplementation through increasing colonicocyte folate and improving folate-related DNA biomarkers of cancer risk.

Effects of dietary red and white meat, with and without high amylose maize starch, on colonic mucosal integrity
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Background – We have previously carried out studies in rats which show that high levels of dietary protein, including cooked red meat, compromise colonic integrity by increasing DNA damage (single-strand DNA breaks) and by thinning the mucus barrier. Inclusion of starch in the diet which is resistant to digestion in the small intestine, termed resistant starch (RS), protected against these changes. The protection was highly correlated with increased production of short chain fatty acids (SCFA), especially butyrate, in the large bowel.

Objectives – To examine whether dietary cooked red or white meat had differential effects on colonic DNA damage and other markers of bowel health in rats and if RS provided protection.

Design – Rats were fed diets containing 15%, 25% or 35% of cooked beef or of chicken at levels to provide equivalent amounts of protein as beef both with or without 20% high amylose maize starch (HAMS; a source of RS) for four weeks. DNA single-strand breaks (SSB) and double-strand breaks (DSB) were measured in isolated colonocytes (by comet assay) along with apoptosis levels, colonic mucus thickness, large bowel SCFA, and phenols and cresols, as well as faecal bacterial population changes.

Outcomes – Both red and white meat increased colonicocyte DNA SSB and DSB dose-dependently but damage was substantially greater with red meat. Dietary HAMS prevented these increases. Apoptotic cell numbers were increased dose-dependently by red meat irrespective of HAMS feeding. Apoptosis was unaffected by dietary white meat inclusion but was increased by HAMS. Red meat induced greater colonic mucus layer thinning than white meat but HAMS was protective in both cases. HAMS induced increases in large bowel SCFA, including butyrate, and significantly lowered concentrations of phenols and cresols.

Conclusions – We have demonstrated that dietary red meat causes greater levels of colonic DNA SSB and DSB than white meat, consistent with the epidemiological data. Dietary resistant starch protects against this damage and also against loss of the mucus barrier, probably through increased butyrate production.