Obesity-Related Hormones and Itaconate in Early-Onset Colon Cancer: a Macrophage Co-Culture Model

Casey Fiechter¹,², Katharina Scheurlen¹, Andrew Littlefield¹, Toriana Alfieri¹, Susan Galandiuk¹

¹Price Institute of Surgical Research, Hiram C. Polk Jr. MD Department of Surgery, Louisville, KY
²University of Louisville School of Medicine, Louisville, KY

• Inflammation is involved in the pathophysiology of both EOCRC & obesity.
• Tumor Associated Macrophages (TAMs) & obesity-related hormones, leptin and adiponectin mediate inflammation.
• TAMs are part of the tumor microenvironment and can switch between a proinflammatory (M1) & anti-inflammatory (M2) phenotype.
• Aconitate Decarboxylase 1 (ACOD1) is an enzyme that produces itaconate from aconitate in the Tricarboxylic Acid Cycle.
• Iaconate is a macrophage-specific metabolite produced by certain macrophage subtypes and has carcinogenic effects.
• M2-like macrophages are associated with tumor progression and worse prognosis.
• The effects of obesity-related hormones and itaconate on the cellular metabolism in EOCRC is unknown.

Background

• Incidence of Early-Onset Colorectal Cancer (EOCRC) in individuals <50 years old
• Incidence of obesity in developing countries

Is there a link between EOCRC and obesity?

Methods

• The human monocyte and colon adenocarcinoma cell lines THP-1 and HT29 were acquired (ATCC®, Manassas, VA).
• THP-1 cells were plated into transwell inserts at a concentration of 200,000 cells/insert and polarized into M2-like macrophages within 14-days using phorbol 12-myristate 13-acetate (PMA), interleukin-4 (IL-4) and IL-13.
• M2-like macrophages were then co-cultured with HT29 cells for 24 hours.
• Co-cultured cells were then treated with either leptin, adiponectin, or one of 2 itaconate metabolites: 4-octyl itaconate (OI) or dimethyl itaconate (DI), for 3 and 6 hours.

Results

• In M2-like macrophages, proinflammatory IL-1β expression was significantly upregulated following adiponectin (30-fold, p=0.014) and leptin treatment (6-fold, p=0.026) for 6 hours (Fig. 1A).
• Expression of ACOD1 in M2-like macrophages was upregulated with adiponectin treatment (50-fold, p=0.002) for 6 hours (Fig. 1B).
• In HT29 cells, OI treatment resulted in decreased expression of the proinflammatory cytokine CXCL10 at 3 hours (-5 fold-regulation, p=0.045) (Fig. 1C).

Acknowledgements

Research supported by the National Cancer Institute grant R25-CA134283, the Mary K. Oxley Foundation and the John W. Price and Barbara Thruston Atwood Price Trust.

Conclusion

• Adiponectin and leptin induce cytokine gene expression and itaconate production in TAMs that promote carcinogenic mechanisms in CRC.
• The effects of obesity-related hormones on macrophage polarization and cytokine expression may provide a link between obesity and EOCRC.

Future Endeavors

• Increase sample size.
• Determine if macrophage specific metabolite itaconate interacts with HT29 cells in co-culture.
• Measure HT29 cell counts before and after co-culture model to determine effects on cellular proliferation.
• Replace HT29 cell line with a different colon cancer cell line in the co-culture model.