Commentary

Obesity, gastrointestinal cancer and the role of visceral fat

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Abstract: Malignancy of the gastrointestinal (GI) tract is over-represented amongst obesity-induced cancer, but the underlying mechanisms remain poorly defined. A recent review has provided an excellent framework for further research and effectively summarised the obesity related pathogenesis of colon, gastric, pancreatic and oesophageal malignancy. In this report we discuss in detail the role of insulin resistance (IR), insulin-like growth factor (IGF)-1, inflammation, adipokines and intestinal microbiota to obesity related GI cancer and highlight the importance of visceral, rather than overall adiposity.

Keywords: Visceral obesity; carcinogenesis; colorectal cancer (CRC); insulin resistance (IR); microbiota

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Rates of obesity have steadily increased over the past 20 years with over 37% of individuals worldwide and up to 70% in developed nations now classified as overweight or obese [Body Mass Index (BMI) ≥25] (1). Obesity is estimated to cause 3.4 million deaths each year, the majority of which are due to cardiovascular disease, diabetes and cancer (2). Malignancy of the gastrointestinal (GI) tract is overrepresented amongst obesity-induced cancer with relative risks ranging from 1.5 for oesophageal and gallbladder cancer to 1.2 for cancer of the colon and liver (3). Given the seeming inability of public health strategies to curb the rise of the obesity pandemic, it is vital we better understand the mechanisms underlying obesity-induced cancer to allow the development of new preventative and therapeutic approaches. Alemán *et al*.'s recent paper in Gastroenterology; Mechanism of Obesity-Induced Gastrointestinal Neoplasia (4), is therefore timely and important. The paper highlights the key role of metabolic, hormonal, inflammatory, genetic and immune factors, in addition to the role of gut microbiota in obesity-induced cancer. They explore how these factors contribute to colon, gastric, pancreatic and oesophageal cancer, but do not discuss liver malignancy.

Appropriately, the initial focus on the paper relates to insulin resistance (IR) and high circulating levels of insulin-like growth factor (IGF)-1, which are common in obesity and likely contribute to mitogenesis via increased nutrient delivery to cancer cells, promotion of cell division and inhibition of apoptosis (4). Excess IGF-1 appears to be particularly important in colorectal cancer (CRC) with overexpression of IGF-1R in colon cancer cells leading to potentiation of disease development, progression and metastases. The high incidence of aggressive CRC in patients with acromegaly and excess IGF-1 highlights this association. Higher levels of IGF-1 in obese patients have been associated with overexpression of IGF-1R in oesophageal adenocarcinoma (OAC) cells, which in turn appears to be a poor prognostic indicator. Similarly, over-expression of IGF-1R in gastric adenocarcinoma (GAC) cells is associated with metastases, local invasion and poorer survival. There is no conclusive evidence, however, that insulin or the IGF-1 system mediates the progression from Barrett's oesophagus or gastric intestinal metaplasia to OAC or GAC.

Inflammation and the role of adipocytokines are considered separately, but are very much linked in the pathogenesis of cancer. Chronic inflammation is a hallmark of both cancer and of obesity, driven by abnormal cytokine production, immune activation and increased inflammatory signalling. T cells and macrophages are the key mediators, producing IL-6, TNF-α, VEGF and MCP-1. The effects of inflammation combine with

expanded adipocyte deposits to increase levels of leptin and reduce adiponectin. The reduction in adiponectin in turn is associated with accentuated IR, cell proliferation, angiogenesis, inflammation and a reduction in apoptosis. Low adiponectin levels are associated with CRC in men, indeed even small increments in serum adiponectin (1 µg/mL) have been associated with a reduced risk of disease (4). These effects may be mediated via alterations in the AMP-kinase and mTOR pathways (5). Inflammation is likely to be an important player in the progression from polyps to established colonic neoplasia, despite the results of many studies being equivocal. TNF-mediated inflammation is definitely associated with CRC and the generalised reduction in early and late colonic neoplasia induced by anti-inflammatory drugs (aspirin and other non-steroidals) suggests a key, if as yet unproven role for inflammation in CRC. Low levels of adiponectin meanwhile, appear strongly associated with OAC and may also contribute to the progression from Barrett's oesophagus to OAC, but their association with gastric and pancreatic cancer is less clear.

A novel and emerging field alluded to by the authors is the potential role of the intestinal microbiome in carcinogenesis. Intestinal microbiota differs between lean and obese subjects with obese subjects having a higher proportion of *Firmicutes* to *Bacteroidetes* species. These differences are highlighted by transplantation of stool from homozygous twins discordant for obesity into germ free mice, with induction of obesity only in mice receiving stool from the obese individual (6). Intestinal microbiota appears to play a vital role in energy harvesting and fat storage and may contribute to the low-grade chronic inflammation of obesity via generation of bacterial lipopolysaccharide and induction of Toll like receptor-4, IL-1, IL-6 and TNF-α (6). The altered intestinal microbiota seen in obesity in turn is associated with dysregulation of bile acid homeostasis and elevated levels of secondary cytotoxic bile acids. In conjunction with the gut dysbiosis of obesity this creates a pro-carcinogenic milieu of excessive inflammation, heightened oxidative DNA damage and increased cell proliferation (7). Although no direct links have yet been made with specific microbiota changes and GI malignancy, it seems highly likely that these will emerge with further study. Given the promising results of faecal microbiota transplantation (FMT) in altering metabolism in animal studies and in treating inflammatory diseases such as ulcerative colitis in humans (8), it is exciting to speculate that FMT could potentially be used to reduce the risk of cancer in the future.

A surprising aspect of this otherwise excellent review is the failure of the authors to emphasize the key importance of visceral fat, rather than overall obesity, to GI carcinogenesis. Waist circumference (WC), one of the best surrogate markers of visceral fat (9), has been shown to be a stronger predictor than BMI for CRC, Barrett's oesophagus and OAC (5) and is associated with a linear increase in risk of pancreatic cancer based on a recent meta-analysis (10). Further compelling evidence comes from the large, prospective Framingham cohort, where elevated WC was associated with a two-fold increase risk of lifetime CRC even after adjusting for BMI, while elevated BMI alone only marginally increased CRC risk and was not significant when WC was added to the multivariate model (11). Significantly, many of the mechanisms underlying obesity related GI carcinogenesis appear to be driven by the extent of visceral, rather than overall, adiposity. Alemán *et al.* (4) acknowledge that the chronic low grade inflammation associated with obesity is most pronounced in visceral fat and that some patients with excess subcutaneous fat appear to have metabolically benign obesity. This is evident in patients undergoing surgical resection for OAC or CRC, where significantly higher levels of leptin, IL-6, NK cells and $CD8^+$ T cells were observed in visceral rather than subcutaneous adipose tissue (5). Similarly, IR and elevations of insulin and IGF-1 are significantly correlated with the extent of visceral fat and largely unrelated to generalised obesity. Indeed each standard deviation (SD) increase in subcutaneous adipose tissue mass decreases the odds of IR by 48%, whereas a SD increase in visceral adipose tissue mass increases the odds of IR by 80% (12). Adiponectin, the most abundant adipocytokine, is predominantly secreted from visceral fat and its levels are inversely correlated with the extent of visceral, rather than overall, adiposity (5). The importance of distinguishing fat depots lies in the targeting of therapies to specifically reduce visceral fat, in the knowledge that this is more likely to alter cancer incidence and progression. Diet and physical activity, for example, appear to preferentially lead to a reduction in visceral adipose tissue independent of overall weight loss, as evidenced by a meta-analysis of over 35 studies where as little as 8 weeks of intense aerobic exercise was shown to significantly reduce visceral fat (13). Pharmacological agents modulating cannabinoid receptors and PPAR-γ agonists appear to preferentially reduce visceral fat, but both classes cannot be recommended due to neuropsychiatric and cardiovascular toxicities, respectively. New agents

are needed, as are targeted studies of bariatric surgery, to determine if visceral fat loss is driving the reduction in cancer incidence in patients who have sustained, long term post-surgical weight loss (5). The article by Alemán *et al*. (4) provides an excellent framework for further investigation and discovery in this rapidly changing field.

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