Obesity and Colon Cancer: What Is the Link?

Betty Schwartz

School of Nutritional Sciences Institute of Biochemistry, Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture, Food and Environment ,The Hebrew University of Jerusalem

Obesity is a key risk factor for the development of colon cancer; however, the endocrine/paracrine/metabolic networks mediating this connection are poorly understood. Our goal was to explore the metabolic networks and molecular signaling pathways linking obesity, adipose tissue and colon cancer. We hypothesize that obesity results in secreted products from adipose tissue that induce malignancy-related metabolic alterations in colonic as well as other cells.

Using in-vivo experiments, we found that mice fed a high-fat diet (HFD) and injected with MC38 colon cancer cells develop significantly larger tumors than their counterparts fed a normal diet. In *in vitro* assays, human colon cancer cells were exposed to conditioned media (CM) from cultured human adipose tissue fragments of obese vs. non-obese subjects. Oxygen consumption rate (OCR, =mitochondrial respiration) and extracellular acidification rate (ECAR, =glycolytic respiration) were examined vis-à-vis cell viability and expression of related genes and proteins. CM from obese (vs. non-obese) subjects decreased OCR and gene expression of mitochondrial proteins without affecting cell viability or expression of glycolytic enzymes. Similar changes could be recapitulated by incubating cells with leptin, whereas, leptin-receptor specific antagonist inhibited the reduced OCR induced by conditioned media from obese subjects.

In additional *in vitro* experiments, MC38 and CT26 murine colon cancer cells exposed to CM from the adipose tissue of HFD-fed mice demonstrated significantly lower OCR. In addition, these colon cancer cells exposed to CM prepared from the visceral fat of HFD-fed mice or to leptin showed downregulated expression of mitochondrial genes. Additionally, we found a close link between the fat adipose tissue and cancer development and demonstrated that this effect is mediated by the JNK/STAT3-signaling pathway. We conclude that obese adipose tissue alters the metabolic networks of colon cancer cells, impinging directly on their metabolism and malignant stage.

We conclude that secreted products from the adipose tissue of obese subjects inhibit mitochondrial respiration and function in colonic cells, an effect that is at least partly mediated by leptin. These results highlight a putative novel mechanism for obesity-

associated risk of gastrointestinal malignancies, and suggest potential new therapeutic avenues.