Homing in on the Fat and Cancer Connection

By Gunjan Sinha

Cancer researchers worldwide are increasingly focusing on the link between obesity and cancer. Epidemiological studies over the past 30 years have consistently shown that diabetics and obese people have a higher risk of getting cancer than lean healthy people, and when they do get it their risk of dying from it is greater.

But not all fat tissue is the same. Now researchers are focusing on how two types of fat tissue—white adipose tissue (WAT) and brown adipose tissue (BAT)—may affect cancer growth.

White Adipose Tissue

Once considered a mere energy storage depot, adipose tissue has revealed itself to be more than just an innocent bystander in promoting chronic disease. White adipose tissue secretes adipokines that include hormones such as insulin and leptin, cytokines and growth factors that may stimulate or inhibit cell growth and cause systemic inflammation. For example, insulin and insulin-like growth factor (IGF), a related hormone, play a role in fueling a range of cancers including breast, prostate, and bladder. Because obese people have more WAT than healthy people, they also have higher levels of certain circulating adipokines. Studies in animal models have shown that tumors can take advantage of adipokines. While systemically circulating adipokines may be important, studies also point to neighboring adipose tissue as a potential contributor.

“The tumor microenvironment is very important and understudied,” explained Mikhail Kolonin, Ph.D., associate professor at the Center for Stem Cell and Regenerative Medicine at the University of Texas Health Science Center in Houston. In some tumors, the majority of cells are not malignant; he said, they are rather infiltrating stromal and vascular cells of mixed origin. The problem for researchers has been that in humans, there is no sure way to identify the cells’ origins. Some research groups have been able to show in animal models and cell culture that mesenchymal stem cells (MSCs) appear to be recruited by tumors in response to inflammatory and hypoxia signals. At tumor sites, they engage in tissue remodeling aimed at normal organ repair. While bone marrow is certainly a source of these progenitor cells, three years ago Kolonin came up with a hypothesis that adipose tissue may also contribute to cancers associated with obesity.

“Most of the focus has been on bone marrow as a source of progenitor cells,” said Francesco Bertolini, M.D., Ph.D., at the European Institute of Oncology in Milan, Italy who is collaborating with Kolonin. “But we think that adipose tissue is an even richer source.”

In fact, when compared to bone marrow, there are more than 250 times more CD45-CD34+ progenitor cells (progenitors with both mesenchymal and endothelial differentiation potential) in 1 gram of fat when compared to 1 gram of aspirated bone marrow [Cancer Res. 2012;72:325-34]. Kolonin reasoned that MSCs from adipose tissue are also recruited by tumors and help them survive. In 2009, Kolonin and his colleagues showed that when fluorescently labeled adipose tissue from mice or humans is transplanted into mice with cancer, the tumors hijack cells from the adipose tissue. This recruitment is associated with increased vascularization and maturation of the tumor. [Cancer Res. 2009; 69:5259–5266.]

Visceral fat is much richer in progenitor cells than subcutaneous fat, which may explain the epidemiologic studies that show a stronger association between disease and visceral fat than subcutaneous fat, Bertolini added. Some evidence to support this comes from Kolonin and his colleagues who recently showed that adipose mesenchymal progenitors from visceral fat are more potent in promoting tumor growth than those from subcutaneous fat [Clin Cancer Res. 2012 Feb 1; 18 (3): 771-82]. And yet, another factor pointing to the potential importance of the proximity of fat tissue to tumors in supporting cancer growth is the observation that cancer progression associated with obesity is typically limited to organs surrounded by adipose tissue such as the breast, prostate and bladder and intestinal organs.

But despite the evidence that tumors do recruit adipose derived cells, these studies don’t show that the cells contribute to the observed growth of the tumors. To help answer this question, Kolonin and his collaborators are presently conducting studies on transgenic mice that carry labeled cell populations. Most experiments to date have looked at what happens to labeled cell populations after they have been injected or transplanted into mice. “The most important thing for us is to prove that cells from adipose tissue are recruited from endogenous cell populations,” he said.

Brown Adipose Tissue

Until recently, BAT has largely been studied as a thermoregulatory organ in rodents. BAT burns fat to generate heat, and it plays an important role in keeping rodents warm. But it was only in 2009 when 3 papers published in The New England Journal of Medicine showed that adult humans also have BAT deposits in the upper back, the neck, between the collarbone and shoulder, and also along the spine, that BAT became a hot research topic.
Stephan Herzig, Ph.D, head of the Joint Research Division of Molecular Metabolic Control at the German Cancer Research Center, the Center for Molecular Biology, and the University Hospital in Heidelberg, Germany, had been interested in the relationship between BAT tissue and metabolic disease, but then he found himself wondering whether adipokines—peptides secreted by adipose tissue—might play an indirect role in either promoting or inhibiting cancer progression. But not just any adipokines, only those specifically secreted by BAT.

In January of this year, Herzig was awarded a €1 million grant by the Deutsche Forschungsgemeinschaft, Germany’s primary science funding agency, to study the role BAT may play in cancer progression. “It’s a very interesting and open question,” said Herzig. Brown adipose cells consume a lot of glucose. In fact, that is how these mice had better insulin sensitivity and thereby have an indirect influence on tumor progression.

### BRITE: Another Type of Fat

Since the discovery of BAT in humans, researchers have also discovered another population of fat cells found within WAT that function like BAT. Some researchers refer to this tissue as BRITE (brown into white). BRITE cells appear de novo under certain conditions in white adipose tissue stores. About two years ago, Herzig and his colleagues showed that the COX-2 enzyme, a key enzyme in the production of prostaglandin, was important in creating BRITE cells in WAT. When the enzyme was inactivated in mice, they lost the ability to convert WAT into BRITE [Science. 2010 May 28; 328 (5982):1158-61]. “This was surprising,” Herzig said. “Prostaglandins have been looked at for 50 years and have been implicated in inflammatory conditions. This was a new function.”

Further study showed that manipulating the prostaglandin pathway, by way of affecting the conversion of WAT into BRITE, had an impact on overall energy regulation. Mice with the COX-2 prostaglandin pathway always active, and consequently with high levels of circulating prostaglandins, were protected against diet induced obesity. These mice had better insulin sensitivity and better glucose regulation, Herzig said. Since the COX-2 pathway is sometimes aberrant in cancer, manipulating the pathway might change the energy balance in cancer patients, particularly in those with cachexia, the wasting syndrome that afflicts up to 50% of cancer patients and can be fatal, Herzig reasoned.

Since both BAT and BRITE cells break down fat tissue to generate heat, and thin people appear to have more active BAT than obese people, many researchers are studying whether the balance of BAT and WAT tissues in people influences obesity and diabetes.

Indeed pharmaceutical companies are deeply interested in this issue because studies show that when activated, typically by cold exposure or certain medications, BAT can increase a person’s metabolic rate—by as much as 1.8 times a person’s resting rate, according to a recent paper published in The Journal of Clinical Investigation by André Carpentier and colleagues at the Université de Sherbrooke in Québec Canada [J Clin Invest. 2012; 122 (2):545-552]. To put that number in perspective, walking increases a person’s metabolic rate by 2 to 3 times, said Carpentier. The study participants’ elevated metabolic rate amounted to roughly 250 extra calories burned after 3 hours of cold exposure, “which isn’t insignificant,” Carpentier said.

Research on BAT may also affect cancer indirectly. If activating BAT or BRITE tissue can help people lose weight, it may cut cancer rates, since obesity can double a person’s chances of getting cancer. “It’s not everyday that a person’s metabolic rate can increase by 2 to 3 times, said Carpentier. “It’s not everyday that researchers rediscover a potentially novel mechanism for metabolism in humans.”

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