tic gene expression and nutrient gradients in the model ocean.

The authors found that although the emergent microbial community differed between model runs, metabolic capacity and thus ocean biogeochemistry remained stable. In other words, the specific activities of microbes mattered more than their species identity.

Many ecologists have been trained to address two key questions: Who is there, and what are they doing? Perhaps, in the ocean, one only needs to know the latter. But before fully embracing this notion, we need to better understand how natural selection acts on marine microbes and how rapidly mutations for new variants arise. These questions could be addressed in Coles *et al.*'s model by allowing for different rates of mutation and selection to occur within a physically and biologically dynamic ocean model.

Future efforts can build on the foundation of the model. Coles *et al.*'s results provide guidance for future improvements of ocean physics models by indicating where the physics in those models is too coarse to resolve the impact of microbial activities. For example, some aspects of nutrient gradients in the Coles *et al.* model differ from observations in the North Atlantic and are more likely due to poor resolution in the physical model than to errors in the parameterization of biological activities. Future iterations of the model could begin to incorporate symbioses. These ubiquitous multispecies and even multikingdom interactions have been fine-tuned over evolutionary time (*12*) and influence rates and magnitudes of nutrient transformations in the global ocean. Last, because the model output can be compared with in situ gene expression, there is a new opportunity to extend the model and integrate global-scale surveys of genes and transcripts, such as the *Tara* Oceans expedition (*3*), with global-scale biogeochemical models. ■

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CANCER BIOLOGY

Obesity and the tumor microenvironment

Obesity-associated inflammation promotes tumor growth and metastatic spread

By **Oakley C. Olson,[1] Daniela F. Quail,[2] Johanna A. Joyce[1]**

Obesity is a growing global epidemic and rivals smoking as the leading preventable risk factor for cancer incidence and mortality, being responsible for an estimated ~20% of cancer-related deaths in adults (*1*). Obesity underlies a number of distinct but interconnected health conditions that have profound consequences for physiology, including hypernutrition, dysbiosis, hypercholesterolemia, metabolic syndrome, and chronic inflammation. Although each of these health conditions may affect cancer pathogenesis, inflammation, in particular, is known to be a potent driver of cancer initiation and progression through its ability to cultivate a microenvironment that is permissive to neoplastic transformation. Thus, as immuno-oncology continues to gain clinical importance, understanding the relationship between cancer and various inflammatory conditions, including obesity, is critical.

> ***"...how cancer biology differs between obese and lean patients..."***

Adipose tissue is found in several anatomical locations, including various subcutaneous and visceral regions, and in bone marrow. Within these depots, the metabolic status of adipose tissue can vary: Brown adipose tissue (BAT) is highly specialized, energy-consuming, thermogenic fat that supports glucose homeostasis and insulin sensitivity. By contrast, white adipose tissue (WAT) stores energy and is relatively more abundant. Clinically, WAT is crudely estimated by using the body mass index (BMI; body mass/height^2 in kg/m^2), where overweight is defined as a BMI between 25 and <30, and obesity as a BMI of 30 or higher (*1*). In obese individuals, increased and deregulated WAT contributes to chronic, systemic inflammation and metabolic syndrome (*2*). Interestingly, ~20% of lean adults display metabolic "obesity," characterized by WAT inflammation, higher proportions of visceral WAT, and insulin resistance (*3*). Conversely, roughly 50% of obese individuals remain metabolically healthy (*3*). Although obesity and WAT inflammation are strongly correlated on a population level, BMI alone cannot accurately capture immunometabolic dysfunction within a given individual. Therefore, preclinical studies that define the causal relationships between WAT inflammation and cancer will potentially have clinical relevance for patients across all weight categories.

Obesity-associated inflammation (OAI) can dramatically alter tissue composition, thereby creating a fertile soil for cancer development; it is conceivable that these changes may lower mutational and epigenetic barriers to tumorigenesis. For instance, in breast (*4*) and pancreas (*5*), OAI is associated with altered extracellular matrix composition that facilitates transformation of premalignant cells. In the colon, epigenetic alterations that occur in cancer are observed in normal epithelial cells in the context of obesity (*6*), thus lowering the mutational threshold that is required for malignant transformation (*7*). These studies suggest that OAI "primes" both the tissue microenvironment and premalignant epithelial cells to facilitate oncogenic transformation. Indeed, obesity is often associated with specific molecular subtypes of cancer (*7*), which may reflect a selective pressure exerted by the obese microenvironment resulting in the altered fitness of specific oncogenic mutations. Accordingly, tumors that evolve within an obese microenvironment may exhibit "obesity addiction" whereby they are driven by a dependency on hypernutrition and inflammatory cytokines.

OAI can also contribute to disease progression at the primary tumor site by perturbing the homeostatic balance of cytokines in the systemic milieu. In breast cancer, tumor-infiltrating myeloid cells producing interleukin-1β (IL-1β), an inflammatory cytokine, are elevated in the obesity-associated tumor microenvironment (TME), and can promote

[1]*Ludwig Institute for Cancer Research, University of Lausanne, Switzerland.* [2]*Goodman Cancer Research Centre, Department of Physiology, McGill University, Montreal, Canada.*
Email: johanna@joycelab.org; daniela.quail@mcgill.ca

tumor angiogenesis and disease progression by stimulating adipocyte production of vascular endothelial growth factor–A (VEGF-A) (*8*). In the pancreas, obesity is associated with increased desmoplasia and inflammation, which enhances IL-1β production by adipocytes. In cancer, this increase in IL-1β promotes the recruitment of immunosuppressive neutrophils to the pancreatic TME, which accelerate tumor growth (*5*). In prostate cancer, periprostatic adipocyte secretion of C-C motif chemokine ligand 7 (CCL7) drives invasion of tumor cells into the surrounding stromal tissue (*9*). Collectively, these studies demonstrate that systemic inflammation resulting from obesity can perturb homeostatic communication between different organs, including WAT, bone marrow, and primary TMEs, to mediate enhanced malignancy.

Obesity is also associated with increased stage at diagnosis for breast cancer (*1*). Although this has been attributed in part to impaired cancer screening efficacy, there is emerging evidence that the systemic effects of OAI can also affect cancer metastasis (see the figure). Indeed, protumorigenic metabolites, cytokines, and growth factors can reprogram the systemic (i.e., blood or circulation) environment to improve metastatic proficiency of the host. For instance, in preclinical diet-induced obesity models, obesity increases circulating concentrations of IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to altered myelopoiesis, enhanced neutrophil trafficking to the lungs, and increased metastatic seeding of breast cancer cells compared with lean controls (*10*). In preclinical models of hypercholesterolemia (a comorbidity of obesity), elevated circulating concentrations of cholesterol metabolites also promote lung metastasis of estrogen receptor–positive (ER^+) breast cancer through enhanced epithelial-to-mesenchymal transition, a cellular process associated with invasion and metastasis (*11*). Given that metastasis is responsible for the vast majority of breast cancer deaths, these observations are consistent with epidemiological data showing increased breast cancer mortality in association with obesity in humans (*1*).

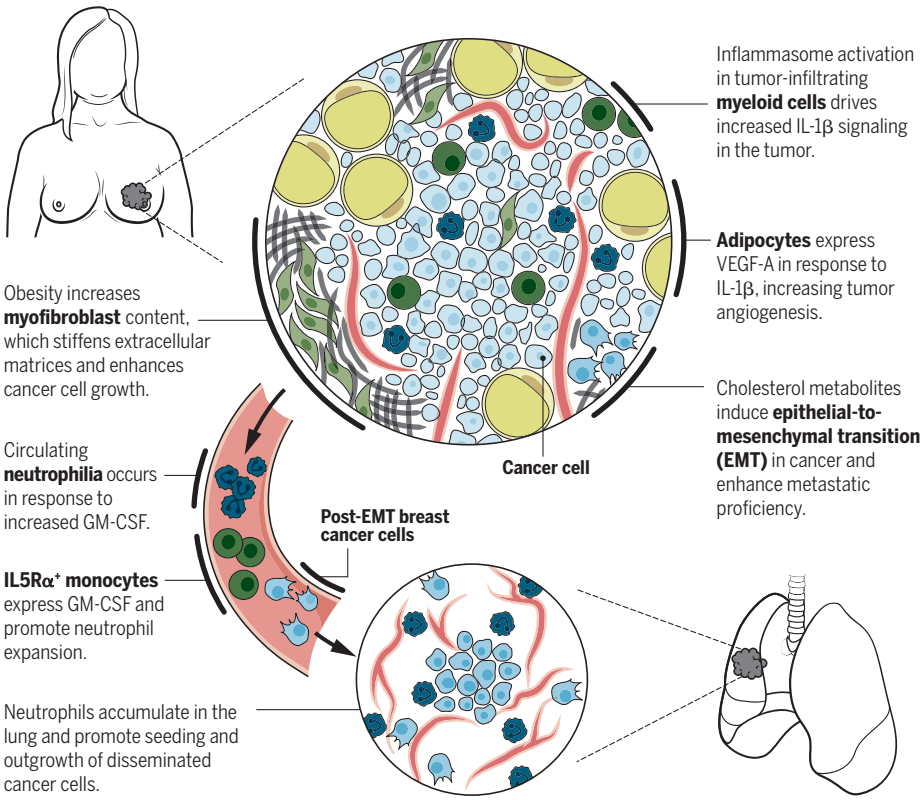
From a translational perspective, there is considerable evidence that resolution of energy imbalance and inflammation may mitigate the protumorigenic effects of obesity. "Obesity addiction" could expose new cancer dependencies that may be vulnerable to intervention. Notably, preventing weight gain using caloric restriction can resolve obesity-associated WAT inflammation in mice (*12*). Weight loss is also associated with a reduction in IL-5, GM-CSF, and circulating neutrophils, resulting in a reversal of the prometastatic effects of obesity in preclinical breast cancer models (*10*). These studies and others suggest that weight loss may be an effective strategy to reverse energy imbalance and WAT inflammation, thereby ultimately improving cancer outcomes.

Additional lifestyle interventions that do not necessarily require reduction in adipose tissue, such as exercise and fasting, have also demonstrated an ability to improve immune function (*13, 14*). Fasting is associated with a reduction of immunosuppressive T regulatory cells within breast tumors and increased lymphopoiesis, which together result in higher numbers of cytotoxic $CD8^+$ tumor-infiltrating lymphocytes, and may thus promote antitumor immune responses (*13*). Exercise and epinephrine lead to activation of natural killer cell–mediated immunosurveillance, and suppress tumor incidence and growth in multiple cancer models (*14*). These interventions, however, have not been rigorously investigated in the obesity context; therefore, further preclinical investigation is required to fully understand their potential application in patients. Furthermore, pharmacological approaches to target the immune system in obese individuals have yielded unpredictable results. For example, certain immunotherapy regimens in aged obese mice have led to lethal inflammatory reactions (*15*), reinforcing a critical need to reexamine what is known about tumor immunology in the obesity setting.

It is essential to understand how cancer biology differs between obese and lean patients, and develop personalized approaches to treat these distinct diseases accordingly. Although pieces of the "cancer-obesity" puzzle are beginning to come together, given the prevalence of obesity in developed countries, we must emphasize the need to incorporate preclinical obesity models and appropriate clinical analysis in all cancer investigations. Obesity is likely to emerge as the dominant pathological state of the future, with considerable implications for patient care. ■

Obesity and cancer progression

The effects of obesity on cancer progression are depicted using breast cancer as a representative example, based on studies from mice and humans. Obesity promotes both primary tumor growth and metastatic progression through systemic alterations that affect tissue homeostasis.



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