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Prostate Cancer Metastasis — Fueled by Fat?

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Obesity is approaching epidemic proportions worldwide and is having an effect on many chronic illnesses, including cancer.¹ The physiological consequences of obesity include a state of chronic inflammation, which has been associated with an increased risk of development of cancer or of progression to more aggressive phenotypes. Although the underlying mechanisms are not yet well defined, the consequences of obesity are thought to include cell-intrinsic effects that allow the metabolic engine of tumor cells to thrive in otherwise hostile environments, as well as physiological effects on the whole organism that promote these altered metabolic states.² Thus, understanding the mechanisms by which obesity promotes the incidence or aggressiveness of cancer may lead to new strategies to prevent and to treat the disease.

A recent study by Chen et al. provides new insights into how obesity induced by a high-fat diet may promote aggressive prostate cancer (Fig. 1).³ Although most prostate cancers are relatively indolent and therefore not life-threatening, highly aggressive and metastatic disease develops in a subgroup of patients, and obesity has been associated with increased aggressiveness of prostate cancer.⁴

Chen et al. analyzed two key tumor-suppressor genes, *PTEN* and *PML*, that protect against prostate cancer. Tumor-suppressor genes promote cell functions that prevent cancer; therefore, their loss is often associated with accelerated development of cancer phenotypes. The loss of both *PTEN* and *PML* often occurs in the most aggressive forms of prostate cancer. Chen et al. investigated the functional consequences of the loss of *PTEN* and *PML* using mice that had been engineered to be deficient in these genes. They found that in mice deficient in *Pten* in the prostate, locally invasive prostate cancer developed, whereas in 30% of mice lacking both *Pten* and *Pml*, prostate cancer that metastasized to lymph nodes developed. These findings were interpreted to indicate that these genes work together to suppress a more aggressive prostate cancer phenotype.

To understand how this might occur, Chen et al. performed molecular profiling of the mouse tumors to identify the genes and biologic pathways that are expressed differentially in aggressive as compared with indolent mouse tumors. They found that among the top genes and biologic pathways affected were those involved in lipid production, a finding that suggests an association between fat production by the prostate cancer cells and an aggressive phenotype. In fact, they showed that the tumors that developed in the mice after the loss of

Pten and *Pml* had high levels of key lipids in their cells. They also found evidence that increased lipid production is triggered by activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which is frequently deregulated in prostate cancer.⁵ These findings led the investigators to consider whether fat may provide a cell-intrinsic signal to promote aggressive subtypes of prostate cancer by activating MAPK signaling. To test this idea, they fed the tumor-prone mice a high-fat diet and investigated whether more prevalent or more aggressive prostate cancer developed in these mice. The high-fat diet mimicked the effect of the loss of tumor-suppressor genes; in particular, the “obese” (as defined by Chen et al.) mice had a greater tendency toward the development of metastases, which occurred not only in lymph nodes but also in soft tissues such as the lung. Leveraging these findings, the authors then investigated whether fatostatin, a small-molecule inhibitor that targets a key regulator of fat production, could prevent metastasis. Indeed, the mice that were given fatostatin had less tumor growth and a lower incidence of metastasis than the control mice. Overall, these findings suggest that reducing levels of fat in prostate cells may improve outcomes of prostate cancer.

A key finding from the study by Chen et al. is that lipids promote aggressive prostate cancer through mechanisms that are intrinsic to tumor cells (Fig. 1). There are many activators of MAPK signaling⁵; *PML* loss may represent only one of many ways that this pathway can be activated in prostate cancer cells. Another point to consider is that obesity, and particularly high-fat diets, have many physiological consequences in the whole organism; perhaps other mechanisms potentiate the cell-intrinsic consequences of lipids in tumor cells to promote aggressive cancer. Furthermore, obesity is not equivalent to high fat intake; certainly, high intake of sugars can lead to substantial weight gain and altered cellular metabolism. This raises questions of whether similar mechanisms would be operable in cases in which weight gain was not the consequence of a high-fat diet and whether we might expect fatostatin to be effective in preventing aggressive prostate cancer in such cases.

Another question is whether these investigators are indeed studying lethal prostate cancer, since most men who die from prostate cancer do not die because of lymph-node metastasis, and metastases to the lung are rare. In particular, it is unclear whether these mouse models are true surrogates for lethal prostate cancer as it occurs in men, in whom bone metastasis is a major cause of lethality.⁵ Furthermore, whether the androgen-receptor–signaling pathway is affected in the prostate tumors of the models used by Chen et al. is unknown. The androgen receptor is a master driver of prostate cancer and is particularly relevant for aggressive subtypes,⁵ yet androgen-receptor signaling is known to be decreased in obesity.⁴ Whether increased levels of fat either affect or are affected by androgen-receptor signaling in the mouse model is unclear.

Finally, the implicit question is whether these studies in mouse models will ultimately prove to be relevant to human prostate cancer. This is a fundamental question because it is ideal to study the physiological consequences of factors that promote or perturb fat production as they arise spontaneously in the whole organism; such a study cannot be accomplished with the use of cell culture or xenograft models. However, although mouse models allow studies in the native host environment, their potential downside is that the physiological processes in mice may be very different from those in humans, and thus the response observed in mouse

models may not fully recapitulate what actually occurs in human prostate cancer. The findings by Chen et al. warrant validation in studies of human prostate cancer; if validated, their findings may be highly relevant for understanding the risk of the development of fatal subtypes of the disease.

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Figure 1. Fat and Metastatic Prostate Cancer.

A recent study in mouse models by Chen et al.³ showed that deletion of two tumor-suppressor genes commonly lost in prostate cancer resulted in the activation of the mitogen-activated protein kinase (MAPK) pathway and increased production of lipids in prostate cancer cells (Panel A). The authors observed a similar effect when the mice were fed a high-fat diet, and they found that the effect was suppressed with the administration of fatostatin, a molecule that blocks adipogenesis (Panel B). Upward arrows indicate increased, and downward arrows decreased.