■ CANCER IMMUNOTHERAPY

Personalized T cells fight cancer

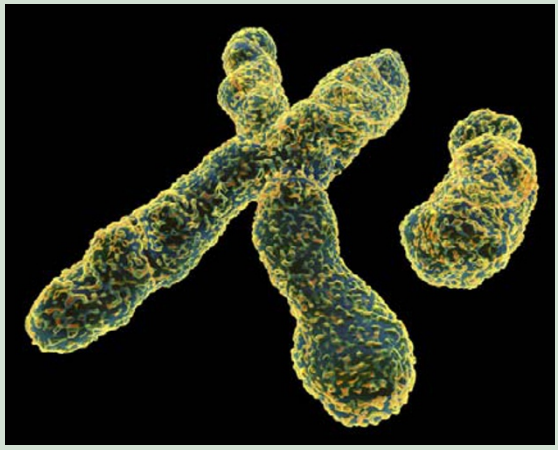
In a recent study, adoptive transfer of a tumor-infiltrating lymphocyte (TIL) population that can target a specific tumor mutation has successfully led to the regression of a metastatic epithelial cancer in one patient. The findings suggest that epithelial cancers, which often have a limited amount of mutations, can also elicit mutation-specific T cell responses, and that these can be harnessed to develop personalized T cell–based immunotherapy (*Science* **344**, 641–645, 2014).

Steven Rosenberg and his colleagues performed whole-exome sequencing of lung metastases in the cancer to identify tumor mutations that were then tested to assess the immunoreactivity of patient-derived T cells and determine which mutation was recognized. After selecting for and expanding the desired TILs, their administration along with interleukin-2 into the patient resulted in an initial tumor regression by 2 months, which reached up to 30% decrease in lung and liver metastatic growth at 6 months. After a second T cell transfer, the patient experienced tumor regression by 1 month, with continuing regression at the 6-month follow-up.

Although personalized T cell immunotherapy has been more widely explored in melanoma, there has not been much evidence to suggest its effectiveness against epithelial tumors, the most common cancers found among patients. Future studies may opt to combine these techniques with additional methods that tackle the immunosuppressive environment in patients with cancer to achieve superior responses.—*KS*

CANCER

Risky Y chromosome loss



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Men are at a higher risk of developing and dying from sex-nonspecific cancers, but the reasons for this are unknown. A recent study with more than 1,000 adult men shows that the mosaic loss of chromosome Y (LOY) in peripheral blood cells may explain this increased cancer risk and related deaths in men (*Nat. Genet.* doi:10.1038/ng.2966, 2014).

Lars Forsberg and his colleagues analyzed copy number variations in peripheral blood DNA of male participants from the Uppsala Longitudinal Study of Adult Men (aged 70.7–83.6 years). Interestingly, the most frequent shared genetic mutation was LOY, which was found in varying proportions of the blood cells of the individuals, and the proportions became progressively larger as patients aged.

The effect of this mosaic LOY on patient survival was examined in 982 subjects, who were cancer free at the beginning of the study. After a medium time of 8.7 years of follow-up, men with LOY were found to survive on average 5.5 years less than those without LOY and to be at a higher risk of nonhematological cancer-related deaths. No subjects developed hematological cancers. These same results were seen in another 488 adult men from the Prospective Investigation of the Vasculature in Uppsala Seniors study.

The findings suggest a protective function for the Y chromosome in cancer, although how this occurs remains unknown. More detailed studies will be required to analyze the degree of LOY in peripheral blood that predisposes to cancer.—*HS*

■ OBESITY

Recruiting inflammatory cells to fat

Adipose tissue–resident macrophages contribute to local inflammation in the fat during states of obesity and can trigger insulin resistance and glucose intolerance. A study in mice adds new insight to this immunometabolic axis in obesity by showing how these macrophages can worsen inflammation and disease by recruiting additional myeloid cells from the bone marrow to the fat (*Cell Metab.* **19**, 821–835, 2014).

Prabhakara Nagareddy and his colleagues found a local elevation of the alarmins S100A8 and S100A9 in fat tissue of obese mice. These molecules were shown to activate the TLR4-MyD88 pathway in fat-resident macrophages, resulting in inflammasome activation in these cells and production of active interleukin-1β (IL-1β). Upon release of this cytokine into the circulation, IL-1β reached the bone marrow, where it signaled in common myeloid progenitors and granulocyte progenitors to induce their maturation into monocytes and neutrophils and their eventual homing to the fat tissue.

In this way, fat tissue–resident macrophages help recruit new macrophages to the fat, thus exacerbating the inflammation of this tissue during obesity. The results also give further credence to the notion of targeting IL-1β signaling to treat the metabolic complications of type 2 diabetes.—*RL*

■ MONOCYTES AND MACROPHAGES

Tissue control of macrophages

The local signals leading to the diversity of tissue-resident macrophages remain largely unknown. Together, the findings of two studies now show that peritoneal-specific signals reversibly induce activation of the transcription factor GATA6 in resident macrophages, which regulates their phenotype and localization in the peritoneum and helps resolve inflammation at this site. The findings highlight the need for tissue-derived signals to induce plasticity of tissue macrophages and adapt to environmental changes (*Cell* **157**, 832–844, 2014 and *Science* **344**, 645–648, 2014).

By comparing mouse macrophages from different tissues, Yasutaka Okabe and Ruslan Medzhitov found GATA6 highly expressed in peritoneal macrophages and responsible for regulating their localization in the peritoneal cavity. The authors identified retinoic acid (found in the fat tissue associated with the peritoneum) as the upstream local signal that activates *Gata6* as well as other peritoneal macrophage–specific genes. Mice lacking vitamin A, a precursor of retinoic acid, had a smaller number of peritoneal macrophages and lower expression of *Gata6* and other specific genes, confirming the role of this axis in