**Metabolism**

**Major finding:** CpG rewires macrophage metabolism to bypass inhibitory CD47 signals and enhance antitumor activity.

**Mechanism:** CpG promotes fatty-acid oxidation and de novo lipogenesis to induce an oxidative state in macrophages.

**Impact:** Targeting core metabolic processes may potentiate macrophage antitumor function in solid tumors.

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**CENTRAL CARBON METABOLISM REGULATES MACROPHAGE ANTITUMOR ACTIVITY**

Macrophages play a dual role in tumorigenesis depending on their polarization phenotype, with proinflammatory M1 macrophages mediating antitumor immunity via phagocytosis of tumor cells and immunosuppressive M2 macrophages supporting tumor growth. These different functions are regulated in part by the balance of stimulatory signals, such as Toll-like receptors (TLR), and inhibitory signals, including CD47, an antiphagocytic protein overexpressed by tumor cells. Liu and colleagues found that, whereas antibody blockade of CD47 was not sufficient to stimulate macrophage antitumor activity in a mouse model of pancreatic ductal adenocarcinoma (PDAC), treatment with CpG oligonucleotide, a TLR9 agonist, enhanced macrophage phagocytosis of PDAC cells and suppressed tumor growth in vivo. This antitumor response was mediated by CSF1R+ tumor-associated macrophages and was sufficient to overcome inhibitory CD47 expression by PDAC cells and other nonhematopoietic tumor cells. Mechanistically, CpG induced a rewiring of macrophage metabolism characterized by enhanced oxidative phosphorylation without polarization to the classic M1 or M2 phenotype. This unique metabolic state was required for CpG-mediated stimulation of macrophage antitumor activity and was dependent on increased fatty-acid oxidation (FAO) and a shift in the use of TCA cycle intermediates for de novo lipogenesis. Inhibition of the FAO enzyme carnitine palmitoyltransferase 1A or ATP citrate lyase, a key enzyme in fatty-acid biosynthesis, prevented the CpG-driven increase in macrophage oxygen consumption and abolished the ability of CpG-stimulated macrophages to phagocytose PDAC cells. These findings establish a critical role for macrophage central carbon metabolism in circumventing inhibitory immune checkpoint signals and suggest that targeted rewiring of the metabolic state in macrophages may potentiate antitumor responses.


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**Metastasis**

**Major finding:** Pathogenic IgG produced by tumor-educated B cells drives formation of a lymph node premetastatic niche.

**Mechanism:** IgG binding to glycosylated HSPA4 on tumor cells activates CXCR4/SDF1α via ITGB5–SRC–NFκB signaling.

**Impact:** HSPA4 expression in tumor cells and anti-HSPA4 IgG levels may be prognostic indicators in breast cancer.

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**B CELL–DERIVED ANTIBODIES PROMOTE LYMPH NODE METASTASIS IN BREAST CANCER**

Primary tumors support the generation of premetastatic niches by recruiting bone marrow–derived cells to secondary tissue sites and secreting factors that educate cells at these sites to establish an immunosuppressive microenvironment. B cells have been implicated in tumor growth and progression via inhibition of antitumor immune responses and production of tumor-promoting humoral immunity; however, the role of B cells and B cell–derived antibodies in the formation of the premetastatic niche remains unclear. In a mouse model of spontaneous breast cancer metastasis, Gu, Liu, and colleagues found that primary tumors stimulated the recruitment of B cells to draining lymph nodes (DLN). B cells from DLNs of tumor-bearing mice produced high levels of pathogenic IgG, which targeted tumor membrane antigens and increased breast cancer cell migration and invasion to selectively enhance lymph node metastasis. This premetastatic effect was mediated by binding of pathogenic IgG to glycosylated heat shock protein family A member 4 (HSPA4), a candidate tumor antigen of the HSP70 family, on the tumor-cell surface, leading to activation of the HSPA4-binding protein integrin β5 (ITGB5) and downstream induction of signaling via SRC kinase and the NFκB pathway. Activation of NFκB signaling was required for HIF1α-dependent induction of C-X-C motif chemokine receptor 4 (CXCR4) in tumor cells and cyclooxygenase 2 (COX2)–driven expression of the CXCR4 ligand stromal-derived factor 1α (SDF1α) in lymph node stromal cells. Pharmacologic inhibition of CXCR4 or COX2 or knockdown of HSPA4 or ITGB5 in tumor cells attenuated lymph node metastasis in tumor-bearing mice. In addition, high tumor HSPA4 expression and elevated serum levels of anti-HSPA4 IgG were associated with lymph node metastasis and poor prognosis in patients with breast cancer. These data define a previously unappreciated role for pathogenic antibodies derived from tumor-educated B cells in establishing the lymph node premetastatic niche and promoting breast cancer metastasis.
