Reinvigorating exhausted immune cells reveals potential therapy target for cancer

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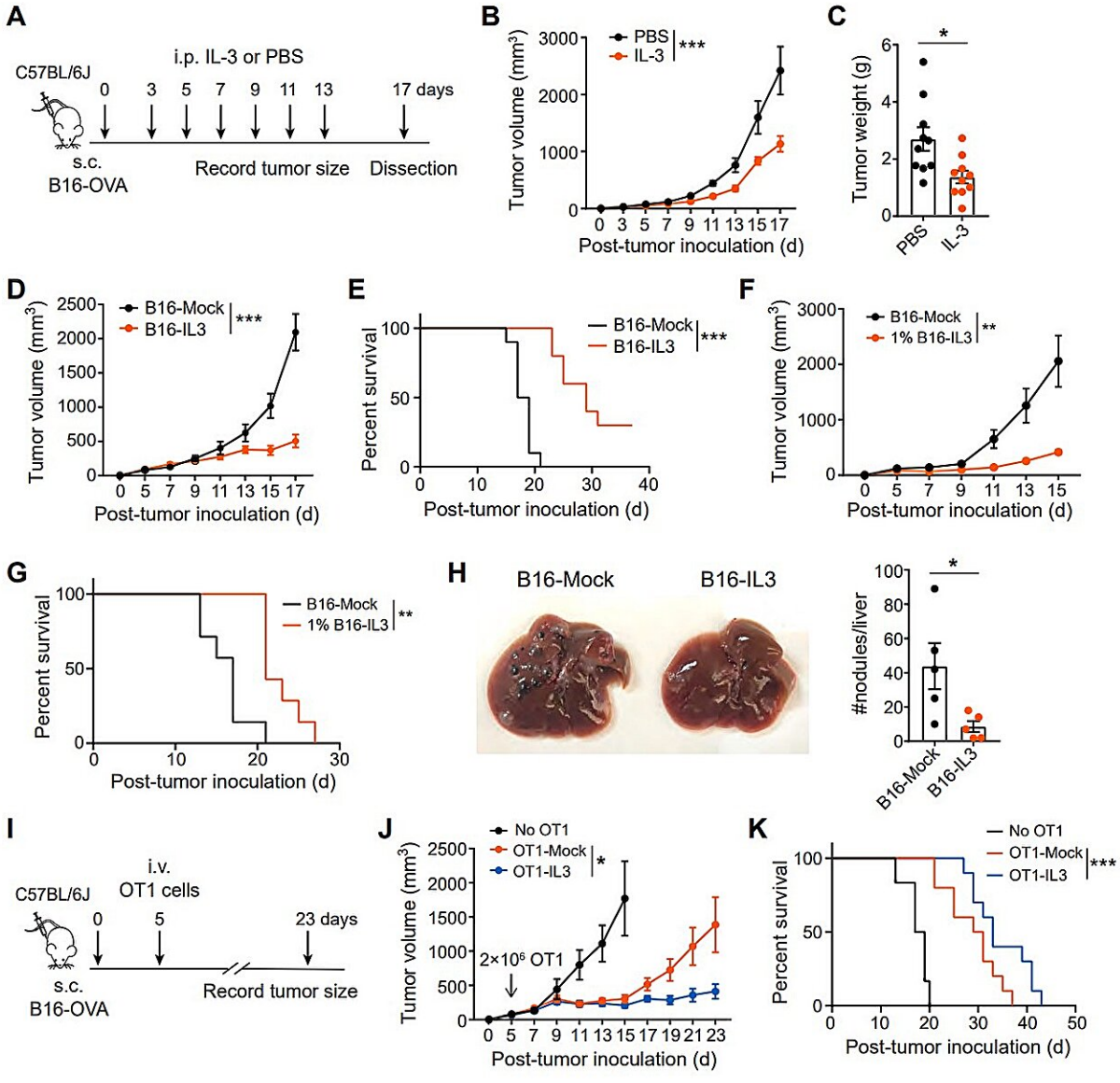

Credit: *Cancer Immunology Research* (2024). DOI: 10.1158/2326-6066.CIR-23-0851

The ecosystem that surrounds a tumor, also known as the tumor microenvironment, includes immune cells, tissues, blood vessels and other cells that interact with each other and with the tumor. Over time, the tumor shapes this ecosystem to its own benefit, monopolizing all of the nutrients and shielding it from immune attack.

In working to understand the ecosystem's role in cancer risk, development and treatment, researchers at The Jackson Laboratory have not only identified how two immune cells work together to fight cancer but also revealed the cascade of molecules that help coordinate this attack.

The work, led by JAX Assistant Professor Chih-Hao "Lucas" Chang, Ph.D., focuses on cytotoxic T-cells, a type of immune cell with many functions, including destroying cells infected with viruses and fighting bacterial infections and other pathogens. They also attack tumor cells.

Our immune systems are able to eliminate most cancerous cells from our body before they can cause a problem. But once a tumor becomes established, cytotoxic T-cells become "exhausted" in the hostile tumor microenvironment and unable to effectively attack tumors. Chang and colleagues are investigating why these immune cells become exhausted, and potential ways to signal them back to targeting tumors.

"T-cells are excellent at identifying and attacking cells that become cancerous, but they can become exhausted in the tumor microenvironment; they can become overworked and overstimulated, while also being starved of glucose and other nutrients by tumor cells.

Helping these cells to function better could improve cancer treatment strategies, particularly immunotherapies," said Chang, whose work appears in *Cancer Immunology Research*.

Previous studies showed that when cytotoxic T-cells are activated, they release signaling molecules called cytokines. Chang and colleagues focused on one of these cytokines, interleukin-3 (IL-3), discovering that as a tumor grows, cytotoxic T-cells progressively lose the ability to produce IL-3 in the tumor microenvironment. Then, when Chang elevated IL-3 levels in mice bearing lymphoma or melanoma tumors, he observed strong antitumor effects.

Chang's team further revealed that IL-3 works to mobilize basophils, a rare immune cell that can also play a role in allergies. In turn, these basophils produce another cytokine known as interleukin-4 (IL-4), which reenergizes cytotoxic T-cells, signaling them to resume detecting and destroying tumors.

"Basophils have not previously been implicated in the signaling cascade for reinvigorating cytotoxic T-cells," said Chang. "These findings are preliminary, but targeting tumor-associated basophils represents a promising avenue for enhancing antitumor immunity and improving patient outcomes."

More information: Jian Wei et al, IL3-Driven T Cell–Basophil Crosstalk Enhances Antitumor Immunity, *Cancer Immunology Research* (2024). DOI: 10.1158/2326-6066.CIR-23-0851

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