Soluble antibodies play immune suppressive role in tumor progression

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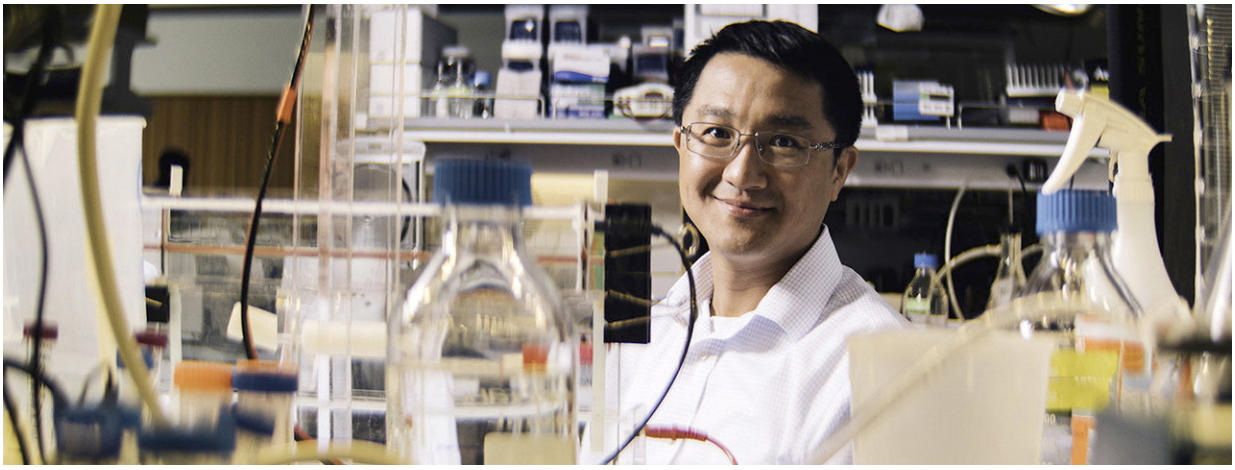

Dr. Andrew Hu in the lab Credit: The Wistar Institute

Wistar researchers have found that soluble antibodies promote tumor progression by inducing accumulation of myeloid-derived suppressor cells (MDSCs) in pre-clinical cancer models. Results were published online in *Cancer Immunology Research*.

Chronic lymphocytic leukemia (CLL) is a malignancy characterized by the progressive accumulation of mature B cells. Several reports indicated that B cells can mediate immune suppression and negatively affect the antitumor immune response in several cancer types. This research, led by Chih-Chi Andrew Hu, Ph.D., associate professor in Wistar's

Immunology, Microenvironment & Metastasis Program, and colleagues, used CLL and lung cancer mouse models to better define the role of soluble antibodies produced by B cells in orchestrating the immune suppressive response.

"Our research highlights the contribution of soluble antibodies in inducing accumulation of MDSCs," said Hu. "These are a population of immune suppressive cells that inhibit the antitumor functions of T cells and cause worse outcomes in many cancer types."

Through elegant crossing experiments, the researchers generated a mouse model of CLL in which malignant B cells produced abundant amounts of soluble antibodies, whereas CLL cells were considered to produce primarily membrane-bound antigen receptors. As a result, the mice developed significantly increased numbers of a specific cell population in the blood, which the researchers characterized as MDSCs.

To examine the role of soluble antibodies in the accumulation of MDSCs, they included an additional model of CLL in which B cells can only produce membrane-bound antigen receptors but not soluble antibodies. Survival was longer and there was a significantly lower number of MDSCs, which also had lower ability to suppress T cells, thus suggesting that soluble antibodies are responsible for accumulation of immune suppressive MDSCs.

Impairing the synthesis of soluble antibodies in tumor-bearing mice may be useful to slow down tumor progression, according to Hu. In fact, genetic and pharmacological targeting of the IRE-1/XBP-1 pathway of the endoplasmic reticulum stress response, which is critical for antibody production, results in decreased numbers and reduced functions of MDSCs. Hu and his collaborator Juan R. Del Valle at the University of South Florida are developing novel small molecule inhibitors against IRE-1 to combat cancers associated with high numbers of MDSCs.

The researchers expanded the relevance of these findings to lung carcinoma, showing that soluble antibodies are generally important in the tumor microenvironment to induce accumulation of MDSCs and promote cancer progression.

"We suggest that soluble antibodies may execute their immune suppressive function by recruiting MDSCs in the tumor microenvironment or promoting their functions", said Chih-Hang Anthony Tang, M.D., Ph.D., a staff scientist in the Hu Lab and the first author of the study. "Another possibility is that soluble antibodies may stimulate other types of immune cells to produce soluble factors that in turn contribute to the expansion of MDSCs and their functions."

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