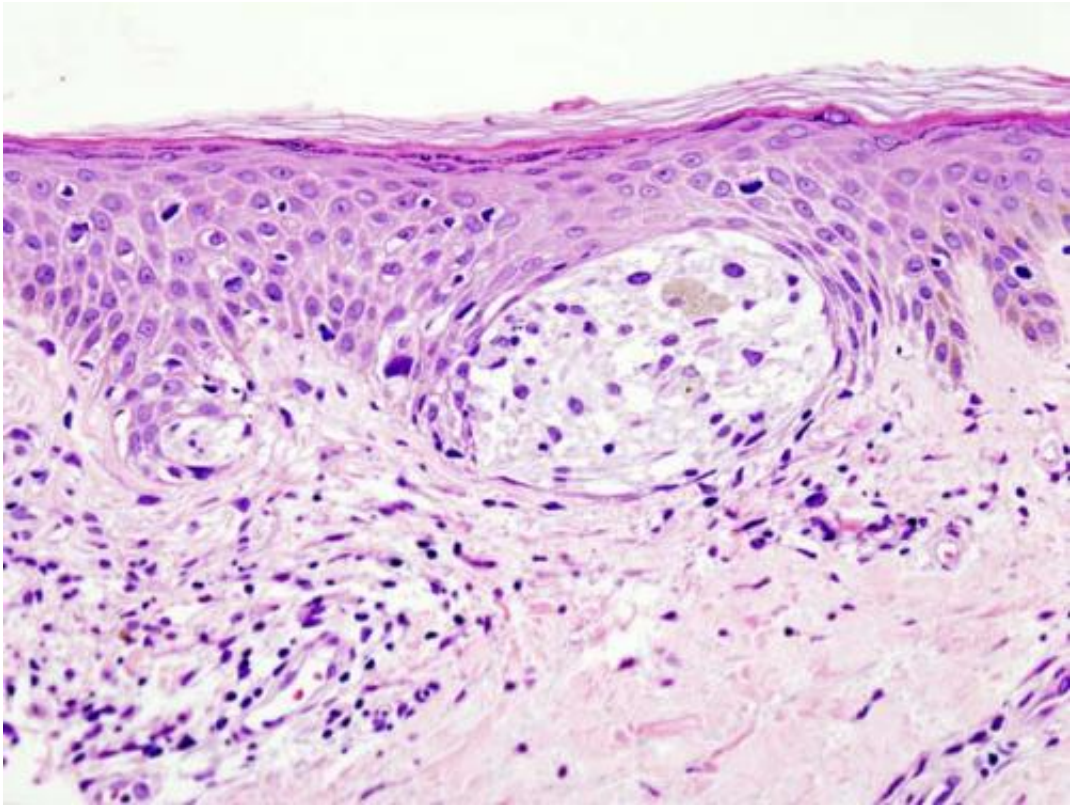
Macrophages surrounding lymph nodes block the progression of melanoma, other cancers

April 11 2016



Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Researchers at Massachusetts General Hospital (MGH) have identified a type of immune cell that appears to block the progress of melanoma and other cancers in animal models. These subcapsular sinus (SCS) macrophages form a protective coating around lymph nodes, preventing

the entry of tiny structures that transport bits of tumor tissue and help the cancer to grow and spread. However, the SCS macrophage barrier appears to be temporary, as it breaks down as the tumor progresses and in response to some cancer treatment drugs.

"Macrophages found within tumors are typically seen as promoting cancer growth, for example, by helping form new blood vessels which deliver nutrients to tumor cells," says Mikael Pittet, PhD, of the MGH Center for Systems Biology, who led the study appearing in the April 8, 2016 issue of *Science*. "My lab studies how tumors communicate with the immune system in the entire body, and we became particularly interested in knowing whether tumors also interact with macrophages that reside away from the tumor."

One potential means by which molecular signals could be transferred from tumors to immune cells are tiny membrane-bound compartments called tumor-derived extracellular vesicles (tEVs), which are known to bind to and activate many different cell types. Measuring tEV levels can be used to predict treatment response and survival, but assessing the impact of tEVs in living animals has been difficult. The MGH team combined genetic and imaging approaches in a novel way to track tEVs and their targets.

In mice carrying tumor cells genetically modified to produce tEVs with a light-emitting marker, the researchers confirmed that tEVs can exit tumors and travel throughout the body and found they were most highly concentrated in nearby lymph nodes to which they are transported via lymphatic vessels. In another group of mice with melanomas carrying different reporter proteins, the team found that tEVs primarily interact with SCS macrophages, which form a layer directly within the fibrous capsule surrounding lymph nodes.

To determine whether this observation in mice was relevant to human

disease, the investigators examined cancer-free sentinel lymph nodes - those closest to the tumor to which it would be expected to spread first—from 13 melanoma patients. Although the nodes themselves were confirmed to be melanoma-free, melanoma-derived material was found in SCS macrophages surrounding nodes from 90 percent of the patients. The presence of tumor-derived material in those macrophages did not reflect how far the primary tumor had progressed.

Further experiments found that SCS macrophages act as tumor suppressors in two mouse models of melanoma and in a lung cancer model. This is in marked contrast to macrophages within tumors, which typically promote cancer. While the current study showed that SCS macrophages suppress cancer by limiting the spread of tEVs, the density of SCS macrophages around lymph nodes begins to decrease as tumors grow. Treatment with chemotherapy and immune therapy drugs was also found to disrupt the SCS macrophage barrier. Once tEVs enter the lymph nodes, they bind to B cells, which produce antibodies that accelerate tumor growth.

An associate professor of Radiology at Harvard Medical School, Pittet says, "Since there currently is interest in developing therapies that deplete tumor-promoting macrophages within tumors, it could be useful to determine whether these treatments also affect protective SCS macrophages. The best outcome would probably be getting rid of the tumor-promoting activities of macrophages within tumors while preserving the tumor-suppressing activities of SCS macrophages. It also would be useful to determine whether SCS macrophages can be strengthened to prevent delivery of tEVs into the lymph nodes and to better understand how tEV-activated B cells promote cancer growth."

More information: F. Pucci et al. SCS macrophages suppress melanoma by restricting tumor-derived vesicle-B cell interactions, *Science* (2016). DOI: 10.1126/science.aaf1328