# Immune responses can be generated locally within human melanoma skin metastases

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In many types of cancer, activated immune cells infiltrate the tumor and influence clinical outcome. It is not always clear where these cells are activated, but results reported in *Cancer Research*, a journal of the American Association for Cancer Research, indicate that in a subset of patients with metastatic melanoma, they can be activated in the tumor microenvironment.

"Our data provide a new concept in melanoma," said Nicolas van Baren, M.D., Ph.D., a clinical and laboratory investigator at the Ludwig Institute for Cancer Research, the de Duve Institute and the Cancer Centre of Cliniques universitaires Saint-Luc in Brussels, Belgium. "Before we began our study, it was thought that immune responses were triggered in specialized structures known as lymph nodes. Lymphocytes, which are an important subset of immune cells, became activated in lymph nodes and then migrated via the blood to the tumor."

Results of his study showed an alternative path whereby naive lymphocytes were activated locally in the tumor microenvironment. "Fundamental knowledge like this is crucial as we seek to understand how tumors escape antitumor immune responses and how we can develop approaches to counter this," he said.

For the majority of immune responses mounted by our bodies, for example in response to invading microbes, the predominant sites of lymphocyte activation are the lymph nodes, spleen and mucosal-associated lymphoid tissues. All these sites are dedicated to supporting

the initiation and maintenance of immune responses. However, in some instances of chronic infection, for example with hepatitis C virus, ectopic lymphoid structures, or lymphoid structures that resemble lymph nodes and develop at aberrant locations, form at the site of the infection and locally support lymphocyte responses directed against the infectious agent.

Ectopic lymphoid structures have also been observed in some malignant tumors, including breast, lung and colorectal tumors, but not melanoma. In some studies, their presence has been linked to improved prognosis.

Van Baren and colleagues observed ectopic lymphoid structures in seven out of 29 skin metastases from patients with melanoma. In contrast, no primary melanoma samples examined contained complete ectopic lymphoid structures. However, some of them hosted small blood vessels that are associated with these structures.

Further analyses indicated that the ectopic lymphoid structures were functional, as features indicative of activation of the B cell lymphocyte subset were observed.

"It is important to have established that immune responses can be generated locally, at least in skin metastases," said van Baren. "In fact, this last point, that we detected functional lymphoid structures in skin metastases and not in primary tumors, is extremely intriguing. We think that understanding the reasons for this difference will be highly informative in determining how antimelanoma immune responses develop during disease progression."

The sample size was too small to allow the researchers to draw clinically meaningful conclusions. "Nonetheless, it will be important to look at this moving forward, as it is not yet clear whether these structures are good for the patient and bad for the tumor or good for the tumor and bad for

the patient. At this point, there is no indication either way, and we could provide a speculative argument for either."

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