A PoEM on breast cancer metastasis

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When breast cancer cells spread through the body, they do so mainly through the lymph system that normally removes excess fluid and waste products from our tissues. Now, scientists from the group of Professor Massimiliano Mazzone (VIB-KU Leuven Center for Cancer Biology) identified a novel subset of immune cells, called Podoplanin-expressing

macrophages (PoEMs), that change the tissues near a tumor in a way that promotes the spreading of cancer cells. Getting rid of these PoEMs in a mouse model strongly reduced the ability of breast cancer cells to move to other parts of the body.

Lymph highways for cancer cells

The lymphatic system drains excessive fluid and removes waste products from our tissues. Lymphatic vessels can also play a role in the spread of breast cancer. Growing tumors often put physical pressure on their environment, which makes these lymphatic vessels leaky and easier accessible for tumor cells.

The cancer cells take advantage of these leaks to move through the body and start growing tumors elsewhere, in a process called metastasis. Previous studies have shown that breast cancer cells prefer to move through the lymph system and that more lymphatic vessels near the tumor correlate with a more dire prognosis for patients.

Therefore, therapies that effectively tackle the development and growth of lymph vessels could reduce metastasis and therefore the death toll from mammary tumors, which remain virtually incurable when not detected in time.

PoEMs that promote metastasis

The development and growth of lymph vessels near tumors is sometimes supported by a certain type of immune cell. In this new study, Pawel Bieniasz-Krzywiec from the Mazzone team identified a subgroup of these cells, called Podoplanin-expressing macrophages (PoEMs).

But what is the importance of the presence of PoEMs in this specific

environment? Prof. Mazzone explains: "PoEMs are characterized by a unique gene signature related to changes in the tumor's environment. Specifically, they are an excellent source of Collagen 1, which constitutes the supporting scaffold for growing lymphatic vessels. PoEMs also digest some parts of this environment. This liberates various growth factors that stimulate the formation of lymph vessels and gives rise to new routes for cancer cells dissemination."

The team further observed that PoEMs loosen up the connections between the cells that form the walls of the lymph vessels, which makes it easier for cancer cells to enter these highways. In mice, preventing PoEMs from 'environmental remodeling' highly decreased lymph node and distant organ metastasis.

Blocking PoEMs to fight cancer

These findings provide supportive evidence to targeting PoEMs in humans. With the help of clinicians and pathologists from KU Leuven and UZ Antwerpen, the researchers further tested their findings in human cancer samples. Pawel Bieniasz-Krzywiec provides more details: "On top of the mice results, human breast cancer sample testing revealed a positive correlation between the presence of PoEMs around tumor lymph vessels and lymph node involvement as well as organ metastasis. These observations pave the road towards the use of PoEM blockers in cancer therapy, specifically targeting the cancer-associated lymphatic vessels, without triggering lymphedema associated with current strategies."

From a broader perspective, the study highlights an emerging concept that properties of immune cells are inherently related to the specific environment they reside in. The study of Prof. Mazzone's team describes for the first time a subset of immune cells specifically associated with tumor lymphatics and promoting their growth.

"Our findings change the way we understand lymph vessel growth near tumors and will surely stimulate new and exciting research in the field," Prof. Mazzone concludes.

More information: Paweł Bieniasz-Krzywiec et al. Podoplanin-Expressing Macrophages Promote Lymphangiogenesis and Lymphoinvasion in Breast Cancer, *Cell Metabolism* (2019). DOI: 10.1016/j.cmet.2019.07.015

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