How do metastatic tumor cells grow in lymph nodes?
7 February 2019

Cancer cells adapt to a challenging lymph node environment through YAP-dependent adjustment to fatty acid oxidation and usage of the plentiful fatty acids as fuel. Highly accumulated bile acids are potential molecular triggers of YAP activation that act mainly through vitamin D receptor (VDR) in metastatic lymph nodes. As a result, the researchers uncovered the genes that regulate fatty acid metabolism are up-regulated in the metastatic tumor cells.

The researchers used animal models with melanoma and breast cancer, which are considered to be most likely to spread first to lymph nodes. With the comparison of cancer cells grown in lymph nodes with those grown in the primary site, the researchers found that the metastatic cancer cells in lymph nodes boost the expression of the genes related to breaking down fatty acids to produce energy in a process known as fatty acid oxidation (FAO).

In the meantime, the cancer cells growing at primary site promote the expression of the genes involved in glucose used as an energy source (the well-known "Warburg" effect). In addition, they also...
found that unlike other organs, lymph nodes are rich in lipids. Dr. Lee says, "These unexpected results gave me strong confidence that lymph node metastatic tumor cells preferentially use fatty acids rather than glucose as a fuel source in the lipid-rich lymph node microenvironment." He confirmed the findings with the almost complete suppression of lymph node metastasis by treating a clinically tested fatty acid oxidation inhibitor to melanoma or breast cancer-bearing mice.

To find out the major stimulator for YAP activation in lymph node metastatic tumors, the researchers looked into biological samples. They found that the abundance of several bile acid species—known to be detected only in the liver and intestinal tract, where they facilitate dietary fat digestion, was strikingly elevated in the lymph node metastatic melanoma.

Dr. Lee says, "It was a very intriguing that bile acids are highly accumulated in the metastatic lymph node, but not in the normal healthy lymph node or primary tumor." The preliminary analyses suggest the lymph node metastatic tumor itself may produce bile acids that can activate YAP and stimulate further growth of the lymph node metastatic tumor. "It requires further extensive verification. Bile acids from blood and lymphatic circulation can be highly accumulated in lymph nodes during metastasis by a certain mechanism," Dr. Koh says.

Cancer cells are smarter than expected in their dissemination in the body. Dr. Koh says, "This study reveals how they adapt to a challenging environment like lymph nodes by switching their energy source to locally abundant molecules such as fatty acids and bile acids to make their way to other organs." Therapies targeting FAO and YAP are currently available or being actively developed. By drawing on the link between FAO /YAP and lymph node metastasis found by this study, doctors may be able to suppress subsequent distant metastasis in patients with melanoma and breast cancers. Dr. Koh adds, "It definitely warrants more extensive investigations in patients with metastatic cancers prior to clinical applications."

The results are published in "Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation" Science (2019). science.sciencemag.org/cgi/doi ... 1126/science.aav0173