Changing cancer's environment to halt its spread

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By studying the roles two proteins, thrombospondin-1 and prosaposin, play in discouraging cancer metastasis, a trans-Atlantic research team has identified a five-amino acid fragment of prosaposin that significantly reduces metastatic spread in mouse models of prostate, breast and lung cancer. The findings suggest that a prosaposin-based drug could potentially block metastasis in a variety of cancers.

The study team, led by Randolph Watnick, PhD, at Boston Children's Hospital, Vivek Mittal, PhD, at Weill Cornell Medical College and Lars Akslen, MD, PhD, at the University of Bergen, released their findings in the May issue of the journal *Cancer Discovery*.

The main cause of cancer mortality is not the primary tumor itself, but rather its spread—metastasis—to other locations in the body and subsequent organ failure. Previous studies by Watnick, a member of Boston Children's Vascular Biology Program, and others have shown that tumors capable of metastasis release proteins that help prepare new homes in distant organs for their metastatic progeny.

Watnick's lab has also previously shown that tumors that cannot metastasize release prosaposin. This protein activates expression of a second protein called thrombospondin-1, a potent anti-angiogenic factor, in tissues where metastatic tumor cells could potentially take root. Thrombospondin-1 makes these otherwise-permissive tissues resistant to metastasis.

"In the past, we've struggled to determine the source of thrombospondin-1 production," Watnick says. "We knew it was coming from the tumor microenvironment, normal cells adjacent to the sites of potential metastasis, but we could not tell if those cells were native to the microenvironment or had been recruited from the bone marrow."

Using mouse models of breast, prostate and lung cancer, Watnick and his colleagues confirmed through bone marrow transplant and gene knockout experiments that both metastatic and non-metastatic tumors induce cells from the bone marrow—specifically, monocytes expressing the Gr1 surface marker—to migrate to the lungs. However, non-metastatic tumors then trigger these monocytes to produce thrombospondin-1 by releasing prosaposin.

"Others have shown that tumors recruit monocytes to future metastatic sites, which help to set up a permissive environment for tumor cells to metastasize, " Watnick notes. "Our results suggest that non-metastatic tumors do the same thing, but instead of creating a permissive environment, the monocytes create a refractory environment by producing thrombospondin-1."

Watnick thinks this finding creates a window of therapeutic opportunity. "If we can trigger monocytes recruited by pro-metastatic tumors to produce thrombospondin-1 like those recruited by non-metastatic tumors, we will be able to hijack the mechanism by which tumors create metastasis-permissive sites to close the door on those sites."

Thrombospondin-1 itself, however, is too large to serve as a drug, and studies using shortened versions of the protein have not been promising. Watnick and his collaborators instead are focusing on prosaposin. To find the smallest part of prosaposin capable of activating thrombospondin-1, the team took an 80-amino acid region of prosaposin and whittled it down bit by bit until they isolated a five amino-acid peptide that could trigger thrombospondin-1 production as strongly as the full-length protein.

When administered in mouse models of metastatic cancer, this peptide significantly reduced metastasis compared to scrambled versions of the peptide (with the same amino acids but in different

sequence), but only in mice with monocytes capable of producing thrombospondin-1.

Strikingly, Watnick and his collaborators also found that prostate cancer patients whose tumors expressed higher levels of prosaposin had significantly greater overall survival than patients whose tumors expressed low levels of prosaposin. Thus, with additional work, Watnick believes the prosaposin peptide could be the foundation for a tumor- and location-agnostic method of treating or preventing metastasis in patients with advanced cancers.

"The size of this peptide makes it ideal for drug development," Watnick says. "It's about as large as tyrosine kinase inhibitors such as Gleevec or Iressa, and could potentially be formulated in multiple ways for different types of cancer. I could also foresee using a therapeutic agent like this peptide as an adjuvant therapy, for example just as we now use chemotherapy or hormonal therapy for breast cancer."

Boston Children's Technology and Innovation Development Office (TIDO) has filed patent applications on these peptides, peptide derivatives and their uses. A start-up company is in the works.

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