T-cadherin affects blood vessel growth in breast cancer, hormone from fat cells may play a role

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Researchers at the Burnham Institute for Medical Research (Burnham) may have found a new option for targeted breast cancer therapy by showing the link between a certain protein and the formation and development of blood vessels that feed breast tumors. Like mortar between bricks in a wall, T-cadherin is a protein that helps cells stick together and collectively form tissues.

Cancer cells that loosen their adhesive tissue bonds stop producing T-cadherin, and in tumors, only the blood vessels that supply oxygen and nutrients express this protein. Now, Barbara Ranscht, Ph.D., and Robert Oshima, Ph.D., at Burnham have led a team that developed the first living model to study this protein's effect on tumor angiogenesis by creating a strain of mice that develops spontaneous mammary gland tumors in the absence of T-cadherin. Their results appeared March 1 in *Cancer Research.*

"Evidence of T-cadherin's role in vascularization has been somewhat controversial," explains Dr. Ranscht, senior author of the study, which includes Drs. Lionel Hebbard and Michèle Garlatti from the Burnham Institute as equally contributing first authors and Drs. Robert Cardiff and Lawrence Young as collaborators from the University of California, Davis. "But our knockout model clearly shows that T-cadherin plays a role in promoting tumor vascularization, with implications for tumor growth and animal survival."

The tumor model developed in Dr. Ranscht's laboratory shows that loss of T-cadherin slows down tumor growth and improves survival compared to controls where T-cadherin is present: The absence of T-cadherin delays tumor growth by an average of 10 days, decreases tumor size, and apoptosis markers, indicators of cell suicide, are six times higher. The tumor-bearing knockouts live an average of 18.5 days longer than their wild-type counterparts, which translates into approximately 18 months of human life span.

The normal models in the study developed solid adenocarcinoma breast tumors, whereas the knockouts formed poorly-differentiated breast tumors with fewer blood vessels. When the adenocarcinoma tumors were transplanted into normal and T-cadherin-deficient mammary glands the knockouts were deficient in growing new blood vessels to the graft.

Stunting blood vessel growth restricts tumors and prolongs survival—a strategy behind anti-angiogenesis cancer drugs like Avastin—so these results were somewhat expected, says Dr. Ranscht. "But what surprised us," she adds, "was that even though our models survived longer, their tumor pathology worsened." Without T-cadherin-mediated vascularization, breast cancer cells consistently metastasized to the lungs, and this did not happen in the control mice where the tumors were highly vascularized.

The reasons for this trend are not clear: loose connections between vascular cells may make it easier for tumor cells to break off and enter the blood stream, or low blood flow and oxygen levels in the tumor environment may cause free radicals to build up, spurring further mutations and malignancy.

Either way, says Dr. Ranscht, "Our work provides a cautionary example that restricting tumor angiogenesis might result in more aggressive disease in the long run. Thus, anti-angiogenic therapies should be

carefully evaluated, because if growth at the primary tumor site slows but at the same time women develop more aggressive, metastatic cancers, then it is imperative to develop and add treatments that prevent this."

This study also showed for the first time in a living model that T-cadherin is essential for binding adiponectin, a hormone produced by fatty tissue that is released in inversely proportional amounts to body fat. Adiponectin has a protective effect against metabolic diseases including diabetes, hypertension, heart disease, and stroke; now for the first time it is linked in a living model with vascular function, a relationship that the Burnham team is still exploring. "While the link between obesity and breast cancer is complex, this study shows that in the mouse, T-cadherin sequesters much of the adiponectin and thus provides a conceptual link between obesity and breast cancer" notes Dr. Oshima.

Source: Burnham Institute