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Serious Infections Can Guard Against Tumor Growth

by Steven Bradt

Serious infections can retard and even halt the growth of tumors in mammals by blocking the formation of blood vessels that nourish those tumors, researchers at the School have found. The finding, reported in the Cutting Edge section of the May 15 issue of the *Journal of Immunology*, offers researchers an important new lead on ways to block angiogenesis, the growth of new small arteries and veins.

“This finding suggests that infected animals could be a source of new, extremely potent inhibitors of angiogenesis, the Holy Grail of modern anti-cancer research,” said lead author **Andrei Thomas-Tikhonenko**, an assistant professor of pathology at the School.

The result also turns on its head decades of dogma among immunologists, who had believed that when the cells of the immune system were mobilized against life-threatening infections, tumors also fell victim to this fortification of the body’s defenses. Now, Thomas-Tikhonenko’s work has shown that during infection tumors don’t grow even in animals with severely weakened immune systems. This indicates that it’s the suppression of angiogenesis, not antigen-battling lymphocytes and macrophages, that holds the key to this long-recognized phenomenon.

“This is a whole new way of looking at how cancer can be inhibited in mammals,” said John Hibbs, professor of internal medicine and chief of the Infectious Disease Division at the University of Utah, who has conducted research on infection-mediated suppression of tumorigenesis. “For a number of years, immunologists have regarded this process as a cytotoxic effect mediated by lymphocytes and activated macrophages. This work shows that infections also inhibit tumors by a surprisingly different mechanism.”

Thomas-Tikhonenko’s research, which has not fingered a specific factor that blocks angiogenesis in infected animals, creates a kind of scientific whodunit. The Penn team is searching for the mystery molecules, pressed into service by infections, that so strongly inhibit the growth of vascular tissues inside the tumors.

“We are very much interested in identification of these ‘culprits’ because we believe that they will be extremely useful therapeutic agents not only for cancer but also for other diseases

where unwanted angiogenesis takes place,” Thomas-Tikhonenko said. Angiogenesis is known to play a role in diabetic retinopathy, a leading cause of blindness, and endometriosis, a major contributor to female infertility.

The first observation that infection interferes with tumor growth was made more than 100 years ago by a New York surgeon, William B. Coley, who noted that streptococcal infection caused regression of soft tissue sarcomas in human patients. Traditionally, this resistance has been explained by stimulation of anti-tumor immunity.

“However, direct proof of this mechanism has never been obtained, and therapies based on it have not materialized,” Thomas-Tikhonenko said. “In our paper, we demonstrate, for the first time, that infection-induced resistance need not involve any of the immune responses that might limit tumor growth.”

Two separate lines of evidence suggested to the Penn researchers that the immune system doesn’t play a crucial role in inhibiting tumors. First, in strains of mice lacking the cells normally found on the front lines of the immune system — T-lymphocytes, macrophages and NK cells — tumor growth was nevertheless suppressed when the protozoan *Toxoplasma gondii* was contracted. Further support came from the earlier observation that the tumor under investigation, the B16 variant of malignant melanoma, produced no antigens recognizable to the mouse’s immune system.

After he had ruled out the immune system as intermediary between infection and tumorigenesis, Thomas-Tikhonenko was tipped off to angiogenesis’ role by co-author and toxoplasmosis expert **Christopher Hunter**, associate professor of parasitology at the School. Hunter suggested that the same mouse proteins designed to guard the host against *Toxoplasma gondii* might also inhibit growth of blood vessels. This suggestion proved correct: in a pilot experiment, the injection of powerful angiogenic compounds into mice with toxoplasmosis failed to induce growth of new blood vessels under the skin, a phenomenon that has important implications for cancer.

The tiniest of tumors don’t require their own blood vessels, relying on simple diffusion of oxygen and nutrients from nearby cells. But by the time they’ve grown to two or three millimeters in size, tumors need the nourishment provided by blood vessels in order to survive.

The laboratories of Thomas-Tikhonenko and William Lee at Penn’s School of Medicine found that at this stage, where angiogenesis becomes crucial, melanomas developing in infected mice experience severe lack of oxygen but are unable to recruit new endothelial cells to produce blood vessels.

Thomas-Tikhonenko’s findings suggest that *Toxoplasma gondii*-infected animals could be used to purify molecules that halt the sustenance of tumors. Although several anti-angiogenic compounds have been recently identified, their efficacies are yet to be proven in clinical trials and none of them has been approved by the Food and Drug Administration for the treatment of cancer patients.

The drive to pinpoint the exact chemical factor that prompts infections to block angiogenesis will likely take months, possibly years. “It might be a combination of well-known molecules such as interferons or an entirely new compound,” Hunter said.

Thomas-Tikhonenko and Hunter’s co-authors on the *Journal of Immunology* paper are **Duonan Yu**, **Cam Ngo**, **Cinzia Sevigiani**, **Michael Goldschmidt** and **Sidney Evans** of Penn’s School of Veterinary Medicine; Michael Gee and William Lee of Penn’s School of Medicine; and Tatyana Golovkina of the Jackson Laboratory in Bar Harbor, Me. Their work was funded by the National Institute of Allergy and Infectious Diseases, the National Cancer Institute and the University of Pennsylvania Cancer Center Pilot Projects Program.

New Faculty Member

Dr. Ilana Reisner has been appointed assistant professor of behavioral medicine and director of VHUP’s behavior clinic. Dr. Reisner came to Penn from Cornell University’s College of Veterinary Medicine where she was a visiting fellow. She received her D.V.M. degree from the Veterinary College at Oregon State University and then went to Cornell for a Ph.D. in behavioral physiology with an interest in canine aggression. During part of her residency in behavioral medicine at Cornell, Dr. Reisner was a Morris Animal Foundation Fellow. Dr. Reisner became a diplomate of the American College of Veterinary Behaviorists in 1995.