Cancer researchers at the University of Pennsylvania discover what makes lymphomas tick

August 29 2007

University of Pennsylvania researchers and their colleagues at the Wistar Institute and University of Oxford have discovered the molecular process by which the PAX5 protein, necessary for lymphocyte development, promotes the growth of common lymphomas, thereby unveiling a potential new target in the fight against cancer.

Researchers found that PAX5 stimulates the growth of cancerous tumors by spurring cell division normally observed during B cell immune response. In a sense, PAX5 “hijacks” the body’s own defense system designed to multiply antibody-making B cells exposed to foreign antigens.

In lymphomas, rather than facilitate an appropriate immune response, PAX5 locks the B cell division switch in the “on” position, regardless of exposure to antigens. This is because PAX5 increases production of several key molecules comprising B cell receptor, which drives B cell expansion. Over-expression of PAX5 in mouse B cell lymphoma cell lines increased tumor growth when these cells were transplanted into mice. Conversely, dampening the expression of PAX5 decreased cancerous growth.

These latest findings on the role of PAX5 are published in the September issue of *The Journal of Clinical Investigation*.

Andrei Thomas-Tikhonenko, an associate professor in the Department of Pathobiology in the School of Veterinary Medicine at Penn, has studied the PAX5 gene for five years, demonstrating that PAX5 shapes the phenotype of bone marrow-derived tumors, a study published in 2003 in the journal Blood.

“We have long believed that PAX5 was involved in B-lymphomagenesis, based on the discovery of PAX-5-specific translocations and somatic hypermutations in diffuse large B cell and other non-Hodgkin lymphomas,” Thomas-Tikhonenko said. “Yet at the molecular and cellular levels, the contribution of PAX5 to neoplastic growth remained undeciphered.”

The study used two B cell lymphoma cell lines from the 2003 Blood paper, Myc5-M5 and Myc5-M12, that spontaneously silence PAX5 and then form slow-growing tumors. Diana Cozma, the first author on the study, reconstituted these cells with the engineered version of PAX5, which required the synthetic estrogen tamoxifen for activity. In her key experiment, tumors grew briskly when mice were treated with tamoxifen but stagnated if tamoxifen were withheld; however, the reason for that became apparent only after large-scale gene-profiling studies.

“It appears that PAX5, which regulates gene expression, instructs B cells to make enough of the components of B cell receptors to spur tumor growth even in the absence of foreign antigens, which normally initiate the immune response,” Thomas-Tikhonenko said.

Studies on human clinical samples corroborated this conclusion. Approximately half of lymphoma samples from the University of Oxford’s John Radcliffe Hospital tumor bank exhibited evidence of abnormal B cell receptor activation.

Source: University of Pennsylvania