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Crucial factors in lymphoma development and survival discovered

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Experiments with new mouse model suggest therapeutic targets
Researchers at National Jewish Medical and Research Center have discovered an important factor in the development of B-cell lymphomas, one of the fastest growing forms of cancer. The B-cell receptor on the surface of B cells can cooperate with the MYC oncogene to accelerate the development of lymphomas. The research team, led by Yosef Refaeli, PhD, Assistant Professor of Pediatrics at National Jewish Medical and Research Center , also showed that disruption of signals from the B-cell receptor can inhibit growth of the tumors. The research is being published in the June 24 issue of the journal, *PLos Biology*.

"Non-hodgkins lymphomas, about 90 percent of which are B-cell lymphomas, have become 85 percent more prevalent in the past 20 years, the only major form of cancer to experience such growth" said Dr. Refaeli. "Our findings have pointed to the B-cell receptor and its signaling pathways as very promising therapeutic targets for B-cell lymphomas."

Non-Hodgkins lymphoma is a cancer of lymphocytes, immune system cells known as T cells and B cells. About 66,000 new cases of non-Hodgkins lymphoma are diagnosed each year in the United States , and about 19,000 people die of it.

It has long been known that the oncogene MYC plays a crucial role in the development of lymphomas. One unanswered question, however, is whether the B-cell receptor on the surface of B cells, may also play an

important role.

When the B-cell receptor binds to molecules on foreign invaders, known as antigens, it sends a signal that causes the B cells to proliferate and produce antibodies. The antibodies bind to the foreign molecules and mark the invaders for destruction. Even if it doesn't bind to an antigen, the B-cell receptor promotes the survival of B cells through an unknown intracellular signal.

Dr. Refaeli and his colleagues at National Jewish and the University of California , San Fransisco developed a series of transgenic mice to evaluate the role of the B-cell receptor in B-cell lymphomas. They found that the presence of a functional B-cell receptor increased the development of tumors in mice with a translocated MYC oncogene.

In a series of experiments, Dr. Refaeli demonstrated that the B-cell receptor cooperated with MYC in the development of tumors both in the presence of an antigen and when no antigen was present. When no antigen was present, the mice developed a lymphoma similar to human B-cell lymphocytic leukemia.

When there was an antigen to bind to the B-cell receptor, the mice developed a lymphoma that closely resembled Burkitt's lymphoma, even to the surprising development of primary tumors in one side of the jaw. The researchers actually used an autoantigen, a molecule produced by the mouse itself, in a situation resembling autoimmune disease. Autoimmune disease increases by 50 to 200 times the chance that a person will develop B-cell lymphoma.

In experiments that both confirmed the crucial role of the B-cell receptor and pointed to potential therapies, Dr. Refaeli and his colleagues also were able to prevent and eliminate tumors by treating the mice with immunosuppressants, which block signals from the B-cell

receptor. Several trials of various immunosuppressants and another inhibitor of B-cell receptor signaling have recently begun.

"Research into B-cell lymphomas has been hampered by the lack of a good mouse model," said Dr. Refaeli. "The mouse we created gives us a very good, predictive model of B-cell lymphomas, which can be used to explore not only these and related cancers, but also autoimmune disease and basic immunology."

Source: National Jewish Medical and Research Center