Experimental drug lets B cells live and lymphoma cells die

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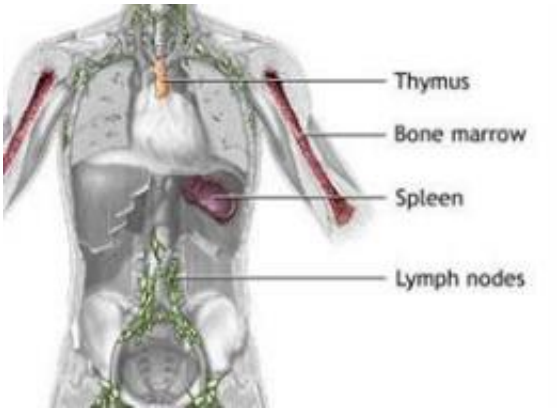

Organs in which White Blood Cells (Lymphocytes) Can Become Cancerous

(PhysOrg.com) -- An investigative drug deprived non-Hodgkin lymphoma cells of their ability to survive too long and multiply too fast, according to an early study published recently in the journal *Experimental Hematology*.

To function normally, the cells that make up bodily tissues must "decide" when to divide and multiply (proliferate) and when to die. Cell death restricts the human cell population as a counterbalance to growth, and billions of cells must die each year just to hold the number constant. Cell growth and death are carefully regulated by signaling networks, which either encourage or discourage survival. When this counterpoise mistakenly shifts too far in favor of growth, tumors result.

One such network revolves around neurotropins, which "tell" nerve cells not to die, and to keep multiplying, as part of normal function. The same neurotrophic signals are known to cause cancers of the central nervous system when unbalanced by carcinogens. The current study found that neurotrophins also cause key immune cells to resist cell death and proliferate as part of the most deadly of lymphomas, and that an experimental compound, the fungal chemical called K252a, restored their ability to die.

Non-Hodgkin Lymphoma (NHL) is the umbrella for more than 30 cancer types that develop in an important type of white blood cell, the lymphocyte. Lymphocytes include B cells, workhorses of the immune system that attach to invaders (e.g. bacteria, viruses) and produce an army of antibodies designed to attack the specific pathogen at hand. In NHL, B cells in the lymphatic system grow abnormally, and most patients are diagnosed too late to benefit from conventional chemotherapy.

"New approaches to the treatment of non-Hodgkin Lymphoma are urgently needed, and the results of this study outline one with unusual promise," said Sanjay Maggirwar, Ph.D., associate professor in the Department of Microbiology & Immunology at the University of Rochester Medical Center, and corresponding author of the study. "We believe we have found a subtle, precise mechanism that shortens the lifespan of many kinds of cancer cells while enabling normal B cells to live on."

Survivor: Cell Edition

Cell death (apoptosis) is controlled by an intricate network of signals, including toxins, hormones and growth factors like the neurotrophins, which have their effect by interacting with specifically shaped proteins called Trk receptors on cell surfaces. When they dock into their

receptors, like ships coming into port, neurotrophins changes the shape of the dock such that chain reactions pass on messages inside the cell. The current study supports the theory that cancerous B lymphocytes secrete neurotrophins that interact with Trk receptors on their surfaces. The results offer the first proof that a self-regulating (autocrine) neurotrophic mechanism drives abnormal survival and proliferation in the most aggressive NHL cell lines.

Among the signaling pathways triggered when a neurotrophin binds to its Trk receptor is that for the nuclear factor kappa B (NFkappaB) protein complex, which turns on genes that vary with the cell type. In cancerous B cells, NFkappaB signaling codes for the building of interleukin 6, a signaling molecule established in past studies to extend the lifespan of B cells.

The intuitive next step would be to block NFkappaB signaling, and more than 900 compounds have been found that do so. None has prevailed in the clinic, however, because this signaling pathway is essential to the function of healthy human cells as well as tumor growth. A successful drug would have to block part of the NFkappaB pathway, but leave other aspects intact. A currently available NFkappaB blocker, Velcade, has achieved some success as chemotherapy because its interference with the pathway is indirect and mild.

The excitement surrounding the study drug, K252a, comes from its evidence that its impact on NFkappaB signaling is also precisely targeted, mild and easily reversed. In cell culture studies, Maggirwar's results suggest that K252a causes one part of the NFkappaB complex, a protein called RelA, to cluster within structures called nucleoli. Once there, RelA can no longer interact with the gene-containing chromosomes that it would otherwise influence (e.g. the one for interleukin 6).

The beauty of the study drug's proposed "RelA redistribution" mechanism would be that it allows other parts of the NFkappaB complex, like RelA relative CRel, to continue signaling. RelA and CRel work interchangeably in many pathways, but only RelA drives the expression of the gene that codes for IL6, encouraging B cell longevity. In experiments, exposure to K252a caused five times as many activated B cells, which closely resemble cancerous B cells, to undergo cell death than normal, resting B cells. Furthermore, experiments revealed that K252a keeps lymphoma-like cells from dividing and multiplying.

To extend their findings to other cancer types, the team then analyzed expression of Trk and neurotrophins in cell lines derived from breast cancer, Burkitt's lymphoma and multiple myeloma, as well as the effect of K252a on them. They found the same autocrine neutrophin signaling cascade to exist in these other cancer cells, which again encouraged abnormal survival, and which K252a countered.

In the next step, the team will test the effect of K252a in live mice with NHL in partnership with oncologists within the James P. Wilmot Cancer Center at the Medical Center, who in September 2008 won a SPORE grant from the National Cancer Institute to support the expansion of lymphoma research and clinical trials.

Along with Maggirwar, the study was led by Lynn Sniderhan, Ph.D., Tatiana Garcia-Bates, Ph.D., Michael Burgart and Richard Phipps, Ph.D., in the Department of Microbiology & Immunology, and by Steven Bernstein, M.D., co-director of Wilmot's Lymphoma Biology Program. The work was supported by the grants from the National Institutes of Health.

"The current study results provide strong evidence for the existence of vicious cycle in Non-Hodgkin Lymphoma, a loop where B cells keep secrete too many neutrophins, which interact with too many Trk

receptors on their surfaces, which drive abnormal survival of these cells," Maggirwar said. "We believe the study drug broke this deadly loop in lymphoma cells."

Source: University of Rochester Medical Center (news : web)