January 2006

Inside this issue...

New Research

ADHD Genetic Risk Factor

DNA Break-ing News

Missing Molecule Stops Signals

New Role for MyD-88

Defect Found in Lupus-like Syndrome

Breaking News

PMH Drug Development Research Program Gets Boost

Research Intranet V2.0 Launched

Visit us at...
uhnresearch.ca

New Research Breakthroughs at UHN

Genetic Risk Factor Gets Attention in ADHD

Dr. Cathy Barr was part of a team including postdoctoral fellow Dr. Nancy Laurin, that identified calcyon—a gene that encodes for a brain-specific protein—as a risk factor for attention deficit/hyperactivity disorder (ADHD).

Although its causes are unknown, ADHD is characterized by difficulties with concentration, hyperactivity and impulsivity. The researchers investigated whether the calcyon gene was significantly associated with ADHD by looking at its genetic inheritance in 215 nuclear families with 260 affected children. They found that certain variants of the calcyon gene were more likely to be transmitted to ADHD-affected children, relating this gene to the disorder.

"Our findings are exciting because calcyon may be involved with multiple signaling pathways in the brain and our results could lead to a better understanding of the causes of ADHD," explains Dr. Barr.

Mol Psychiatry. 2005 Dec;10(12):1117-25. [PubMed abstract]
Funded by the Canadian Institutes of Health Research and The Hospital for Sick Children Psychiatric Endowment Fund.

Breaking News at DNA Break Sites

UHN researchers Drs. Robert Bristow and Lothar Lilge, in collaboration with researchers in Toronto, US and the UK, recently found evidence that damaged DNA in a cell binds a specific form of the tumour suppressor protein p53—a molecule essential to the cell's ability to sense and repair damaged DNA.

Using novel microscopy methods developed within UHN, the team recorded where p53 was found in the cell following different types of DNA damage. They discovered that only a phosphorylated form of p53 (modified by the addition of phosphate groups) interacted with DNA repair proteins and accumulated at sites of DNA damage.

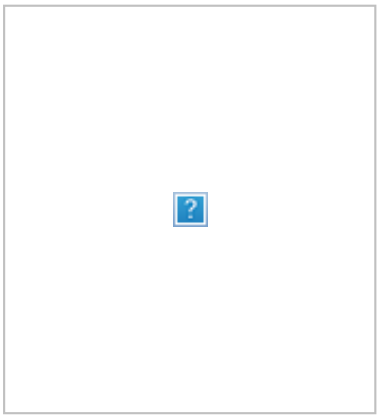
Mutation and altered phosphorylation of p53 proteins are common in cancer cells and can reduce the response to cancer therapy. "Determining what specific forms of p53 direct DNA repair opens up new possibilities for cancer therapies that work by targeting the cancer cell's response to DNA damage," says Dr. Bristow.

Cancer Res. 2005 Dec 1;65(23):10810-21. [PubMed abstract]

Research supported by the Canada Foundation of Innovation, the Princess Margaret Hospital Foundation, the National Cancer Institute of Canada, Canadian Institutes of Health Research, U.S. Department of Energy and Cancer Research UK.

Missing Molecule Stops Signals in Their Tracks

Drs. Gregory Downey and Patrick Shannon led a team that discovered that the Meg2 protein has a crucial role in the early development of mice and the activation of white blood cells in adult mice. Meg2 is an enzyme that helps cells develop properly and communicate with each other by regulation secretion.



By transplanting embryonic liver stem cells lacking Meg2 into a strain of mice, the researchers discovered that Meg2 is important to the correct functioning of lymphocytes and platelets. Lymphocytes that lacked Meg2 could not properly respond to the immune system's activation signals.

"These findings could help to understand diseases related to defects in the activation of white blood cells during innate and inflammatory responses," says Dr. Downey. "Further research into Meg2's role in cell signaling could lead to treatments for inflammatory diseases."

J Exp Med. 2005 Dec 5;202(11):1587-97. [PubMed abstract]
Funded by the Canadian Institutes of Health Research, the Ontario Thoracic Society and the National Institutes of Health.

New Role for MyD-88 in Inflammatory Response

A team led by Drs. Peter Liu, Mansoor Husain and Wen-Chen Yeh has discovered that myeloid differentiation factor-88 (MyD-88), a protein critical to the innate immune response to pathogens, appears to have a novel function mediating the host inflammatory response to viral infection.

Viral myocarditis is a leading cause of heart congestion and failure, stemming from the inflammation of the heart's muscular walls.

Using MyD-88 deficient mice as models, the researchers examined the impact of MyD-88 on the host response to coxsackievirus B3 infection, which causes a heart disease similar to myocarditis. Surprisingly, MyD-88 deficient mice had dramatically improved survival, excellent heart function and higher intrinsic interferon levels. Thus, MyD-88 may be the critical switch responsible for heart inflammation after injury.

"The results support the emerging idea that the acquired immune system may be in part regulated by elements of the innate immune system, like MyD-88," says Dr. Liu. "Our findings also suggest that the MyD-88 pathway could be a new target for therapeutic interventions for infections like myocarditis."

Circulation. 2005 Oct 11;112(15):2276-85. [PubMed Abstract]
Research support provided by the Canadian Institutes of Health Research, the Heart and Stroke Foundation, and partnership programs of CHFNET, TACTICS and CHF-CORE.

Cell Death-Defying Defect Found in Lupus-like Syndrome

UHN researcher Dr. Joan Wither and her team recently discovered that a strain of mice used to model the autoimmune disease systemic lupus erythematosus (lupus) have a cell signaling defect that may lie at the cause of the disease.

The immune system normally has checkpoints to ensure that its antibodies do not recognize (and destroy) its own cells. In autoimmune diseases such as lupus, however, the immune system targets and attacks its own tissues —with devastating consequences.

New Zealand Black mice, a common research model for lupus, spontaneously develop a lupus-like syndrome.

“In the New Zealand Black strain, we discovered that a defect in signaling programmed cell death increases the levels of factors that help self-targeting immune cells survive instead of being deleted,” says Dr. Wither. “Our research could help determine whether similar cell signaling defects play a role in lupus susceptibility in humans.”

J Immunol. 2005 Dec 1; 175(11): 7363-71. [PubMed abstract]
Funded by the Canadian Institutes of Health Research and the Arthritis Society of Canada.

Breaking News from UHN Research

Flagship PMH Drug Development Research Program Gets Boost

Congratulations to Drs. Amit Oza, Malcolm Moore and Lillian Siu on the successful renewal of the Phase II Drug Development program. This program was one of nine successful applications across North America—and the only Canadian network—chosen by the US National Cancer Institute to develop new anti-cancer agents.

Research Intranet V2.0 Launched

With new features such as Webmail, a community calendar, a search engine and an integrated message board, the new Research Intranet launched in late 2005 and has proven a hit with the UHN Research community.

The improved Research Intranet was the result of extensive feedback from Research Intranet users and outstanding effort from the Research Intranet Development team.
