October 2008

Immunity: Mechanics Behind Signal Control

Immunity: a

The benefits of calcium for bones are well-known; however, calcium also plays a very important role in other biological processes important to survival—regulating cell death, fertilization and the human immune response—and for the first time, an OCI team is providing protein evidence to better understand the mechanics behind a specific kind of calcium regulation in some immune diseases.

"Understanding the structure of proteins and how proteins are affected by changes to their structures is very important in learning how basic biological processes happen," comments Dr. Mitsu Ikura, study lead.

By using a variety of structural and molecular biology strategies, Dr. Ikura and his team are now able to draw out, section by section, the mechanics required by the protein STIM1 to detect calcium levels. The structure determined by Peter Stathopulos, an OCI Knudson fellow in Dr. Ikura's lab, has led to the discovery of the previously unidentified 'EF-hand' domain which, in combination with the SAM domain, is how calcium is detected and responded to accordingly.

Explains Dr. Ikura, "When blood cells are stimulated, STIM1 responds by letting calcium in. We now know this gate is opened only when the EF-hand and SAM domains let the "hand shake" go. Mutations in this machinery found in some diseases lead to dysfunctional immune cell activity. With continued research we can work towards finding targets for treatment right at the root of the problem."

The discovery was made possible by an award from CFI and the Ontario government which purchased a state-of-the-art 800-MHz NMR installed in Dr. Ikura's lab in 2005. "The high resolution of this instrument was critical for revealing how these structures interact," notes Dr. Ikura.

Cell, Vol 135, 110-122, 03 October 2008. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research and Canada Foundation for Innovation, Ontario Innovation Trust and Ontario Ministry of Economic Development & Trade. Dr. Stathopoulos is supported by the OCI Knudson Fellowship.*

Thyroid Cancer: The Importance of Anchoring the Cell

Ministry Awards UHN Researchers

The Ministry of Research and Innovation's Ontario Research Fund has awarded UHN researchers Drs. Tak Mak, Elise Stanley, Rudiger von Harsdorf, Lakshmi Kotra, James Pan and Gang Zheng a total of $1.4M in the most recent round of funding competition.

Dr. Mak will receive funding to develop targeted therapies for breast cancer; Dr. Stanley has been awarded support for neuroscience research laying the groundwork for more effective psychiatric treatments; Dr. von Harsdorf will use the provincial funding to develop non-invasive treatment for heart failure; and the group award to Drs. Kotra, Pan and Zheng will enhance efforts to design new drugs for infectious diseases.

$2M Boost to Krembil Hepatitis Program

UHN congratulates a multidisciplinary team of investigators led by Dr. Jenny Heathcote for recently being awarded $2M NIH funding towards the creation of a Clinical Centre for Chronic Hepatitis B at TWH.

The only clinical centre in Canada to be funded from this NIH RFA, the new centre will support a clinical therapeutic trial examining dual antiviral therapy and the creation of a database that will be used to connect a network of up to 10 hepatitis B centres, the others all being in the USA.

Renewed Chair for UHN Researcher

UHN congratulates OCI's Dr. Pamela Ohashi on the recent renewal of her Tier I Canada Research Chair. Dr. Ohashi's Chair in Autoimmunity and Tumor Immunity, will receive $1.4M to support her research program over the next 7

Recent findings out of OCI add to our understanding of how thyroid cancer cells grow and migrate, causing metastases.

When lead investigator Dr. Shereen Ezzat and colleagues Dr. Sylvia Asa and graduate students genetically removed fibronectin (FN)—a protein responsible for preventing cells from migrating uncontrollably—from a mouse model of thyroid cancer, tumor growth significantly increased and larger, more numerous lung metastases developed.

"Turning off FN, effectively shut off the process involved in anchoring cells. This clearly created an environment conducive to dangerous cancer growth. Our next studies looked at how this was happening, not just where," explains Dr. Ezzat.

Cells lacking FN were shown to have elevated levels of the protein MAGE A3—a molecule responsible for promoting invasive cancer cell growth. MAGE A3 promotes growth of cancer cells by shutting down protective proteins like p21 and enhacing cell motility.

In collaboration with the newly developed STTARR Innovation Centre at UHN, Dr. Ezzat and colleagues were also able to track the development of cancer metastases in this mouse model.

"FN proteins target MAGE A3 proteins to prevent them from working and effectively keep cell growth in check," says Dr. Ezzat. "When this balance is disrupted, cancer progress is promoted. This points to the potential of MAGE-A3 as a diagnostic and even immunotherapeutic target in cancer treatment."

Cancer Res.2008 Oct 1;68(19):8104-12. [Pubmed abstract]. *Research support provided by the Canadian Institutes of Health Research, the Toronto Medical Laboratories, and the Rita Banach Thyroid Cancer Research Fund.*

Imaging: Focusing on Alleviating Pain

TGRI researchers have discovered a safe alternative treatment option to decrease pain associated with bone metastasis and increase the quality of life in these patients.

"For the first time we've been able to show that using a sophisticated type of ultrasound—called MR imaging-guided focused ultrasound—holds tremendous potential for almost complete pain relief associated with bone metastases," says lead author Dr. David Gianfelice.

With colleagues Drs. Walter Kucharczyk, Mark Clemons, Patrice Bret and colleagues, a total of 11 patients received the new treatment in a non-invasive outpatient procedure. All patients reported progressive decrease in pain in treated areas and reduction in pain medication use up to 3 months following the study.

"Using this non-invasive technique, forty-five percent of patients saw increased bone density at the site of treatment including hip bones, shoulder blade and collar bone," notes Dr. Gianfelice. "This is an incredible result and we look forward to expanding the study to show the effects in a larger population."

Radiology. 2008 Oct;249(1):355-63. Epub 2008 Aug 11. [Pubmed

years.

Dr. Ohashi will also receive in excess of $400,000 in infrastructure from the Canada Foundation for Innovation (CFI) to continue investigations into the molecular mechanisms regulating T-cell tolerance in function.

OCI Welcomes Dr. Hal Berman

The Ontario Cancer Institute (OCI) is pleased to welcome Dr. Hal Berman as a new investigator in the Campbell Family for Breast Cancer Research.

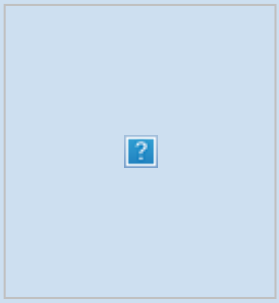
Following his residency and postdoctoral training at the University of California, San Francisco, Dr. Berman came to Canada in the summer of 2007 as a clinical fellow in Breast Pathology at the Toronto General Hospital. Following the completion of his fellowship, Dr. Berman has started his own lab on the 9th floor of 610 University to study early events in breast carcinogenesis.

Dr. Berman will be studying breast cancer with 80% protected time for research. "It's a wonderful opportunity for someone like me with dual training," he noted. "The goal is to take the information and make it meaningful - it's an exciting time. To do so, we need to continue to learn to work together as the challenges of tomorrow require teamwork and communication."

abstract].

Regenerative Medicine: 'Current' Findings in Neuronal Stem Cell Migration

'Current' findings out of Krembil showcase the potential benefits of marrying direct-current electrical fields with neuronal stem cells to promote neuronal regeneration—or rebuilding the lines of information transmission in the brain—after stroke or brain injury.



With colleagues from China and the US, UHN study lead Dr. Qi Wan has provided the first evidence that electrical fields guide and control the direction of stem cells migrating in the brain through a specific pathway.

Says Dr. Wan, "Understanding how endogenous stem cells are controlled is incredibly important in developing regenerative strategies for the treatment of diseases like stroke."

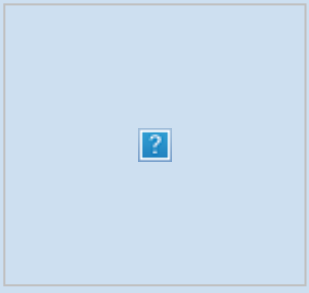
Applying these fields to a rat model, they found that stem cell migration is mediated through a pathway of protein interaction involving cell migration (the NMDA receptor/Rac1/actin cytoskeleton signal transduction pathway).

"Electricity activates the NMDR receptor and prepares the cell for move and new building," notes Dr. Wan. "These results suggest that controlled stimulation of electrical fields may be safe for clinical application and serve as a practical therapeutic strategy for brain repair by directing stem cells to injured regions to replace cell loss."

Stem Cells Vol. 26 No. 8 August 2008, pp. 2193 -2200. [Pubmed abstract]

Neurology: A First in Determining Injury Mechanics

Intracerebral hemorrhage (ICH) is a common and devastating form of stroke, but there are no drug treatments. Progress in understanding this injury has focused almost entirely on grey matter damage (nerve cells), with little understanding of white matter injury or the result of delayed inflammation. Worse yet, experimental studies have used young animals, despite this stroke normally affecting older people.



A UHN study provides a plausible explanation for the poorer functional recovery of the elderly after ICH, despite a similar loss of grey matter in young and aged animals. "To our knowledge, we're the first team to map injury progression after ICH over time and space; and to show that white matter injury is worse in the aged," comments study lead Dr. Lyanne Schlichter, who conducted the study with graduate student, Jason Wasserman.

Using a rat model of ICH, the team has discovered that in and around the bleeding zone (the core), nerve cells lose their insulating layer and die. Surprisingly, the axons of nerve cells were progressively damaged far outside this region, and this damage was worse in the old animals. The results also show that delayed inflammation might kill nerve cells in the

core, but is unlikely to cause the axon damage further away.

Says Dr. Schlichter: "This is important because it shows that older rats have a more difficult time recovering from brain hemorrhage than their younger counterparts, despite experiencing a similar injury. More importantly, we've provided hard evidence that there is a large window of opportunity (upwards of 3 days) for therapy, and that we need to focus on strategies to reduce white matter injury after ICH."

Experimental Neurology. [Pubmed abstract]. *Research supported by the Heart & Stroke Foundation, Ontario Chapter.*