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New Research Breakthroughs at UHN

Heart Failure: Unraveling the Role of Statins

Researchers at TGRI recently revealed a mechanism of action for the popular cardiac drug family statins.

Statins are commonly prescribed to treat overproduction of cholesterol in cardiovascular patients. Findings from a UHN study of heart cells, led by Dr. Rudiger von Harsdorf, show that lovastatin—a type of statin—uses the molecule FoxO3a as a signal to activate the protein p21. The p21 protein is responsible for hindering cell growth and division, preventing overgrowth of heart tissue leading to heart failure.

“Heart failure is characterized by pathological overgrowth of the heart muscle. Statins have been shown to prevent this; however, up to now, the cellular pathway for this event was unclear,” says Dr. von Harsdorf. “We have now identified the cell cycle suppressor p21 as the target molecule for the growth-inhibitory effect of statins in the heart. This may lead to novel therapies aiming at the stability of p21 in heart failure patients.”

Circ Res. 2007 Jan 5;100(1):50-60. Epub 2006 Dec 7. [Pubmed abstract]. *Research was supported by the Deutsche Forschungsgemeinschaft.*

Brain Trauma and Stroke: Channel Has Potential Therapeutic Benefits

A new finding from UHN may offer novel treatment strategies for stroke by “turning off” harmful immune reactions in the brain.

The brain harbours immune cells called microglia which normally function to dispose of harmful products. In brain trauma, stroke and other disorders, overactive microglia can contribute to the death of neurons leading to lasting neurological problems.

A team led by Krembil’s Dr. Lyanne Schlichter recently showed that the microglial KCa3.1 channel is involved in their overactivation. When this channel was inhibited by specific chemicals, microglia-induced neuroinflammation and cell death were reduced.

“We have been the first to show that this channel contributes to microglia neurotoxicity,” says Dr. Schlichter. “Our research reveals that it could be used as a potential therapeutic target for the treatment of brain trauma, stroke and other inflammatory diseases involving the immune system.”

J. Neurosci. 2007 Jan 3;27(1):234-44. [Pubmed abstract] *Research was*

supported by Canadian Institutes of Health Research and Heart and Stroke Foundation.

Neurological Diseases: Determining the Function of RalA and RalB Proteins

A Krembil research team has made an important discovery about the mechanisms of cell communication in the brain by determining the function of two proteins involved in this key process.

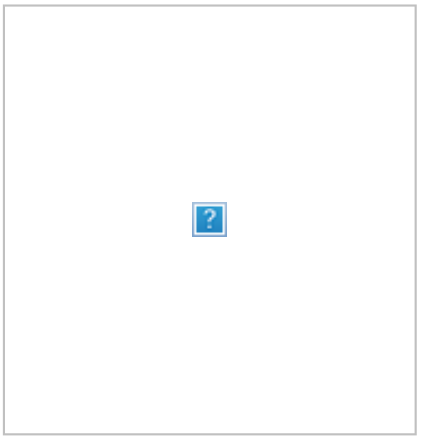
Cells communicate when molecules called transmitters are released from one cell, a process called exocytosis, and sent out to another cell. Normally exocytosis can occur through an energy molecule such as GTP or calcium.

To determine how RalA and RalB proteins were involved in GTP-dependent and calcium-dependent pathways, Dr. Shuzo Sugita and colleagues knocked down RalA and RalB in a cell model. They determined that both RalA and RalB work as GTP sensors in the GTP-dependent exocytosis process.

“Malfunctions in neuronal communication are the basis of many neurological and psychiatric diseases and aging,” says Dr. Sugita. “Our findings demonstrate that RalA and RalB are the long-sought sensors in this process. Our future work will be to determine what function they play in physiology.”

J. Neurosci. 2007 Jan 3;27(1):190-202. [Pubmed abstract] *Research was supported by the Canada Research Chair program, Natural Sciences and Engineering Research Council of Canada, and Canadian Institutes of Health Research.*

Cancer: Putting the Brakes on Tumour Growth



The relaxin hormone receptor may play a role in the impairment of prostate tumour growth, according to an OCI study conducted by researcher Dr. Jeffrey Medin and colleagues.

Receptors receive and process signals from outside the cell. This study focused on altering the portion of the relaxin molecule thought to bind to its receptor called the binding domain. The authors found that this altered relaxin molecule demonstrated antagonistic properties against the normal hormone, thus blocking prostate tumour growth in mice.

“Our study suggests that changes to the relaxin molecule are sufficient to interfere with the growth of tumour cells.” says Dr. Medin. “This opens the door to the development of other agents or modified molecules that may block this signaling pathway by other mechanisms and thereby offer treatment possibilities for prostate and potentially other cancers.”

FASEB J. 2006 Dec 28; [Epub ahead of print]. [Pubmed abstract]

Breaking News from UHN Research

SORL1 Gene Plays a Role in Late-Onset Alzheimer's Disease

An international study co-led by Krembil and Centre for Research in Neurodegenerative Diseases director Dr. Peter St George-Hyslop has found a new gene that is implicated in the etiology of late-onset Alzheimer's disease.

Read the UT Media release and Pubmed abstract

Major UHN Study Implicates Tissue Density in Breast Cancer Risk

Ontario Cancer Institute and The Campbell Family Institute for Breast Cancer Research scientist Dr. Norman Boyd has led a national study that has identified breast tissue density as a major risk factor for breast cancer.

For more information, see the UHN press release.

Potential New Mechanism for Preventing Cardiovascular Disease

Researchers at TGRI and The Albert Einstein College of Medicine in New York have found that the brain controls liver fat production, revealing new ways to lower fat levels in those who are overweight, prediabetic and diabetic and who are predisposed to developing cardiovascular disease.

For more information, see the UHN press release.
