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# Helping Damaged Heart Cells to Heal

*Researchers sought to clarify how and what types of cells can be mobilized to aid the heart in repairing itself after a heart attack. What they found surprised them…*

(Monday, February 6, 2006, Toronto) – The role of a major naturally-occurring protein which can promote healing after heart attacks has been discovered by researchers at Toronto General Hospital, University Health Network.

In a ground-breaking paper entitled, "Stem cell factor receptor induces progenitor and natural killer cell-mediated cardiac survival and repair after myocardial infarction," and published today in the prestigious Washington-based **Proceedings of the National Academy of Sciences** (PNAS), the researchers uncovered how stem and other immune cells can be activated to quickly move to the site of injury in the heart to help in cell repair. PNAS is one of the world's most-cited multidisciplinary scientific journals.

"This study gives us hope that one day we may be able to stop the damaged heart muscle from dying, and will be able to promote healing soon after any damage to prevent heart failure", says Dr. Peter Liu. He added that "after a heart attack damaged heart muscle cells cannot regenerate, resulting in the heart having to struggle to pump blood throughout the body". Additionally, heart tissue damage can lead to congestive heart failure. Despite advances in surgical procedures and drug therapy, more than half of patients with congestive heart failure die within five years of diagnosis. Dr. Liu is a cardiologist and scientist at the Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, the Heart and Stroke/Polo Chair, and Professor of Medicine and Physiology at the University of Toronto. He is also the Director of the Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research. The research was performed in the laboratories of Dr. Liu at the Toronto General Research Institute and Dr. Jeffrey Medin at the Ontario Cancer Institute, Princess Margaret Hospital.

"Given the estimated over 70,000 heart attacks in Canada each year, the potential benefits of Dr. Liu and his team's findings to heart attack patients and to the health care system are considerable," says Dr. Alan Bernstein, President of the Canadian Institutes of Health Research. "This new understanding of cellular mechanisms involved in heart disease could translate into novel approaches for the treatment of heart muscle after a heart attack."

All over the world, researchers are racing to develop new methods to repair impaired heart cells and restore cardiac function. Many are trying to infuse the patient's own cells -- stem, bone marrow or other cells – into the damaged heart muscle to try and improve the outcome after a heart attack. Although results have been encouraging, success has been limited and results are often temporary.

Using mice models and sophisticated gene chip technology, Dr. Liu's research team in collaboration with Dr. Medin's laboratory wanted to find a way in which the heart repair process could be strengthened, so they sought to clarify how and what types of cells can be mobilized to aid the heart in repairing itself. What they found surprised them.

Using genetically-engineered mice, the researchers found that those mice without specific specialized proteins called stem cell factor receptors had worse heart function as well as

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significantly decreased heart repair capacity after heart attacks than mice with the stem cell factor receptors. These specialized proteins are important because they have the capability to activate other “signaling” molecules as a way of communicating with them in order to carry out specific functions. These receptor proteins are frequently found on stem cells in the bone marrow. Once activated, the stem cells leave the bone marrow through the blood stream and migrate to the injured heart tissue.

Moreover, when the knock-out mice underwent bone marrow transplantation with normal mouse donors, the stem cell factor receptor signaling was restored and cardiac function was improved.

“After a heart attack, we need to create the right environment or ‘niche’ for the heart to heal itself. Our work shows that we can help the damaged heart to give off a louder type of ‘‘SOS distress signal’’ which can mobilize more repair cells from other parts of the body to come and rescue the damaged heart,” explains Dr. Liu, noting that this research identifies two key types of cells necessary for heart repair: adult stem cells and white blood cells known as natural killer cells.

Natural killer (NK) cells are part of the body’s early immune system defense mechanism against foreign invaders. They reside in the bone marrow and spleen and are able to recognize and kill bacteria, viruses and abnormal cells. “For the longest time, everybody assumed these cells are killers and only killers,” says Dr. Liu, noting that this is no longer true. “Our research shows that there is a ‘kindler and gentler’ side to NK cells that can help injured hearts.

In this study, the research found that after a heart attack, the death rate doubled for mice deficient in both the stem cell factor receptor protein and NK immune cells. Working with stem cells, these NK cells can help the heart repair itself by producing new blood vessels, thereby restoring blood flow to the heart.

Dr. Liu says that there may be other proteins that work together and signal various other cells to come in aid of dying heart cells. “Our goal is to find the most potent combination of factors which together would produce the best outcome after a heart attack,” he noted, adding that the team is presently investigating other cell protein signaling mechanisms and other types of cells that may be best able to help in healing the heart.

In addition to Dr. Liu, Dr. Medin, and first author Bill Ayach, a PhD candidate at the University of Toronto, other authors of this study include: Makoto Yoshimitsu, Fayez Dawood, Mei Sun, Sara Arab, Manyin Chen, Koji Higuchi, Christopher Siatskas, Paul Lee, Hilda Lim, Jane Zhang, Eva Cukerman and William L. Stanford.

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Toronto General Hospital is a partner in the University Health Network, along with the Toronto Western Hospital and the Princess Margaret Hospital. These teaching hospitals are affiliated with the University of Toronto. The scope of research at Toronto General Hospital has made this institution a national and international source for cardiovascular discovery, education and patient care, as well as for its innovations in transplantation, surgical innovation, infectious diseases, diabetes and genomic medicine. In addition, the Peter Munk Cardiac Centre at Toronto General Hospital trains more cardiologists and cardiovascular surgeons than any hospital in Canada.

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