Offering hope for tissue regeneration

February 26 2010

Researchers at Rhode Island Hospital have discovered how cells communicate with each other during times of cellular injury. The findings shed new light on how the body repairs itself when organs become diseased, through small particles known as microvesicles, and offers hope for tissue regeneration. The paper is published in the March 2010 edition of the journal *Experimental Hematology* and is now available online in advance of publication.

Lead author Jason Aliotta, MD, a physician researcher in the pulmonary/critical care and hematology/oncology departments at Rhode Island Hospital, and his colleagues focused their work on the microvesicles. These particles are several times smaller than a normal cell and contain genetic information such as messenger ribonucleic acid (RNA), other species of RNA and protein. The paper shows a novel mechanism by which the cells communicate with each other through these microvesicles. During times of cellular injury or stress, or with certain diseases like cancer, infections and cardiovascular disease, these particles are shed and then taken up by other cells in the body. The genetic information and protein in the microvesicles helps to reprogram the accepting cell to behave more like the cell from which the particle was derived.

Aliotta is also an assistant professor of medicine at The Warren Alpert Medical School of Brown University and a physician with University Medicine Foundation, Inc. He says, "What we attempted to understand is how cells within the bone marrow are able to repair organs that are unrelated to those bone marrow cells, such as the lung. Our work suggests that when the lung is injured or diseased and cells within the lung are stressed or dying, they shed microvesicles. Those microvesicles are then consumed by cells within the bone marrow, including stem cells, which are present in small numbers within the circulatory system. Those bone marrow cells then turn into lung cells."

Other researchers have reported similar findings over the last couple of years, however, microvesicles have been known about for over 40 years and have often been considered irrelevant.

Aliotta adds, "We are now recognizing the relevance of microvesicles: They are important mediators of cell-to-cell communication. What is unique to our research is the finding that microvesicles not only supply information to stem cells with lung injury, but this process also occurs in other organs as well, like the heart, liver and brain."

The researchers report unique findings, noting that the change in those stem cells that have consumed microvesicles made by injured lung cells is very stable - the change appears to be permanent. Stem cells are reprogrammed due to the transfer of microvesicle-based transcription factors. These factors cause cells to behave atypically. As Aliotta says, "This would be relevant to any type of disease - if you want to repair damaged tissue, these microvesicles potentially provide a durable fix, and the hope is that it would be fixed forever."

The study is part of ongoing stem cell research at Rhode Island Hospital under the direction of Peter Quesenberry, MD, director of hematology/oncology at Rhode Island Hospital, who is a co-author on the paper. He is the principal investigator for a recent $11 million Center of Biomedical Research Excellence (COBRE) grant to Rhode Island Hospital from the National Center for Research Resources of the National Institutes of Health (NIH).

Quesenberry says, "We believe this research presents a novel finding in the understanding of stem cells and signifies practical implications for the world of medicine. These microvesicles can change the basic nature of adjoining cells, and that presents a world of possibilities in tissue restoration efforts." Quesenberry, who is a physician with University Medicine Foundation, Inc., also holds the Paul Calabresi, MD, professorship in oncology and is director of the division of hematology/oncology at Alpert Medical School.

Among the practical implications from their findings is an understanding of the mechanism of tissue repair and determining whether or not microvesicles can be used in a therapeutic fashion. Aliotta explains, "If you have an injured organ, our hope is that if we were to deliver large numbers of microvesicles to that injured organ, it would help the repair process."

Based on their findings, the researchers also hypothesize that microvesicles could potentially be mediators of cancer metastasis. It is known that in cancer there are higher levels of circulating microvesicles, and these microvesicles may be responsible for transferring the traits of the cancer to other organs. Aliotta notes, "If we can define the microvesicles that are shed from cancer cells, we can identify unique characteristics, which might help us to block their uptake into normal cells. This could, in theory, stop the metastasis of cancer."

Quesenberry concludes, "Our work explained in this paper and the work still to come from our COBRE grant hold great promise in terms of future treatment of tissue repair and cancer."

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