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Tiny Exosomes Extracted From Donor Cells May Be 'Magic Bullet' For Drug-free Transplants

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Summary: Bubble-like nano-scale particles that are shed by dendritic cells may hold the key to achieving transplant tolerance – the long-term acceptance of transplanted organs without the need for drugs, suggests a study by University of Pittsburgh researchers published in the Nov. 15 issue of the journal Blood.

FULL STORY

PITTSBURGH, Nov. 10 – Bubble-like nano-scale particles that are shed by dendritic cells may hold the key to achieving transplant tolerance – the long-term acceptance of transplanted organs without the need for drugs, suggests a study by University of Pittsburgh researchers published in the Nov. 15 issue of the journal Blood. The results provide some of the first information about what these structures called exosomes actually do.

Exosomes are no larger than 65-100 nanometers – 1,000 times smaller than the diameter of a human hair – yet each contains a potent reserve of major histocompatibility complex (MHC) molecules. MHC molecules are gene products that cells use to determine self from nonself. Millions of exosomes scurry about within the bloodstream, and while their function has been somewhat of a mystery, researchers are beginning to surmise that they play an important role in immune regulation and response.

Adrian Morelli, M.D., Ph.D., of the University of Pittsburgh's Thomas E. Starzl Transplantation Institute, became intrigued by the tiny exosomes while researching ways to harness dendritic cells, specialized white blood cells that present antigens to other immune system cells, as a means to donor-specific immune tolerance. Considered the "Holy Grail" of transplantation, tolerance means a recipient's immune system fully accepts a donor graft without immunosuppressive drugs and without compromising its ability to respond appropriately to infections. Because certain dendritic cells have tolerance-enhancing qualities, several approaches under study involve giving recipients donor dendritic cells that have been modified in some way. The idea is that the modified donor cells would convince recipient cells that a transplanted organ from the same donor is not foreign.

"What may be a more effective approach is to make use of these tiny, MHC-rich vesicles that we can siphon from donor dendritic cells and that we have found are captured by recipient dendritic cells and processed in a manner important for cell-surface recognition. What this means is that we can efficiently deliver donor antigen

using the exosomes as our magic bullet. Further research will determine if we can actually influence transplant tolerance," explained Dr. Morelli, assistant professor of surgery at the University of Pittsburgh School of Medicine.

The function and mechanisms for dendritic cell-derived exosomes had never before been elucidated, so Dr. Morelli and colleagues sought to do so by following the fate of exosomes that they extracted from dendritic cells of one mouse strain and injected into the bloodstream of mice of a different strain. The exosomes were labeled with a dye, and methods such as flow cytometry, confocal microscopy and immuno-electron microscopy helped the researchers track their every movement and activity within the mouse.

Very quickly and efficiently, the donor exosomes were captured by one of three recipient immune system cell types: antigen-presenting dendritic cells and macrophages, both originating in the spleen, and Kupffer cells of the liver.

Of particular interest to the researchers were those exosomes that were caught by the dendritic cells of the spleen, the site where dendritic cells typically present antigens as bounty to T cells that do their part to destroy the foreign invaders. Yet, what the researchers discovered was that these dendritic cells internalized the exosomes instead of displaying them to T cells, this despite the exosomes' rich endowment of donor MHC molecules.

Once internalized, the exosomes were ushered inside larger vesicles, special endosomes called MHC-II enriched compartments, where they were processed with the dendritic cell's own MHC molecules. This hybrid MHC-II molecule, now loaded with a peptide of donor MHC, was then expressed on the cell's surface. As one family of MHC molecules, MHC-II serves as a beacon for a specific population of T cells called CD4+ T cells. Such cells are activated during chronic rejection in a process associated with the indirect pathway of immune recognition.

"This finding is significant because current immunosuppression therapies used in the clinical setting are not able to efficiently prevent T cell activation via the indirect pathway. Perhaps the CD4+ T cells normally involved in this pathway would retreat from attack if they encountered a cell surface marker that is of both donor and recipient origin, such as that which we observed following the dendritic cell's internalization of the donor-derived exosomes," said Dr. Morelli.

Also significant, the researchers report, was that the process of internalizing the donor exosomes did not affect maturation of the dendritic cell. Only immature dendritic cells can capture antigens efficiently and are believed to participate in the induction of transplant tolerance. By contrast, once mature, dendritic cells are capable of triggering the T cell activation that leads to transplant rejection.

Additional research will be required to determine whether donor-derived exosomes will enhance the likelihood that an organ transplant from the same donor will be accepted. Under a recently awarded National Institutes of Health grant, Dr. Morelli plans to address this question with studies involving mice that receive heart transplants following infusion with exosomes from the same donor. A recent French study in rats, while offering no clues as to why, suggests the approach will be successful. In addition, animal studies conducted at Pitt by Paul Robbins, Ph.D., professor of molecular genetics and biochemistry, provide evidence that exosomes can reverse arthritis. Drs. Morelli and Robbins plan to collaborate in future research.

"This is an exciting new area of investigation, which appears to hold great promise in the area of transplant tolerance. So much more remains to be understood, but this current study, whereby we have offered the first details about the mechanism of dendritic cell-derived exosomes, is a significant start," commented senior au-

thor, Angus W. Thomson, Ph.D., D.Sc., professor of surgery and immunology at the Starzl Transplantation Institute and the University of Pittsburgh School of Medicine.

According to the Pitt authors, few research groups are engaged in active study of exosomes with most of the research taking place in Europe.

In addition to Drs. Morelli and Thomson, other authors of the study published in Blood include Adriana T. Larregina, M.D., Ph.D.; William J. Shufesky; Mara G. Sullivan; Donna Beer Stolz, Ph.D.; Glenn D. Papworth, Ph.D.; Alan F. Zahorchak; Alison J. Logar; Zhiliang Wang, M.D.; Simon C. Watkins, Ph.D.; and Louis D. Falo, Jr., M.D., Ph.D.

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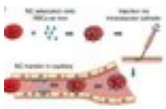

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