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NCCS' APPROACH MAKES BONE MARROW TRANSPLANTATION MORE SUCCESSFUL

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Compared with controls, there was 30-40% increase in the engraftment of hematopoietic stem cells, say Vaijayanti Kale (right) and Sapana Jalnapurkar.

One of the reasons why the efficiency of bone marrow transplantation gets compromised is due to fewer hematopoietic stem cells available for transplantation. Researchers from the Pune-based National Centre for Cell Science (NCCS) have addressed this by using a novel way to multiply or expand the number of hematopoietic stem cells before transplantation. Importantly, the procedure also improves the body's ability to accept the transplanted stem cells and begin producing new blood cells (engraftment potential). Increase in the engraftment potential improves the success rate of bone marrow transplantation.

A team led by Dr. Vaijayanti Kale from NCCS had earlier found that treating hematopoietic stem cells with nitric oxide improved the engraftment potential of juvenile cells. However, adult hematopoietic stem cells lost the engraftment potential when treated with a nitric oxide. "So in the latest study we treated the mesenchymal stem cells with a nitric oxide-producing compound (a nitric oxide donor)," says Dr. Kale.

The nitric oxide donor-treated mesenchymal stem cells (MSCs) secreted micro-vesicles that were enriched in certain factors have the ability to increase the engraftment potential of hematopoietic stem cells. "Micro-vesicles are normally secreted by all cells. But the micro-vesicles secreted by MSCs treated with the nitric oxide donor are rich in two mRNAs — Jagged-1 and VEGF-A," says Sapana Jalnapurkar from NCCS and first author of a paper published in the journal *Stem Cells.* There was about 200-fold increase in Jagged-1-specific mRNA and about 7-fold increase in VEGF-A-specific mRNA in these micro-vesicles.

Micro-vesicles secreted by naïve mesenchymal stem cells do not show such high expression of Jagged-1 or VEGF-A-specific mRNAs.

The micro-vesicles enriched with these two mRNAs were cultured with hematopoietic stem cells for three days. There was an increase in the number (expansion) of hematopoietic stem cells at the end of three days of culture. Two signalling pathways involving Jagged-1 and VEGF-A were also induced when the micro-vesicles entered the hematopoietic stem cells. The pathway involving Jagged-1 plays an important role in self-renewal or multiplication of the stem cells whereas the pathway involving VEGF-A is required for HSCs to reach the bone marrow (homing) and be retained there.

After culturing with micro-vesicles, the hematopoietic stem cells were infused into mice that had undergone whole body irradiation to kill the stem cells in the bone marrow. "We found that the infused stem cells reached the bone marrow (homing) and produced new blood cells (engrafted). Compared with controls, there was 30-40% increase in the engraftment of hematopoietic stem cells. This is quite significant," says Dr. Kale.

After four weeks, the peripheral blood contained 50-55% of blood cells that were derived from the donor stem cells; it was 40% after 16 weeks. In the case of bone marrow, the engraftment of HSCs was 30% after 16 weeks. "This is 5-6-fold more engraftment compared with control," Dr. Kale says.

To test the engraftment efficiency, the researchers extracted the cells from the bone marrow of mice 16 weeks after receiving the donor stem cell infusion. The HSCs were separated and then infused into another set of mice that had undergone whole body irradiation. Blood cells in the peripheral blood after four and 16 weeks of infusion were 40% and 20-25% respectively. In the case of bone marrow, the stem cell engraftment was 7% after 16 weeks; the control mice had only about 1% engraftment. “There is 6-fold more engraftment in the bone marrow of the secondary mice, which is significant,” Dr. Kale says.

“Nitric oxide-donors are already being used as drugs for certain cardiac conditions. Similarly, mesenchymal stem cells are already in clinical use. So it will be relatively straight forward to use them in clinical settings to vastly improve engraftment and achieve greater bone marrow transplantation success. This finding has an important application in transplantation done with gene-edited hematopoietic stem cells,” says Dr. Kale.

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