Scaffolds Seeded With Molecule-Releasing Stem Cells Shows Promise In Treating Fatal Bone Disease

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DURHAM, N.C. (PRWEB) September 05, 2018 -- A team of researchers developed a biocompatible scaffold seeded with molecule-releasing stem cells that, when implanted in mice with a rare but deadly bone disease called autosomal recessive osteopetrosis (ARO), showed potential to help these animals. The findings, recently published in STEM CELLS Translational Medicine (SCTM), might someday yield a treatment for humans afflicted by the same devastating condition.

One of every 250,000 babies born has ARO. ARO is caused by mutations in several genes involved in the formation, development and function of specialized cells called osteoclasts. Osteoclasts break down bone tissue during bone remodeling, a normal process in which old or damaged bone is removed and new bone is produced to replace it. In ARO the osteoclasts fail to resorb bone, leading to restriction of bone marrow cavity and cranial nerve spaces.

People with ARO have a high risk of bone fracture from minor bumps and falls or for no apparent reason. Abnormally dense skull bones pinch nerves in the patient’s head and face, often causing vision and hearing loss, facial paralysis or seizures. Anemia, slow growth, short stature and dental abnormalities are just some of the other symptoms. The condition leads to a high mortality rate in the child’s first years of life — mainly due to bone marrow failure and infection. A bone marrow transplant is the only treatment that has a favorable outcome for ARO patients — unless the ARO is due to lack of Receptor Activator of Nuclear Factor k B Ligand (RANKL), a molecule that is essential to the formation of osteoclasts and, thus, bone formation.

In the SCTM study, a research team led by Anna Villa, M.D., and Cristina Sobacchi, Ph.D., at the Italian National Research Council (CNR), Milan, evaluated how biomimetic scaffolds seeded with mesenchymal stromal cells (MSCs) that have been transduced with a viral vector producing soluble RANKL might help ARO patients lacking this molecule. (MSCs are isolated from bone marrow, adipose and other adult tissue sources, and have the capacity to differentiate into various cell types.)

“Defining a cure for RANKL-ARO is currently an unmet medical need whose solution is unfairly complicated, owing to the extreme rarity of these patients,” Dr. Sobacchi said. In collaboration with Prof. Anna Tampieri, at ISTEC-CNR, the team turned to biomimetic scaffolds because, she explained, “They are extremely versatile in terms of chemical composition and physical properties, which can be defined to accomplish specific applications. One property that can be added is the production/release of bioactive soluble factors, either directly from the biomaterial or from cells embedded within the biomaterial. We reasoned that pursuing this strategy would be appropriate to set up a cell-based therapy for RANKL-deficient ARO.”

The team tested their strategy on RANKL-/ mice, subcutaneously implanting them with the scaffolds. One group received MSC-seeded scaffolds transduced with human-soluble RANKL; one group received mock-
transduced MSC-seeded scaffolds (which did not release RANKL); and the last group received WT MSC-seeded scaffold, as controls.

“We followed the groups for two months, and saw no major side effects, indicating that this treatment was safe,” said Ciro Menale, Ph.D., a CNR colleague and lead author of the work. Mice implanted with RANKL-releasing cell constructs showed restoration of the presence of the cell type completely absent in bone in untreated RANKL-/− mice.

“On the other hand,” Dr. Menale continued, “the biological effect attained in the mice was limited and no amelioration of the osteopetrotic phenotype was observed. These results prompted us to conceive a strategy that could possibly enhance the benefit gained on the skeletal tissue by increasing the amount of cytokine delivered in vivo.”

To reach their goal, the team increased the number of cells seeded on each scaffold and the number of cell constructs implanted in each mouse. These changes to the protocol led to an increase in cell formation in the bones of the mice receiving RANKL-producing cell constructs, although again there was no major improvement in skeletal defect.

“Still, the cell constructs in the human-soluble RANKL group were well tolerated, colonized by host cells and intensely vascularized. In particular, the chemical and physical properties of this scaffold enhanced MSC proliferation and human-soluble RANKL production,” Dr. Sobacchi reported.

“Our strategy proved to have the potential to elicit an effect on the bone. Further work is required to maximize these benefits and achieve improvements of the skeletal pathology in the treated RANKL-/− mice,” Dr. Menale added. “As a perspective, we might pursue further implementation of this system using patients-derived cells for a future possible autologous cell and gene therapy approach.”

“This research has progressed to provide proof of principle that MSC-seeded biomimetic scaffolds might provide a beneficial effect in restoring osteoclastogenesis in bone, leading to possible future translational application toward the treatment of this rare skeletal genetic disease,” said Anthony Atala, M.D., Editor-in-Chief of STEM CELLS Translational Medicine and director of the Wake Forest Institute for Regenerative Medicine.

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