Microscopic packets of stem cell factors could be key to preventing lung disease in babies

October 31 2012

Researchers at Boston Children's Hospital have found that microscopic particles containing proteins and nucleic acids called exosomes could potentially protect the fragile lungs of premature babies from serious lung diseases and chronic lung injury caused by inflammation.

The findings explain earlier research suggesting that while transplanting a kind of stem cell called mesenchymal stem cells (MSCs) could help reduce lung injury and prevent inflammation in a mouse model, the fluid in which the cells were grown was more effective than the cells themselves.

The research team—led by Stella Kourembanas, MD, and S. Alex Mitsialis, PhD, and spearheaded by led by Changjin Lee, PhD, all of the Division of Newborn Medicine at Boston Children's—published their findings online on October 31 in the journal *Circulation*.

Premature babies often struggle to get enough oxygen into their underdeveloped lungs, resulting in hypoxia and the need for ventilator assistance to breathe. Their lungs are particularly susceptible to inflammation, which can lead to poor lung growth and chronic lung disease. Inflammation is also often associated with pulmonary hypertension (PH)—dangerously high blood pressure in the pulmonary artery (the vessel that carries blood from the heart to the lungs), which can have both short- and long-term consequences.

"PH is a complex disease fueled by diverse, intertwined cellular and molecular pathways," according to Kourembanas, who chairs Boston Children's Newborn Medicine division. "We have treatments that improve symptoms but no cure, largely because of this complexity. We need to be able to target more than one pathway at a time."

In 2009, Kourembanas, Mitsialis and others showed that injection of MSCs could prevent PH and chronic lung injury in a newborn mouse model of the disease. The results were puzzling, though, because the team found that few of the injected stem cells actually engrafted within the lungs. They also found that they could achieve better results by injecting just conditioned media—the fluid the cells had been grown in—than by injecting the cells themselves.

"We knew, then, that the significant anti-inflammatory and protective effects we saw had to be caused by something released by the MSCs," Kourembanas explained. "The question was, what?"

To answer that question, the research team grew mouse MSCs in the laboratory and searched the conditioned media for any secreted factors. They came upon exosomes, which many cell types, including MSCs, produce and release as a kind of communication vehicle.

The team found that injecting just purified exosomes from MSCs reduced lung inflammation and prevented the occurrence of PH in their animal model of PH. In contrast, neither MSC-conditioned media depleted of exosomes nor exosomes purified from other cell types had any effect on inflammation or PH in the model, indicating that something unique to the MSC-produced exosomes is required for their protective effect.

"We are actively working to figure out what exactly within the MSC-produced exosomes causes these anti-inflammatory and protective

effects," Kourembanas said. "But we know that these exosomes contain microRNAs as well as other nucleic acids. They also induce expression of specific microRNAs in the recipient lung."

MicroRNAs are small pieces of RNA that regulate gene activity in very specific ways. Thousands of microRNAs have been identified in species up and down the evolutionary tree since their initial discovery in worms nearly 20 years ago, suggesting they play a fundamental role in the cell's regulatory machinery.

"What we may be seeing is the effect of these microRNAs on the expression of multiple genes and the activity of multiple pathways within the lungs and the immune system all at once," she continued.

Looking to the future, Kourembanas thinks exosome research could open a new venue in the development of stem cell-based therapies. She also hopes that, with further study, MSC-produced exosomes could one day be developed into a direct therapy for premature infants at risk of or suffering from chronic lung disease and PH, or even for other diseases with an inflammatory component.

"Exosomes can be isolated from MSCs from several sources, including the umbilical cord" she says. "And unlike donor cells, exosomes are not immunogenic. As such, they could potentially be collected, banked and given like a drug, without the risks of rejection or tumor development that can theoretically come with donor cell or stem cell transplantation."

Provided by Children's Hospital Boston