Enzyme delivered in smaller package protects cells from radiation damage

June 1 2007

A University of Pittsburgh School of Medicine research team, collaborating with scientists from Stanford University, have developed a new, smaller gene therapy vector that may be effective in delivering a radioprotective enzyme systemically throughout the body which may spare healthy tissue the long-term consequences of therapeutic irradiation. These results are being presented at the 10th annual meeting of the American Society of Gene Therapy, being held May 30 to June 3 at the Washington State Convention & Trade Center, Seattle.

Combined with intensive chemotherapy, high dose whole-body irradiation often is given to patients with blood and lymphatic cancers to wipe out their bone marrow cells prior to subsequent transplantation of hematopoietic stem cells, bone marrow stem cells or peripheral blood progenitor stem cells. However, there is increasing concern that such high doses of radiation may have long-term negative effects on healthy tissues and organs, such as the kidney, liver and thyroid gland.

Based on previous studies showing that intravenous gene therapy delivery of the enzyme manganese superoxide dismutase (MnSOD) could protect mice from whole body irradiation, and in preparation for a potential clinical trial of systemic MnSOD in humans, the University of Pittsburgh and Stanford researchers, led by Joel S. Greenberger, M.D., professor and chair of the department of radiation oncology, University of Pittsburgh School of Medicine, delivered the human MnSOD enzyme into mouse hematopoietic progenitor cells using a newly constructed gene therapy vector called a "minicircle" plasmid.

To determine if the cells transfected with the MnSOD minicircle plasmid retained radioprotective capacity, they irradiated those cells as well as another cell line transfected with MnSOD in a full-sized plasmid. They also irradiated a parent mouse cell line that had not been transfected with MnSOD. After irradiation, the cells were plated in a growth medium and incubated at body temperature for 7 days at which time colonies of greater than 50 cells were counted.

The MnSOD transfected cells were significantly more resistant to ionizing radiation than the non-tranfected cells. However, there was no significant difference in survival between MnSOD-minicircle and MnSOD full plasmid transfected cells. According to Dr. Greenberger, whose group is currently conducting a phase I/II clinical trial in lung cancer patients consisting of twice-weekly swallowed MnSOD for protection of the esophagus from chemoradiotherapy damage, these results suggest that minicircle DNA containing the human MnSOD transgene confers undiminished radioprotection to cells.

"Because we now can deliver MnSOD in this very small vector, we will be able to get this radioprotective enzyme more efficiently into all of the cells of the body and give patients receiving total body radiation for systemic cancers better long-term outcomes. This also has implications for the prophylactic protection of those who may be the first responders to a nuclear accident or a terrorist attack, such as a "dirty bomb," he explained.

Source: University of Pittsburgh Schools of the Health Sciences