MedicalXpress

Boosting blood system protein complex protects against radiation toxicity

June 24 2012

New research in *Nature Medicine* shows that boosting a protein pathway in the body's blood making system protects mice from otherwise fatal radiation poisoning.

Scientists in the multi-institutional study – posted online by the journal on June 24 – say their findings open the potential for new treatments against radiation toxicity during cancer treatment or environmental exposures – such as in a nuclear explosion or accident.

By identifying a target-specific intervention to protect the hematopoietic system against radiation toxicity, the study addresses a largely unmet challenge, according to the researchers.

"These findings suggest that pharmacologic augmentation of the activity of the Thbd-aPC pathway by recombinant Thbd (thrombomodulin) or aPC (activated protein C) might offer a rational approach to the mitigation of tissue injury and lethality caused by ionizing radiation," the scientists write in their manuscript. "Recombinant human aPC has undergone extensive clinical testing in patients, and recombinant soluble human Thbd is currently being investigated for efficacy in antithrombotic therapy in humans. Our data encourage the further evaluation of these proteins for their radio-mitigating activities."

The study reveals a previously unknown function of the Thbd-aPC pathway in radiation mitigation. The pathway is normally known for its ability to prevent the formation of blood clots and help the body fight

infections. The researchers found the pathway helps blood cells in the bone marrow recover from injury caused by radiation exposure. They demonstrated that pharmacologic boosting of this pathway with two drugs tested for the treatment of thrombosis or infection (recombinant Thbd and aPC respectively) can be used in mice to prevent death caused by exposure to lethal doses of radiation.

In all instances of treatment with recombinant soluble Thbd or aPC, the result was accelerated recovery of hematopoietic progenitor cell activity in bone marrow and a reduction in the harmful effects of lethal total body irradiation. When treatment was with aPC, these benefits occurred even when treatment was delayed for 24 hours.

The scientists caution their study involves early laboratory research in mice, so it remains to be tested how the findings may translate to human treatment. Researchers also need to determine exactly why the protective function of the targeted Thbd-aPC protein pathway seems to work so well in mice.

Researchers noted that the protective benefits of Thbd-aPC occurred only in vivo in irradiated mouse models. The researchers reported that overexpressed Thbd in irradiated laboratory cell cultures did not offer the same protective benefits, as the cells did not survive. This indicates the protective benefits of Thbd on blood making cells in irradiated mouse models depends on the help of additional cells or molecules in the body, which the researchers are trying to identify in a follow-up study.

The study involves extensive multi-scientist collaborations that combined previously independent lines of research by groups at Cincinnati Children's Hospital Medical Center and the University of Ulm, Germany (led by Hartmut Geiger, PhD, Division of Experimental Hematology/Cancer Biology and the Department of Dermatology/Allergic Diseases); the University of Arkansas, Little Rock

(led by Martin Hauer-Jensen, MD, PhD, Division of Radiation Health, the College of Pharmacy and the Central Arkansas Veterans Healthcare System); the Blood Research Institute in Milwaukee, Wis. (led by Hartmut Weiler, PhD); and The Scripps Research Institute in La Jolla, Calif. (led by John H. Griffin, PhD, Department of Molecular and Experimental Medicine).

The research team said the current study exemplifies a global shift to multi-investigator projects that allow a combination of varied expertise by scientists tackling complex problems from the perspective of their respective fields. This approach requires the willingness of investigators to share unpublished data and engage in an open collaboration. The researchers also said the study underscores the importance of continued federal funding for leading edge basic research that can benefit human health.

Provided by Cincinnati Children's Hospital Medical Center