Endothelial Cells Mitigate DNA Damage and Restore Function in Irradiated Hematopoietic Stem Cells

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Disclosures

We have no conflicts of interest to report.
• The hematopoietic system is exquisitely sensitive to ionizing radiation-induced injury and dysfunction.

• Radiation injury results in chronic oxidative stress and genomic aberrations in hematopoietic stem cells (HSCs).

• Chronic HSC injury can result in early hematopoietic failure and may contribute to the development of hematologic disorders, including leukemia.

• Discovering means to regenerate and repair irradiated HSCs may improve treatments for hematopoietic dysfunction following controlled and unexpected radiation exposure.
Endothelial cells are microenvironmental components that can rescue hematopoiesis after lethal irradiation

- HSCs reside in niches in the bone marrow, where signals from the microenvironment modulate their behavior.

- Previous studies by our lab and others have shown that endothelial cells (ECs) rescue hematopoiesis after otherwise lethal doses of $^{137}$Cs irradiation.

- Our goal was to establish an assay system to ultimately identify EC-derived factors that mediate HSC regeneration.

**1° FACS-sorted ECs or saline**

1200 cGy $^{137}$Cs (split dose)
Direct co-culture with ECs resulted in a 24-fold expansion in HSCs relative to control conditions.
EC-regenerated HSCs are pluripotent and self-renewing.

EC-rescued HSCs provide long-term, multilineage reconstitution in vivo and are serially transplantable.
Endothelial-dependent HSC regeneration is robust to post-irradiation delay.

ECs remained capable of regenerating *in vivo* functional HSCs up to 48 hours after HSC irradiation.
ECs mitigate hematopoietic suppression while simultaneously expanding HSCs and progenitor populations (HSPCs)

Following a 48 hr post-irradiation delay, ECs expanded HSCs and progenitors (HSPCs) more effectively than granulocyte colony-stimulating factor (G-CSF).
ECs reduce DNA damage in regenerating HSPCs

Co-culture with ECs after radiation exposure reduced HSPC DNA damage 50-70% relative to control culture.
Conclusions and future direction

• Direct co-culture with an endothelial monolayer is sufficient to regenerate functional, long-term HSCs after ionizing radiation exposure.

• EC-mediated HSC regeneration rescues functional HSC activity following a post-irradiation delay of up to 48 hours.

• ECs promote expansion of HSCs and non-lineage committed hematopoietic populations.

• EC-derived signals reduce DNA damage in HSCs and progenitors.

• *We are currently utilizing this regeneration assay to identify soluble EC-derived candidates that mediate HSC regeneration and repair following radiation injury.*
Acknowledgements

Oregon Health & Science University
Department of Pediatrics
Department of Radiation Medicine
Albert Einstein College of Medicine
Department of Radiation Oncology

Funding
U19: W.H.F., C.G.
T32: D.K.Z.