ABSTRACT FORM DEADLINE: December 15, 2021

Association of University Cardiologists
January 19-21, 2022
Belmond Charleston Place
Charleston, SC

Protecting mitochondrial function to prevent cardiovascular toxicity of cancer therapies.

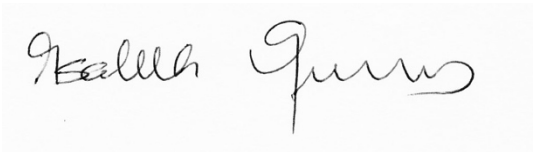
Isabella Grumbach, MD, PhD, University of Iowa

Background: Approximately 18 million cancer survivors currently live in the U.S. These individuals represent more than 5.0% of the U.S. population. With improving therapies, the number of cancer survivors is projected to increase to > 25 million by 2040. At least 40% of this population received radiation therapy (RT) as part of their cancer treatment.
A major concern related to these predictions is that, despite dramatic improvements in techniques that target RT to malignant tissue, some radiation is always dispensed to normal tissue. Despite a well-documented high incidence of heart failure, premature valvular and occlusive vascular diseases, the mechanisms of radiation injury to the heart, large arteries and are not completely understood. Endothelial damage within the microvasculature, also termed "radiation endotheliopathy" is believed to be the major driver of radiation-induced injury to normal tissue in all organs, including acute gastrointestinal syndrome, lung and skin fibrosis, and heart failure. One striking understudied example of such syndrome is radiation-induced cognitive impairment. Radiation-induced cognitive impairment occurs in up to 90% of adult survivors of brain tumors after RT.

Methods and Results: Our studies *in vivo* and *in vitro* in endothelial cells from different vascular beds confirm that mitochondria are particularly susceptible to damage by RT. In our studies, we established the concept that the repair of mitochondrial DNA after RT is rudimentary, leaving DNA only partially repaired and altering the expression and activity of electron transport chain complexes.
These events cause a chronic increase in the production of mitochondrial oxidative stress and ultimately leads to cell senescence and further epigenetic changes that are propagated upon cell division. We also demonstrate that mitochondrial Ca^{2+} uptake is augmented in irradiated cells because of an increase in the mitochondrial membrane potential. Influx of Ca^{2+} into mitochondria via the mitochondrial Ca^{2+} uniporter (MCU) leads to increases in the activity of the Krebs cycle as well as of the electron transport chain, thereby promoting generation of oxidative stress. RT-induced oxidative stress can be blocked by inhibiting mitochondrial Ca^{2+} uptake. These findings suggest that either scavenging mitochondrial oxidative stress or reducing mitochondrial Ca^{2+} overload might prevent radiation endotheliopathy, potentially by promoting efficient repair of mitochondrial DNA. Indeed, blocking either event prevents endothelial dysfunction in vivo in larger arteries after RT as well as blood brain barrier dysfunction.
We also tested the effects of statins in our models given that incidental use of statins has been reported to decrease the progression of macrovascular disease after RT. Surprisingly, we found differential effects of statins on mitochondrial function and vascular reactivity *in vivo* after RT.

Conclusions: Despite the growing number of cancer survivors that have been treated with to RT, there are no proven mitigators that prevent RT-induced cardiovascular dysfunction. Our research program has identified mitochondrial pathways that drive endothelial dysfunction after RT and may be druggable. Lastly, our data point towards differential effects of statins in experimental models that require urgent validation in humans.

1) Please identify members by underlining their name.
2) Please use box above, Abstract (with spaces) = 500 Word limit
3) Talk duration 15 min, questions 10 min (total time 25 min)



Member's Signature

NOTE: This form is also available on the AUC website at https://www.aucard.org/scientific-abstract-form