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# The modulating effect of Oxidative Metabolism and Oxygen Partial Pressure on Propagation of Radiation Bystander Effects

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## Introduction:

Redox modulated pathways play important roles in out-of-field effects of ionizing radiation. We investigated how the redox environment impacts the propagation of stressful effects from irradiated to bystander cells.

## Materials and Methods:

- Normal human fibroblasts that have incorporated [<sup>3</sup>H]-thymidine were intimately co-cultured with bystander cells during 24 h in a strategy that allowed isolation of bystander cells with high purity. The antioxidant glutathione peroxidase (GPX) was maintained either at wild-type conditions or overexpressed in the bystanders.
- Confluent cell cultures pre-treated with t-butyl-hydroperoxide (t-BOOH), an oxidizing agent, or maintained in low oxygen pressure environment approaching *in vivo* conditions were exposed alongside respective controls to low fluences of 3.7 MeV  $\alpha$  particles.

## Results:

- Following 24 h of coculture with [<sup>3</sup>H]-thymidine-labelled cells, levels of stress-responsive p21<sup>Waf1</sup>, p-Hdm2, and connexin43 proteins were increased in bystander cells expressing wild-type GPX relative to respective controls. These levels were significantly attenuated when GPX was ectopically overexpressed in the bystanders, demonstrating by direct approach the involvement of oxidative metabolism.
- By exposing confluent cell cultures to 3.7 MeV  $\alpha$  particles wherein only ~2 % of cells are traversed through the nucleus by a particle track, increases in chromosomal damage 3 h post-exposure were greater than expected ( $p < 0.001$ ) and further enhanced in presence of t-BOOH ( $p < 0.05$ ). While maintaining and irradiating cell cultures at low oxygen pressure (3.3 or 6.7 mmHg) still supported the participation of bystander cells in responses assessed by chromosomal damage and stress-responsive protein levels ( $p < 0.001$ ), the effects were attenuated compared to ambient pO<sub>2</sub> (141 mm Hg) ( $p < 0.05$ ).

## Conclusions:

Together, the results show that bystander effects are attenuated at below ambient pO<sub>2</sub> and when metabolic oxidative stress is reduced but increased when the basal redox environment tilts towards oxidizing conditions. They are consistent with bystander effects being independent of radiation dose rate.