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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 [^{3}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 α particles.

Results:

- Following 24 h of coculture with [^{3}H]-thymidine-labelled cells, levels of stress-responsive $p21^{Waf1}$, 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 α 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_2 (141 mm Hg) ($p<0.05$).

Conclusions:

Together, the results show that bystander effects are attenuated at below ambient pO_2 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.