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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 [³H]-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 [³H]-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 pO₂ (141 mm Hg) ($p < 0.05$).

Conclusions:

Together, the results show that bystander effects are attenuated at below ambient pO₂ 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.