

## **Molecular mediators of radio-adaptation in human cells**

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Low doses of ionizing radiation (IR) can protect cells and organisms from the loss of viability caused by a subsequent dose of IR, a phenomenon known as radio-adaptation or radiation hormesis. We find that low (priming) levels of IR (0.5-2 cGy) accelerate the rate at which human cells repair DNA double strand breaks (DSBs) after receiving a subsequent high (challenge) dose of IR. Of particular importance, we find that priming IR doses protect human cells from undergoing a senescence response to challenge IR doses. Several lines of evidence suggest that senescent cells can have long-lasting deleterious effects within tissues, and that the presence of these cells can drive both aging and cancer. The deleterious effects of senescent cells are thought to derive from their secretory phenotype, which in turn is thought to result from a senescence-associated reorganization of chromatin. To understand the molecular pathways responsible for this ability of low IR doses to abrogate the senescence response, we studied human cells deficient in several proteins known to be crucial mediators of DNA repair and the senescence response. Low IR doses were fully capable of protecting human cells deficient in NBS1, and largely, although not completely, capable of protecting cells deficient in ATM, ATR and p53. Strikingly, cells defective in WRN were unable to mount a radio-adaptive response. WRN encodes a DNA helicase and exonuclease that participates in several DNA transactions, including telomere maintenance and DSB repair. Humans who are genetically deficient in this protein age at an accelerated rate and are cancer-prone, and cells from such humans undergo premature senescence. This finding suggests that the radio-adaptation caused by low doses of IR act via a pathway or mechanisms in which WRN also participates. An important clue regarding how low dose IR might abrogate the senescence response is our finding that cells must undergo at least one S phase in order to experience the protective effects. S phase is often required to 'reset' chromatin organization. Indeed, we find that a major chromatin-associated protein, HMGB1, is actively exported from nuclei and secreted by senescent cells, and that low dose IR prevents HMGB1 nuclear export and secretion. Our findings uncover novel connections between the biological effects of low dose radiation and proteins that participate in the senescence response, which in turn is thought to drive aging and cancer phenotypes.