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The role of TGFbeta3 and induced nitric oxide activity in connection with induced resistance against low dose hyper-radiosensitivity

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We have previously found that protracting a priming dose of 0.3 Gy over 1 hour resulted in permanent elimination of low dose hyper radio-sensitivity (HRS) instead of the transient elimination by an acute priming with the same dose. The cells exposed to the low dose-rate priming secreted a factor into the medium, which removed HRS transiently in recipient cells. The factor could also be induced by low dose-rate irradiation of cell conditioned medium but only when serum was present in the medium during conditioning.
We have now identified the serum factor as interleukin-13 and the factor secreted by the low dose-rate primed cells as TGFβ3 and propose a model for a self-sustaining molecular mechanism responsible for permanent elimination HRS transmitted to the progeny.
Two cell lines known to display HRS were used, T-47D breast cancer cells and T98G glioblastoma cells. The change to a HRS-negative phenotype was found to be transiently induced by extracellular TGFβ3, which could be activated through iNOS activity by low dose-rate irradiation (0.2-0.3 Gy/h for 1 h) of cell conditioned medium. However, direct cell irradiation at low dose-rate induced a permanent elimination of HRS by activation of a self-sustaining mechanism found to depend on iNOS activity and resulting in continuously elevated cytoplasmic levels of TGFβ3. The HRS-negative phenotypes of T-47D and T98G were reversed by iNOS inhibitor 1400W. Interestingly, HRS was induced by 1400W in the HRS-negative cervix cancer cell line NHIK 3025. The effect of low dose-rate irradiation could be mimicked by high dose-rate irradiation or reoxygenation after hypoxia in combination with NO.
The data show how resistance against low levels of DNA-damage can be turned on (by TGFβ3) or off (by iNOS inhibition) in cells. In addition, the data contributes to the understanding of the importance of distinguishing between dose-rates in relation to radiation protection issues and indicate that the effects induced by low dose-rate irradiation are related to NO production and independent of DNA-damage.
Preliminary results confirm the findings in a mouse model.

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