Irradiation-induced regulation of plasminogen activator inhibitor type-1 and vascular endothelial growth factor in six human squamous cell carcinoma lines of the head and neck.

Abstract:
It has been shown that plasminogen activator inhibitor type-1 (PAI-1) and vascular endothelial growth factor (VEGF) are involved in neo-angiogenesis. The aim of this study was to investigate the irradiation-induced regulation of PAI-1 and VEGF in squamous cell carcinomas of the head and neck (SCCHN) cell lines of varying radiation sensitivity. Six cell lines derived from SCCHN were investigated in vitro. The colorimetric AlamarBlue assay was used to detect metabolic activity of cell lines during irradiation as a surrogate marker for radiation sensitivity. PAI-1 and VEGF secretion levels were measured by enzyme-linked immunosorbent assay 24, 48, and 72 h after irradiation with 0, 2, 6, and 10 Gy. The direct radioprotective effect of exogenous PAI-1 was measured using the clonogenic assay. For regulation studies, transforming growth factor-beta1 (TGF-beta1), hypoxia-inducible factor-1alpha (HIF-1alpha), hypoxia-inducible factor-2alpha (HIF-2alpha), or both HIF-1alpha and HIF-2alpha were downregulated using siRNA. Although baseline levels varied greatly, irradiation led to a comparable dose-dependent increase in PAI-1 and VEGF secretion in all six cell lines. Addition of exogenous stable PAI-1 to the low PAI-1-expressing cell lines, XF354 and FaDu, did not lead to a radioprotective effect. Downregulation of TGF-beta1 significantly decreased...
VEGF secretion in radiation-sensitive XF354 cells, and downregulation of HIF-1alpha and HIF-2alpha reduced PAI-1 and VEGF secretion in radiation-resistant SAS cells. Irradiation dose-dependently increased PAI-1 and VEGF secretion in all SCCHN cell lines tested regardless of their basal levels and radiation sensitivity. In addition, TGF-beta1 and HIF-1alpha could be partly responsible for VEGF and PAI-1 upregulation after irradiation.

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