Induction of plasminogen activator inhibitor type-1 (PAI-1) by hypoxia and irradiation in human head and neck carcinoma cell lines.

BACKGROUND: Squamous cell carcinoma of the head and neck (SCCHN) often contain highly radioresistant hypoxic regions, nonetheless, radiotherapy is a common treatment modality for these tumours. Reoxygenation during fractionated radiotherapy is desired to render these hypoxic tumour regions more radiosensitive. Hypoxia additionally leads to up-regulation of PAI-1, a protein involved in tumour progression and an established prognostic marker for poor outcome. However, the impact of reoxygenation and radiation on PAI-1 levels is not yet clear. Therefore, we investigated the kinetics of PAI-1 expression and secretion after hypoxia and reoxygenation, and determined the influence of ionizing radiation on PAI-1 levels in the two human SCCHN cell lines, BHY and FaDu. METHODS: HIF-1alpha immunoblot was used to visualize the degree of hypoxia in the two cell lines. Cellular PAI-1 expression was investigated by immunofluorescence microscopy. ELISA was used to quantify relative changes in PAI-1 expression (cell lysates) and secretion (cell culture supernatants) in response to various lengths (2-4 h) of hypoxic exposure (< 0.66% O2), reoxygenation (24 h, 20% O2), and radiation (0, 2, 5 and 10 Gy). RESULTS: HIF-1alpha expression was induced between 2 and 24 h of hypoxic exposure. Intracellular PAI-1
expression was significantly increased in BHY and FaDu cells as early as 4 h after hypoxic exposure. A significant induction in secreted PAI-1 was seen after 12 to 24 h (BHY) and 8 to 24 h (FaDu) hypoxia, as compared to the normoxic control. A 24 h reoxygenation period caused significantly less PAI-1 secretion than a 24 h hypoxia period in FaDu cells. Irradiation led to an up-regulation of PAI-1 expression and secretion in both, BHY and FaDu cells. CONCLUSION: Our data suggest that both, short-term (approximately 4-8 h) and long-term (approximately 20-24 h) hypoxic exposure could increase PAI-1 levels in SCCHN in vivo. Importantly, radiation itself could lead to PAI-1 up-regulation in head and neck tumours, whereas reoxygenation of hypoxic tumour cells during fractionated radiotherapy could counteract the increased PAI-1 levels.

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