Airway stem cells from Chronic Obstructive Pulmonary Disease (COPD) patients preserve patient phenotypes and have increased radiation sensitivity.

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Abstract

In 30% of lung cancer patients, radiation therapy results in radiation-induced lung injury (RILI): a dose-limiting complication that can lead to irreversible loss of pulmonary function and death. RILI is further exacerbated by pre-existing co-morbidities such as chronic obstructive pulmonary disease (COPD) in many lung cancer patients reducing their tolerance to treatment and chance of tumour control. The cause for the increased sensitivity of COPD patients to RILI is poorly understood, and there are no mitigating treatments or predictive biomarkers to identify patients at risk. We hypothesised that airway stem cells might be involved in the acute- and late response to radiotherapy. Here we used the Air-Liquid Interface (ALI) model: a 3D polarised and pseudostratified culture system, to compare the radiation response of primary human airway stem cells from healthy and COPD patients. We exposed patient-derived healthy- and COPD ALI cultures to irradiation (2-4 Gy) and characterised their DNA damage response (53BP1/EdU co-staining, Comet assay), self-renewal (incucyte, EdU/PI, Annexin-V), differentiation capacity (TP63, AcTub, Mu5ac) and secreted pro-inflammatory cytokine profile. In ALI, COPD airway stem cells recapitulated the aberrant histopathological features of COPD in mucociliary differentiation (a 2-fold increase in mucous cells and a 30% reduction of ciliated cells). Irradiated COPD stem cells accumulate more DNA damage, as shown by the 1,5-fold increase of 53BP1 foci in the Edu+ stem cells, 6 and 24h post-RT, respectively, suggesting an impaired non-homologous end joining pathway that may attenuate their repair capacity. These results correlated with 2-fold increased DNA damage with the Alkaline comet assay. Irradiated COPD stem cells responded with a 1,5-fold higher G2/M accumulation and a 4-fold reduced S-phase, and a 2-fold increase in apoptotic cells, with higher C-PARP, TP53 and P21CIP levels. In response to irradiation, we found 22 pro-inflammatory cytokines differentially secreted (1,5-2-fold) by COPD versus healthy airway stem cells and 29 pro-inflammatory cytokines differentially secreted three days post-irradiation.

These data show that ALI cultures of primary human upper airway lung epithelium reflect part of RILI and clinical behaviour of COPD patients and disclose novel insights into the role of airway stem cells and their sensitivity to irradiation.