Radiation-induced lung fibrosis is associated with M2 interstitial and hybrid alveolar macrophages

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Radiation-induced fibrosis is a delayed complication of radiotherapy often associated with chronic inflammatory process and macrophage infiltration. Nowadays, macrophages are suggested to be important cellular contributors to fibrogenic process, but their implication in the context of RIF is not well known. To investigate the role of macrophages in RIF we have used a classical experimental model of lung fibrosis developed in C57Bl/6 mice after 16Gy thorax-IR. We then profiled both alveolar macrophages (AM) and interstitial macrophages (IM) during the various steps of the fibrogenic process. We confirmed the fact that total lung irradiation at 16Gy (IR) induces an interstitial fibrosis associated with delayed recruitment of pulmonary macrophages. We found a transient depletion of AM associated with cytokine secretion during the acute post-IR phase (15 days), followed by an active repopulation and an enhanced number of AM during the late post-IR phase (20 weeks). Interestingly, AM were mostly recruited from the bone marrow and exhibit a hybrid polarization (M1/M2) associated with up-regulation of Th1 and Th2 cytokines. The number of M2-polarized IM significantly increased during the late time points after irradiation and a down-regulation of Th1 cytokine was measured in tissue lysate. These results suggest a differential contribution of hybrid AM vs M2-IM to fibrogenesis. Interestingly, in contrast to activated hybrid AM, activated M2-IM were able to induce fibroblast activation in vitro mediated by an enhanced TGF-B1 expression suggesting a profibrotic role of M2-IM. Specific depletion of hybrid AM using intranasal administration of clodrosome increased radiation-induced fibrosis score and enhanced M2-IM infiltration suggesting a protective role of hybrid AM. These present study shows a dual and opposite contribution of aleular versus interstitial macrophages in radiation-induced fibrosis and identify M2-IM as a potential therapeutic target to treat radiation-induced fibrosis.

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The internal mammary chain - should we treat it in every node-positive patient?

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Locoregional radiation therapy (RT) improves locoregional control and survival for patients treated with breast conserving therapy and for patients after mastectomy with risk factors including involved axillary lymph nodes. In the past, however, this treatment could be linked to an increased risk for late cardiovascular morbidity and mortality as a result of cardiac exposure to radiation. This was especially the case for the treatment of the internal mammary lymph node target volume, for which this was abandoned by many