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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- β 1 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 alveolar *versus* interstitial macrophages in radiation-induced fibrosis and identify M2-IM as a potential therapeutic target to treat radiation-induced fibrosis.

Symposium: Regional nodal irradiation for breast cancer

SP-0015

The axilla- less surgery, more radiotherapy?

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Irradiation of lymph node areas in breast cancer patients, especially in early stages of the disease is a controversial topic. The recommendation to irradiate lymph nodes is

clearly indicated in patients with more than three involved nodes. In these cases, after standard lymphadenectomy, the volumes to irradiate include supraclavicular fossa and axillary level III nodes. Until a few years ago, irradiation of axillary levels I and II, are reserved for cases of very large axillary involvement, or in patients whom lymphadenectomy was insufficient (less than 10 lymph nodes resected). However, when only 1 to 3 nodes are involved, there is no unanimity on the radiotherapy recommendations, despite several studies having show clearly a disease free survival improvement in irradiated patients. The Canadian trial NCIC-CTG MA20, including high risk patients, most of them with 1 to 3 involved nodes, showed that local irradiation with regional lymph node irradiation improved disease-free survival, both loco-regional and distant disease control. The EORTC trial also demonstrates the same findings: regional irradiation in breast cancer patients improve even the overall survival. Therefore the current trend, described in international guidelines, lymph node irradiation is recommended for all patients regardless of the number of positive nodes. Nevertheless, the therapeutic value of axillary lymphadenectomy has been questioned for a long time. The ACOSOG Z0011 study results have caused clinical practice changes since many axillary dissections are being avoided. Even several clinical practice guidelines, including prestigious ones such as those of National Comprehensive Cancer Network, don't recommend lymphadenectomy. The ACOSOG Z0011 does not exactly describe the irradiated nodal volumes exactly. Therefore, the nodal volumes to include in the irradiation treatment of early stages of breast cancer remains under discussion, especially without axillary lymphadenectomy despite involvement of sentinel lymph nodes. In most cases, breast irradiation with tangent fields implies certain "incidental" of axillary level I, and also in some cases the level II. For this reason, some groups have decided to avoid intentional irradiation of these axillary areas, while others advocate to irradiate them intentionally, without clear evidence to do that. The AMAROS trial demonstrated that lymph node radiotherapy obtains the same results as axillary dissection in node-positive patients without primary systemic treatment, with less morbidity. Therefore, it is possible to replace the surgery with radiation. The current situation is that some groups decide to irradiate lymph node in cases with positive sentinel node without lymphadenectomy and other groups in these cases do not treat the lymph node, and accept that some incidental irradiation will arrive by tangential fields. But, we do not know which patients, with positive nodes, do not require lymph node irradiation. It is possible that in patients with low axillary involvement intentional irradiation would not be necessary. In order to demonstrate this hypothesis, we have started the OPTYMAL trial (www.clinicaltrials.gov/ct2/show/NCT02335957?term=osna&rank=7) to investigate the non-inferiority of incidental versus intentional irradiation of axillary nodes in patients with axillary involvement of 250-15000 copies/uL with One Step Nucleic Acid Amplification method (OSNA). We decided to use this method to unify the pathological reports. This international multicenter trial must help us to elucidate the necessity of node area irradiation by combining with reliable information about the tumor load involvement in axillary nodes.

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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