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Title: A myeloid NF-κB response in malignant pleural effusion

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Body: Malignant pleural effusion (MPE) is a phenotype of cancer that heavily rests on inflammatory tumor-host interactions (Stathopoulos, G.T. et al. Am J Respir Crit Care Med 2012;186:487-92). The impact of host nuclear factor (NF)-κB, a key proinflammatory pathway, on MPE development has not been elucidated. Here we used bioluminescence imaging of relevant reporter mice, adoptive bone marrow transfer (BMT) and molecular phenotyping to map host NF-κB activation during MPE formation. For this, MPE-competent (LLC lung adenocarcinoma, MC38 colon adenocarcinoma and AE17 pleural mesothelioma) and –incompetent (B16F10 melanoma) wild-type tumor cells were delivered to the pleural space of NF-κB reporter mice (NF-κB.GFP.Luciferase; NGL) followed by serial bioluminescent imaging. In this model, GFP and luciferase reporter expression is restricted to host cells with active NF-κB. A strong thoracic NF-κB response was triggered specifically by MPE-competent tumor cells and coincided with MPE development. Using BMT of wt or NGL bone marrow to wt or NGL recipients, we identified that this host NF-κB response was transplantable with NGL-donated bone marrow. Immunophenotyping of GFP+ cells identified myeloid cells as the source of the NF-κB signal. Clodronate-mediated ablation of pleural myeloid cells during MPE formation significantly abrogated the potential of MPE-competent tumor cells to give rise to MPE. These studies suggest a tumor-promoting role for myeloid NF-κB activation in the malignancy-affected pleural space, providing evidence that, in addition to tumor cell-NF-κB, activation of the transcription factor in host immune cells may present a marked therapeutic target in patients with MPE. These studies were supported by a ERC Grant.