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Title: Inhibition of osteopontin modulates tumor-stimulated immune response and suppresses mesothelioma progression

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Body: Rationale: Osteopontin (OPN) is overexpressed in mesothelioma tissue and has been associated with impaired patient survival. However, whether OPN is involved in mesothelioma growth and regulation of tumor-stimulated immune reaction is unknown. Aim: To examine the functional importance of OPN in experimental malignant pleural mesothelioma. Methods: AE17 murine mesothelioma cells which express high levels of OPN, engineered to stably express short hairpin RNAs (shRNAs) targeting the OPN transcript. To mimic pleural mesothelioma we intrapleurally injected syngeneic C57/Bl6 mice with AE17/OPNshRNA or AE17/vector cells. Tumor tissue and pleural fluid were harvested 15 days post-injection. The presence of pro-tumor cells including CD11b(+)/F4/80(+)/CD206(+) macrophages and CD11b(+)/Gr1(+) myeloid suppressor cells were evaluated using FACS. Results: Pleural tumors in mice injected with AE17/shRNA were significantly smaller than those developed in mice injected with AE17/vector (mean tumor weight 428.3±41.2mg versus 107.2±25.6mg, $P<0.05$). In addition, animals bearing AE17/shRNA tumors had significantly less pleural fluid compared to those bearing control tumors (451.3±48.8μl versus 41.67±4.52μl, $P< 0.05$). Pleural fluid CD206(+) macrophages were significantly less in mice with AE17/shRNA tumors compared to those with AE17/vector. Similarly, pleural fluid CD11b(+)/Gr1(+) myeloid-suppressor cells were significantly reduced respectively. Conclusion: OPN promotes experimental mesothelioma growth and formation of malignant pleural effusion. Importantly, OPN substantially contributes in pro-tumor inflammatory cell recruitment in the mesothelioma-affected pleural cavity.