HMGB-1 RELEASE AND THE CD8 T CELL RESPONSE ELICITED BY RADIATION TREATMENT IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: Malignant pleural mesothelioma (MPM) is a cancer of the lung lining that is difficult to treat and linked with the inhalation of asbestos fibers. Cytotoxic T lymphocytes circulate through the body and are able to kill tumor cells. However, an inhibitory tumor microenvironment renders T cells unable to inhibit tumor growth. Furthermore, MPM has few known tumor associated antigens; making it difficult to target interventions. Danger associated molecular pattern (DAMP) molecules offer a new avenue of treatment. DAMPs, released from cells undergoing cell death, are implicated in stimulating the antigen uptake, maturation, and antigen presentation of dendritic cells; crucial activators of cytotoxic T cells that mediate tumor killing. We are keen to observe the role of HMGB-1 in the context of radiation treatment for mesothelioma.

Purpose: To investigate the CD8+ T cell immune response elicited by HMGB-1 release and to correlate HMGB-1 released by MPM to survival.

Hypothesis: Radiation treatment of MPM results in tumor cell death and the subsequent release of HMGB-1, recruitment of CD8 T cells, and stimulation of tumor cell killing.

Methods: Transwell filters were used to assess migration towards recombinant HMGB-1 protein, *in vitro*. Tumor killing assay assessed the ability of recombinant HMGB-1 to promote MPM cell death by CD8 T cells. C57BL/6 mice received radiation, radiation and anti-HMGB-1 Ab or no treatment to MPM tumors that were established by MPM cell line subcutaneous injection.

Results: *In vitro*, HMGB-1 is able to stimulate CD8 T cell migration and MPM tumor cell line killing. Mice with radiated tumors displayed an increase in tumor CD8 T cell number and serum HMGB-1 levels. Anti-HMGB-1 Ab treatment decreased tumor infiltrating CD8 T cell numbers in radiated mice and resulted in lower survival than radiation alone.

Conclusion: HMGB-1 is crucial for the immunogenicity of radiation treatment in MPM.