ME-15. INTERACTION BETWEEN CANCER STEM CELLS AND MYELOID DERIVED SUPPRESSOR CELLS DRIVES IMMUNOSUPPRESSION AND GLIOBLASTOMA GROWTH
Balint Otvos, Alvaro Alvarado, James Hale, Kevin Stoltz, Maksim Sinyuk, Pat Rayman, William Flavahan, Qulian Wu, Awad Jarrar, Jeremy Rich, Richard Ransohoff, James Finke, Michael Vogelbaum, and Justin Lathia; Cleveland Clinic, Cleveland, OH, USA

Cellular and molecular regulation of the immune system is exquisitely controlled in the brain and disrupted in neoplasia. Glioblastoma (GBM) has an immunosuppressive phenotype, and despite the accumulation of immune cells in the tumor microenvironment, tumor growth persists. Myeloid derived suppressor cells (MDSCs) are a class of immature immune cells that mitigate cytotoxic T cell responses and promote immunosuppression in a variety of cancers. MDSCs are increased in the peripheral blood of GBM patients, but their role in the GBM microenvironment is undefined. We observed co-localization between arginase (Arg1) producing immunosuppressive MDSCs and cancer stem cells (CSCs) in GBM patient specimens and xenografts, leading to the hypothesis that CSCs stimulate MDSCs to promote immunosuppression. Intracranial injections of CSCs into mice led to GBM formation, expansion of the Arg1-producing MDSCs within the marrow of GBM-bearing mice, and increased levels of MDSCs within the GBM microenvironment. CSC conditioned media increased Arg1 production of murine marrow MDSCs which were then able to modulate cytotoxic T cell responses in co-culture models. Screening of conditioned media revealed cytokines secreted selectively by CSCs that activated MDSCs suppression. Removal of CSC-secreted factors decreased MDSCs in the GBM microenvironment, increased cytotoxic T cell infiltration, and had a pronounced survival benefit. Peripheral targeting of MDSCs through a subtherapeutic dose of 5-fluorouracil (5-FU) in an immunocompetent syngeneic mouse model led to a similar phenotype to CSC-secreted factor removal in the GBM microenvironment, and an even greater survival benefit. Taken together, our results suggest a critical role of MDSC-mediated immunosuppression in GBM, a novel paradigm of immunomodulation by CSCs, and demonstrate that peripheral removal of MDSCs leads to increased T cell infiltration into GBM, and consequently suggest a novel chemotherapeutic strategy that is not generally toxic to bone marrow and that is not dependent on agents crossing the blood brain barrier.

Published by Oxford University Press on behalf of the Society for Neuro-Oncology 2014.