degradation is the optimal source to fuel protein translation in T cells in the stress of solid tumors. We demonstrate that Rapamycin-primed T cells are preferentially powered by pro-teosomal proteolysis and are able to sustain protein translation in tumors and control tumor growth.

Conclusions Our data establish that canonical protein translation governed by mTORC1 and glucose metabolism is subject to inhibition in the TME and promotion of protein catabolism is a new strategy to support antitumor immunity.

Ethics Approval All animal experiments were in accordance with the MUSC Institutional Animal Care and Use Committee (IACUC), protocol # IACUC-2018-00422 and # IACUC-2018-00347.

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523 A SUBSET OF MATURE NEUTROPHILS CONTAINS THE STRONGEST PMN-MDSC ACTIVITY IN BLOOD AND TISSUE OF PATIENTS WITH HEAD AND NECK CANCER

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Background A high neutrophil-to-lymphocyte ratio in the circulation and high frequencies of tumor-associated neutrophils (TAN) in malignant tissue are associated with poor outcome and tumor progression in patients with cancer. It is hypothe-sized that immunosuppressive neutrophil activity (aka PMN-MDSC activity) contributes to this effect. In addition, this MDSC activity represents a major resistance mechanism in different types of immunotherapy. The exact cellular identity of human PMN-MDSC is still under debate. Improved immunomonitoring and functional characterization of MDSC is needed in order to exploit these cells as novel biomarkers and targets for combination immunotherapy.

Methods In this study, we sought to identify the neutrophil subset that contained the highest T cell suppressive activity. To this end, we purified different subsets of circulating neutrophils by FACS and performed multi-parameter immunofluorescence together with digital pathology on 2-D and 3-D tumor tissue samples.

Results We found that a population of circulating, mature, arginine 1+ neutrophils that co-purified with mononuclear cells in density gradients, most potently suppressed T cell function in multiple in vitro assays. These PMN-MDSC were also superior to monocytic MDSC in T cell suppression. Using a novel technology of tissue whole mount labelling, clearing and imaging we derived 3-D spatial maps of neutrophil – T cell interaction in human tumors. We found that T cells, which were conjugated to arginase I+, myeloperoxidase + TAN, had significantly reduced expression of proliferation and cytotoxicity markers. In patients, frequent conjugation of T cells to those PMN-MDSC was associated with poor prognosis. In contrast to circulating PMN-MDSC, tissue PMN-MDSC expressed high amounts of LOX-1 (oxidized low density lipoprotein receptor 1) and a high intratumoral frequency of LOX-1+ PMN-MDSC was associated with poor survival.

Conclusions We identified and characterized PMN-MDSC activity in human cancer patients. Our findings will facilitate and improve MDSC immunomonitoring and MDSC targeting in combination therapies.