ABSTRACT:

Myeloid-derived suppressor cell accumulation in secondary target organs promotes metastatic growth in breast cancer

A role for bone marrow-derived cells (BMDCs) in promoting metastatic tumour growth is emerging. Previous work has shown accumulation of CD11b+ BMDCs in pre-metastatic niches in the lungs of mice bearing metastatic breast tumours, although questions remain about the precise identity of these cells and their potential long-term influence on metastatic growth. We studied the induction, identity, longevity, and function of CD11b+ BMDCs in tissues of mice bearing murine mammary tumours. Metastatic, but not non-metastatic, mammary tumours induced the accumulation of CD11b+Gr1+ cells, which we functionally identified as immunosuppressive myeloid-derived suppressor cells (MDSCs) using ex vivo assays. Unlike BMDCs associated with pre-metastatic niches in other breast tumour models, MDSCs were induced systemically, with levels increasing in metastatic target organs (lung, liver, bone-marrow) and in tissues that do not harbor metastases from these tumours (kidney, spleen). We also found that circulating MDSC levels can be used as a surrogate marker for monitoring MDSC accumulation in tissues.

Primary tumour resection caused decreased serum levels of granulocyte-colony stimulating factor and MDSCs, but functional MDSCs remained elevated in the lungs for several weeks after tumour resection. These MDSCs were associated with enhanced subsequent pulmonary metastatic growth, providing evidence that MDSC induction by metastatic primary tumours helps create a long-lasting metastasis-promoting environment in lung tissue. In addition to surgery, we utilized gemcitabine (GEM), 5-fluorouracil (5-FU) and tirapazamine (TPZ) to target MDSCs in the lungs and spleen of tumour bearing mice. Aside from its classification as a hypoxia-specific cytotoxic, we report TPZ as a novel MDSC cytotoxic, comparable in potency to other well characterized MDSC specific chemotherapeutics. We administered GEM to mice with resected tumours in order to target residual MDSCs. Our data shows that GEM significantly eliminates residual MDSC levels in the lungs which resulted in a decreased ability of 4T1 tumour cells to colonize the metastatic target organ. While we were able to target the tumour-potentiating fraction of MDSCs, our data indicates that significant levels of residual MDSCs still remain in the lungs, whose function and phenotype remains to be characterized.

Taken together, our findings suggest that metastatic murine mammary carcinomas induce systemic elevation of MDSCs and highlight the potential importance of identifying patients with elevated MDSC levels. Additionally, our research provides support for therapeutic targeting of MDSCs in patients at risk of developing or re-developing metastatic disease.