Exploiting myeloid cells as prognostic biomarker and therapeutic target in cancer patients

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It has been known for long time that myeloid cells, in their different cell subsets including monocytes, granulocytes, macrophages and dendritic cells, may provide a key support to tumor growth and development in a immunocompetent host. What is instead emerging only recently is the increasing contribution that the study of myeloid cells may provide to the identification of prognostic biomarkers and therapeutic targets in cancer patients. Within the febrile race to identify criteria for selecting patients responsive or resistant to immunotherapy with immune checkpoint inhibitors, myeloid cells represent a hot field of investigation. The evidence then that cancer-related myeloid cell dysfunctions are a systemic process that can be thus intercepted in the peripheral circulation, makes these cells a perfect sensor of patient immune suppression and potential source of blood tests that could be easily translated into clinical practise.

Myeloid-derived suppressor cells (MDSC) represent a major subset of circulating dysfuctional myeloid cells in cancer patients, playing a crucial role in cancer development, progression and metastatization. Representing immature myeloid precursors mobilized from the bone marrow by soluble or nanoparticle-related factors produced by the tumor, they progressively accumulate in blood of cancer patients in association with disease progression and poor prognosis. Through a large screening of myeloid markers applied to multicolor cytofluorimetry, we recently defined that broad alterations in the frequency of monocytic MDSC, inflammatory monocytes and granulocytic MDSC, are detected in blood of melanoma patients in association with poor prognosis. On the basis of these data, we defined a Myeloid Index Score (MIS) that predicts prognosis and response to therapy (including immune checkpoint inhibitors) in restrospective and prospectively validated settings. We are presently testing whether MIS does indeed reflect the accumulation of myeloid cells at tumor site.

To identify the mechanisms by which MDSC accumulation occurs, we recently defined an MDSC in vitro model based on the coincubation of normal CD14+ cells with melanoma exosomes (Exo-MDSC). This model likely resembles the process of MDSC genesis in vivo, possibly involving the trafficking of tumor exosomes to the bone marrow and the conditioning of myleoid precursors, with the consequent release and systemic spreading of MDSC. We and others have recently performed studies in murine models clearly showing that melanoma exosomes home to the bone marrow of tumor-bearing mice and induce MDSC accrual and activation. We have also collected evidence that Exo-MDSC highly resembles blood MDSC from melanoma patients, in terms of gene expression profiling, cyto/chemokine secretion and suppressive activity in T cells.

Melanoma exosomes induce MDSC through the direct transfer, from melanoma to CD14+ cells, of a panel of miRs; this processa has a clear relevance in vivo, as MDSC-miR result upregulated in circulating CD14+ cells and plasma of melanoma patients, and in tumor lesions in association with myeloid cell accrual. The silencing of these miRs blocks the protumor and immunosuppressive effect of myeloid cells both in vitro and in murine setting. We are presently using the miR-MDSC model to screen for new MDSC-blocking drugs, that could have a broad application in clinical setting in improving the response of cancer patients to immune checkpoint inhibitors.

Altogether, solid evidence support the protumor and immunosuppressive role of myeloid cells in human cancer, and point to this pathway as a promising source of immune-related prognostic biomarkers and modulating targets in cancers.