Metabolic re-programming of monocytes-macrophages in tumor settings regulates their pro-tumor functions

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Metabolic re-programming is a hallmark of cancer cells, wherein they change their metabolism to adapt to the tumor microenviromment. However, whether immune cells like monocytes and macrophages which are key regulators of cancer progression, also undergo such metabolic changes in a tumor setting is still not known. To address this, we studied the expression of metabolic genes, metabolites, and metabolic flux distribution of targeted metabolic pathways in tumor-conditioned monocytes and macrophages in vitro and in vivo in tumor preclinical model and patients with ovarian cancer. We also performed mechanistic dissections with metabolic inhibitors and knockouts to dissect effect of such metabolic changes on macrophage function in tumors and identify molecular mechanisms involved therein. The results from our integrated metabolic profiling demonstrated a re-wiring of energy metabolism in the tumor-conditioned monocytes/macrophages in presence of tumor cells. This was also validated in vivo in tumor associated macrophages in mice and those from patients, where immuno-metabolic markers associated with this metabolic re-wiring correlated with clinical prognosis. Finally, mechanistic studies linked the metabolic rewiring of these cells to regulate their tumor promoting functions. Collectively, these results indicate a new aspect of the tumor microenvironment, where we identify a metabolic re-programming of monocyte-macrophages to be a key regulator of the tumor promoting functions of these cells, thereby opening roads for using metabolic drugs in combination with conventional therapy.