Impact of lactic acid on human macrophage polarization

Introduction: In established tumors, tumor-associated macrophages (TAM) orchestrate unresolving cancer-related inflammation (M1 properties) and produce growth factors that favor tumor growth, metastasis and angiogenesis (M2-like properties). To date, factors that confer M1 and M2 functional properties to human macrophages remain unknown.
Objective: Elevated levels of lactic acid (LA) being common in most solid tumors, we analyzed the impact of lactic acidosis on human monocyte differentiation.
Methods: Human monocytes were differentiated in GM-CSF, in the absence or presence of 10 mM LA and their phenotype was analyzed at different time-points.
Results: We report that prolonged lactic acidosis induces monocyte differentiation into macrophages (GM+LA-Mφ) harboring an unconventional mixed M1 and M2 functional phenotype. In addition to producing high levels of many inflammatory cytokines and low levels of IL-10, GM+LA-Mφ produce many growth factors (i.e. VEGF, PDGF, OSM, HB-EGF and IL-20) and express prototypic M-CSF-dependent genes. These effects were partly due to the ability of lactic acid to allow autocrine M-CSF consumption by monocytes under differentiation, despite the presence of GM-CSF.
The impact of LA on macrophages is not mimicked by acidosis. It requires the import of lactate into the cells, its oxidation into pyruvate, which induces HIF-1 stabilization. Finally, primary ovarian cancer cells are glycolytic and induce M1/M2 cell generation through an MCT-dependent mechanism. Finally, we show for the first time that most of the TAM present in human ovarian tumors exhibit a mixed M1 (production of IL-8 and IL-1) and M2 (secretion of VEGF) phenotype.
Conclusion: These results identify tumor-derived LA as a missing link reconciling the M2-like features of human TAM with their inflammatory properties and reinforce the potential of therapies that reduce tumor glycolysis or tumor-associated acidosis.

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