After being largely disregarded for decades, tumor immunology has recently come back into prominence, at least in part because of the approval by the US Food and Drug Administration (FDA) of a monoclonal antibody targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4) and the development of dendritic cell (DC)-based therapies. There is widespread consensus on the notion that the optimal efficacy of these immunotherapeutic agents depends upon the elimination of immunosuppressive tumor-infiltrating cells. Indeed, malignant transformation is generally accompanied by the secretion of soluble factors that stimulate the production of immunosuppressive bone marrow and recruit them to the tumor microenvironment. Imhaus suppressive cells are involved in the regulation of a variety of processes, including angiogenesis, inflammation and immunosuppression. The most prominent bone marrow-derived cell population that exerts broadly immunosuppressive functions is constituted by myeloid-derived suppressor cells (MDSC). These cells potently suppress both innate and adaptive immunity by inhibiting T-cell activation, suppressing natural killer (NK)-cell cytotoxicity, favoring the development of regulatory T cells (Tregs) and preventing the maturation of DCs. While Otto Warburg reported his milestone discovery more than 80 years ago, only recently has progress been made in understanding the role of metabolism in oncogenesis and tumor progression. Many tumor types are indeed characterized by enhanced glycolytic flux and convert a major fraction of pyruvate into lactate, even under normoxic conditions. The latter effect is mediated by lactate dehydrogenase A (LDHA), a hypoxia-inducible factor 1α (HIF-1α) target. It is clear that the Warburg effect serves to generate biosynthetic precursors, thus facilitating the survival and rapid proliferation of malignant cells. Is it possible that a tumor environment enriched in lactate also influences antitumor immune responses? It has recently been suggested that the production of lactate by tumor cells impairs immune effectors by inhibiting the cytolytic functions of T cells and by polarizing immune responses toward a Th1/Th17/Th23 pro-inflammatory profile. In addition, lactate is known to inhibit the maturation of DCs. Finally, our recent study adds lactate to the long list of cancer-derived factors that stimulate the generation of MDSCs, which already included interleukin IL-1β, IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte monocyte colony stimulating factor (GM-CSF), prostaglandin E2 (PGE2), tumor necrosis factor α (TNFα), and vascular endothelial growth factor (VEGF). In particular, lactate turned out to exacerbate immunosuppression (by increasing the frequency of MDSCs) and to limit the activity of innate immune effectors (by inhibiting the functions of NK cells), further demonstrating that lactate contributes to the establishment of an immunosuppressive microenvironment for developing tumors (Figure 1). Moreover, a recent study suggests that lactate operates as an endogenous inhibitor of histone deacetylases, hence regulating (at the transcriptional level) a number of genes that not only are involved in metabolism and transcriptional control but also participate in immune responses, such as natural cytotoxicity triggering receptor 1 (NCR1), which encodes an NK-cell activating receptor. Since it has been reported that effector T cells and
Tregs differ from each other with regard to bioenergetic metabolism, high levels of lactate (and/or the consequent decrease in microenvironmental pH) may affect these T-cell subsets in a different fashion. We observed an increased frequency of T cells to infiltrate LDHA-deficient tumors as well as LDHA-proficient lesions developing in mice subjected to a ketogenic diet, a suboptimal surrogate for LDHA inhibition. These observations suggest that reduced levels of lactate may be associated with an improved survival or recruitment of effector T cells. Interestingly, a recent report demonstrates that a ketogenic diet lowers the levels of lactate in head and neck cancer lesions. It would be interesting to investigate how the kinetic of lactate reduction affects the generation of MDSCs and the overall immunological profile in this setting.

Several reports indicate that the pH of the tumor microenvironment can impact on antitumor immune responses. Our study also shows that lowering the local pH from 6.8 to 6.0 results in a significant decrease in the activity of NK cells. Moreover, by utilizing a system for the in vitro generation of MDSCs from mouse bone marrow cells, we demonstrated a decrease in the individual cytotoxic activity of NK cells against target cells at low pH.

In summary, our study highlights a role for tumor-derived lactate in the regulation of NK cells, MDSCs and Tregs, lending further support to the notion that tumor metabolism and immunity are tightly interconnected.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
