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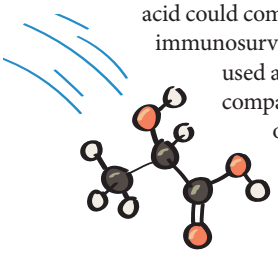
TUMOUR IMMUNOLOGY

Suppressive metabolites

> tumour-derived lactic acid could perturb cytokine production of tumour-infiltrating T and NK cells

Continuous metabolism of glucose to lactate by tumour cells, through upregulation of glycolytic enzymes, such as lactate dehydrogenase A (LDHA), creates a tumour microenvironment rich in lactic acid. Previous studies have suggested a correlation between increased lactate production and tumour progression. Now, Brand *et al.* report that lactic acid accumulation by highly glycolytic tumours is a strategy for immune evasion, thereby affording the tumour a growth advantage.

To investigate whether lactic acid could compromise tumour immunosurveillance, the authors used a melanoma model to compare the growth rate of mouse melanoma B16.SIY cells with reduced levels of *Ldha* (LDHA^{low}) in immunocompetent (C57BL/6) versus immunodeficient (*Rag2*$^{-/-}$*gc*$^{-/-}$) mice. LDHA^{low} tumours, which secreted less lactate, grew at a slower rate and with increased infiltration of T cells and natural killer (NK) cells in immunocompetent mice than control tumours (formed from B16.SIY cells with comparatively higher levels of *Ldha* expressed). By contrast, in *Rag2*$^{-/-}$*gc*$^{-/-}$ mice LDHA^{low} and control tumours developed at the same rate, indicating that immune cell infiltration of LDHA^{low} tumours is effective at limiting tumour expansion. Interestingly, this effect of tumour-induced lactic acid production on the immune cell infiltration seems to be restricted to the local tumour environment, as the composition of immune cells in the blood and spleen of LDHA^{low} tumour-bearing mice was unchanged.



Brand *et al.* identified the immune infiltrate in LDHA^{low} tumours as containing a higher proportion of CD8^{+} T cells and NK cells, with both effector cell types expressing increased levels of interferon-γ (IFNγ). Moreover, IFNγ production was necessary for the control of LDHA^{low} tumour volume, as the growth difference between control and LDHA^{low} tumours was lost in *Ifng*$^{-/-}$ mice. To establish the mechanism by which tumour-derived lactic acid could perturb cytokine production of tumour-infiltrating T and NK cells, the authors incubated CD8^{+} T cells in the presence of $^{13}C_{1}$-labelled lactate and hydrochloric acid to replicate conditions of high lactic acid in the tumour microenvironment. This experiment revealed that lactic acid uptake was sufficient to cause intracellular acidification and suppress expression of nuclear factor of activated T cells (NFAT), a regulator of *IFNG* gene expression during T and NK cell activation.

Finally, the authors related their mouse findings to human melanoma data by analysing a cohort of 44 patients with metastatic melanoma and showed that LDHA expression negatively correlated with survival. Furthermore, biopsy samples from cutaneous melanoma metastases were found to have higher lactate levels with fewer activated T cells than those of normal skin. In summary, this work highlights how LDHA-mediated lactic acid can be used by a tumour as an immunosuppressive metabolite to induce immune tolerance and promote tumour growth.

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ORIGINAL ARTICLE Brand, A. *et al.* LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab.* https://dx.doi.org/10.1016/j.cmet.2016.08.011 (2016)