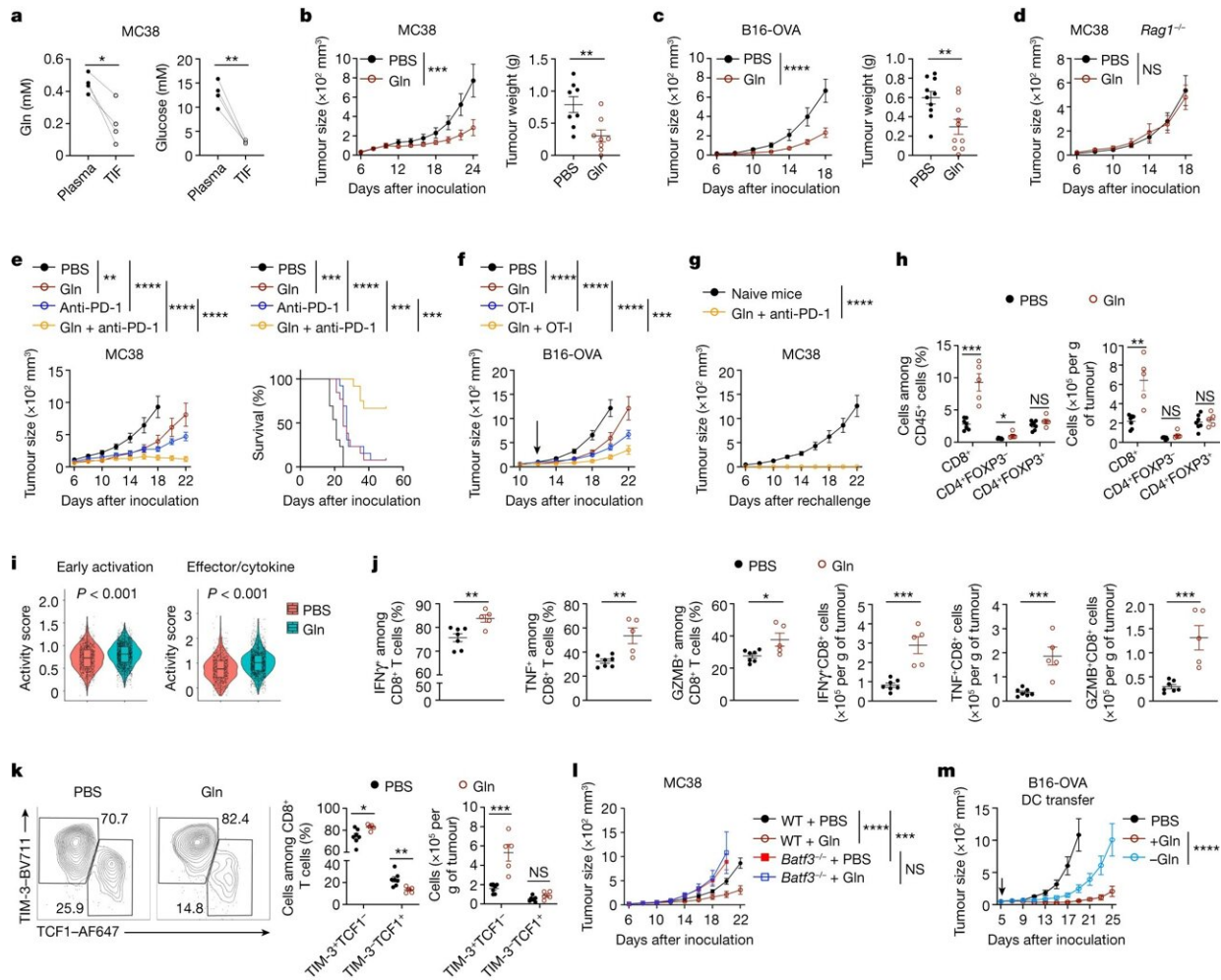


# Immune and tumor cell 'tug-of-war' controls anti-cancer activity, study finds

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Intratumoral glutamine supplementation promotes cDC1-mediated anti-tumor immunity. **a**, Levels of glutamine and glucose in plasma and TIF of mice bearing MC38 tumors at day 15 ( $n = 4$  per group). **b,c**, Growth and endpoint weight of MC38 (**b**;  $n = 8$  per group) and B16-OVA (**c**;  $n = 10$  per group) tumors (day 24

and 18, respectively) after intratumoral PBS or glutamine supplementation. **d**, MC38 tumor growth in *Rag1*<sup>-/-</sup> mice after PBS or glutamine treatment ( $n = 7$  per group). **e**, MC38 tumor growth and mouse survival after indicated treatments ( $n = 12$  for Gln + anti-PD-1,  $n = 13$  for all other groups). **f**, Growth of B16-OVA tumors in mice receiving intratumoral PBS or glutamine with activated OT-I cells (indicated by arrow) ( $n = 10$  per group). **g**, MC38 tumor growth in tumor-free (having received prior glutamine + anti-PD-1 treatment;  $n = 8$ ) or naive mice ( $n = 5$ ) upon challenge with MC38 cells. **h**, Indicated T cell populations at day 15 in MC38 tumors treated with PBS ( $n = 7$ ) or glutamine ( $n = 5$ ). **i**, DCs, CD45<sup>+</sup> non-macrophage immune cells, macrophages and CD45<sup>-</sup> cells were sorted from PBS- and glutamine-treated MC38 tumors and mixed for scRNA-seq analysis. Violin plots show activity scores of early activation and effector/cytokine signaling signatures in intratumoral CD8<sup>+</sup> T cells from MC38 tumors treated with PBS ( $n = 1,113$  cells) or glutamine ( $n = 2,031$  cells). Box plots show the median (center line) with interquartile range of 25% to 75%. **j,k**, IFN $\gamma$ <sup>+</sup>, TNF<sup>+</sup> and granzyme B<sup>+</sup> (GZMB<sup>+</sup>) (**j**) or effector-like (TIM-3<sup>+</sup>TCF1<sup>-</sup>) and stem-like (TIM-3<sup>-</sup>TCF1<sup>+</sup>) (**k**) CD8<sup>+</sup> T cells at day 15 from MC38 tumors treated with PBS ( $n = 7$ ) or glutamine ( $n = 5$ ). **l**, MC38 tumor growth in indicated mice treated with PBS ( $n = 10$  for wild-type,  $n = 8$  for *Batf3*<sup>-/-</sup>) or glutamine ( $n = 9$  for wild-type,  $n = 8$  for *Batf3*<sup>-/-</sup>). WT, wild-type. **m**, Growth rate of B16-OVA tumors after transfer of OVA-pulsed cDC1s activated in the presence or absence of glutamine ( $n = 9$  for DCs treated with glutamine,  $n = 8$  for DCs treated without glutamine). Non-transfer control mice ( $n = 10$ ) received PBS. Data are mean  $\pm$  s.e.m., except in **i**. **a**, Two-tailed paired Student's *t*-test. **b, c,h,j,k**, Two-tailed unpaired Student's *t*-test (**b,c**, tumor weight). **b-g,l,m**, Two-way ANOVA for tumor size. **e**, Mantel-Cox test for survival. **i**, Two-tailed Wilcoxon rank sum test. Data are representative of two (**a,d-h,j,l,m**) or at least three (**b,c,k**) independent experiments. \**P*

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