Cancer Cell

CellPress

Commentary

Immunometabolic gatekeeping: How tissue metabolism conditions tumor immunity

Naomi Iris van den Berg,[1,2,*] Matouš Elphick,[1,2,3,4] Kevin Mulder,[1,2] Omar Bouricha,[1,2] Omid Sadeghi-Alavijeh,[1,5] Xiao Fu,[6,7,9] and Samra Turajlic[2,1,8,9,*]
[1]The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK
[2]Cancer Research UK Manchester Institute, The University of Manchester, Wilmslow Road, Manchester M20 4BX, UK
[3]Department of Bioengineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
[4]The Institute of Cancer Research, 123 Old Brompton Road, London SW7 3RP, UK
[5]Centre for Genetics and Genomics, UCL Department of Renal Medicine, UCL Medical School, London, UK
[6]Cancer Research UK Scotland Institute, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, UK
[7]School of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Bearsden, Glasgow G61 1BD, UK
[8]The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
[9]Senior author
*Correspondence: naomi.vandenberg@crick.ac.uk (N.I.v.d.B.), samra.turajlic@crick.ac.uk (S.T.)
https://doi.org/10.1016/j.ccell.2026.03.002

Why the link between immune infiltration and tumor control varies so strongly across tissues remains unresolved. We propose the "immunometabolic gatekeeping" framework, whereby tissue-intrinsic metabolic activity and waste-handling capacity shape anti-tumour immunity. In high-flux tissues, metabolic stress impairs immune surveillance, decoupling infiltration from control and allowing tumor outgrowth. This framework explains cancer paradoxes—including T cell prognostic heterogeneity, hereditary and pediatric tumor tropisms, sex-biased tumor incidence, and cancer-resistant species—and suggests metabolism-aware strategies for cancer prevention and immunotherapy.

Introduction: Cancer risk through a metabolic lens

Traditional models of cancer emphasize mutations, cell-intrinsic transformation, and immune surveillance, yet tissues differ dramatically in their energetic demands and in their ability to clear metabolic intermediates and byproducts. These differences are not incidental; they determine the biochemical environment in which immune cells operate and in which early lesions evolve. Here, we outline a framework of immunometabolic gatekeeping, in which the metabolic intensity and waste-handling capacity of healthy tissues shape local immune competence and cancer susceptibility. This metabolic constraint helps explain why pediatric and certain hereditary solid cancers show specific tissue tropisms, why men exhibit higher incidence of several tumors, and why T cell infiltration predicts good outcomes in some cancers but poor outcomes or no benefits in others. Note we focus here on solid tissues and cancers, where constrained diffusion makes local waste accumulation particularly relevant; hematological malignancies are beyond the scope of this discussion.

Metabolic tone of healthy tissues as an immune constraint

Mammalian tissues can vary in their metabolic rate by an order of magnitude,[1] the global composite of which is the body's basal metabolic rate. High metabolic rates lead to the production of abundant reactive oxygen species (ROS), lactate, protons, and other organic waste. If diffusion or perfusion cannot match production, metabolic byproducts accumulate locally, even in the absence of disease. Single-cell transcriptomic profiles of fibroblasts and endothelial cells from high-flux organs (e.g., kidney, brain, and eye) reveal elevated expression of key glucose transporter (GLUT1) and pH-handling genes, indicating high energy demand and high homeostasis management following waste production (Table 1). Lineage-encoded tissue metabolism is also expected to shape how resident cells respond to (oncogenic) stress. Here, we focus on immunity without excluding relevant effects on tumor and stromal compartments.

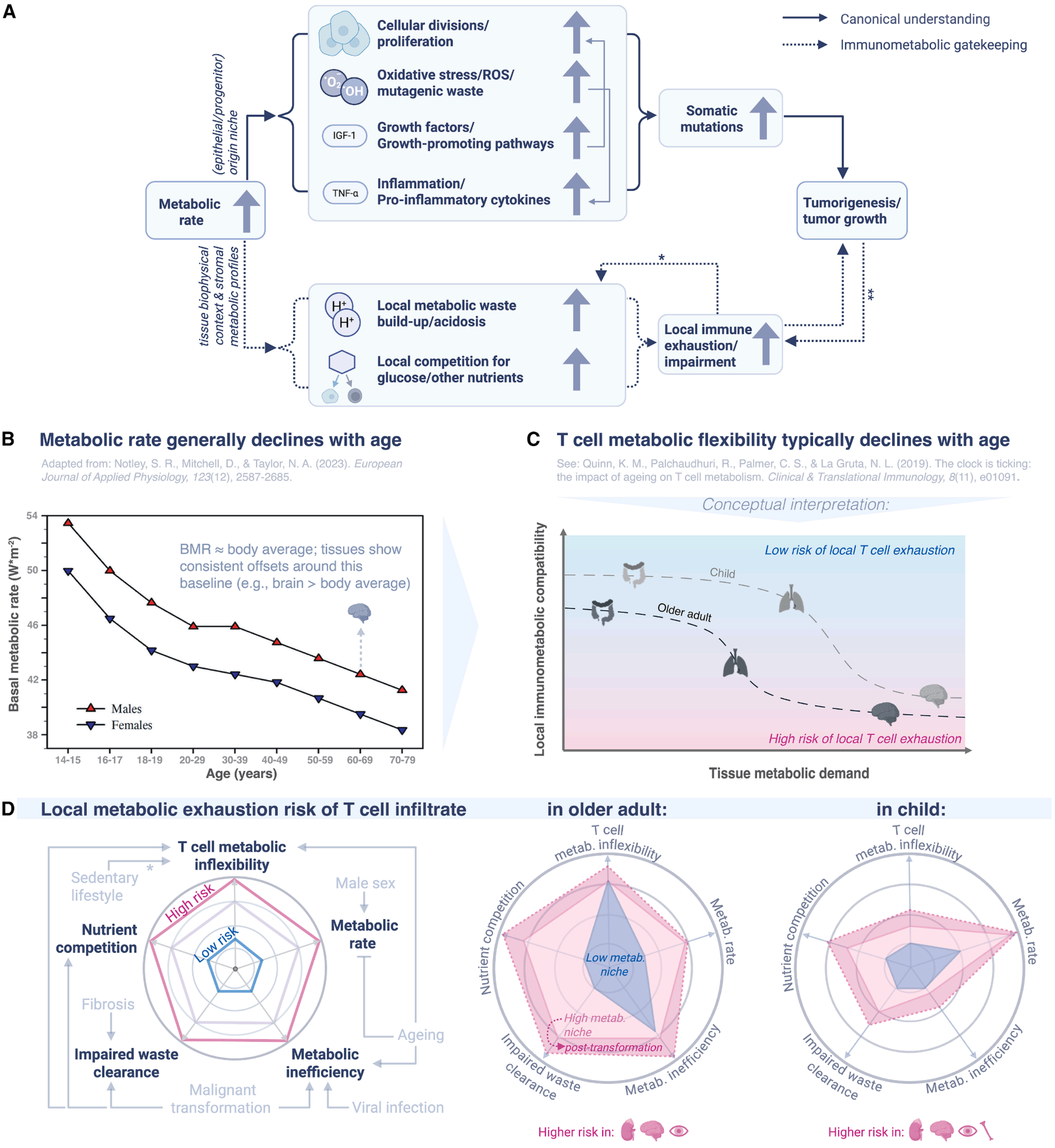
Metabolic byproducts or associated acidosis suppress nearly every arm of antitumor immunity, impairing T cell motility, infiltration, and cytokine production; promoting checkpoint expression; skewing macrophage polarisation toward M2-like phenotypes; and dampening dendritic and natural killer cell cytotoxicity. Moreover, metabolic stress and acidosis can disrupt proteostasis, promoting proteotoxic stress responses that further impair immune cell viability and effector function.[7] In addition, highly active stromal and tumor cells can outcompete T cells for nutrients via, e.g., overexpression of GLUT1, impairing T cell glycolysis and IFNγ production. Glycolysis-dependent effector T cells, particularly cytotoxic CD8$^+$ T and Th1 subsets, may therefore be especially susceptible to metabolic dysfunction in high-flux niches.

This suggests that some tissues are predisposed to form immune-exhausting niches that can be intensified by emerging lesions through metabolic rewiring and genetic programs of immune evasion, rather than needing to create such conditions *de novo*. Primary cancers are notably rare in tissues at metabolic extremes—such as white adipose (low) versus heart/red skeletal muscle (high). While differences in proliferative capacity and lineage-specific programs clearly contribute to this rarity, their minimal metabolic flux or highly efficient, tightly

Table 1. Comparison of CD8⁺ T cell infiltration, prognostic impact, and proxied baseline metabolic activity across 15 normal tissues associated with cancer initiation[a]

Normal tissue (cancer type)	CD8⁺ T cell infiltration → prognosis[2]	*SLC2A1* (GLUT1) expression by fibroblasts and endothelial cells in normal human tissue[13]	pH homeostasis expression by fibroblasts and endothelial cells in normal human tissue[13]	*TOX* expression by T cells in normal human tissue[13]	Mitochondrial resp. average (complex IV) in healthy young mice[1]	No. of publ./ratio of endo. + fib. cells to T cells[13]	Notes
Kidney (renal cell carcinoma)	very poor	high	high	very high	very high	13/3:1	The renal proximal tubule, where many RCCs originate, is among the highest in mitochondrial density and oxygen use
Brain (glioma, glioblastoma)	poor	very high	int-high	very high	very high	23/38:1	–
Eye (uveal melanoma)	poor[3]	very high	high	very high	int-high	6/27:1	Not included in Bruni et al.[2]
Esophageal (esophageal cancer)	poor	very high	very high	high	N/A	4/10:1	–
Prostate gland (prostate cancer)	int-poor	int-high	very high	int-high	N/A	4/2:1	–
Stomach (gastric cancer)	intermediate	int-high	int-high	intermediate	high	4/1:1	–
Pancreas (pancreatic ductal adenocarcinoma)	int-good	high	very high	int-high	intermediate	5/8:1	–
Lung (lung cancers, incl. adenocarcinoma)	int-good	high	high	high	int-high	24/1:1	–
Head and neck	good	N/A	N/A	N/A	N/A	N/A	–
Breast (breast cancer)	very good	intermediate	intermediate	high	N/A	4/9:1	–
Liver (hepatocellular carcinoma)	very good	intermediate	intermediate	low	high	11/1:1	–
Bladder (bladder cancer)	very good	low	low	intermediate	N/A	3/3:1	2 scRNA-seq datasets for "bladder organ," 1 for "urinary bladder"
Fallopian tubes (ovarian cancer)	very good	low	low	low	int-low	3/3:1	–
Skin (melanoma)	very good	low	low	low	low	7/3:1	–
Colon (colorectal cancer)	very good	low	low	low	low	11/1:1	–

[a] Tissues are ordered by the strength and direction of the cross-cohort CD8⁺ T cell infiltration-prognosis relationship as reported in Bruni et al.[2] and Zuo et al.[3] "Poor" = predominantly adverse or null prognostic effect[2]; "very good/poor" = uniformly beneficial/adverse.[2] Tissue-level, cross-publication aggregated "expression" values were extracted from CELLxGENE[13] (Feb. 2026, "disease" = "normal") for "cell type" = "fibroblast," "endothelial cell," or "T cell," filtered to retain "tissue" × "cell type" × "gene" combinations with $\geq$ 10 cells expressing. We calculated cell-count-weighted averages across stromal cell types for each stromal marker panel: *i. SLC2A1*, *ii*. pH-homeostasis genes *SLC9A1*, *SLC4A2*, *SLC4A3*, *CA2*, *CA9*, *CA4*, *SLC4A7*, *SLC4A4,* and *SLC4A5* (gene-level weighted expressions were normalized across tissues to their maximum and then averaged). *TOX* was used as a marker of baseline T cell exhaustion propensity, as it stabilizes the exhausted transcriptional program. "No. of publications" reflects the number of independent single-cell RNA sequencing (scRNA-seq) studies contributing fibroblast, endothelial cell, and/or T cell expression data for the indicated tissue after filtering; stromal to T cell ratios reflect relative cell representation therein. Full analysis and regular updates with database can be found on https://github.com/NaomiIrisvdBerg/immunometabolic_gatekeeping.



B Metabolic rate generally declines with age

Adapted from: Notley, S. R., Mitchell, D., & Taylor, N. A. (2023). *European Journal of Applied Physiology, 123*(12), 2587-2685.

C T cell metabolic flexibility typically declines with age

See: Quinn, K. M., Palchaudhuri, R., Palmer, C. S., & La Gruta, N. L. (2019). The clock is ticking: the impact of ageing on T cell metabolism. *Clinical & Translational Immunology, 8*(11), e01091.

D Local metabolic exhaustion risk of T cell infiltrate

Figure 1. Immunometabolic gatekeeping across tissues and development

(A) Immunometabolic gatekeeping as a complement to canonical models of tumor development. The schematic illustrates how tissue-intrinsic metabolic activity and waste-handling capacity establish baseline biochemical conditions that shape local immune surveillance even prior to transformation. While accumulation of metabolic intermediates and byproducts is known to contribute to cancer development via, e.g., promoting inflammation and mutagenesis, we emphasize a complementary mechanism in which metabolic and proteotoxic debris impair infiltrating immune cells[7] and facilitate tumor initiation and growth.*T cells themselves—especially when metabolically inflexible—may further contribute to an immunometabolically hostile environment.[4] **Tumors directly impose metabolic dysfunction in immune cells by, e.g., tumors transferring mutant mtDNA to infiltrating T cells[14] or by tumors hijacking functional mitochondria from immune cells, including CD8$^+$ T cells.[15]

(B) Basal metabolic rate (BMR) generally declines with age. At any given age, males tend to have higher BMR than females. High-flux tissues such as the brain will have higher metabolic rates than the whole-body average represented by the BMR.

(legend continued on next page)

buffered metabolism may further reduce the likelihood of establishing recurrent waste-rich, immune-suppressive niches.

Reconciling the paradox of T cell infiltration

Although immunometabolic gatekeeping may begin pre-transformation, its consequences extend into tumor progression. When transformation occurs in organs whose parenchyma are normally high flux, the emerging lesion does not arise in a metabolic vacuum; it "inherits" both the surrounding stromal and diffusive baseline and lineage-encoded metabolic wiring of its cell of origin. Even as normal organ function is lost within the transformed tissue, oncogenic reprogramming (e.g., HIF, MYC, and p53 pathway alterations) becomes layered onto this metabolically demanding foundation, extending and intensifying pre-existing metabolic plasticity and potential (Figure 1A). In the early stages, nascent lesions are still embedded in the original hostile environment; immune surveillance is recruited, and immune cells must operate in niches already close to their immunometabolic limits. As the tumor evolves, cancer and (reprogrammed) stromal cells add further glycolytic/oxidative stresses and acquire additional immune-evasive adaptations, progressively tightening local immunometabolic constraints. As the tumor grows, declining surface-area-to-volume ratios may further limit the diffusion and clearance of tumor-generated waste, amplifying local metabolic stress and potentially contributing to size-dependent tipping points in immune control (consistent with, e.g., the ~3 cm clinical threshold in small renal masses).

In cancers such as melanoma, bladder, and colorectal—particularly following surgical resection of the primary tumor with curative intent—high T cell infiltration (e.g., "brisk" infiltration in melanoma) is linked to reduced risk of recurrence and improved outcomes.[2] By contrast, in renal cell carcinoma (RCC), uveal melanoma, lower grade glioma, and glioblastoma multiforme (GBM), cross-cohort analyses indicate that within a given tumor type, patients whose tumors are most heavily infiltrated by effector T cells do not consistently fare better and in some cases do worse than those with lower T cell densities.[2,3] These cancers originate in metabolically high-flux tissues (Table 1), suggesting a unifying explanation: effector immune cells can enter but cannot properly function—and may in fact contribute to an even more immunosuppressive tumor microenvironment (TME) themselves.[4]

Clear cell renal cell carcinoma (ccRCC) illustrates how cell-of-origin context and oncogenic rewiring can entrench immunometabolic failure. Proximal tubule epithelium—ccRCC's likely cell of origin—is among the most metabolically demanding tissues (Table 1), and near-universal VHL loss overlays an HIF-driven glycolytic and angiogenic program onto this high-flux background. Consistent with this, ccRCC CD8$^+$ TILs were shown to be abundant but metabolically impaired—even in early stages of disease[5]—and that metabolic rescue (via pyruvate supplementation or ROS scavengers) partially restored their activation.[6]

Indeed, immune cells themselves are metabolically active participants in this ecosystem; during effector activity they shift toward glycolysis, adding to local lactate and proton production, particularly when metabolically constrained.[4] In already nutrient-limited, waste-rich microenvironments, this can create a positive feedback loop in which infiltrating T cells both experience and reinforce metabolic stress, deepening exhaustion. This dynamic may help explain why, in some tumor types with especially hostile metabolic microenvironments, high T cell infiltration associates with poorer rather than better prognosis (Table 1; Figure 1A).

Rather than viewing infiltration as universally beneficial, immunometabolic gatekeeping argues that the prognostic value of infiltration depends on both tumor-intrinsic evolution and tissue metabolic context. In metabolically quiescent tissues, infiltrating T cells are more likely to retain metabolic compatibility and function, and immune suppression is driven predominantly by tumor-acquired mechanisms. In metabolically intense tissues, infiltrating T cells begin at a disadvantage—entering niches already competitive for nutrients, high in organic waste, and prone to acidification—onto which tumor evolution can superimpose additional (epi)genetic modes of immune escape, further decoupling infiltration from effective control.

Fibrosis and physical barriers as immunometabolic modulators

Physical microenvironmental features shape metabolic and immune dynamics. Fibrosis and cell-dense stromal remodeling restrict diffusion and perfusion of oxygen, nutrients, and waste, effectively increasing local byproduct concentrations. Stiff extracellular matrices also induce glycolytic reprogramming in fibroblasts—even in the absence of cancer—via upregulation of GLUT1 and MCT4.[8] Within the immunometabolic gatekeeping framework, such effects may create waste-rich niches that blunt immune surveillance, offering a complementary

(C) Age-dependent decline in T cell metabolic flexibility and conceptual relationship to tissue demand. Increasing tissue metabolic demand constrains local immunometabolic compatibility, raising the risk of local T cell exhaustion. Age-related declines in T cell metabolic flexibility (i.e., ability to change fuel sources to meet energy demands) shift this relationship downward, such that a given tissue is more likely to exceed the functional tolerance of T cells in older adults than that in children. Pediatric solid tumors, while rare, arise disproportionately in metabolically intense organs, consistent with tissue-specific metabolic priming during development. Primary bone tumors (osteosarcoma and Ewing sarcoma) similarly emerge during periods of rapid skeletal growth, when local metabolic demand is transiently high.

(D) Local metabolic exhaustion risk of T cell infiltration across tissues and ages. This qualitative schematic illustrates how multiple metabolic factors—tissue metabolic rate, metabolic inefficiency, nutrient competition, impaired waste clearance, and T cell metabolic inflexibility—combine to shape local T cell metabolic exhaustion risk. Axes represent qualitative contributors to local immunometabolic stress; increased radial extent reflects greater constraint on T cell function. Following transformation, local metabolic stress in high-flux tissues increases due to tumor, (reprogrammed) stromal, and immune cell demand and reduced metabolic efficiency (via Warburg effect), even as overall organ function may decline. A shared color scheme is used across the example spider plots. *The aging-induced decline in T cell metabolic flexibility can be mitigated by physical activity; older active adults' T cells show better mitochondrial-glycolytic switching, a higher mitochondrial dependence and lower glucose dependence at rest, as well as a reduced inflammatory phenotype and lower metabolic demand compared to T cells of less active peers.[10]

Figure made using BioRender.

explanation for increased cancer risk in fibrotic diseases (e.g., cirrhosis, chronic pancreatitis, and pulmonary fibrosis) beyond chronic inflammation, aberrant repair, physical immune blockage, or dysregulated signaling.

Viral oncogenesis as natural immunometabolic reprogramming

Oncogenic viruses commonly reprogram and upregulate host-cell metabolism toward higher aerobic glycolysis to support replication. These shifts increase lactate and ROS, mirroring tumor-driven (i.e., Warburg-mediated) immunosuppression and demonstrating that metabolic reprogramming can precede transformation. Viral-induced fibrosis or stromal signals further metabolically stress the tissue, impairing immune function. Viral oncogenesis therefore offers a natural experiment in immunometabolic gatekeeping; viral infections can impose Warburg-like and fibrotic metabolic stresses on tissues, narrowing the window for effective immune surveillance even before overt transformation, complementing established genetic and inflammatory mechanisms of virus-induced cancer.

Tissue tropism in hereditary and pediatric cancers

Hereditary cancer syndromes driven by germline mutations in metabolic pathways (e.g., *VHL*, *SDH*, and *FH*) often show organ tropism that is not easily accounted for by the ubiquity of the germline mutation or by simple cell-of-origin models. In VHL disease, individuals carry a germline *VHL* mutation in all tissues, yet clinically apparent lesions arise predominantly in metabolically intense sites (i.e., the renal cortex, eye, brain/CNS, and adrenal medulla). This tropism is usually interpreted as reflecting tissue-specific metabolic advantages of *VHL* loss in high-flux organs. Within our framework, these same tissues may also impose stronger immunometabolic constraints, potentially contributing to where VHL-deficient clones progress versus remain controlled.

Pediatric solid tumors show similar patterns; while rare overall, they arise disproportionately in metabolically intense organs, such as the brain/CNS (glioma and medulloblastoma), adrenal gland (neuroblastoma), kidney (renal tumors and Wilms), and eye (retinoblastoma). Germline or early developmental mutations and tissue-specific developmental programs clearly play central roles, yet pediatric tumor tropism suggests that both immune and metabolic state shape the selective landscape in which emerged clones progress. Periods of high metabolic demand and rapid remodeling may transiently narrow the functional margin of the pediatric immune system and alter the fitness costs and benefits of oncogenic events, allowing transformed progenitors to expand in particular tissues (Figures 1B–1D), without implying that immune surveillance failure is the sole driver of pediatric tumorigenesis.

Sex differences and systemic metabolic tone

Men have higher incidence of numerous solid tumors, including kidney, liver, esophageal, and bladder cancers. While lifestyle and hormone differences can play a role, the etiology for these disparities remains inconclusive. However, emerging data points to sex-specific metabolic dimorphism. For instance, male kidneys exhibit approximately 2-fold higher lactate production than females in non-diseased rat models.[9] Higher basal metabolic rate in males compared to females (matched for age and body weight) may both increase intrinsic mutagenic/metabolic stress and generate more acidic or waste-prone microenvironments (Figure 1A). In our framework, this systemic dimorphism narrows the functional margin for immune surveillance across tissues, providing a complementary layer to tumor-intrinsic explanations for male-biased cancer risk in most shared/non-reproductive anatomic sites (Figures 1B–1D).

Systemic metabolic states, including obesity, hyperglycemia, and chronic inflammation, also modulate immunometabolic tone. Hyperglycemia increases substrate availability for glycolysis while inflammation and insulin resistance impair immune metabolic flexibility. Sedentary behavior reduces adult mitochondrial adaptability in T cells,[10] making them more vulnerable to acidic or nutrient-competitive environments. These systemic states are well known to influence tumor-intrinsic evolution and signaling (e.g., via growth factors and insulin/IGF axes); in parallel, our framework highlights how they can also erode immune metabolic fitness and thereby intensify tissue-level vulnerability.

Cross-species patterns and cancer-resistant mammals

Immunometabolic gatekeeping offers a unifying explanation for several cross-species cancer paradoxes. Large mammals have lower mass-specific metabolic rates, producing fewer metabolic byproducts per gram of tissue, in accordance with allometric scaling laws (Kleiber's law). However, the physical process of passive diffusion of small molecules (governed by Fick's laws) does not scale allometrically with body size, such that diffusion coefficients are largely conserved across species. Therefore, improved metabolic homeostasis may help explain why large, long-lived species show lower spontaneous tumorigenesis despite greater cellularity and longevity. While taxon-specific genetic factors contribute (e.g., *TP53* expansions in elephants), inherently lower predisposition to metabolic waste accumulation may be a complementary, universal layer to explain cancer resistance in large animals.

Conversely, some small mammals show remarkable cancer resistance, such as naked mole rats (NMRs). Living in chronically hypoxic burrows, NMRs exhibit extreme metabolic suppression—up to 85% in acute hypoxia—and downregulate glycolysis, β-oxidation, and ATP-consuming processes, thereby sparing small carbohydrate stores and minimizing the accumulation of anaerobic end products.[11] Accordingly, it may be the NMR's unusual metabolic programs (and resulting microenvironmental states) that help prevent early transformed clones from ever reaching permissive, immune-evading niches, shifting emphasis from purely cell-intrinsic resistance mechanisms to an immunometabolic barrier to tumor outgrowth.

Both large, long-lived animals with improved metabolic homeostasis and small mammals with specialized metabolic adaptations maintain tissue ecosystems less prone to immune-suppressive byproduct accumulation, illustrating that cancer resistance may in part be aided by metabolic suppression and efficient waste management.

Beyond cancer-resistant species on metabolic extremes, the immunometabolic gatekeeping model holds in broader cross-species comparisons; a comparative genomics study across nearly 200 vertebrates found that genes whose conservation levels correlate negatively with cancer resistance are enriched for metabolic functions,[12] suggesting that metabolic activity contributes to cancer incidence disparities across species. Direct cross-species measurements of immune surveillance efficiency are scarce, so this signal does not by itself demonstrate enhanced immunity in cancer-resistant taxa. Rather, this signal is consistent with the hypothesis that differences in tissue metabolism shape the conditions under which immune surveillence operates, as proposed in our framework (Figure 1A), now viewed across species.

Therapeutic and preventive implications

Viewing tumors as arising within pre-existing metabolic constraints highlights key strategies:

1. **Buffering local acidity and reducing glycolytic flux**: sodium bicarbonate, MCT inhibitors, GLUT1 inhibitors, and LDHA inhibitors have shown efficacy in preclinical models. These interventions aim to reduce the metabolic hostility of the environment, potentially synergizing with checkpoint blockade.
2. **Modulating systemic metabolic tone**: caloric restriction, dietary amino-acid modulation, GLP-1 receptor agonists, and physical activity have been associated with reduced cancer risk and improved immune metabolic function.
3. **Stratifying tumors by metabolic ecology**: the metabolic intensity of the tissue of origin may help predict which tumors will respond to immunotherapy, where metabolic interventions should be prioritized, and which early lesions require active surveillance.
4. **Intervening in high-risk tissues**: For genetically predisposed individuals (e.g., *VHL* mutation carriers), interventions targeting early metabolic shifts—buffering acidification, modulating glycolytic tone, or enhancing perfusion—may delay transformation or progression.

While caution is warranted and further clinical evidence is needed, the overall principle remains: restoring and optimizing immunometabolic compatibility may be an important synergist in achieving successful (immuno)therapy of solid cancers.

Conclusion

Immunometabolic gatekeeping reframes anti-tumor immunity as a property of tissue metabolism rather than exclusively of tumor genetics or the TME. On its own, immunometabolic gatekeeping does not predict cancer incidence, which is often dominated by mutational load, cell-intrinsic programs and the exposome. However, when mutational load is low (i.e., in children) or constrained (i.e., when the first event is defined by germline mutations in metabolic genes), immunometabolic tone is expected to align more closely with tissue tropism and incidence. Tissues with high metabolic flux and limited waste clearance create environments where immune cells can rapidly lose functional capacity, explaining why some tumors grow despite abundant infiltration and why certain organs and species are strikingly cancer resistant. By integrating metabolic ecology with immune dynamics, this framework provides a unifying way to bridge paradoxes in cancer biology and to design metabolism-aware strategies for prediction, prevention, and therapy.

ACKNOWLEDGMENTS

We thank Anne-Laure Cattin, Matthew Vander Heiden, Karen Vousden, Husayn Pallikonda, Ilaria Malanchi, and Max Emmerich for their helpful insights in discussions about the concept of this framework. We thank Andrew Porter for his useful feedback on the manuscript. We also thank the Wellcome Cancer Evolution summer school and Cambridge University Isaac Newton Institute's Mathematical Foundations of Oncological Digital Twins workshop (OOEW07) for helpful insights and discussions driving the further development of the framework. We thank the MANIFEST program, supported by the UK Government's Office for Life Sciences and the Medical Research Council (grant ref.: MR/Z505158/1), which funds this work.

DECLARATION OF INTERESTS

S.T. has received speaking fees from Roche, AstraZeneca, Novartis, and Ipsen and has filed patents on Indel mutations as a therapeutic target and predictive biomarker (PCTGB2018/051893) and Clear Cell Renal Cell Carcinoma Biomarkers (P113326GB).

REFERENCES

1. Sarver, D.C., Saqib, M., Chen, F., and Wong, G.W. (2024). Mitochondrial respiration atlas reveals differential changes in mitochondrial function across sex and age. eLife *13*, RP96926. https://doi.org/10.7554/eLife.96926.4.
2. Bruni, D., Angell, H.K., and Galon, J. (2020). The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat. Rev. Cancer *20*, 662–680. https://doi.org/10.1038/s41568-020-0285-7.
3. Zuo, S., Wei, M., Wang, S., Dong, J., and Wei, J. (2020). Pan-Cancer Analysis of Immune Cell Infiltration Identifies a Prognostic Immune-Cell Characteristic Score (ICCS) in Lung Adenocarcinoma. Front. Immunol. *11*, 1218. https://doi.org/10.3389/fimmu.2020.01218.
4. Chen, C., Zheng, H., Horwitz, E.M., Ando, S., Araki, K., Zhao, P., Li, Z., Ford, M.L., Ahmed, R., and Qu, C.-K. (2023). Mitochondrial metabolic flexibility is critical for CD8+ T cell antitumor immunity. Sci. Adv. *9*, eadf9522. https://doi.org/10.1126/sciadv.adf9522.
5. Annels, N.E., Denyer, M., Nicol, D., Hazell, S., Silvanto, A., Crockett, M., Hussain, M., Moller-Levet, C., and Pandha, H. (2023). The dysfunctional immune response in renal cell carcinoma correlates with changes in the metabolic landscape of ccRCC during disease progression. Cancer Immunol. Immunother. *72*, 4221–4234. https://doi.org/10.1007/s00262-023-03558-5.
6. Siska, P.J., Beckermann, K.E., Mason, F.M., Andrejeva, G., Greenplate, A.R., Sendor, A.B., Chiang, Y.-C.J., Corona, A.L., Gemta, L.F., Vincent, B.G., et al. (2017). Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma. JCI Insight *2*, e93411. https://doi.org/10.1172/jci.insight.93411.
7. Wang, Y., Ma, A., Song, N.-J., Shannon, A.E., Amankwah, Y.S., Chen, X., Wu, W., Wang, Z., Saadey, A.A., Yousif, A., et al. (2025). Proteotoxic stress response drives T cell exhaustion and immune evasion. Nature *647*, 1025–1035. https://doi.org/10.1038/s41586-025-09539-1.
8. Ponce, I., Garrido, N., Tobar, N., Melo, F., Smith, P.C., and Martínez, J. (2021). Matrix Stiffness Modulates Metabolic Interaction between Human Stromal and Breast Cancer Cells to Stimulate Epithelial Motility. Metabolites *11*, 432. https://doi.org/10.3390/metabo11070432.
9. Wen, Y., Qi, H., Østergaard Mariager, C., Mose Nielsen, P., Bonde Bertelsen, L., Stødkilde-Jørgensen, H., and Laustsen, C. (2020). Sex Differences in Kidney Function and Metabolism Assessed Using Hyperpolarized [1-13C]Pyruvate Interleaved Spectroscopy and Nonspecific Imaging. Tomography *6*, 5–13. https://doi.org/10.18383/j.tom.2020.00022.
10. Hazeldine, J., Withnall, E., Llibre, A., Duggal, N.A., Lord, J.M., and Sardeli, A.V. (2025). Physical Activity Modifies the Metabolic Profile of CD4 + and CD8 + T-Cell Subtypes at Rest and Upon Activation in Older Adults. Aging Cell *24*, e70104. https://doi.org/10.1111/acel.70104.

11. Farhat, E., Devereaux, M.E.M., Pamenter, M.E., and Weber, J.-M. (2020). Naked mole-rats suppress energy metabolism and modulate membrane cholesterol in chronic hypoxia. Am. J. Physiol. Regul. Integr. Comp. Physiol. *319*, R148–R155. https://doi.org/10.1152/ajpregu.00057.2020.

12. Nair, N.U., Cheng, K., Naddaf, L., Sharon, E., Pal, L.R., Rajagopal, P.S., Unterman, I., Aldape, K., Hannenhalli, S., Day, C.-P., et al. (2022). Cross-species identification of cancer resistance–associated genes that may mediate human cancer risk. Sci. Adv. *8*, eabj7176. https://doi.org/10.1126/sciadv.abj7176.

13. CZI Cell Science Program, Abdulla, S., Aevermann, B., Assis, P., Badajoz, S., Bell, S.M., Bezzi, E., Cakir, B., Chaffer, J., Chambers, S., et al. (2025). CZ CELLxGENE Discover: a single-cell data platform for scalable exploration, analysis and modeling of aggregated data. Nucleic Acids Res. *53*, D886–D900. https://doi.org/10.1093/nar/gkae1142.

14. Ikeda, H., Kawase, K., Nishi, T., Watanabe, T., Takenaga, K., Inozume, T., Ishino, T., Aki, S., Lin, J., Kawashima, S., et al. (2025). Immune evasion through mitochondrial transfer in the tumour microenvironment. Nature *638*, 225–236. https://doi.org/10.1038/s41586-024-08439-0.

15. Terasaki, A., Bhatnagar, K., Weiner, A.T., Tan, Y., Szeifert, V., Huang, H.-L., Wiggers, L., Rodrigues, V., Rada, C.C., Shankar, V., et al. (2026). Mitochondrial transfer from immune to tumor cells enables lymph node metastasis. Cell Metab. *38*, 388–398.e7. https://doi.org/10.1016/j.cmet.2025.12.014.