Metabolism - A cornerstone of cancer initiation, progression, immune evasion and treatment response

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Highlights

- Crosstalk between metabolism and epigenetics can be a driver of cancer
- Nucleotide metabolism is a common metabolic vulnerability of proliferating tumors
- Metastasis formation depends on energy and antioxidant metabolism
- Cancer cells impair the anti-tumor immune response
- Metabolic rewiring and microbiota metabolism can define therapy response

Abstract

Cancer is not a single disease, but a spectrum of diseases with common hallmarks. One of these hallmarks is deregulated metabolism. Changes in the metabolism of cancers are not a mere downstream event of an oncogenic transformation; rather, metabolism is an essential cornerstone enabling various aspects of cancer. In this review, we highlight the role of metabolism in cancer initiation, proliferation, metastasis formation, immune evasion, and therapy response. We further provide metabolic concepts by which metabolic pathways support these different aspects of cancer.

Introduction

Metabolism is a cellular process required for the survival and proliferation of all cells. Increased proliferation and sustained survival are hallmarks of cancer (1) that can be targeted for therapy (2). Thus, it is not surprising that cancer cells exhibit an altered metabolism to fuel their increased energy and biomass requirements. However, it has become clear that metabolic alterations in cancer are not only a consequence of an

oncogenic transformation, but essential changes that support and/or drive cancer initiation, progression and treatment response. In this review, we present the current knowledge on the role of metabolism in different aspects of cancer.

Crosstalk between metabolism and epigenetics can be a driver of cancer

Only few changes in metabolism can be considered drivers of tumor initiation. A common feature of all such metabolic changes is the induction of epigenetic remodeling. In particular, metabolite concentrations alter the activity of enzymes that modify DNA and/or histones (3, 4). Consequently, a change in the global transcriptional program occurs, which can result in tumor initiation (Figure 1a). Examples are mutations or loss of the TCA cycle enzymes isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) (5-7). Each of these tumor-driving alterantion results in the accumulation of a particular metabolite (2-hydroxyglutarate with IDH mutation, succinate with SDH mutation, and fumarate with FH mutation) that inhibits ten-eleven translocation methylcytosine dioxygenase (TET) enzyme activity by preventing the conversion of the substrate α-ketoglutarate to succinate and consequently the demethylation of DNA (8-12). However, epigenetic remodeling may only be a part of the mechanism that enables metabolism-driven tumor initiation. While hereditary SDH mutations disrupt epigenetic homeostasis in each organ, only particular cell types and tissues, such as paraganglia, are prone to tumor initiation (13). Additionally, mutations in SDH are found in each subunit of the enzyme and always result in succinate accumulation, but aggressive tumors predominantly arise from SDH mutations in subunit B (13). Interestingly, SDH mutations are not only associated with tumor initiation, but can also lead to neurodegeneration (14), which constitutes the opposite of a proliferation-defined disease. These findings indicate that further cellular changes, beyond epigenetic remodeling, are necessary to enable metabolism to initiate tumors (15, 16). One reason for the inability of metabolite concentration-induced epigenetic remodeling to drive tumor initiation in any cell might be the basal metabolism of the tumor-originating cell (17). In conclusion, crosstalk with epigenetics is required, but likely not sufficient, to explain the ability of metabolic changes to initiate tumors.

Nucleotide metabolism is a converging metabolic vulnerability of proliferating tumors

A hallmark of tumors is uncontrolled proliferation (18, 19). Any biosynthetic pathway supporting proliferation may therefore be considered a drug target in cancer treatment. Yet, cancer therapy drug screens conducted in the 1950s mainly identified compounds that target nucleotide biosynthesis, and some are still used as chemotherapeutics today (2, 20, 21). Accordingly, recent research has identified changes in nucleotide metabolism as a converging metabolic vulnerability of tumors (22-27) (Figure 1b). While targeting the enzymes of nucleotide biosynthesis in tumors also impairs proliferating non-transformed cells, this limitation could be overcome by targeting metabolic pathways that fuel nucleotide biosynthesis. There is evidence suggesting that such metabolic pathways depend predominantly on the tumor microenvironment (28-30) (Figure 1b). This observation provides an opportunity for cancer treatment: tumors within the same organ could be treated

with the same drugs regardless of their origin. However, the tumor microenvironment is quite flexible, as tumor cells and tumor-associated stromal cells continually shape the microenvironment (4). Thus, intra-tumor heterogeneity and instability can arise over time, contributing to treatment resistance. Taken together, proliferation is the most targeted phenotype of cancer cells, and agents targeting directly or indirectly nucleotide metabolism are still heavily used in the clinic; however, modulating cancer phenotypes beyond proliferation could lead to more specific and effective drug targets.

Metastasis formation depends on energy and antioxidant metabolism

Metastasis, the progression of cancer to distant organs, accounts for up to 90% of cancer mortality (17, 31). During metastasis formation, cancer cells undergo multiple cellular changes that support each metastatic step (32). First, cancer cells disseminate from the primary tumor via the circulatory system to distant organs. Upon survival and a possible dormancy state, they colonize a distant organ, which results in the formation of metastases. These will eventually grow and build secondary tumors. Given that each of these metastatic steps is defined by one or more different cellular phenotypes, it is not surprising that metabolism changes accordingly. While the initial invasive phase that allows cancer cells to disseminate to the circulatory system seems metabolically diverse (33-40), the later steps – particularly survival in the circulation and colonization of a site – require increased antioxidant (41) and energy metabolism, respectively (Figure 2a). In particular, antioxidant treatment increases the survival of cancer cells in the circulation (41, 42). Moreover, cancer cells without matrix attachment (in vitro abstraction of circulating tumors cells) upregulate the pentose phosphate pathway (43) and enrich their reactive oxygen species scavenging capacity, predominately in the mitochondria (44). Moreover, recent data suggest that cancer cells colonizing a distant organ have an increased energy need. In addition, metabolic rewiring driven by this energy requirement seems to be organ- and potentially oxygen tension-dependent. In support of this, energy production from proline catabolism (45) and upregulated mitochondrial metabolism (46) support lung colonization, while cancer cells undergoing liver colonization can scavenge extracellular bioenergetics (47) and rely on glycolysis (48). Interference of specific energy-providing pathways in colonizing cancer cells has shown promising results in mouse models (45, 48). While the reasons for these particular metabolic patterns in circulating and colonizing cancer cells remain to be fully determined, effectively preventing and treating metastasis formation is expected to have a major impact on patient survival. Further mechanistic insight, including research in multiple metastatic niches, on cancer cells of different origin and genetic drivers is needed to evaluate the extent to which these emerging metabolic vulnerabilities can be translated to the clinic.

Cancer cells impair the anti-tumor immune response by metabolic competition, inhibition and reprograming

Both innate and adaptive immunity contribute to cancer initiation, proliferation, and progression. Impaired anti-tumor innate immune programs of macrophages (with subsequent activation of a pro-tumorigenic immune response) have been implicated

in supporting cancer progression towards metastasis formation (49, 50). On the other hand, the failure of anti-tumor, lymphocyte-mediated adaptive immunity can boost cancer initiation and proliferation (50, 51). While the lack of anti-tumor immunity may be due to various factors, the metabolism of cancer cells certainly contributes by changing metabolite availability in the tumor microenvironment (Figure 2b). Cancer metabolism can suppress the anti-tumor immune response through: 1) metabolite excretion; and/or 2) nutrient deprivation. First, cancer cells can release metabolites (such as lactate (52) and fatty acids (53)) that hinder the proliferation and/or effector function of anti-tumor lymphocytes (while promoting proliferation and regulator function of pro-tumor lymphocytes (54)). Moreover, metabolites released by cancer cells (such as lactate) can reprogram macrophages from an anti-tumor to a pro-tumor polarization (55). Second, cancer cells reduce the availability of nutrients that anti-tumor lymphocytes require for proliferation and/or effector function. This latter change of the microenvironment can be induced by a direct competition between cancer cells and anti-tumor lymphocytes for nutrients such as glucose (56, 57), or indirectly when cancer cells initiate the release of nutrient degradation enzymes by tumor associated macrophages or tolerogenic dendritic cells to the microenvironment. Examples include cancer cells releasing indoleamine-2,3-dioxygenase (IDO) to reduce tryptophan (58), and arginase (ARG) 1 to reduce arginine (55, 59)). Catabolites of tryptophan (kynurenines) and arginine (nitric oxide) have been further implicated in immunosuppression (60, 61). Interestingly, some cancer cells themselves express IDO and thereby contribute to the inhibition of anti-tumor lymphocytes (62). Taken together, these data suggest that cancer metabolism is an important determinate of the immune response inhibiting anti-tumor and promoting pro-tumor immunity (Figure 2b).

Metabolic rewiring and microbiota metabolism can define therapy response

Poor response to therapy, including drug resistance, is a major challenge in cancer treatment. Often, the reasons for therapy failure are not known. Yet, it has recently emerged that cancer cell and host metabolism can dictate therapy response (Figure 3). Recent studies have identified several metabolic rewiring mechanisms that enable the resistance of cancer cells to drugs. Pancreatic cancer cells can overcome nucleotide metabolism inhibition (with gemcitabine, a nucleoside analog) by metabolic activation of counteracting signaling pathways (63) and increased pyrimidine biosynthesis from glucose (64). Thus, targeting multiple metabolic pathways will be required to counteract drug resistance mechanisms in pancreatic cancers (65). Similarly, MYC-activated glutamine metabolism is a response to CDK4/6 blockade that could be targeted to overcome therapy resistance (66). Moreover, energy metabolism emerges as a metabolic vulnerability of cancer cells resistant to non-metabolic chemotherapeutic agents (67-69). Thus, we have limited knowledge on how and to what extent metabolic rewiring causes therapy resistance, but initial data are promising and might lead to rational combinations of metabolic drugs with chemotherapeutic agents and targeted therapy.

In addition to cancer metabolism, the host metabolism impacts therapy response (Figure 3). In particular, the metabolism of the gut microbiota has been recently identified to modulate therapy response. Two studies investigated the efficacy of

typical chemotherapies in the presence of different microbes using *C. elegans* as a model system for rapidly proliferation. Interestingly, *E. coli* in the gut microbiota of *C. elegans* convert the anti-pyrimidine drugs 5-fluorouracil (5-FU) and 5-fluoro-2'-deoxyuridine (FUDR) to 5-fluorouridine monophosphate (FUMP), which in turn increases treatment response (70, 71). This enhancing effect could be further boosted or impaired based on dietary supplements (70). Another microbiota species, namely *Comamonas,* decreased FUDR efficacy, but increased the efficacy of the topoisomerase I inhibitor camptothecin through an unknown mechanism (71). Strikingly, in humans, response to immunotherapy is at least partly defined by the microbiota (72), urging the need to better understand how the microbiota alters drug metabolism (Figure 3). These findings collectively suggest that metabolism directly or indirectly (via the microbiota) drives therapy response in cancer patients. Consequently, comprehensive treatment concepts shaping the metabolism of cancer cells and the host could be combined with targeted treatment and chemotherapy to overcome treatment failure.

Conclusion

Metabolism has emerged as a key player in cancer. Its central role in all stages of the disease suggests that metabolism-based drugs are essential for effective treatment and eventual cure of cancer (2). Mechanistic understanding and further integration of cancer, immune, and host metabolism with other drivers of cancer such as the (epi)genetic landscape are needed to develop innovative strategies against this deadly disease.

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References

1. Hanahan D & Weinberg Robert A (2011) Hallmarks of Cancer: The Next Generation. *Cell* 144(5):646-674.
2. Fendt S-M (2017) Is There a Therapeutic Window for Metabolism-Based Cancer Therapies? *Frontiers in Endocrinology* 8:150.

3. Lorendeau D, Christen S, Rinaldi G, & Fendt S-M (2015) Metabolic control of signaling pathways and metabolic auto-regulation. *Biology of the Cell* 107(8):251–272.
4. Rinaldi G, Rossi M, & Fendt S-M (2017) Metabolic interactions in cancer: Cellular metabolism at the interface between the microenvironment, the cancer cell phenotype and the epigenetic landscape. *WIREs Syst Biol Med* 2018 Jan;10(1). doi: 10.1002/wsbm.1397.
5. Frezza C & Gottlieb E (2009) Mitochondria in cancer: Not just innocent bystanders. *Seminars in cancer biology* 19(1):4-11.
6. Linehan WM, Srinivasan R, & Schmidt LS (2010) The genetic basis of kidney cancer: a metabolic disease. *Nat Rev Urol* 7(5):277-285.
7. Cohen A, Holmen S, & Colman H (2013) IDH1 and IDH2 Mutations in Gliomas. *Current neurology and neuroscience reports* 13(5):345-345.
8. Lu C*, et al.* (2012) IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature* 483(7390):474-478.
9. Xiao M*, et al.* (2012) Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. *Genes & Development* 26(12):1326-1338.
10. Letouze E*, et al.* (2013) SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer cell* 23:739-752.
11. Laukka T*, et al.* (2016) Fumarate and Succinate Regulate Expression of Hypoxia-inducible Genes via TET Enzymes. *Journal of Biological Chemistry* 291(8):4256-4265.
12. Sciacovelli M*, et al.* (2016) Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition. *Nature* 537(7621):544-547.
13. Evenepoel L*, et al.* (2015) Toward an improved definition of the genetic and tumor spectrum associated with SDH germ-line mutations. *Genet Med* 17(8):610-620.
14. de Moura MB, dos Santos LS, & Van Houten B (2010) Mitochondrial dysfunction in neurodegenerative diseases and cancer. *Environmental and molecular mutagenesis* 51(5):391-405.
15. Lorendeau D*, et al.* (2016) Dual loss of succinate dehydrogenase (SDH) and complex I activity is necessary to recapitulate the metabolic phenotype of SDH mutant tumors. *Metabolic engineering*. 2017 Sep;43(Pt B):187-197. doi: 10.1016/j.ymben.2016.11.005
16. Tyrakis PA*, et al.* (2017) Fumarate Hydratase Loss Causes Combined Respiratory Chain Defects. *Cell Reports* 21(4):1036-1047.
17. Elia I, Schmieder R, Christen S, & Fendt S-M (2016) Organ-Specific Cancer Metabolism and Its Potential for Therapy. *Handbook of Experimental Pharmacology* 233:321-353.
18. Lunt SY & Vander Heiden MG (2011) Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. *Annu Rev Cell Dev Biol* 27:441-464.
19. Hanahan D & Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144.
20. Luengo A, Gui DY, & Vander Heiden MG (2017) Targeting Metabolism for Cancer Therapy. *Cell Chemical Biology* 24(9):1161-1180.

21. Vander Heiden MG (2011) Targeting cancer metabolism: a therapeutic window opens. *Nature reviews. Drug discovery* 10(9):671-684.
22. Lunt S*, et al.* (2015) Pyruvate Kinase Isoform Expression Alters Nucleotide Synthesis to Impact Cell Proliferation. *Molecular Cell* 57(1):95-107.
*This study suggests that PKM1 expression impairs nucleotide biosynthesis and consequently cellular proliferation in proliferating cells.
23. Cox AG*, et al.* (2016) Yap reprograms glutamine metabolism to increase nucleotide biosynthesis and enable liver growth. *Nature Cell Biology* 18:886.
*This study establishes a link between signaling de-regulation and nucelotide biosynthesis suppporting cancer proliferation.
24. Maddocks Oliver DK, Labuschagne Christiaan F, Adams Peter D, & Vousden Karen H (2016) Serine Metabolism Supports the Methionine Cycle and DNA/RNA Methylation through De Novo ATP Synthesis in Cancer Cells. *Molecular Cell* 61(2):210-221.
25. Labuschagne Christiaan F, van den Broek Niels JF, Mackay Gillian M, Vousden Karen H, & Maddocks Oliver DK (2014) Serine, but Not Glycine, Supports One-Carbon Metabolism and Proliferation of Cancer Cells. *Cell Reports* 7(4):1248-1258.
26. Keibler MA*, et al.* (2016) Metabolic requirements for cancer cell proliferation. *Cancer & Metabolism* 4(1):16.
*This study comprehensivley dissects the metabolic requirments of cancer cell proliferation.
27. Gatto F, Nookaew I, & Nielsen J (2014) Chromosome 3p loss of heterozygosity is associated with a unique metabolic network in clear cell renal carcinoma. *Proceedings of the National Academy of Sciences of the United States of America* 111:E866-E875.
28. Davidson Shawn M*, et al.* (2016) Environment Impacts the Metabolic Dependencies of Ras-Driven Non-Small Cell Lung Cancer. *Cell metabolism* 23(3):517-528.
*This study suggests that the the change from an in vitro to an in vivo environment alters cancer cell metabolism.
29. Christen S*, et al.* (2016) Breast cancer-derived lung metastasis show increased pyruvate carboxylase-dependent anaplerosis. *Cell Reports* 17(3):837-848.
**This study suggests that different in vivo environments are sufficient to change the metabolism of the same cancer cells.
30. Elia I & Fendt S-M (2016) In vivo cancer metabolism is defined by the nutrient microenvironment. *Translational Cancer Research* 5:S1284-S1287.
31. Siegel R, Ma J, Zou Z, & Jemal A (2014) Cancer statistics, 2014. *CA: a cancer journal for clinicians* 64(1):9-29.
32. Massagué J & Obenauf AC (2016) Metastatic colonization by circulating tumour cells. *Nature* 529:298.
33. Anderson M, Marayati R, Moffitt R, & Yeh JJ (2016) Hexokinase 2 promotes tumor growth and metastasis by regulating lactate production in pancreatic cancer. *Oncotarget*:8:56081-56094.

34. Nokin M-J, *et al.* (2016) Methylglyoxal, a glycolysis side-product, induces Hsp90 glycation and YAP-mediated tumor growth and metastasis. *eLife* 5:e19375.
35. Payen VL, *et al.* (2017) Monocarboxylate Transporter MCT1 Promotes Tumor Metastasis Independently of Its Activity as a Lactate Transporter. *Cancer research* 77(20):5591.
36. Torrano V, *et al.* (2016) The metabolic co-regulator PGC1[alpha] suppresses prostate cancer metastasis. *Nat Cell Biol* 18(6):645-656.
37. LeBleu VS, *et al.* (2014) PGC-1α mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. *Nat Cell Biol* 16(10):992-1003.
38. Camarda R, *et al.* (2016) Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer. *Nature medicine* 22:427.
39. Li J, *et al.* (2017) Lipid Desaturation Is a Metabolic Marker and Therapeutic Target of Ovarian Cancer Stem Cells. *Cell stem cell* 20(3):303-314.e305.
40. Shi X, *et al.* (2017) The abundance of metabolites related to protein methylation correlates with the metastatic capacity of human melanoma xenografts. *Science Advances* 3(11).

**This study links post-transcriptional modifications to melanoma invasiveness.

41. Piskounova E, *et al.* (2015) Oxidative stress inhibits distant metastasis by human melanoma cells. *Nature* 12(527(7577)):186-191.

**This study suggests antioxidant metabolism as a vulnerability of circulating tumor cells.

42. Le Gal K, *et al.* (2015) Antioxidants can increase melanoma metastasis in mice. *Science Translational Medicine* 7(308):308re308.

*This study provides translational relevance to the finding that antioxidant metabolism promotes metastasis formation.

43. Schafer ZT, *et al.* (2009) Antioxidant and oncogene rescue of metabolic defects caused by loss of matrix attachment. *Nature* 461:109-113.
44. Jiang L, *et al.* (2016) Reductive carboxylation supports redox homeostasis during anchorage-independent growth. *Nature* 532(7598):255-258.
45. Elia I, *et al.* (2017) Proline metabolism supports metastasis formation and could be inhibited to selectively target metastasizing cancer cells. *Nature communications* 8:15267.

**This study suggests energy production from proline catabolism as a requirment for lung metastatis formation.

46. Andrzejewski S, *et al.* (2017) PGC-1α Promotes Breast Cancer Metastasis and Confers Bioenergetic Flexibility against Metabolic Drugs. *Cell metabolism*:S1550-4131(1517)30557-30550.
47. Loo Jia M, *et al.* (2015) Extracellular Metabolic Energetics Can Promote Cancer Progression. *Cell* 160(3):393-406.

*This study suggests that cancer cells metastasizing to the liver scavenge extracellular metabolic energetics.

48. Dupuy F, *et al.* (2015) PDK1-Dependent Metabolic Reprogramming Dictates Metastatic Potential in Breast Cancer. *Cell metabolism* 22(4):577-589.

49. Geeraerts X, Bolli E, Fendt S-M, & Van Ginderachter JA (2017) Macrophage Metabolism As Therapeutic Target for Cancer, Atherosclerosis, and Obesity. *Frontiers in Immunology* 8:289.
50. Buck MD, Sowell RT, Kaech SM, & Pearce EL (2017) Metabolic Instruction of Immunity. *Cell* 169(4):570-586.
51. Ho P-C & Kaech SM (2017) Reenergizing T cell anti-tumor immunity by harnessing immunometabolic checkpoints and machineries. *Current Opinion in Immunology* 46:38-44.
52. Brand A*, et al.* (2016) LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell metabolism* 24(5):657-671.
53. Ma C*, et al.* (2016) NAFLD causes selective CD4+ T lymphocyte loss and promotes hepatocarcinogenesis. *Nature* 531(7593):253-257.
54. Angelin A*, et al.* (2017) Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. *Cell metabolism* 25(6):1282-1293.e1287.
55. Colegio OR*, et al.* (2014) Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 513(7519):559-563.
56. Chang C-H*, et al.* (2015) Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* 162(6):1229-1241.

*This paper suggests metabolic competition as an important driver of cancer cells to evade the immune response.

57. Ho P-C*, et al.* (2015) Phosphoenolpyruvate Is a Metabolic Checkpoint of Anti-tumor T Cell Responses. *Cell* 162(6):1217-1228.

*This paper provides a mechanistic link between glycolysis and an anti-tumor immune response.

58. Adams JL, Smothers J, Srinivasan R, & Hoos A (2015) Big opportunities for small molecules in immuno-oncology. *Nature reviews Drug discovery* 14(9):603-622.
59. Geiger R*, et al.* (2016) L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* 167(3):829-842.
60. Fallarino F*, et al.* (2003) T Cell Apoptosis by Kynurenines. *Adv Exp Med Biol.* 2003;527:183-90*.*
61. Bingisser RM, Tilbrook PA, Holt PG, & Kees UR (1998) Macrophage-Derived Nitric Oxide Regulates T Cell Activation via Reversible Disruption of the Jak3/STAT5 Signaling Pathway. *The Journal of Immunology* 160(12):5729-5734.
62. Ninomiya S*, et al.* (2015) Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs. *Blood* 125(25):3905.
63. Jin X*, et al.* (2017) Fructose-1,6-bisphosphatase inhibits ERK activation and bypasses gemcitabine resistance in pancreatic cancer by blocking IQGAP1-MAPK interaction. *Cancer Research*.
64. Shukla SK*, et al.* (2017) MUC1 and HIF-1alpha Signaling Crosstalk Induces Anabolic Glucose Metabolism to Impart Gemcitabine Resistance to Pancreatic Cancer. *Cancer Cell* 32(1):71-87.e77.

65. Biancur DE, *et al.* (2017) Compensatory metabolic networks in pancreatic cancers upon perturbation of glutamine metabolism. 8:15965.
66. Tarrado‐Castellarnau M, *et al.* (2017) De novo MYC addiction as an adaptive response of cancer cells to CDK4/6 inhibition. *Molecular systems biology* 13(10).
67. Le Grand M, *et al.* (2017) Akt targeting as a strategy to boost chemotherapy efficacy in non-small cell lung cancer through metabolism suppression. *Scientific Reports* 7:45136.
68. Farge T, *et al.* (2017) Chemotherapy-Resistant Human Acute Myeloid Leukemia Cells Are Not Enriched for Leukemic Stem Cells but Require Oxidative Metabolism. *Cancer Discovery* 7(7):716-735.
*This paper links chemotherapy resistance to metabolic rewiring.
69. Lee K-m, *et al.* (2017) MYC and MCL1 Cooperatively Promote Chemotherapy-Resistant Breast Cancer Stem Cells via Regulation of Mitochondrial Oxidative Phosphorylation. *Cell metabolism* 26(4):633-647.e637.
70. Scott TA, *et al.* (2017) Host-microbe co-metabolism dictates cancer drug efficacy in C. elegans. *Cell* 169(3):442-456.
71. García-González AP, *et al.* (2017) Bacterial metabolism affects the C. elegans response to cancer chemotherapeutics. *Cell* 169(3):431-441.
72. Gopalakrishnan V, *et al.* (2017) Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. *Science*.
**This paper suggests the microbiota as an important determinant of the immunotherapy response.

Figures

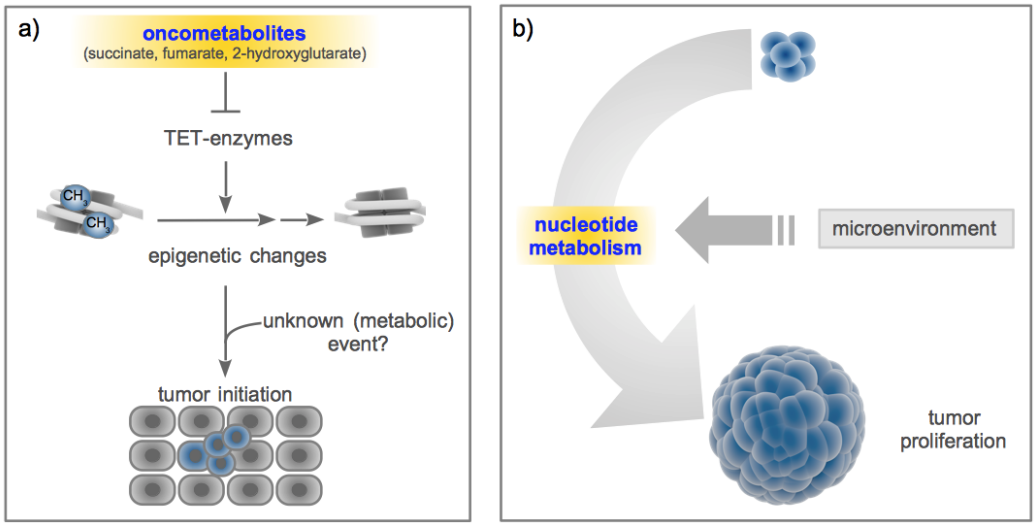

Figure 1: Metabolism in tumor initiation and proliferation. **a)** The link between metabolism and epigenetics can enable tumor initiation. Increased metabolite concentrations inhibit TET-enzyme mediated epigenetic modifications such as DNA methylation, promoting transcriptional programs that can lead to tumor initiation. Normal cells are shown in gray, and cells undergoing oncogenic transformation are shown in blue. **b)** Altered nucleotide metabolism is a common vulnerability of many

proliferating cancers. The microenvironment can define the particular pathways within nucleotide metabolism on which cancer cells rely for proliferation. Cancer cells are shown in blue.

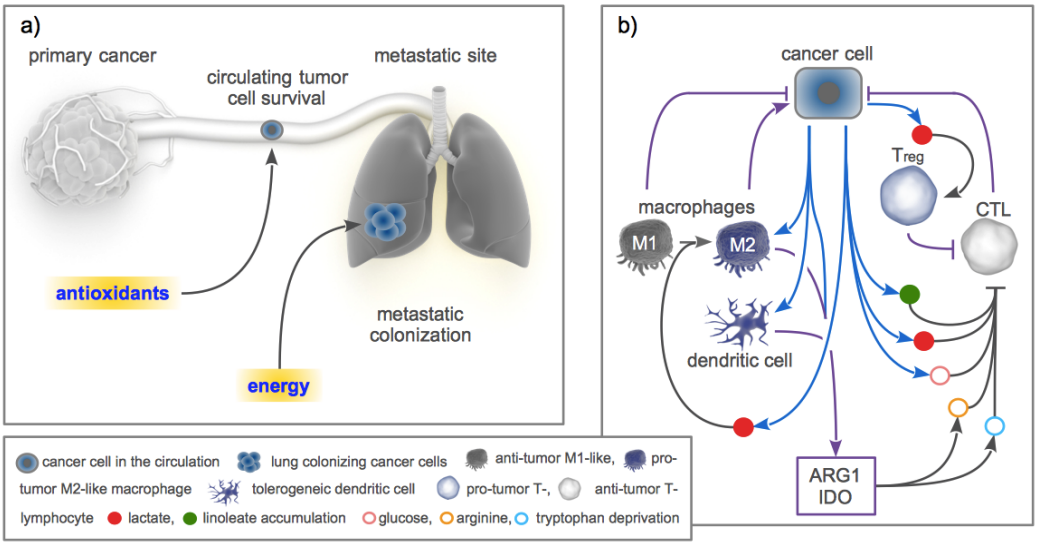

Figure 2: Metabolism during metastasis formation and cancer-immune cell interaction. **a)** Circulating tumor cells rely on increased antioxidant defense for survival, while cancer cells colonizing the metastatic site depend on increased energy availability. Cancer cells are shown in blue. **b)** Cancer cells reprogram the immune response by inhibiting anti-tumor immune cells and inducing pro-tumor immune cells. Mechanistically, cancer cells induce an accumulation of metabolites in the microenvironment that impair anti-tumor immune cells and promote pro-tumor immune cells. Moreover, cancer cells can directly or indirectly deprive nutrients from pro-tumor immune cells. ARG1 refers to arginase 1, and IDO refers to indoleamine 2,3-dioxygenase. Gray arrows indicate metabolite- or enzyme-mediated effects. Purple arrows indicate immune cell-mediated effects. Blue arrows indicate cancer cell-mediated effects.

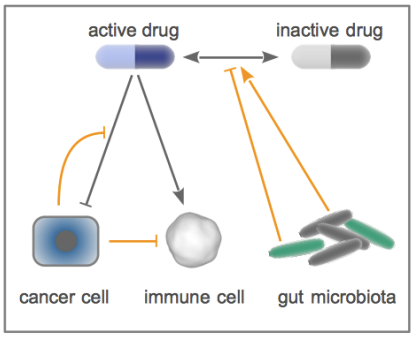

Figure 3: Metabolism defines therapy response. Cancer cells can acquire drug resistance (and immune cell evasion) by rewiring their metabolism. Drug metabolism by the host microbiota can improve or impair therapy response. Gray arrows indicate drug effects. Yellow arrows indicate metabolism-mediated effects.