# An Interaction Network for Fluctuation of Glucose and Lactate in Triple-negative Breast Cancer

# Abstract

**Summary:** Due to the lack of expression of ER, PR, and overexpression of HER2, triple-negative breast cancer is lack of valid treatment method and has an overall worse prognosis. However, the interactions among molecules as well as cells are yet to be elucidated. In this article, we aim to elucidate the effect of lactate and glucose on the tumor microenvironment and the underlying molecular interaction mechanism. We provide an overview of the TNBC microenvironment and the metabolic pathways altered to illustrate the central importance of two key metabolites, glucose, and lactate, plus glutamine for generality in the first place, in which an interaction network is established. Moreover, we provided another interaction network among cells on the basis of molecular interactions. We look forward to using mathematical tools from network theory to conduct more detailed analyses in the future.

**Keywords**: Triple-Negative Breast Cancer, Metabolic Pathway, Network Theory, Warburg Effect

# Contents

**1. Introduction** ..... **4**

1.1 Overview ..... 4

1.2 Glucose and Lactate in Tumor Microenvironment ..... 4

**2. Mathematical Model** ..... **5**

2.1 Intake of Glucose ..... 5

2.2 Intake of Glutamine ..... 6

2.3 Lactate Production ..... 6

2.4 Lactate Shuttling ..... 7

2.5 Tumor Microenvironment Interaction Network ..... 8

2.6 Cells in Tumor Microenvironment ..... 8

2.6.1 Normal Cells ..... 8

2.6.2 Tumor-related Cells ..... 9

**3. Conclusions** ..... **10**

**Citations** ..... **11**

# 1. Introduction

## 1.1 Overview

Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) are three vital biomarkers for breast cancer staging and classification, owing to their predictability for prognosis.[1–3] According to epidemiology research, young women as well as black women have a higher risk of having TNBC.[4–6] Due to the lack of expression of ER, PR, and overexpression of HER2, triple-negative breast cancer is lack of valid treatment method and has an overall worse prognosis.[7] As hormone therapy is unsuitable for treatment, currently only chemotherapy is a systematic approach for TNBC treatment.[8,9] Of note, TNBC has a higher probability of metastasis and is usually observed higher incidence to the brain, liver, and lungs.[10–12]

Due to the heterogeneity of breast cancer, therapeutic targets may not be universal to all TNBC patients. Thus, there have been multiple approaches applied in TNBC stratification, namely, the subtyping of TNBC for more targeted therapy. Lehmann et al. stratified TNBC into 6 subtypes based on gene profiling: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR).[13] In a follow-up study, Masuda et al. proved the validity of such a subtyping method using prognosis analysis, factors including distant metastasis-free survival rate, overall survival rate (OS), and 3-year recurrence rate are considered.[14] Liu et al. proposed a TNBC subtyping based on the mRNA and lncRNA transcriptome profiles, separating tumors into 4 main subtypes.[15] However, such a stratification method rose from the information of 165 TNBC tumor samples.

Based on the established TNBC subtypes, endeavors have been made in seeking new therapeutic targets. Poly ADP-ribose polymerase (PARP) inhibition is one of the extensively studied molecular targets, as clinical trial outcomes indicate, monotherapy with these agents is not sufficient and requires more combination regimens.[16–18] Another target is the PI3K/mTOR/S6 pathway since it has been recognized as a driver in TNBC.[13,19] Some pieces of evidence suggest that the cytoskeleton, cell migration, and vascular system are also potential targets for therapeutics.[20–22]

## 1.2 Glucose and Lactate in Tumor Microenvironment

In the later part of this passage, we aim to elucidate the effect of lactate and glucose on the tumor microenvironment and the underlying molecular interaction mechanism. Here, we provide an overview of the TNBC microenvironment and the metabolic pathways altered to illustrate the central importance of two key metabolites, glucose, and lactate, plus glutamine for generality.

Glucose uptake is vital for biological processes since it is the main energy source and carbon source. Metabolic pathways in both somatic cells and cancer cells involve glucose. In somatic cells, oxidative phosphorylation (OXPHOS) functions as the main energy source.[23] In cancer cells, as observed by Warburg, OXPHOS is usually replaced by glycolysis for accelerated production of metabolic fuels as well as energy despite oxygen level, which is named the Warburg effect.[24] The rate of ATP production is about 100 times that of oxidative phosphorylation. For somatic cells under oxygen deprivation conditions, they switch to anaerobic OXPHOS to reduce the stress from hypoxia, in which lactate is one of the final products.[25]

In recent years, more models describing the phenomenon that arise in cancer cells have been established. The reverse Warburg effect proposed by Stephanos et al. establishes the contact between glycolytic stromal cells and oxidative tumor cells.[26] The inverse Warburg effect proposed by Carla et al. focused on the obesity-triggered abnormal metabolism pattern.[27] Additionally, comprehensive models have been proposed. For instance, the hybrid model models the metabolic state of the coexistence of glycolytic activity and OXPHOS activity.[28] Among all the mentioned models, lactate is the key that connecting various cells. Hence the significance of lactate.

Since we are discussing breast cancer, we cannot ignore the characteristics of the breast. During lactation, the glucose uptake level rises, and some of the consumed glucose is transported to the Golgi apparatus to produce lactose, which is a rich component of breast milk.[29,30]

We organize the text as follows. Firstly, we establish a mathematical model of tumor microenvironment focusing on three key metabolites, glucose, glutamine, and lactate in *Section 2* and discuss the effect of acidic microenvironment on various types of cells and draw conclusions in *Section 5*. The data obtained from the experiment can be found in **Appendix A**.

# 2. Mathematical Model

Given the central importance of glucose and lactate, we organize the text centered around them. As mentioned earlier, we also take glutamine into account. The first two subsections aim to model the intake of energy, and the following two focus on the production and shuttling of lactate. Finally, we give a comprehensive network for summarization in *Section 2.5* and discuss the effect of acidified tumor microenvironment on various types of cells in *Section 2.6*, in which a cell interaction network is established.

## 2.1 Intake of Glucose

GLUT transporters are a group of transporters encoded by SLC2 genes controlling the inflow of glucose, the process of glucose transporting through GLUTs is categorized as facilitated diffusion.[31] Glucose transportation based on sodium-dependent glucose transporters (SGLT) is based on the $Na^+$ electrochemical gradient provided by the $Na^+ - K^+$ ATPase pump despite the concentration difference.[32] Among them, GLUT1 is expressed as the most common. The silencing of GLUT1 in TNBC by Sunhwa et al. exhibits that GLUT1 promotes cell proliferation, migration, and invasion by regulating HER and integrin signaling in TNBC cells.

Now we introduce a set of transcription factors named hypoxia-inducible factors (HIFs). Since they emerge under the condition of hypoxia, we first give the definition of the hypoxia state. Oxygen concentrations below 21% is called hypoxia and is graded as: physiological hypoxia: 2–9%; mild hypoxia: 1–5%; hypoxia: <1%, and anoxia: <0.1%.[33] Hypoxia-inducible factor 1 (HIF-1) is composed of two subunits, i.e., HIF-1$\alpha$ and HIF-1$\beta$.[34] c-Myc is a transcription factor regulating multiple pathways involving cancer metabolism and has a direct effect on GLUT1 expression, we combine the discussion of c-Myc with HIF-1$\alpha$ since the similar mechanisms.[35] Firstly, the rate-limiting steps in glycolysis is accelerated by HIF-1$\alpha$ or c-Myc-induced hexokinase 2 and fructose-2,6-bisphosphate.[36] Secondly, pyruvate dehydrogenase-mediated pyruvate mitochondrial metabolism is suppressed with the induced pyruvate dehydrogenase kinase-1.[37] Thirdly, the activity of LDHA is promoted and the activity of LDHB is suppressed, whose functions will be discussed in later sections.[38]

Thioredoxin-inducing protein (TXNIP) is a protein that downregulates the expression of GLUT1 and its induction is MondoA-dependent.[39] MondoA is a transcription factor functions as a sensor that adapt cells to changes in microenvironmental glycolytic changes, the work by Carrie et al. suggests that MondoA likely accounts for the induction of TXNIP by glucose and the TXNIP-dependent down-regulation of glucose uptake.[40,41] C-Myc competitively binds to the promotor region of TXNIP, upregulating the uptake of glucose.[42,43]

Now we introduce two important molecules, mTOR and PKM2, whose corresponding metabolic pathway enhances the uptake of glucose.[44] The mammalian target of rapamycin (mTOR) is a kinase encoded by the MTOR gene, which serves as a component for the synthesis of two major protein complexes, mTORC1, and mTORC2.[45] mTOR is able to control the proliferation and growth of cells by responding to diverse environmental signals.[46] Similarly, USP6NL is a GTPase-activating protein that contributes to the stabilization of the expression level of GLUT1 by suppressing GLUT1 endocytosis and the Akt-mediated degradation.[47] An illustration of the associations discussed above is depicted in **Figure 1** below.

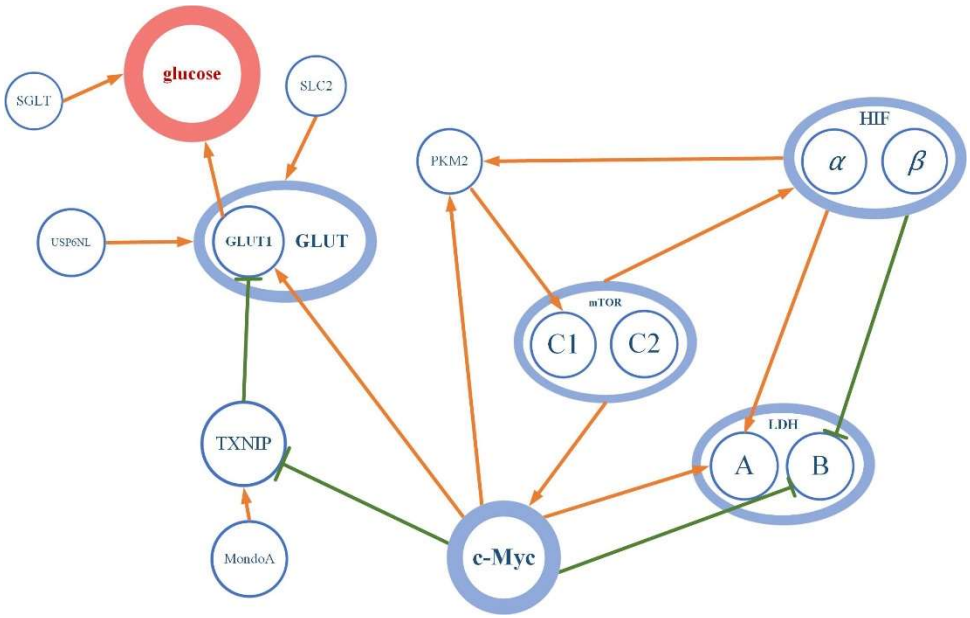


**Figure 1**

## 2.2 Intake of Glutamine

Glutamine (Gln) is an $\alpha$-amino acid used in multiple biochemistry processes, especially the synthesis of proteins. In cancer, glutamine metabolism acts as a carbon and nitrogen source.[48] Increased glutamine metabolism is recognized as a hallmark of cancer. In cancer cells, glutamine is converted to glutamate under the mitochondrial enzyme glutaminase, which is under the regulation of the c-Myc factor.[49–51] The product glutamate then enters the tricarboxylate acid (TCA) cycle in the form of $\alpha$-ketoglutarate as an alternative source of carbon other than glucose and is finally converted to malate.[52] The malate is then transported into the cytoplasm to convert to pyruvate, which will be mentioned later, is a precursor of lactate. Thus, the upregulated glutaminolysis contributes to the production of lactate.

Of note, the glutaminolysis level is dependent on the tumor type. In our case, the TNBC cells are glutamine dependent and the expression of glutaminase was significantly associated with a low level of TILs and poor disease-free survival in TNBCs presenting with lymph node metastasis and high levels of TILs.[53] An illustration of the relationships in glutaminolysis is shown in **Figure 2**.

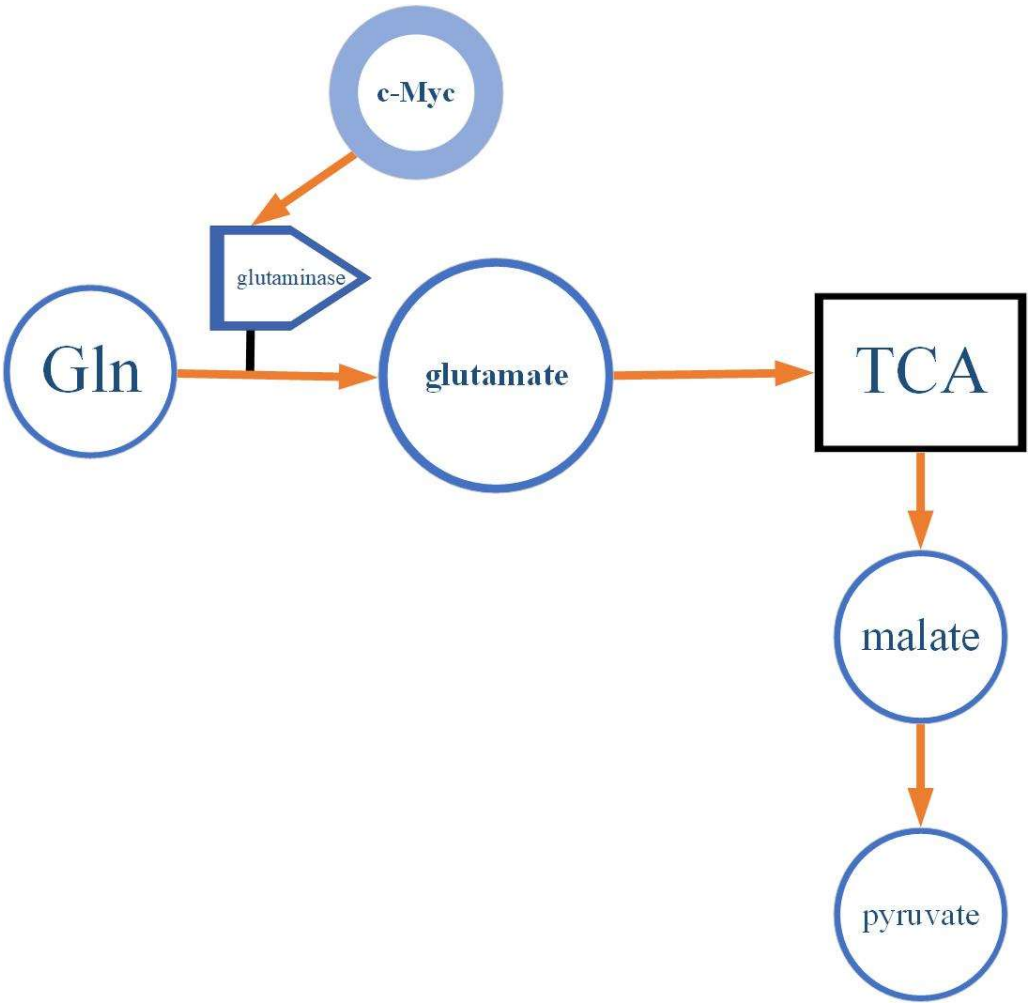


**Figure 2**

## 2.3 Lactate Production

From the analysis earlier, we conclude that there are 3 main sources for the production of lactate: anaerobic OXPHOS, glycolysis, and glutaminolysis. The common product of the three processes is pyruvate. Here we discuss the involved elements in the conversion of pyruvate to lactate.

The conversion between pyruvate and lactate is controlled by a family of enzymes called lactate dehydrogenases (LDHs).[54] There are 5 major isoforms of LDHs, and each of them is composed of subunits, namely LDH-M and LDH-H.[55] The specified combination of each isoform is listed in *Table 1*. LDH-M and LDH-H are encoded by the LDHA gene and LDHB gene, respectively. Different isoforms express in different locations, the LDHA isoform mainly expresses in muscles and preferentially converts pyruvate to lactate, while the LDHB isoform mainly expresses in the heart and brain and preferentially converts lactate to pyruvate.[56] The overexpression of LDHA is a necessity for transformations

mediated by transcriptional factor c-Myc.[57]

*Table 1*

| **Isoform** | LDH1 | LDH2 | LDH3 | LDH4 | LDH5 |
|---|---|---|---|---|---|
| **Subunits** | H4 | H3M1 | H2M2 | H1M3 | M4 |
| **Alternative Name** | LDHB | | | | LDHA |

The forkhead box protein M1 (FoxM1) is a transcriptional factor ensuring the fidelity of the cell division process and it supports the proliferation of tumor cells by stimulating the expression of the antioxidant genes and reducing oxidative stress.[58,59] Moreover, the increased expression level of FOXM1 binds to the promotor region of LDHA and thus upregulates the activity of LDHA at mRNA level as well as protein level.[60]

The krüppel-like factor 4 (KLF4) is a transcription factor that inhibits cancer EMT and metastasis via transcriptionally downregulating CAV-1 expression.[61] KLF4 binds to the promoter regions of the LDHA gene, thus negatively regulating the expression of LDHA.[62] An illustration of the associations discussed above is depicted in **Figure 3** below.

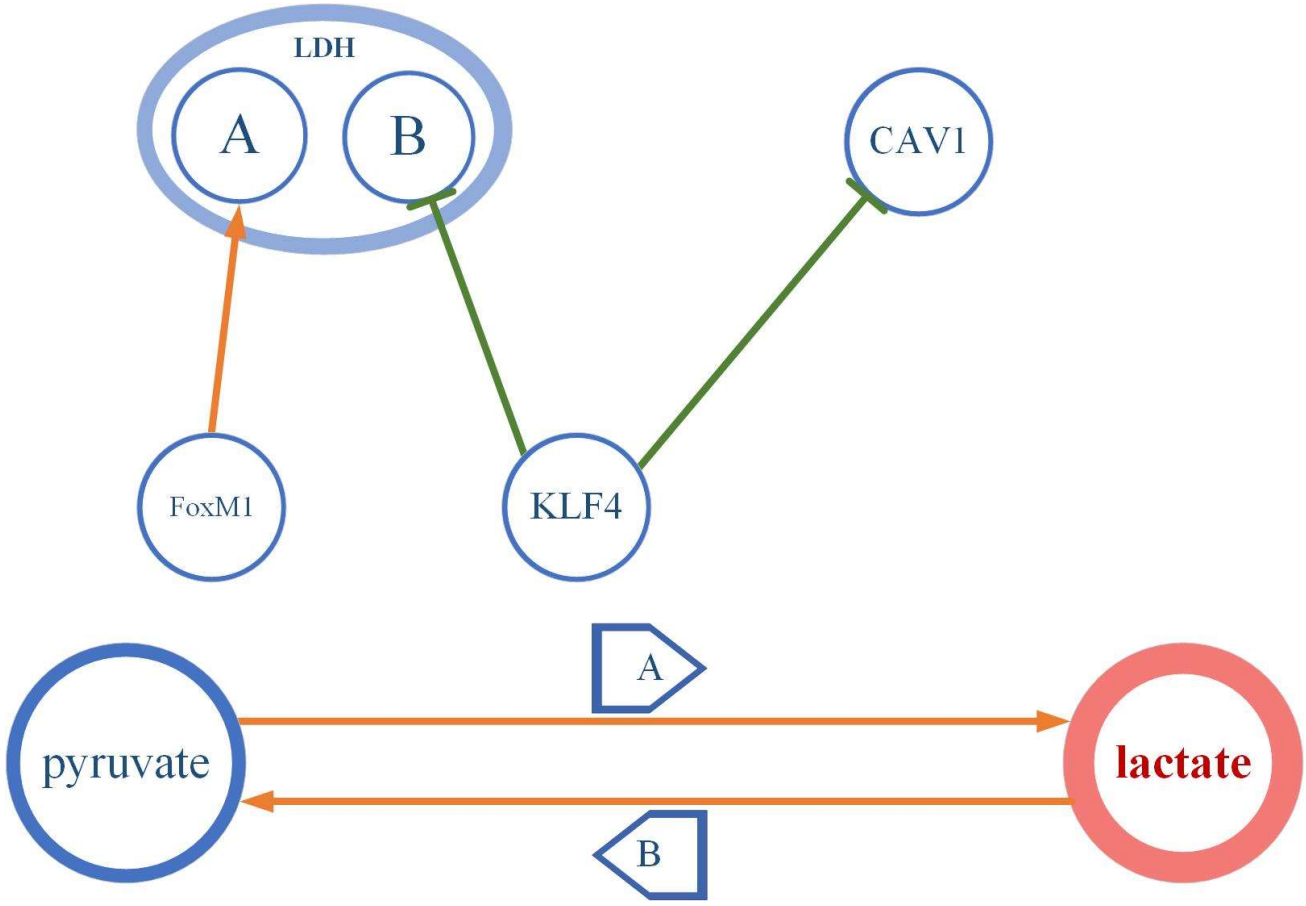


**Figure 3**

## 2.4 Lactate Shuttling

The monocarboxylate transporter family (MCT) is a family of transporters expressed mainly on cell membranes that are encoded by solute carrier 16 (SLC16) genes and are vital for the intake and efflux of lactate.[63] MCTs have various expression patterns depending on tissue type and microenvironment, MCT1 and MCT4 are of vital importance where MCT1 is bidirectional while MCT4 only controls the efflux of lactate.[64,65] The upregulation of MCT1 is directly linked to the oxidative metabolism of oxygenated tumor cells as observed by Pierre et al.[66]

CD147 is a hypoxia-inducible small molecule transporter ancillary protein that chaperones to the MCTs, which has the function of stabilizing their expression levels.[67,68] According to Renaud et al., CD147 controls the stability and functional plasma membrane insertion of the MCTs in many tissues.[69] Moreover, CD147 was shown to ensure the polarization of MCT1.[70]

The G-protein-coupled receptor 81 (GPR81), also named the hydrocarboxylic acid receptor 1 (HCAR1), is reported to function as a receptor for lactate and is able to mediate the anti-lipolytic effect of the lactate, the activation of GPR81 by lactate directly leads to increased expression of

MCTs, CD147 and PGC-1.[71,72] An examination of tumors resected from patients with pancreatic cancer by Craig et al. indicated that 94% (148 of 158) expressed high levels of GPR81.[73] A main regulator of GPR81 is the signal transducer and activator of transcription 3 (STAT3), which determines the immune responses in the tumor microenvironment.[74] STAT3 is able to bind to the promotor region of GPR81, thus downregulating the expression of GPR81.[75] An illustration of the associations discussed above is depicted in **Figure 4** below.

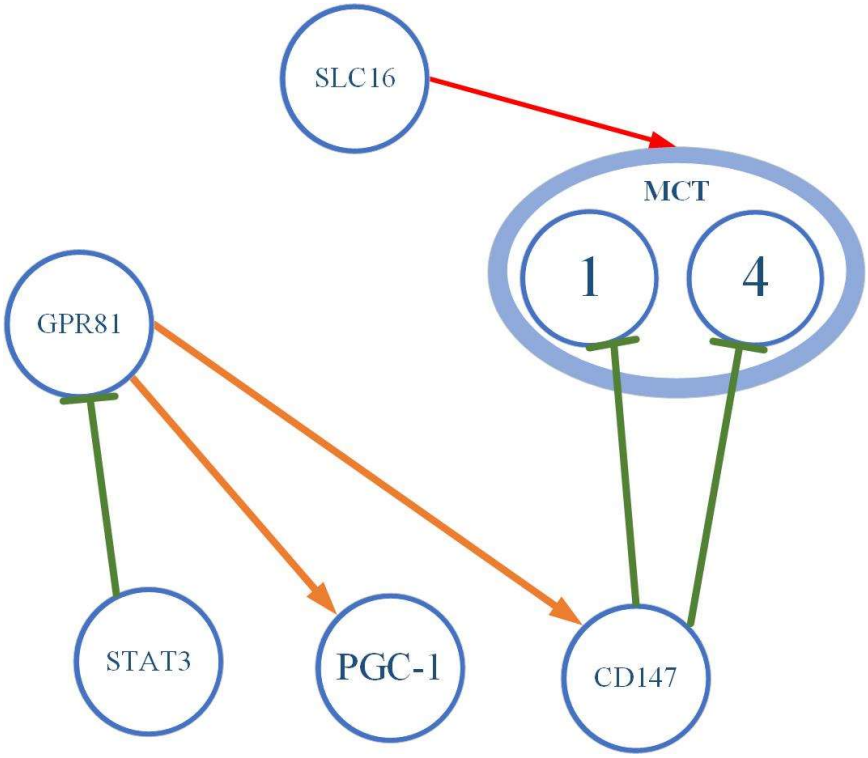


**Figure 4**

## 2.5 Tumor Microenvironment Interaction Network

Here we summarize the interlinked 4 networks. **Figure 5** depicts the overall network. Since **Figure 5** is large in scale, we put it in **Appendix A** for convenience.

## 2.6 Cells in Tumor Microenvironment

Tumor microenvironment consists of various types of cells, including tumor cells, myeloid-derived suppressor cells, dendritic cells, fibroblast cells, T lymphocyte cells, et cetera. Here we simplify our discussion to the relationship among the cells along with the interaction between cells and the tumor microenvironment, forming an interaction network. The tumor microenvironment interaction network established above is integrated into this cell-environment network model.

### 2.6.1 Normal Cells

Adipocytes are cells that store the energy as fat.[76] The need to maintain a constant supply of lipids and lipid precursors to fuel membrane production in the highly proliferating cancer cell population is widely acknowledged, adipocytes contribute to tumor progression as a fuel reservoir. Moreover, adipocytes are able to secrete growth factors and hormones that facilitate tumor growth.[77,78] According to cancer epidemiology surveys, obesity is estimated to contribute to up to 20% of cancer-related deaths.[79,80] Thus, elucidating the relationship between adipocytes and cancer cells is of significance.

Stomal cells are usually found in bone marrows and the interaction between stromal cells and tumor cells play a critical role in cancer growth and progression.[81] As the tumor progresses, stromal cells transform into tumor-associated fibroblasts (CAFs) or tumor-associated adipocytes and further enhance the tumor invasiveness.[82] CAFs make up the bulk of cancer stroma and affect the tumor microenvironment by promoting cancer initiation, angiogenesis, invasion, and metastasis.[83]

According to the definition provided by NIH, a fibroblast is a type of cell that contributes to the formation of connective tissue, a fibrous cellular material that supports and connects other tissues or organs in the body. Fibroblasts secrete collagen proteins that help maintain the structural framework of tissues.[84] The transformation from normal fibroblasts to CAFs is a basic link in tumor invasion.[85] The aged fibroblasts express IL6

and multiple suppressing signals to promote tumor invasion. IL6 limits the maturation of dendritic cells and stimulates angiogenesis.[86]

Since the blood vessel functions as the transportation station for tumor cells by delivering nutrition and providing the environment for metastasis, we involve the blood vessel in our discussion. The cells in the tumor microenvironment stimulate angiogenesis by secreting vascular endothelial growth factor (VEGF) and fibroblast growth factor.[87]

### 2.6.2 Tumor-related Cells

Myeloid-derived suppressor cell (MDSC) is cancer-promoting by limiting the function and proliferation of T cells and promoting the differentiation of T regulatory cells, thus inducing angiogenesis.[88] However, the underlying mechanism of how MDSC thrives by metabolism competition in the glycolysis tumor microenvironment is yet to be understood.

T lymphocyte is one of the important white blood cells of the immune system and plays a central role in the adaptive immune response.[89,90] As the tumor progresses, metabolic competition is introduced, which damages the activities of immune cells.[91]

Dendritic cells (DCs) are bone marrow-derived cells that seed all tissues, in which they sample their environment and transmit information to adaptive immune cells.[92] Tumor-derived factors can alter DC maturation to yield cells that indirectly help tumor growth.[93] The experiment by Isabelle et al. concluded that the infiltration by pDC of primary localized breast tumor correlates with an adverse outcome, suggesting their contribution to breast cancer progression.[94] The resistance to DC proliferation and antigen presentation may induce resistance to T cells' activation in the tumor microenvironment.[95]

A macrophage is categorized as a white blood cell, which consumes and digests pathogens. The two most intensively studied macrophages are M1 macrophage and M2 macrophage, they are inflammation-promoting and inflammation-suppressing respectively.[96] M2 macrophages secrete immune suppressing cell factors and suppress the toxicity of TIL cells, promoting the differentiation of T regulatory cells.[97]

In summary, the effect of tumor cells on immune cells is: creating a lactate overexpressed environment, in which the dysfunction of mitochondria and accumulated ROS lead to the apoptosis of immune cells.[98] **Figure 6** depicts the relationship among cells.

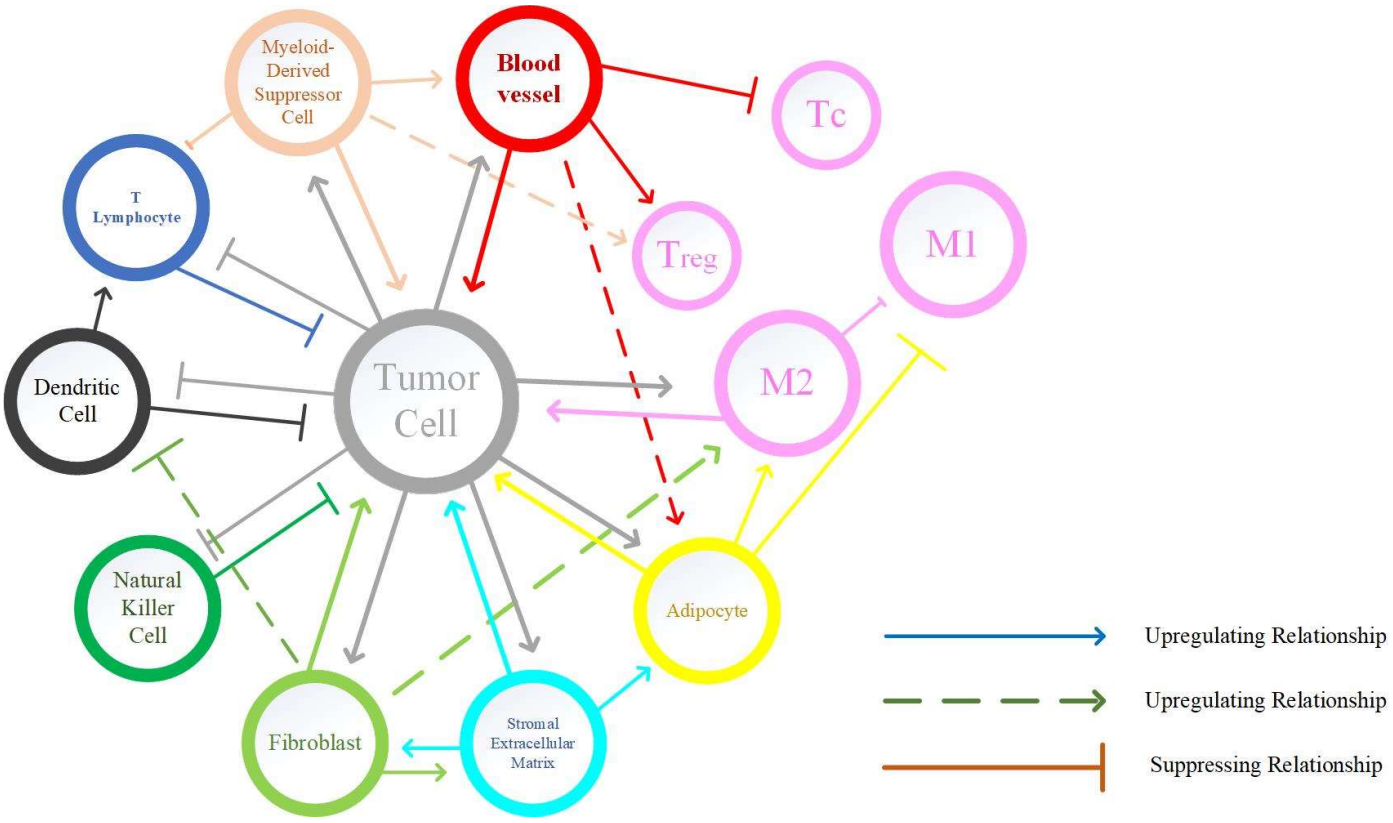


**Figure 6**

# 3. Conclusions

In this article, we constructed a network among gene-regulated molecules and a cell interaction network concomitantly. We will use mathematical tools from network theory to conduct a more detailed analysis in the future. We hope our work can elucidate the current interaction relationships for future researchers.

**Author Contributions:** Conceptualization, Hongying Zhong, Ruotao Yu, Shengqi Liu, Yichen Wang; draft preparation, Ruotao Yu, Shengqi Liu, Yichen Wang, Jiarui Chen, Qianhui Li; writing, review, and editing, Ruotao Yu, Shengqi Liu, Yichen Wang, Jiarui Chen, Qianhui Li; figure: Ruotao Yu, Shengqi Liu, Yichen Wang; supervision, Hongying Zhong;

All authors have read and agreed to the published version of the manuscript.

**Funding:** No funding received.

**Conflicts of Interest:** The authors declare no conflict of interest.

# Citations


1. Ensenyat-Mendez, M. *et al.* Current Triple-Negative Breast Cancer Subtypes: Dissecting the Most Aggressive Form of Breast Cancer. *Front Oncol* 2311 (2021).
2. Costa, R. L. B. & Gradishar, W. J. Triple-negative breast cancer: current practice and future directions. *J Oncol Pract* **13**, 301–303 (2017).
3. Perou, C. M. *et al.* Molecular portraits of human breast tumours. *Nature* **406**, 747–752 (2000).
4. Liu, Y. *et al.* Prognosis in very young women with triple-negative breast cancer: retrospective study of 216 cases. *Medical oncology* **31**, 1–4 (2014).
5. Stead, L. A. *et al.* Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Research* **11**, 1–10 (2009).
6. Malorni, L. *et al.* Clinical and biologic features of triple-negative breast cancers in a large cohort of patients with long-term follow-up. *Breast Cancer Res Treat* **136**, 795–804 (2012).
7. Tsang, J. & Tse, G. M. Molecular classification of breast cancer. *Adv Anat Pathol* **27**, 27–35 (2020).
8. Collignon, J., Lousberg, L., Schroeder, H. & Jerusalem, G. Triple-negative breast cancer: treatment challenges and solutions. *Breast Cancer: Targets and Therapy* **8**, 93 (2016).
9. Yin, L., Duan, J.-J., Bian, X.-W. & Yu, S. Triple-negative breast cancer molecular subtyping and treatment progress. *Breast Cancer Research* **22**, 1–13 (2020).
10. Al-Mahmood, S., Sapiezynski, J., Garbuzenko, O. B. & Minko, T. Metastatic and triple-negative breast cancer: challenges and treatment options. *Drug Deliv Transl Res* **8**, 1483–1507 (2018).
11. Malorni, L. *et al.* Clinical and biologic features of triple-negative breast cancers in a large cohort of patients with long-term follow-up. *Breast Cancer Res Treat* **136**, 795–804 (2012).
12. O'Reilly, D., al Sendi, M. & Kelly, C. M. Overview of recent advances in metastatic triple-negative breast cancer. *World J Clin Oncol* **12**, 164 (2021).
13. Lehmann, B. D. *et al.* Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest* **121**, 2750–2767 (2011).
14. Masuda, H. *et al.* Differential Response to Neoadjuvant Chemotherapy Among 7 Triple-Negative Breast Cancer Molecular SubtypesDifferential Response to Chemotherapy by TNBC Subtype. *Clinical cancer research* **19**, 5533–5540 (2013).
15. Liu, Y.-R. *et al.* Comprehensive transcriptome analysis identifies novel molecular subtypes and subtype-specific RNAs of triple-negative breast cancer. *Breast Cancer Research* **18**, 1–10 (2016).
16. Tutt, A. *et al.* Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *The Lancet* **376**, 235–244 (2010).
17. Gelmon, K. A. *et al.* Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* **12**, 852–861 (2011).
18. Ibrahim, Y. H. *et al.* PI3K Inhibition Impairs BRCA1/2 Expression and Sensitizes BRCA-Proficient Triple-Negative Breast Cancer to PARP InhibitionCombined PI3K and PARP Inhibition in TNBC. *Cancer Discov* **2**, 1036–1047 (2012).
19. Speers, C. *et al.* Identification of Novel Kinase Targets for the Treatment of Estrogen Receptor–Negative Breast CancerKinase Targets for ER-Negative Breast Cancer Treatment. *Clinical cancer research* **15**, 6327–6340 (2009).
20. Tung, N. M. & Garber, J. E. BRCA1/2 testing: therapeutic implications for breast cancer management. *Br J Cancer* **119**, 141–152 (2018).
21. Jeong, H., Ryu, Y., An, J., Lee, Y. & Kim, A. Epithelial–mesenchymal transition in breast cancer correlates with high histological grade and triple-negative phenotype. *Histopathology* **60**, E87–E95 (2012).
22. Bissell, M. J. & Hines, W. C. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nat Med* **17**, 320–329 (2011).
23. Barrientos, A. In vivo and in organello assessment of OXPHOS activities. *Methods* **26**, 307–316 (2002).
24. vander Heiden, M. G., Cantley, L. C. & Thompson, C. B. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science (1979)* **324**, 1029–1033 (2009).
25. Stojan, G. & Christopher-Stine, L. 151 - Metabolic, drug-induced, and other noninflammatory myopathies. in *Rheumatology (Sixth Edition)* (eds. Hochberg, M. C., Silman, A. J., Smolen, J. S., Weinblatt, M. E. & Weisman, M. H.) 1255–1263 (Mosby, 2015).

doi:https://doi.org/10.1016/B978-0-323-09138-1.00151-0.

26. Pavlides, S. *et al.* The reverse Warburg effect: aerobic glycolysis in cancer associated fibroblasts and the tumor stroma. *Cell cycle* **8**, 3984–4001 (2009).
27. Luis, C. *et al.* Warburg Effect Inversion: Adiposity shifts central primary metabolism in MCF-7 breast cancer cells. *Life Sci* **223**, 38–46 (2019).
28. Jia, D. *et al.* Elucidating cancer metabolic plasticity by coupling gene regulation with metabolic pathways. *Proceedings of the National Academy of Sciences* **116**, 3909–3918 (2019).
29. Gidrewicz, D. A. & Fenton, T. R. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr* **14**, 1–14 (2014).
30. Farmer, C., Trottier, N. L. & Dourmad, J. Y. Current knowledge on mammary blood flow, mammary uptake of energetic precursors and their effects on sow milk yield. *Can J Anim Sci* **88**, 195–204 (2008).
31. Wood, I. S. & Trayhurn, P. Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. *British journal of nutrition* **89**, 3–9 (2003).
32. Mueckler, M. & Thorens, B. The SLC2 (GLUT) family of membrane transporters. *Mol Aspects Med* **34**, 121–138 (2013).
33. Koh, M. Y. & Powis, G. Passing the baton: the HIF switch. *Trends Biochem Sci* **37**, 364–372 (2012).
34. Semenza, G. L. Hypoxia-inducible factors in physiology and medicine. *Cell* **148**, 399–408 (2012).
35. Gordan, J. D., Thompson, C. B. & Simon, M. C. HIF and c-Myc: sibling rivals for control of cancer cell metabolism and proliferation. *Cancer Cell* **12**, 108–113 (2007).
36. Clem, B. *et al.* Small-molecule inhibition of 6-phosphofructo-2-kinase activity suppresses glycolytic flux and tumor growth. *Mol Cancer Ther* **7**, 110–120 (2008).
37. Dang, C. v, Hamaker, M., Sun, P., Le, A. & Gao, P. Therapeutic targeting of cancer cell metabolism. *J Mol Med* **89**, 205–212 (2011).
38. Feng, Y. *et al.* Lactate dehydrogenase A: A key player in carcinogenesis and potential target in cancer therapy. *Cancer Med* **7**, 6124–6136 (2018).
39. Wilde, B. R. & Ayer, D. E. Interactions between Myc and MondoA transcription factors in metabolism and tumourigenesis. *Br J Cancer* **113**, 1529–1533 (2015).
40. Billin, A. N., Eilers, A. L., Coulter, K. L., Logan, J. S. & Ayer, D. E. MondoA, a novel basic helix-loop-helix–leucine zipper transcriptional activator that constitutes a positive branch of a max-like network. *Mol Cell Biol* **20**, 8845–8854 (2000).
41. Stoltzman, C. A. *et al.* Glucose sensing by MondoA: Mlx complexes: a role for hexokinases and direct regulation of thioredoxin-interacting protein expression. *Proceedings of the National Academy of Sciences* **105**, 6912–6917 (2008).
42. Wu, N. *et al.* AMPK-dependent degradation of TXNIP upon energy stress leads to enhanced glucose uptake via GLUT1. *Mol Cell* **49**, 1167–1175 (2013).
43. Choi, J., Jung, W.-H. & Koo, J. S. Metabolism-related proteins are differentially expressed according to the molecular subtype of invasive breast cancer defined by surrogate immunohistochemistry. *Pathobiology* **80**, 41–52 (2013).
44. Guertin, D. A. & Sabatini, D. M. Defining the role of mTOR in cancer. *Cancer Cell* **12**, 9–22 (2007).
45. Mossmann, D., Park, S. & Hall, M. N. mTOR signalling and cellular metabolism are mutual determinants in cancer. *Nat Rev Cancer* **18**, 744–757 (2018).
46. Sun, Q. *et al.* Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. *Proceedings of the National Academy of Sciences* **108**, 4129–4134 (2011).
47. Avanzato, D. *et al.* High USP6NL Levels in Breast Cancer Sustain Chronic AKT Phosphorylation and GLUT1 Stability Fueling Aerobic GlycolysisUSP6NL Fuels Aerobic Glycolysis in Breast Cancer. *Cancer Res* **78**, 3432–3444 (2018).
48. Souba, W. W. Glutamine and cancer. *Ann Surg* **218**, 715 (1993).
49. Masisi, B. K. *et al.* The role of glutaminase in cancer. *Histopathology* **76**, 498–508 (2020).
50. Bhutia, Y. D., Babu, E., Ramachandran, S. & Ganapathy, V. Amino acid transporters in cancer and their relevance to "glutamine addiction": novel targets for the design of a new class of anticancer drugs. *Cancer Res* **75**, 1782–1788 (2015).
51. Márquez, J., de la Oliva, A. R. L., Matés, J. M., Segura, J. A. & Alonso, F. J. Glutaminase: a multifaceted protein not only involved in generating glutamate. *Neurochem Int* **48**, 465–471 (2006).
52. DeBerardinis, R. J. *et al.* Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement

for protein and nucleotide synthesis. *Proceedings of the National Academy of Sciences* **104**, 19345–19350 (2007).

53. Kim, J. Y. *et al.* Glutaminase expression is a poor prognostic factor in node-positive triple-negative breast cancer patients with a high level of tumor-infiltrating lymphocytes. *Virchows Archiv* **470**, 381–389 (2017).
54. Markert, C. L., Shaklee, J. B. & Whitt, G. S. Evolution of a gene: multiple genes for LDH isozymes provide a model of the evolution of gene structure, function and regulation. *Science (1979)* **189**, 102–114 (1975).
55. Mishra, D. & Banerjee, D. Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. *Cancers (Basel)* **11**, 750 (2019).
56. Valvona, C. J., Fillmore, H. L., Nunn, P. B. & Pilkington, G. J. The regulation and function of lactate dehydrogenase a: therapeutic potential in brain tumor. *Brain pathology* **26**, 3–17 (2016).
57. Shim, H. *et al.* c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proceedings of the national academy of sciences* **94**, 6658–6663 (1997).
58. Raychaudhuri, P. & Park, H. J. FoxM1: a master regulator of tumor metastasis. *Cancer Res* **71**, 4329–4333 (2011).
59. Laoukili, J., Stahl, M. & Medema, R. H. FoxM1: at the crossroads of ageing and cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* **1775**, 92–102 (2007).
60. Cui, J. *et al.* FOXM1 Promotes the Warburg Effect and Pancreatic Cancer Progression via Transactivation of LDHA ExpressionFOXM1 Regulates the Warburg Effect. *Clinical Cancer Research* **20**, 2595–2606 (2014).
61. Rowland, B. D. & Peeper, D. S. KLF4, p21 and context-dependent opposing forces in cancer. *Nat Rev Cancer* **6**, 11–23 (2006).
62. Shi, M. *et al.* A Novel KLF4/LDHA Signaling Pathway Regulates Aerobic Glycolysis in and Progression of Pancreatic CancerRegulation of Pancreatic Cancer Metabolism by KLF4. *Clinical Cancer Research* **20**, 4370–4380 (2014).
63. Payen, V. L., Mina, E., van Hée, V. F., Porporato, P. E. & Sonveaux, P. Monocarboxylate transporters in cancer. *Mol Metab* **33**, 48–66 (2020).
64. Halestrap, A. P. & Wilson, M. C. The monocarboxylate transporter family—Role and regulation. *IUBMB Life* **64**, 109–119 (2012).
65. Halestrap, A. P. The monocarboxylate transporter family—Structure and functional characterization. *IUBMB Life* **64**, 1–9 (2012).
66. Sonveaux, P. *et al.* Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J Clin Invest* **118**, 3930–3942 (2008).
67. Kendrick, A. A. *et al.* CD147: a small molecule transporter ancillary protein at the crossroad of multiple hallmarks of cancer and metabolic reprogramming. *Oncotarget* **8**, 6742 (2017).
68. Deora, A. A., Philp, N., Hu, J., Bok, D. & Rodriguez-Boulan, E. Mechanisms regulating tissue-specific polarity of monocarboxylate transporters and their chaperone CD147 in kidney and retinal epithelia. *Proceedings of the National Academy of Sciences* **102**, 16245–16250 (2005).
69. le Floch, R. *et al.* CD147 subunit of lactate/H+ symporters MCT1 and hypoxia-inducible MCT4 is critical for energetics and growth of glycolytic tumors. *Proceedings of the National Academy of Sciences* **108**, 16663–16668 (2011).
70. Settle, P. *et al.* Polarized lactate transporter activity and expression in the syncytiotrophoblast of the term human placenta. *Placenta* **25**, 496–504 (2004).
71. Cai, T.-Q. *et al.* Role of GPR81 in lactate-mediated reduction of adipose lipolysis. *Biochem Biophys Res Commun* **377**, 987–991 (2008).
72. Liu, C. *et al.* Lactate inhibits lipolysis in fat cells through activation of an orphan G-protein-coupled receptor, GPR81. *Journal of Biological Chemistry* **284**, 2811–2822 (2009).
73. Roland, C. L. *et al.* Cell Surface Lactate Receptor GPR81 Is Crucial for Cancer Cell Survival. *Cancer Res* **74**, 5301–5310 (2014).
74. Yu, H., Pardoll, D. & Jove, R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* **9**, 798–809 (2009).
75. Xie, Q. *et al.* A lactate-induced Snail/STAT3 pathway drives GPR81 expression in lung cancer cells. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* **1866**, 165576 (2020).
76. Birbrair, A. *et al.* Role of pericytes in skeletal muscle regeneration and fat accumulation. *Stem Cells Dev* **22**, 2298–2314 (2013).
77. Quail, D. F. & Dannenberg, A. J. The obese adipose tissue microenvironment in cancer development and progression. *Nat Rev Endocrinol* **15**, 139–154 (2019).
78. Choi, J., Cha, Y. J. & Koo, J. S. Adipocyte biology in breast cancer: From silent bystander to active facilitator. *Prog Lipid Res* **69**, 11–20 (2018).
79. Tan, J., Buache, E., Chenard, M.-P., Dali-Youcef, N. & Rio, M.-C. Adipocyte is a non-trivial, dynamic partner of breast cancer cells. *International Journal of Developmental Biology* **55**, 851–859 (2011).

80. Santander, A. M. *et al.* Paracrine interactions between adipocytes and tumor cells recruit and modify macrophages to the mammary tumor microenvironment: the role of obesity and inflammation in breast adipose tissue. *Cancers (Basel)* **7**, 143–178 (2015).
81. Mao, Y., Keller, E. T., Garfield, D. H., Shen, K. & Wang, J. Stromal cells in tumor microenvironment and breast cancer. *Cancer and Metastasis Reviews* **32**, 303–315 (2013).
82. Gioiella, F., Urciuolo, F., Imparato, G., Brancato, V. & Netti, P. A. An Engineered Breast Cancer Model on a Chip to Replicate ECM-Activation In Vitro during Tumor Progression. *Adv Healthc Mater* **5**, 3074–3084 (2016).
83. Wiseman, B. S. & Werb, Z. Stromal effects on mammary gland development and breast cancer. *Science (1979)* **296**, 1046–1049 (2002).
84. NIH. https://www.genome.gov/genetics-glossary/Fibroblast#:~:text=%E2%80%8BFibroblast&text=A%20fibroblast%20is%20a%20type,the%20structural%20framework%20of%20tissues.
85. Ruhland, M. K. *et al.* Stromal senescence establishes an immunosuppressive microenvironment that drives tumorigenesis. *Nat Commun* **7**, 1–18 (2016).
86. Guo, X., Oshima, H., Kitmura, T., Taketo, M. M. & Oshima, M. Stromal fibroblasts activated by tumor cells promote angiogenesis in mouse gastric cancer. *Journal of Biological Chemistry* **283**, 19864–19871 (2008).
87. Jain, R. K. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science (1979)* **307**, 58–62 (2005).
88. Fleming, V. *et al.* Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression. *Front Immunol* 398 (2018).
89. Frauwirth, K. A. & Thompson, C. B. Regulation of T lymphocyte metabolism. *The Journal of Immunology* **172**, 4661–4665 (2004).
90. Carvalho, M. I., Pires, I., Prada, J. & Queiroga, F. L. A role for T-lymphocytes in human breast cancer and in canine mammary tumors. *Biomed Res Int* **2014**, (2014).
91. Chang, C.-H. *et al.* Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* **162**, 1229–1241 (2015).
92. Banchereau, J. & Steinman, R. M. Dendritic cells and the control of immunity. *Nature* **392**, 245–252 (1998).
93. Palucka, K., Coussens, L. M. & O'Shaughnessy, J. Dendritic cells, inflammation and breast cancer. *Cancer J* **19**, (2013).
94. Treilleux, I. *et al.* Dendritic cell infiltration and prognosis of early stage breast cancer. *Clinical Cancer Research* **10**, 7466–7474 (2004).
95. Gottfried, E. *et al.* Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood* **107**, 2013–2021 (2006).
96. Choi, J., Gyamfi, J., Jang, H. & Koo, J. S. The role of tumor-associated macrophage in breast cancer biology. (2018).
97. Santoni, M. *et al.* Triple-negative breast cancer: Key role of Tumor-Associated Macrophages in regulating the activity of anti-PD-1/PD-L1 agents. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* **1869**, 78–84 (2018).
98. Brand, A. *et al.* LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. *Cell Metab* **24**, 657–671 (2016).